EXHIBIT 86

Clinical guidelines for children and adolescents experiencing gender dysphoria or incongruence: a systematic review of guideline quality (part 1)

Jo Taylor, Ruth Hall, Claire Heathcote, Catherine Elizabeth Hewitt, Trilby Langton, Lorna Fraser

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/archdischild-2023-326499).

Department of Health Sciences, University of York, York, UK

Correspondence to
Dr Jo Taylor, Department of Health Sciences, University of York, York, UK; dohs-gender-research@york.ac.uk

Received 24 October 2023
Accepted 15 December 2023

► http://dx.doi.org/10.1136/archdischild-2023-326347
► http://dx.doi.org/10.1136/archdischild-2023-326348
► http://dx.doi.org/10.1136/archdischild-2023-326112
► http://dx.doi.org/10.1136/archdischild-2023-326500
► http://dx.doi.org/10.1136/archdischild-2023-326669
► http://dx.doi.org/10.1136/archdischild-2023-326670
► http://dx.doi.org/10.1136/archdischild-2023-326760
► http://dx.doi.org/10.1136/archdischild-2023-326681

To cite: Taylor J, Hall R, Heathcote C, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2023-326499

ABSTRACT

Background Increasing numbers of children and adolescents experiencing gender dysphoria/incongruence are being referred to specialist gender services. There are various guidelines outlining approaches to the clinical care of these children and adolescents.

Aim To examine the quality and development of published guidelines or clinical guidance containing recommendations for managing gender dysphoria/incongruence in children and/or adolescents (age 0-18). A separate paper reports the synthesis of guideline recommendations.

Methods A systematic review and narrative synthesis. Databases (Medline, Embase, CINAHL, PsycINFO, Web of Science) were searched to April 2022 and web-based searches and contact with international experts continued to December 2022, with results assessed independently by two reviewers. The Appraisal of Guidelines for Research and Evaluation tool was used to examine guideline quality.

Results Twenty-three guidelines/clinical guidance publications (1998–2022) were identified (4 international, 3 regional and 16 national). The quality and methods reporting in these varied considerably. Few guidelines systematically reviewed empirical evidence, and links between evidence and recommendations were often unclear. Although most consulted with relevant stakeholders, including 10 which involved service users or user representatives, it was often unclear how this influenced recommendations and only two reported including children/adolescents and/or parents. Guidelines also lacked clarity about implementation. Two international guidelines (World Professional Association for Transgender Health and Endocrine Society) formed the basis for most other guidance, influencing their development and recommendations.

Conclusions Most clinical guidance for managing children/adolescents experiencing gender dysphoria/incongruence lacks an independent and evidence-based approach and information about how recommendations were developed. This should be considered when using these to inform service development and clinical practice.

PROSPERO registration number CRD42021289659.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Increasing numbers of children and adolescents are being referred to specialist gender services.
⇒ Several clinical guidelines of varying quality exist to support the clinical care of children and adolescents experiencing gender dysphoria/incongruence and their families.
⇒ Current systematic reviews have focused on a subset of guidelines and there is a need to assess all guidelines that may be influencing care provision for these children/adolescents.

WHAT THIS STUDY ADDS

⇒ This review identified 23 guidelines or clinical guidance publications that contain recommendations about the management of children and/or adolescents experiencing gender dysphoria/incongruence.
⇒ Few guidelines are informed by a systematic review of empirical evidence and lack transparency about how recommendations were developed. Only two reported consulting directly with children and/or adolescents during their development.
⇒ Most national and regional guidance has been influenced by the World Professional Association for Transgender Health and Endocrine Society guidelines, which themselves lack developmental rigour and are linked through cosponsorship.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Healthcare services and professionals should take into account the poor quality and inter-related nature of published guidance to support the management of children and adolescents experiencing gender dysphoria/incongruence.

INTRODUCTION

Internationally, there has been a reported increase in the number of children and adolescents describing themselves as gender questioning or identifying as transgender.[1] For some, this experience may not be distressing and require limited professional input; however, for others, difficulties in gender development can be associated with significant distress.[2] Gender dysphoria is the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition diagnostic category referring to psychological distress and/or functional impairment that results from incongruence between experienced or expressed

gender and sex registered at birth.[3] The more recently published International Classification of Diseases, 11th edition uses the broader term of gender incongruence,[4] although both terms continue to be used in clinical practice. The prevalence of gender dysphoria/incongruence in children and adolescents is currently unknown due to lack of population-level data.[2 5] However, referrals to specialist paediatric gender services have increased considerably over the last 10-15 years.[2] For example, the UK paediatric gender service received 3585 referrals in 2021–2022 compared with 210 in 2011–2012.[6]

Alongside this overall rise in numbers, there has been recognition that this population have high rates of mental health and well-being needs as well as broader psychological and social complexity.[7–10] There is a need to ensure that the increasing numbers of children and adolescents presenting with experiences of gender-related distress receive timely, appropriate and evidence-based care. Guidelines for the management of gender dysphoria/incongruence can help to ensure the needs of children and adolescents are met, and that provision is equitable and evidence based.[11]

Several clinical guidelines exist to inform care provision for this population.[12 13] Recent systematic reviews have identified and appraised guidelines for transgender care, raising concerns about their quality.[12–14] However, they each focus on a subset of guidelines: Dahlen *et al*[12] only included international guidelines and Ziegler *et al*[13 14] focused on guidelines for primary care. This systematic review builds on these reviews by appraising and synthesising all published guidance that includes recommendations regarding the care of children and adolescents experiencing gender dysphoria/incongruence. The review is reported in two papers, with this first paper describing the guidelines and examining their quality and development, and the second synthesising recommendations.[15]

METHODS

This review forms part of a linked series examining the epidemiology, care pathways, outcomes and experiences for children and adolescents experiencing gender dysphoria/incongruence (protocol registered on PROSPERO: CRD42021289659[16]). The review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17]

Search strategy

A single search strategy was used comprising two combined concepts: 'children', which included all terms for children and adolescents; and 'gender dysphoria', which included associated terms such as gender-related distress and gender incongruence, and gender identity terms including transgender, gender diverse and non-binary.

MEDLINE (online supplemental table 1), EMBASE and PsycINFO through OVID, CINAHL Complete through EBSCO and Web of Science (Social Science Citation Index) were searched (13–23 May 2021; updated 27 April 2022).

Reference lists of included guidelines and relevant systematic reviews were assessed.[12–14] International experts were contacted and key organisational websites reviewed to December 2022.

Inclusion criteria

Published articles or documents that provide at least one specific recommendation for the assessment and/or care of children and/or adolescents (age 0–18) experiencing gender dysphoria/incongruence, and which were developed by or for a professional, healthcare or government organisation or from a research study, were included in the review.

These criteria enabled us to include documents like blueprints and position statements that include recommendations developed for practice and that are available for clinicians to use. Adopting these broad criteria enabled us to map and assess the quality of all clinical guidance that is potentially influencing practice regardless of method of development or year of publication and to examine any changes in guidance and its development over time. In making this decision, we also considered the knowledge that clinical guidelines are not always informed by a systematic review of evidence or developed robustly, despite this being implied in guideline definitions.[11] The document type or title is, therefore, potentially misleading as a criterion for inclusion.

Guidelines for adults, all ages or those not specifying a target population were included if they contained explicit recommendations for children/adolescents.

Originally we planned to include publications in the English language[16]; however, in order to include the increasing number of national guidelines published in Europe, we expanded this to include those that could be reliably translated. For guidance not published in English, we requested official or reliable translations from international experts or used DeepL Pro translation services[18] where these were not available.

Selection

The results of database and other searches were uploaded to Covidence[19] and screened independently by two reviewers. Full texts for potentially relevant articles were reviewed against inclusion criteria by two reviewers independently. Disagreements were resolved through discussion and inclusion of a third reviewer where necessary.

Data extraction

We extracted data on guidance characteristics, development and content into prepiloted data extraction templates. All extraction was undertaken by a single reviewer and second checked by another.

Quality appraisal

To be eligible for appraisal, guidance needed to describe the methodology in the main or auxiliary documents,[11] in addition to meeting inclusion criteria for the review.

We used the Appraisal of Guidelines for REsearch & Evaluation (AGREE) II instrument to assess quality.[20] This validated tool was designed to assess the quality of practice guidelines but has been successfully applied to other types of guidance in this practice area.[12 13] The tool contains 23 criteria organised around six quality domains (scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence), followed by an overall assessment on quality and whether a guideline should be recommended for use in practice. The criteria and overall assessment are rated on a 7-point scale from 1 'strongly disagree' to 7 'strongly agree'. Response options for recommendation for use are 'yes', 'yes, with modifications' or 'no'. A quality score is calculated for each domain, which represents the total summed score of all reviewers' ratings as a percentage of the maximum possible domain score.[21]

Guidance was appraised independently by three reviewers using My AGREE PLUS, an online appraisal platform.[21] Following the Dahlen *et al* systematic review,[12] a colour coding

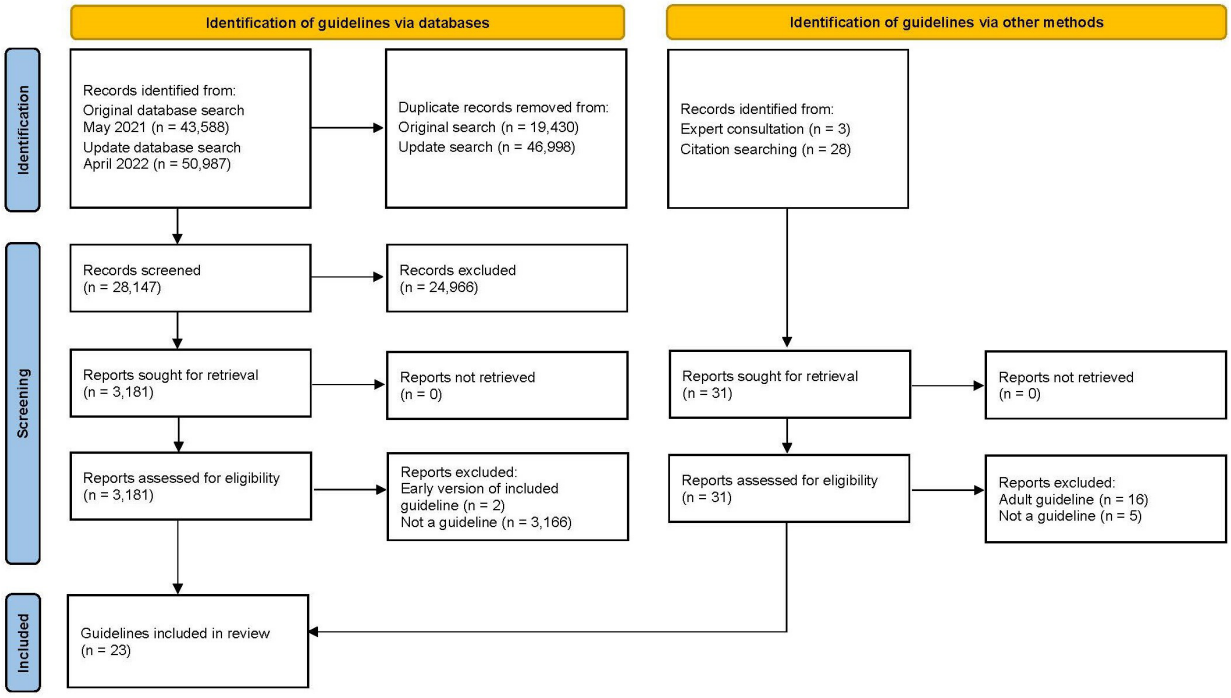


Figure 1 Study flow diagram.

scheme was used to aid visual comparison of domain scores (≤30%, 31%–69%, ≥70%). All reviewers undertaking appraisal read the AGREE II User Manual[21] and appraised and discussed the same two guidance publications first to improve reviewer competence.

Synthesis

Synthesis was undertaken using a narrative approach and involved a series of team discussions to ensure accurate interpretation of included guidance. To examine development, we reviewed reported methods against AGREE II domains, considering both quality of reporting and methods described. This included exploring how evidence was used to inform recommendations, how recommendations were developed and agreed and who was involved in this process and how the guidance referenced and used other included guidance during their development. For the latter, we produced a visual map to show these links.

RESULTS

Database searches yielded 28 147 records, 3181 of which were potentially relevant for the linked series of reviews. From these, 13 guidelines or other clinical guidance meeting our criteria were identified.[22–34] An additional 31 sources were identified as potential guidelines (via citation searching and expert consultation), 10 of which met inclusion criteria.[35–44] In total, 23 distinct clinical guidance publications (referred to in the synthesis as guidelines) were identified (see figure 1 and online supplemental table 2).

The 23 guidelines were published from 1998 to 2022, with all but two published after 2010. Four guidelines are international,[25 31 33 34] three regional (one covering Europe,[26] one Asia and the Pacific[38] and one the Caribbean[40]), and others are national, with four from the US,[22–24 44] two from Spain[32 42] and one each from Australia,[29] Canada,[37] Denmark,[36] Finland,[35] Italy,[27] New Zealand,[28] Norway,[39] South Africa,[41] Sweden[43] and the UK[30] (see figure 2). Three guidelines were translated into English.[35 39 43]

Five guidelines are position or policy statements from professional societies or organisations,[23 26 27 31 32] two are blueprints developed by multiple regional and international organisations,[38 40] and one is a practice parameter developed by a professional organisation.[22] The remaining 15 are guidelines: four were developed for national government bodies,[35 36 39 43] seven for or adopted by professional organisations,[24 25 28 30 34 41 42] three for healthcare organisations[29 37 44] and one a research study.[33]

Seven guidelines reference a previous version,[25 28 34 36 40 43 44] two of which have multiple updates.[34 36] Three guidelines were published by the developer[45–47] and as an academic paper.[28 29 41]

Seven guidelines focus on the care and/or treatment of children and adolescents experiencing gender dysphoria/incongruence[22 23 29 30 32 35 43] (one also covers practice for sexual minority children/adolescents[22]). Four guidelines cover adolescents only,[27 31 33 37] one of which is about co-occurring autism spectrum condition and gender dysphoria/incongruence.[33] One guideline, which has a specific focus on sexual function and satisfaction, covers adolescents and adults,[26] and 10 guidelines cover all transgender and/or gender diverse people but include chapters or sections specific to children/adolescents.[25 28 34 36 38–42 44] The final guideline is about psychological practice for adults but contains one section about adolescents.[24]

The target audience is generally broad, with 11 guidelines targeting healthcare providers[27–29 31 32 34–36 39 41 44] and five healthcare providers plus other stakeholders, for example, social care professionals or policymakers.[26 37 38 40 43] Two are for psychiatrists,[22 30] one for psychologists,[24] one for paediatricians,[23] one for endocrinologists[25] and two do not specify.[33 42]

Multiple areas of practice are covered in the guidelines. These include care models, principles and practices; service composition, roles and expertise; assessment; psychosocial care; information and advocacy; social transition; puberty suppression; masculinising/feminising hormones; surgical interventions;

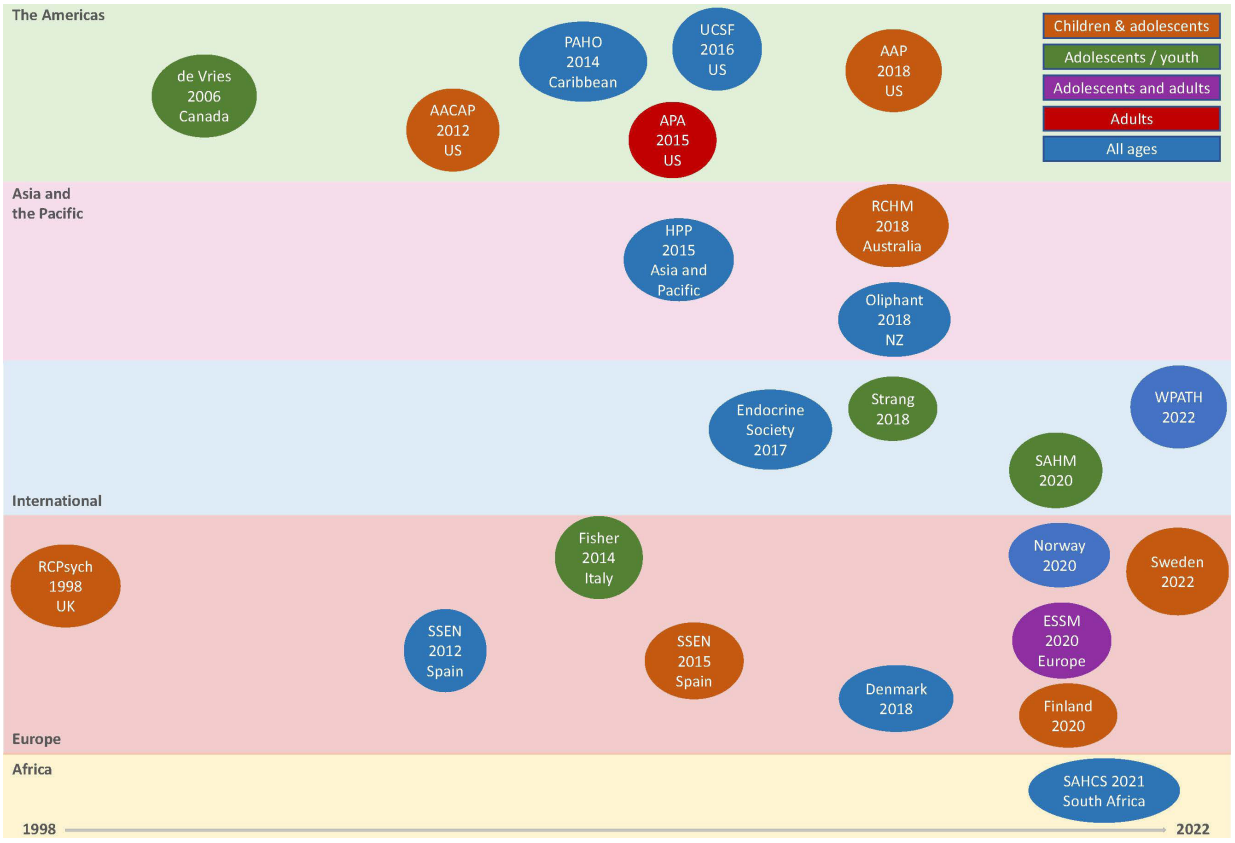


Figure 2 Regional timeline for guidelines. Presents a timeline for the included guidelines by geographical region, country and target population. AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; APA, American Psychological Association; ESSM, European Society for Sexual Medicine; HPP, Health Policy Project; PAHO, Pan American Health Organisation; RCHM, Royal Children's Hospital Melbourne; RCPsych, UK Royal College of Psychiatrists; SAHCS, South African HIV Clinicians Society; SAHM, Society for Adolescent Health and Medicine; SSEN, Spanish Society for Endocrinology and Nutrition; UCSF, University California, San Francisco; WPATH, World Professional Association for Transgender Health.

fertility care; other interventions (eg, voice therapy); sexual health and functioning; and physical health and lifestyle. Content varies depending on guideline scope and audience. More guidelines focus on medical treatments than psychosocial care.

Guideline methods and quality

Of the 23 guidelines, four provided no information about the process of development and could not be appraised.[30 32 36 42]

The 19 guidelines reporting methods varied in approach and quality of reporting. Most were developed by a core group of clinical experts with broader consultation with other professional stakeholders, although the nature of consultation and stakeholders varied. Few provided clear information about how experts were recruited or selected. Of the 16 that reported wider consultation,[22–25 28–30 33 34 37–41 43 44] only two described a formal consensus methodology[33 34] and a third reported a modified consensus process, but no details are provided.[44] Across guidelines, it was unclear how input from wider stakeholders informed recommendations.

Ten guidelines reported engaging with service users or service user representatives.[24 28 29 34 35 38–41 43] Methods varied, with two reporting separate research or consultation,[24 35] but most consulting with service users alongside other stakeholders during development or by obtaining their views on draft guidelines, although details are limited. Three of these guidelines also published a draft guideline for public comment,[24 34 39] which may have involved contributions from the transgender and gender diverse community although again details are limited. Only two guidelines reported consulting directly with children/adolescents or their parents,[29 43] and a second guideline listed them as potential stakeholders but it was unclear whether their views were included.[34] Others consulted with transgender or gender diverse adults or organisations representing children/adolescents experiencing gender dysphoria/incongruence or the broader transgender community.

Most guidelines reference evidence sources to support recommendations. However, only five described using a systematic approach to searching and/or selecting evidence, and in most cases, this covered one or two specific aspects of practice.[22 25 34 35 43] Three of the guidelines that reviewed evidence,[25 34 43] and another guideline not reporting a systematic approach to finding evidence,[44] reported appraising the quality and strength of evidence they reviewed. The Finnish guideline chose not to appraise quality in their systematic review because they determined all studies were poor quality on the basis of study design.[35]

Across guidelines, it was difficult to detect what evidence had been reviewed and how this informed development of recommendations, and the links between specific recommendations and evidence were often unclear or missing. For example, all but seven guidelines[27 28 30 38 40–42] describe insufficient evidence about the risks and benefits of medical treatments for adolescents, particularly in relation to long-term outcomes. At the same time, many of these guidelines then cite this evidence or

Table 1 Critical appraisal domain scores

Guideline ID	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial independence
AACAP 2012	65	39	44	63	7	31
American Academy of Paediatrics 2018	70	26	12	30	6	69
American Psychological Association 2015	74	74	24	50	18	14
Council for Choices in Healthcare Finland 2020	91	69	51	72	56	0
de Vries 2006	63	31	10	74	17	6
Endocrine Society 2009	65	33	44	70	22	31
Endocrine Society 2017	63	33	42	72	21	92
European Society for Sexual Medicine 2020	63	52	39	70	7	58
Fisher 2014	65	20	12	35	17	44
Health Policy Project 2015	63	63	16	24	33	6
Norwegian Directorate of Health 2020	76	81	30	57	47	17
Oliphant 2018	44	39	12	33	21	0
Pan American Health Organisation 2014	52	44	13	31	21	0
Royal Children's Hospital Melbourne 2018	81	59	19	41	19	14
Society for Adolescent Health and Medicine 2020	41	24	17	41	7	0
South African HIV Clinicians Society 2021	59	59	21	43	24	69
Strang 2018	87	31	18	37	15	19
Swedish National Board of Health & Welfare 2022	91	87	71	83	25	36
UCSF 2016	70	41	23	37	26	0
WPATH 2012	85	61	26	56	17	17
WPATH 2022	83	63	35	56	24	39

≥70%, 31%–69%, ≤30%.
AACAP, American Academy of Child & Adolescent Psychiatry; UCSF, University of California, San Francisco; WPATH, World Professional Association for Transgender Health.

refer to guidelines that recommend these treatments to support a similar recommendation. Only the Swedish guideline makes a different recommendation, linking the lack of evidence about medical treatments to their recommendation that these should be provided under a research framework and for exceptional cases until this is established.[43] The Finnish guideline also takes a more cautious approach and recommends that medical interventions, which are described as experimental on the basis of their own evidence review, must be provided at the two central research clinics in Finland, and that data on the effects of these treatments should be systematically collected.[35]

Table 1 shows the AGREE II domain scores for the appraised guidelines. Most scored well regarding clarity of scope and purpose and scored poorly regarding applicability, editorial independence and rigour of development. Guidelines often differed between domains, although overall few guidelines scored highly across the domains. Only six guidelines scored higher than 30% for rigour,[22 25 26 34 35 43] and only the Swedish guideline scored higher than 70%.[43] In the stakeholder involvement and clarity of presentation domains, guidelines varied considerably. For example, in certain guidelines, it was not always easy to discern a recommendation from a suggestion, and recommendations were not always specific or unambiguous. Additionally, in guidelines covering all age groups, the terms adults and people were sometimes used interchangeably without defining them, making it difficult to assess whether recommendations about people were referring to children and/or adolescents.

Online supplemental table 3 shows the overall scores and assessment of whether guidelines should be recommended for practice. Only two guidelines were recommended for practice by all three appraisers: the Swedish[43] and Finnish[35] guidelines. These guidelines were the only two that scored higher than 50% for rigour of development due to their evidence-based approach and transparent reporting of this. They were also the only guidelines, which included a formal ethics review and they both scored highly on stakeholder involvement.

Links and influences between guidelines

All but two guidelines,[30 36] both of which contain no reference list and do not report methods of development, cite at least one other guideline. Figure 3 shows the different ways in which guidelines reference or use other guidelines and the level of influence guidelines have on each other. Examples of different links include citing another guideline as a resource for the reader, citing a guideline to justify or support a single or multiple recommendations, explicitly adopting another guideline's recommendation(s), recommending that another guideline be used alongside their own or reviewing other guidelines to inform the development of recommendations.

The links examined show that early versions of two international guidelines, the Endocrine Society[25] and World Professional Association for Transgender Health (WPATH)[34] guidelines (specifically the 2009 Endocrine Society guideline[48] and WPATH V.7 published in 2012)[49] have influenced nearly all the national and regional guidelines identified. The two guidelines also have close links, with WPATH adopting Endocrine Society recommendations in its own guideline and acting as a cosponsor for and providing input on drafts of the Endocrine Society guideline. Due to the considerable influence of these two guidelines, the quality of the current and preceding versions for both was appraised.

The type of relationship between the Endocrine Society and WPATH guidelines and other guidelines varied. For example, WPATH V.7[49] formed the basis of an initial draft of the Australian guideline[29]; the American Psychological Association (APA)[24] recommends using their guideline in tandem with WPATH[49] and Endocrine Society[48] guidelines; the guideline developed in New Zealand[28] is offered as additional guidance to WPATH[49] and adopts numerous recommendations from this and Endocrine Society[25] guidelines; the regional blueprints[38 40] adopt WPATH[49] criteria for hormone treatments; and the Norwegian guideline[39] describes their overall approach and principles as consistent with WPATH[49] and Endocrine Society,[25] along with

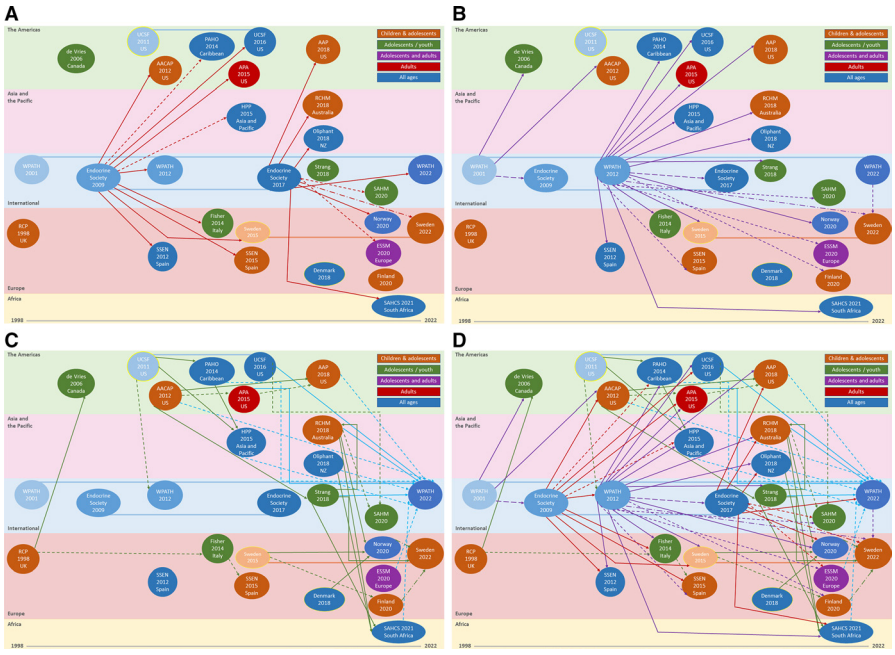


Figure 3 Links between guidelines. (A–D) show how the guidelines have influenced each other using the regional timeline shown in figure 2. (A) Shows how guidelines have cited and drawn on the Endocrine Society guidelines (indicated by red arrows). (B) Shows how guidelines have cited and drawn on the World Professional Association for Transgender Health (WPATH) guidelines (indicated by purple arrows). (C) Shows how guidelines have cited and drawn on other guidelines (indicated by green arrows). A different colour (blue) was used to show how the latest Endocrine Society and WPATH guidelines have cited and drawn on these other guidelines. (D) Shows all the links between the guidelines. Link symbol: Solid line: guideline has been adapted from the source guideline, has adopted numerous key recommendations from the source guideline or used the source guideline as evidence to support numerous key recommendations or recommends using the source guideline alongside its own. Short-dashed line: included reference to the source guideline or has adopted one or two key recommendations or used the source guideline as evidence to support these. Long dashed line: co-sponsor with direct involvement in development process. Long and short dashed line: critically reviewed recommendations from source guideline as key element of development process. Guidelines circled in yellow are those for which there are no available references to assess any potential links with other guidelines.

the Australian,[29] Danish[36] and Swedish 2015[50] guidelines. The updated 2022 Swedish guideline[43] took a different approach, which involved examining the WPATH,[49] Endocrine Society,[25] Finnish[35] and Norwegian[39] recommendations against their own evidence review and knowledge base to consider whether to adopt them (with the process reported in a separate Appendix published alongside the guideline[51]). The basis for decisions to adopt WPATH or Endocrine Society recommendations in other guidelines is unclear.

The Endocrine Society and WPATH V.7 guidelines contain few references to other guidelines. However, WPATH V.8 published in 2022 identifies numerous national and regional guidelines published as early as 2012 as potentially valuable resources and cites the APA,[24] Australian,[29] New Zealand[28] and University California, San Francisco[44] guidelines multiple times to support recommendations, all of which were themselves influenced considerably by WPATH V.7.

DISCUSSION

This systematic review identified 23 guidelines or clinical guidance publications (4 international, 3 regional and 16 national), nine of which focus solely on the management of children and/or adolescents experiencing gender dysphoria/incongruence.[23 27 29–32 35 37 43] Guidance quality and methods reporting varied considerably, and only five reported using a systematic approach to using evidence to inform recommendations.[22 25 34 35 43] Links between evidence and recommendations are often unclear, and information about how recommendations were developed in the absence of reviewing evidence is limited. There is also limited guidance on how to implement recommendations, and in some cases, a lack of clarity as to what is being recommended and for who. Although consultation with stakeholders was common, only 10 involved service users or their representatives, and it was unclear how this influenced recommendations. Only two reported consulting directly with children/adolescents or their parents, so few guidelines have been informed by an understanding of the needs and preferences of this population.

The findings from this review, therefore, raise questions about the credibility of currently available guidance, despite the majority being published in the last 5 years. Most guidelines have not followed international standards for guideline development set out by the AGREE2 initiative,[20] and/or provide insufficient information about their development. Because of this, the review team only recommended two guidelines for practice—the Finnish guideline published in 2020[35] and the Swedish guideline published in 2022,[43] neither of which were included in previously published systematic reviews.[12 13] These are the only guidelines to publish details of how developers reviewed and utilised the evidence-base and the decision-making behind their recommendations. For example, they explicitly link the lack of robust evidence about medical treatments for adolescents, as established from their own systematic reviews,[52 53] with the recommendation for a more cautious approach to treatment and the need for gender services providing these treatments to collect outcome data, with Sweden recommending that medical

treatments should only occur under a research framework. They are also the only guidelines which have been informed by an ethical review conducted as part of guideline development. However, even these guidelines, like others, lack clear recommendations regarding certain aspects of practice and would benefit from more detailed guidance regarding implementation of recommendations.

Although other guidance mostly acknowledges the lack of robust evidence regarding medical treatments for adolescents, some then suggest existing evidence is sufficient to recommend them. Others have instead used a consensus or expert-led approach that results in the same recommendation or have adopted recommendations from the Endocrine Society guideline[25 48] or WPATH V.7,[49] despite the latter having been published a decade earlier in some cases. These two guidelines are themselves linked through cosponsorship and like other guidelines lack a robust and transparent approach to their development. Although it is not uncommon to adopt an expert consensus-based approach when evidence is limited, it is less common for guideline developers to draw so heavily on other guidelines.[11] This relationship may explain why there has until recently been an apparent consensus on key areas of practice for which evidence remains lacking.[54]

Previous systematic reviews have also found guidelines to be lacking in methodological quality, transparency and clarity,[12 13] and Dahlen *et al* recommend clinicians proceed with caution due to the gap between clinical practice and research in this area. Although neither highlight the interdependent nature of available guidance, this is not surprising due to their focus on a subset of mainly international guidelines. However, a recent BMJ article,[55] which too highlights the lack of an evidence-based approach, draws attention to the different conclusions in the Swedish and Finnish guidelines about the risks and benefits of medical treatments, which marks a considerable departure from all other guidance.

The different conclusions in recently published guidelines and concerns about guideline quality, combined with limited evidence about the most appropriate assessment and care pathways for children and adolescents experiencing gender dysphoria/incongruence has led to clinical uncertainty in practice and changing service provision and policy.[55] Large well-designed and conducted research that assesses long-term care outcomes for this population is urgently needed to inform future clinical guidelines, which themselves must be underpinned by an evidence-based and transparent approach that includes direct consultation with children and adolescents and their families.

Strengths and limitations

This review followed a published protocol and used robust search strategies. A systematic approach to appraise quality was used, although the AGREE2 tool was developed to appraise clinical guidelines rather than the broader set of guidance included in this review. A detailed examination of how guidance was developed facilitated new insights about the links between published guidelines. The search strategy may not have identified all guidelines not published in English. As searches were conducted to April 2022, this review does not include more recently published guidance; as this is a rapidly evolving area this is a limitation.

CONCLUSIONS

Most clinical guidance lacks an evidence-based approach and provides limited information about how recommendations were developed. The WPATH and Endocrine Society international guidelines, which like other guidance lack developmental rigour and transparency have, until recently, dominated the development of other guidelines. Healthcare professionals should consider the lack of quality and independence of available guidance when utilising this for practice. Future guidelines should adhere to standards for guideline development and provide greater transparency about how recommendations are developed and links between evidence and recommendations. The views of children, adolescents, parents and carers should also inform future guideline development.

Contributors LF and TL contributed to the conception of the review. JT, RH, LF, and TL designed the review methods. JT, RH and CH carried out screening, extraction and critical appraisal. JT, CEH, RH, LF, and TL contributed to data synthesis. JT drafted the manuscript. All authors contributed to interpretation of results and reviewed the manuscript prior to submission. CEH accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was funded by NHS England to inform the Cass Review (Independent review of gender identity services for children and young people). The funder and Cass Review team had a role in commissioning the research programme but no role in the study conduct, interpretation or conclusion.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer-reviewed.

Data availability statement Data sharing is not applicable as no datasets were generated and/or analysed for this study.

ORCID iDs
Jo Taylor http://orcid.org/0000-0001-5898-0900
Catherine Elizabeth Hewitt http://orcid.org/0000-0002-0415-3536

REFERENCES

1 Zhang Q, Goodman M, Adams N, *et al*. Epidemiological considerations in transgender health: a systematic review with focus on higher quality data. *Int J Transgend Health* 2020;21:125–37.
2 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender dysphoria literature: 1) epidemiology. *PLOS Glob Public Health* 2022;2:e0000245.
3 American Psychiatric Association. *Diagnostic and statistical Manual of mental disorders: DSM-5*5th edn. Washington, DC: American Psychiatric Publishing, 2013.
4 World Health Organisation. ICD-11: International classification of diseases for mortality and Morbidiy Statistics (11th revision); 2022.
5 Zucker KJ. Epidemiology of gender dysphoria and transgender identity. *Sex Health* 2017;14:404–11.
6 The Tavistock and Portman NHS Foundation Trust. Number of referrals to GIDS (gender identity development service). 2023. Available: https://gids.nhs.uk/about-us/number-of-referrals/
7 Frew T, Watsford C, Walker I. Gender dysphoria and psychiatric comorbidities in childhood: a systematic review. *Aust J Psychol* 2021;73:255–71.
8 Surace T, Fusar-Poli L, Vozza L, *et al*. Lifetime prevalence of suicidal Ideation and suicidal behaviors in gender non-conforming youths: a meta-analysis. *Eur Child Adolesc Psychiatry* 2021;30:1147–61.
9 Kozlowska K, McClure G, Chudleigh C, *et al*. Australian children and adolescents with gender dysphoria: clinical presentations and challenges experienced by a multidisciplinary team and gender service. *Human Systems* 2021;1:70–95.

10 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender dysphoria literature: 2) mental health. *PLOS Glob Public Health* 2022;2:e0000426.
11 Lunny C, Ramasubbu C, Puil L, *et al*. Over half of clinical practice guidelines use non-systematic methods to inform recommendations: a methods study. *PLoS One* 2021;16:e0250356.
12 Dahlen S, Connolly D, Arif I, *et al*. International clinical practice guidelines for gender minority/Trans people: systematic review and quality assessment. *BMJ Open* 2021;11:e048943.
13 Ziegler E, Charnish E, Carroll B, *et al*. A critical review of clinical practice guidelines for care of transgender and gender diverse children and youth for use by primary care practitioners. *Transgend Health* 2022;7:397–406.
14 Ziegler E, Carroll B, Charnish E. Review and analysis of international transgender adult primary care guidelines. *Transgend Health* 2021;6:139–47.
15 Taylor J, Hall R, Heathcote C, *et al*. Clinical guidelines for children and adolescents experiencing gender Dysphoria or Incongruence: a systematic review of recommendations (part 2). *Arch Dis Child* 2024;0:1–10.
16 Fraser L, Hall R, Taylor J, *et al*. The epidemiology, management and outcomes of children with gender-related distress / gender dysphoria: a systematic review. PROSPERO 2021 CRD42021289659; 2021.
17 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
18 DeepL SE. Deepl pro; 2023.
19 Veritas Health Innovation. *Covidence systematic review software*. Melbourne, Australia: Veritas Health Innovation, 2023.
20 Brouwers MC, Kho ME, Browman GP, *et al*. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010;182:E839–42.
21 AGREE Next Steps Consortium. The AGREE II Instrument [Electronic Version].2017. Available: http://www.agreetrust.org
22 Adelson SL, American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter on gay, lesbian, or bisexual sexual orientation, gender nonconformity, and gender discordance in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 2012;51:957–74.
23 Rafferty J, COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, COMMITTEE ON ADOLESCENCE, *et al*. Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. American academy of paediatrics (AAP). *Pediatrics* 2018;142:e20182162.
24 American Psychological Association. Guidelines for psychological practice with transgender and gender nonconforming people. *Am Psychol* 2015;70:832–64.
25 Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-dysphoric/gender-Incongruent persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017;102:3869–903.
26 T'Sjoen G, Arcelus J, De Vries ALC, *et al*. European society for sexual medicine position statement "assessment and hormonal management in adolescent and adult trans people, with attention for sexual function and satisfaction. *J Sex Med* 2020;17:570–84.
27 Fisher AD, Ristori J, Bandini E, *et al*. Medical treatment in gender dysphoric adolescents endorsed by SIAMS-SIE-SIEDP-ONIG. *J Endocrinol Invest* 2014;37:675–87.
28 Oliphant J, Veale J, Macdonald J, *et al*. Guidelines for gender affirming healthcare for gender diverse and transgender children, young people and adults in aotearoa. *N Z Med J* 2018;131:86–96.
29 Telfer MM, Tollit MA, Pace CC, *et al*. Australian standards of care and treatment guidelines for transgender and gender diverse children and adolescents. *Med J Aust* 2018;209:132–6.
30 The Royal College of Psychiatrists. Gender identity disorders in children and adolescents guidance for management, council report Cr63, January 1998. *Int J Transgend* 1998.
31 Society for Adolescent Health and Medicine. Promoting health equality and nondiscrimination for transgender and gender-diverse youth. *J Adolesc Health* 2020;66:761–5.
32 Esteva de Antonio I, Asenjo Araque N, Hurtado Murillo F, *et al*. Position statement: gender dysphoria in childhood and adolescence. working group on gender identity and sexual development of the Spanish society of endocrinology and nutrition (GIDSEEN). *Endocrinol Nutr* 2015;62:380–3.
33 Strang JF, Meagher H, Kenworthy L, *et al*. Initial clinical guidelines for co-occurring autism spectrum disorder and gender dysphoria or Incongruence in adolescents. *J Clin Child Adolesc Psychol* 2018;47:105–15.
34 Coleman E, Radix AE, Bouman WP, *et al*. Standards of care for the health of transgender and gender diverse people, version 8. *Int J Transgend Health* 2022;23(Suppl 1):S1–259.
35 Council for Choices in Healthcare in Finland. Medical treatment methods for Dysphoria associated with variations in gender identity in minors – recommendation. 2020. Available: https://palveluvalikoima.fi/en/recommendations#genderidentity
36 Danish Health Authority. Guide on Healthcare related to gender identity. 2018. Available: https://www.sst.dk/-/media/English/Publications/2018/Guide-on-healthcare-related-to-gender-identity.ashx?sc_lang=en&hash=0FF626604C50D5EED94852CA5D042A8E
37 de Vries AL, Cohen-Kettenis PT, Delemarre-Van de Waal H. Clinical management of gender Dysphoria in adolescents. caring for Transgender adolescents in BC: suggested guidelines. Transcend Transgender Support & Education Society and Vancouver Coastal Health's Transgender Health Program; 2006. Available: https://rainbowhealth.wpenginepowered.com/wp-content/uploads/2009/05/Guidelines-adolescent.pdf
38 Health Policy Project, Asia Pacific Transgender Network, United Nations Development Programme. Blueprint for the provision of comprehensive care for Trans people and Trans communities in Asia and the Pacific. Futures Group, Health Policy Project; 2015. Available: https://www.undp.org/asia-pacific/publications/blueprint-provision-comprehensive-care-trans-people-and-trans-communities-asia-and-pacific
39 Norwegian Directorate of Health. Gender Incongruence: national professional guideline; 2020. Available: https://www.helsedirektoratet.no/retningslinjer/kjonnsinkongruens
40 Pan American Health Organisation, World Professional Association for Transgender Health. Blueprint for the provision of comprehensive care for Trans persons and their communities in the Caribbean and other Anglophone countries. John Snow, Inc; 2014. Available: https://www.paho.org/en/node/50469
41 Tomson A, McLachlan C, Wattrus C, *et al*. Southern African HIV clinicians' society gender-affirming healthcare guideline for South Africa. *South Afr J HIV Med* 2021;22:1299.
42 Moreno-Pérez O, Esteva De Antonio I, Grupo de Identidad y Diferenciación Sexual de la SEEN (GIDSEEN). Clinical practice guidelines for assessment and treatment of transsexualism. SEEN identity and sexual differentiation group (GIDSEEN). *Endocrinol Nutr* 2012;59:367–82.
43 The Swedish National Board of Health and Welfare. Care of children and young people with gender Dysphoria - national knowledge support with recommendations for the profession and decision makers. 2022. Available: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-12-8302.pdf
44 University of California San Francisco Gender Affirming Health Program. Guidelines for the primary and gender-affirming care of Transgender and gender Nonbinary people. University of California San Francisco; 2016. Available: https://transcare.ucsf.edu/guidelines
45 Oliphant J, Veale J, Macdonald J, *et al*. Guidelines for gender affirming Healthcare for gender diverse and Transgender children, young people and adults in Aotearoa, New Zealand. Transgender Health Research Lab, University of Waikato; 2018. Available: https://researchcommons.waikato.ac.nz/handle/10289/12160
46 Telfer M, Tollit MA, Pace CC. Australian standards of care and treatment guidelines. for Trans and gender diverse children and adolescents. The Royal Children's Hospital; 2020. Available: https://www.rch.org.au/uploadedFiles/Main/Content/adolescent-medicine/australian-standards-of-care-and-treatment-guidelines-for-trans-and-gender-diverse-children-and-adolescents.pdf
47 Tomson A, McLachlan C, Wattrus C, *et al*. Southern African HIV Clinicians society gender-affirming Healthcare guideline for South Africa – expanded version. Southern African HIV Clinicians Society; 2021. Available: https://sahivsoc.org/Files/SAHCS%20GAHC%20guidelines-expanded%20version_Oct%202021(3).pdf
48 Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, *et al*. Endocrine treatment of transsexual persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2009;94:3132–54.
49 Coleman E, Bockting W, Botzer M, *et al*. Standards of care for the health of Transsexual, Transgender, and gender-Nonconforming people, version 7. *Int J Transgend* 2012;13:165–232.
50 The Swedish National Board of Health and Welfare. Good care for children and young people with gender Dysphoria. National knowledge support. 2015. Available: https://etik.barnlakarforeningen.se/wp-content/uploads/sites/16/2022/03/1.-SoS-God-va%CC%8Ard-av-barn-....pdf
51 The Swedish National Board of Health and Welfare. Appendix - knowledge base with method description - care of children and young people with gender Dysphoria. 2022. Available: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-12-8302-kunskapsunderlag-med-metodbeskrivning.pdf
52 Pasternack I, Söderström I, Saijonkari M, *et al*. Medical approaches to treatment of Dysphoria related to gender variations. A systematic review. n.d. Available: https://app.box.com/s/y9u791np8v9gsunwgpr2kqn8swd9vdtx
53 Ludvigsson JF, Adolfsson J, Höistad M, *et al*. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatr* 2023;112:2279–92.
54 Biggs M. The Dutch protocol for juvenile transsexuals: origins and evidence. *J Sex Marital Ther* 2023;49:348–68.
55 Block J. Gender dysphoria in young people is rising—and so is professional disagreement. *BMJ* 2023;380:382.

Supplementary Table S1: Final search strategy for Ovid MEDLINE

1 exp Child/ or Child Behavior/ or Child Health/ or Child Welfare/ or Psychology, Child/ or Child Psychiatry/ or Child Health Services/ or Child Development/ (1984459)
2 Minors/ (2638)
3 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or emerging adult$).ti,ab,kf,jn. (1862660)
4 (young$ adj (people$ or person$1 or adult$ or man$1 or men$1 or woman$ or women$ or male$1 or female$1)).ti,ab,kf,jn. (224878)
5 pediatrics/ (55388)
6 (pediatric$ or paediatric$ or peadiatric$).ti,ab,kf,jn. (543516)
7 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Psychology, Adolescent/ or Adolescent Psychiatry/ or Adolescent Health Services/ or Adolescent Medicine/ or Adolescent Development/ (2088552)
8 Puberty/ (13562)
9 (adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or underage$ or under-age$).ti,ab,kf,jn. (522801)
10 Schools/ or Schools, Nursery/ (42221)
11 exp Child Day Care Centers/ or Child Care/ (11287)
12 (school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1).ti,ab,kf,jn. (356157)
13 or/1-12 (4333601)
14 Gender Dysphoria/ (581)
15 "Sexual and Gender Disorders"/ (79)
16 Transsexualism/ (3895)
17 Transgender Persons/ (3835)
18 Health Services for Transgender Persons/ (152)
19 exp Sex Reassignment Procedures/ (969)
20 "Sexual and Gender Minorities"/ (4924)
21 ((gender$ and dysphori$) or (gender$ adj5 incongru$) or sexual dysphori$).ti,ab,kf. (1784)
22 (gender$ adj (disorder$ or identi$)).ti,ab,kf. or (gender identity/ and dysphori$.ti,ab,kf.) (4568)
23 (GID or GIDS or GIDC or GIDCS).ti,ab,kf. (456)
24 (gender$ adj5 (confusion or confused or questioning or distress$ or discomfort)).ti,ab,kf. (980)
25 (gender$ adj5 (minority or minorities)).ti,ab,kf. (1593)
26 (gender$ adj5 (variant$ or variance$ or nonconform$ or non-conform$ or diverse or diversity or atypical$)).ti,ab,kf. (3409)
27 (non-binary or nonbinary or enby or genderqueer or gender-queer or neutrois).ti,ab,kf. (796)
28 (agender$ or genderless$ or gender-less$ or genderfree or gender-free or ungender$ or un-gender$ or non-gender$ or nongender$ or bigender$ or bi-gender$ or dual gender$ or dualgender$ or demi-gender$ or demigender$ or genderfluid$ or gender-fluid$ or trigender$ or tri-gender$).ti,ab,kf. (315)

29 two spirit$.ti,ab,kf. (84)
30 (trans adj3 (female$ or feminin$ or woman$ or women$ or male$1 or man or mans or men or mens or masculin$ or person$1 or peopl$ or population$ or individual$)).ti,ab,kf. (1362)
31 (transgend$ or trans-gend$ or transex$ or transsex$ or trans-sex$ or transfemale$ or transfeminin$ or transwom$ or transmale$ or transman$ or transmasculin$ or transmen$ or transperson$ or transpeopl$ or transpopulation$ or transindividual$).ti,ab,kf. (10832)
32 (trans adj3 identi$).ti,ab,kf. or (gender identity/ and trans.ti,ab,kf.) or (trans and dysphori$).ti,ab,kf. (1447)
33 (crossgender$ or cross-gender$ or crossex$ or crosssex$ or cross-sex$).ti,ab,kf. (836)
34 ((sex or gender$) adj3 (reassign$ or re-assign$ or affirm$ or confirm$ or transition$)).ti,ab,kf. (3963)
35 ((gender$ or sex) adj (change or changes or changing or changed)).ti,ab,kf. (825)
36 (detransition$ or de-transition$ or desister$ or de-sister$).ti,ab,kf. (134)
37 ((desist$ or persist$) adj5 (transition$ or trans or dysphori$)).ti,ab,kf. (823)
38 or/14-37 (28731)
39 (trans and (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ti. (339)
40 (trans adj5 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ab,kf. (397)
41 (transchild$ or transminor$ or transboy$ or transgirl$ or transkid or transkids or transyoung$ or transyouth$ or transteen$ or transtween$ or transadoles$ or transjuvenil$).ti,ab,kf. (15)
42 13 and 38 (9819)
43 39 or 40 or 41 or 42 (10343)
44 exp animals/ not humans/ (4823832)
45 (editorial or news or comment or case reports).pt. or case report.ti. (3692318)
46 43 not (44 or 45) (9429)
47 limit 46 to english language (9029)

Key to Ovid symbols and commands:
$ Unlimited right-hand truncation symbol
$N Limited right-hand truncation - restricts the number of characters following the word to N

ti,ab,kf,	Searches are restricted to the Title (ti), Abstract (ab), Keyword Heading Word (kf) fields
.jn	Searches are restricted to the Journal name field
adj	Retrieves records that contain terms next to each other (in the shown order)
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-12	Combines sets 1 to 12 using OR

Supplementary Table S2 - Guideline characteristics*

Guideline ID, Year	Type of guideline	Country	Summary of guideline	Target audience	Population	Stated Aim	Produced by	Weblink	Version
American Academy of Child & Adolescent Psychiatry (AACAP) 2012 [21]	Practice Parameter	US	Sets out principles for practice but does not include specific treatment recommendations	Psychiatrists	Children and adolescents (includes sexual minority care as well)	To foster clinical competence in those caring for children and adolescents	American Academy of Child & Adolescent Psychiatry (AACAP)	https://doi.org/10.1016/j.jaac.2012.07.004	1
American Academy of Paediatrics (AAP) 2018 [22]	Policy Statement	US	Sets out nine recommendations regarding role of paediatricians but does not include specific treatment recommendations	Paediatrians	Children and adolescents	To provide suggestions for paediatric providers that are focused on promoting the health and positive development of youth that identity as transgender and gender diverse while eliminating discrimination and stigma	American Academy of Paediatrics	https://doi.org/10.1542/peds.2018-2162	1
American Psychological Association (APA) 2015 [23]	Guideline	US	Sets out 16 guidelines which are principles for psychological practice but within these are recommendations for assessment and psychological care	Psychologists	Adults (includes guideline specific to children and young people)	To assist psychologists in the provision of culturally competent, developmentally appropriate, and trans-affirmative psychological practice	American Psychological Association	https://www.apa.org/practice/guidelines/transgender.pdf	1
Council for Choices in Healthcare in (COHERE) Finland 2020 [34]	Guideline	Finland	National guideline focusing on medical research and treatment methods for the treatment of gender dysphoria	All healthcare providers	Minors (<18) - guidelines for adults and minors developed together but published separately	To provide a recommendation on medical treatment methods for dysphoria associated with variations in gender identity of minors	Council for Choices in Healthcare in Finland	https://palveluvalikoima.fi/en/recommendations#genderidentity	1
Danish Health Authority 2018 [35]	Guideline	Denmark	National guideline covering all aspects of care and broad recommendations	All healthcare providers	All (includes chapter on under 18s)	To ensure a high quality and equal access to healthcare related to gender identity in Denmark.	Danish Health Authority	https://www.sst.dk/-/media/English/Publications/2018/Guide-on-healthcare-related-to-gender-identity.ashx?sc_lang=en&hash=0FF626604C50D5EED94852CA5D042A8E	3
de Vries 2006 [36]	Guideline	Canada	Covers all aspects of care including assessment, psychosocial care and medical interventions	Health and social service professionals	Adolescents (not defined)	To provide professionals working with adolescents with gender-dysphoric feelings practical clinical guidelines for diagnosis and treatment.	Trans Care Project - initiative of Transcend Transgender Support & Education Society and Vancouver Coastal Health's Transgender Health Program	https://rainbowhealth.wpenginepowered.com/wp-content/uploads/2009/05/Guidelines-adolescent.pdf	1

Endocrine Society 2017 [24]	Guideline	International	Covers all aspects of hormone treatment and surgery, including assessment for these	Endocrinologists	All (includes sections on children and adolescents)	To make recommendations and suggestions, based on existing literature and clinical experience, that will enable treating physicians to maximize benefit and minimize risk when caring for individuals diagnosed with gender dysphoria/gender incongruence.	Endocrine Society	https://doi.org/10.1210/jc.2017-01658	2
European Society for Sexual Medicine (ESSM) 2020 [25]	Position statement	Europe	Covers assessment and hormone treatments with emphasis on sexual functioning - includes general principles and treatment recommendations	European sexologists and healthcare providers who encounter trans people in clinical practice.	Adolescents and Adults	To provide an up-to-date overview of clinical consensus statements on trans health care with attention for sexual function and satisfaction.	European Society for Sexual Medicine	https://doi.org/10.1016/j.jsxm.2020.01.012	1
Fisher 2014 [26]	Position Statement	Italy	Covers psychological support and medical intervention including specific recommendations regarding hormone treatments	All healthcare providers	Adolescents	To develop and subscribe Italian guidelines for treatment of gender dysphoria in adolescents, based on the ''Dutch Approach'', and in line with the Endocrine Society (ES), and the WPATH guidelines.	Fisher et al. (2014)	https://doi.org/10.1007/s40618-014-0077-6	1
Health Policy Project (HPP) 2015 [37]	Blueprint	Asia and the Pacific	Covers all aspects of policy affecting trans people and includes specific guidance about assessment, psychological care and medical care	Health providers, policymakers and governments	All (includes section on children and adolescents)	To improve access to competent primary and specialised care for trans people in Asia and the Pacific.	The Health Policy Project (HPP), Asia Pacific Transgender Network APTN), United Nations Development Programme (UNDP)	https://www.undp.org/asia-pacific/publications/blueprint-provision-comprehensive-care-trans-people-and-trans-communities-asia-and-pacific	1
Norwegian Directorate of Health 2020 [38]	Guideline	Norway	Naitonal guideline containing broad assessment and care recommendations and some criteria for medical treatments	Healthcare managers and staff working in general and specialist services	All (includes specific recommendations for children and young people)	To prepare recommendations on the treatment of gender dysphoria and gender incongruence, and to confirm the health services offered to people who experience gender incongruence.	Norwegian Directorate of Health	https://www.helsedirektoratet.no/retningslinjer/kjonnsinkongruens	1
Oliphant 2018 [27, 44]	Guidelines	New Zealand	Includes principles for care and covers all aspects of care and includes specific recommendations regarding hormone treatments	All healthcare providers	All (includes specific recommendations for children and young people)	To present guidance for the provision of gender affirming health care in Aotearoa, New Zealand, which is in step with current practice and international standards.	Oliphant et al. (2018)	https://nzmj.org.nz/journal/vol-131-no-1487/guidelines-for-gender-affirming-healthcare-for-gender-diverse-and-transgender-children-young-people-and-adults-in-aotearoa-new-z	2
Pan American Health Organisation (PAHO) 2014 [39]	Blueprint	The Caribbean	Covers all aspects of policy affecting trans people and includes specific guidance about assessment, psychological care and medical care	Health providers, programme planners and managers, policymakers, community leaders, and other stakeholders	All (includes section on children and adolescents)	To provide guidance on improving access to competent primary and specialized care for trans persons in the Latin American and Carribbean region	Pan American Health Organisation (PAHO), John Snow Inc. and WPATH are named as co-authors	https://www.paho.org/en/node/50469	2

Royal Children's Hospital Melbourne (RCHM) 2018 [28, 45]	Guidelines	Australia	Includes general principles and covers all aspects of care including specific recommendations regarding hormone treatments	All healthcare providers	Children and adolescents	To maximise quality care provision for trans and gender diverse children and adolescents across Australian	The Royal Children's Hospital, Melbourne	https://doi.org/10.5694/mja17.01044	1
Royal College of Psychiatrists (RCPsych) 1998 [29]	Guideline	UK	Covers psychological assessment and management and broad recommendations about medical treatments	Psychiatrists	Children and adolescents	Not reported	Royal College of Psychiatrists (UK)	http://web.archive.org/web/20070503090525/http://www.symposion.com/ijt/ijtc0402.htm	1
Society for Adolescent Health and Medicine (SAHM) 2020 [30]	Position Statement	International	Includes broad recommendations relating to care approach and model, and medical intervention - does not include specific treatment recommendations	All healthcare providers	Young people	Not reported	Society for Adolescent Health and Medicine	https://doi.org/10.1016/j.jadohealth.2020.03.016	1
South African HIV Clinicians Society (SAHCS) 2021 [40, 46]	Guideline	South Africa	Covers all aspects of care and treatment and includes detailed guidance on hormone treatments	All healthcare providers, particularly those working in a primary care setting, public or private	All (includes sections on children and adolescents)	To provide evidence-informed best practice recommendations to enable South African healthcare providers to offer quality, affirming services to transgender and gender diverse clients. The term 'client', for the purposes of this guideline, includes service users, patients and participants.	South African HIV Clinicians Society	https://doi.org/10.4102/sajhivmed.v22i1.1299	1
Spanish Society of Endocrinology and Nutrition (SSEN) 2012 [41]	Guideline	Spain	Covers assessment and treatment with main focus on hormone treatments	Not reported	All (includes section on children and adolescents)	To meet the need for implementing a coordinated action protocol for comprehensive health care for transgender people in the [Spanish] National Health System.	SSEN Identity and Sexual Differentiation Group (GIDSEEN)	https://doi.org/10.1016/j.endonu.2012.02.001	1
Spanish Society of Endocrinology and Nutrition (SSEN) 2015 [31]	Position Statement	Spain	Sets out broad recommendations for evaluation and treatment (no specific details)	All healthcare providers	Children and adolescents	To set out recommendations for evaluation and treatment of gender dysphoria in children and adolescents.	SSEN Working Group on Gender Identity and Sexual Development (GIDSEEN)	https://doi.org/10.1016/j.endonu.2015.03.004	1
Strang 2018 [32]	Guideline	International	Covers all aspects of care but does not include specific guidance on hormone treatments	Not reported	Adolescents (time of onset of puberty to age 19) with autism spectrum disorder and gender dysphoria	To develop initial clinical consensus guidelines for the care of adolescents with co-occuring autism spectrum disorder and gender non-conformity/gender dysphoria.	Strang et al. (2018)	https://doi.org/10.1080/15374416.2016.1228462	1

Swedish National Board of Health and Welfare 2022 [42]	Guideline	Sweden	National guideline covering all aspects of assessment and care including psychosocial care and hormone treatments	Health professionals in health care sector and decision-makers with responsibility for health care activities concerned	Children and adolescents	To contribute to good and equal care for children and young people with gender inequality and gender dysphoria.	Swedish National Board of Health and Welfare	https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-12-8302.pdf	2
University of California San Francisco (UCSF) 2016 [43]	Guideline	US	Covers all aspects of care including assessment, psychosocial care, medical and other interventions	All healthcare providers	All (includes chapter on children and adolescents)	To equip primary care providers and health systems with the tools and knowledge to meet the health care needs of their transgender and gender nonconforming patients.	Center of Excellence for Transgender Health, University of California, San Francisco (UCSF)	https://transcare.ucsf.edu/guidelines	2
World Professional Association for Transgender Health (WPATH) 2022 [33]	Guideline	International	Covers all aspects of assessment, care and treatment including specific recommendations regarding medical treatment	All healthcare providers	All (includes sections on children and adolescents)	To provide clinical guidance to assist transgender and gender diverse people in accessing safe and effective pathways to achieving lasting personal comfort with their gendered selves with the aim of optimizing overall physical health, psychological well-being, and self-fulfillment.	World Professional Association for Transgender Health (WPATH)	https://doi.org/10.1080/26895269.2022.2100644	8

* The terminology and language used by guidelines has been retained in this summary

Supplementary Table S3 – Critical appraisal overall rating and recommendations for use

Guideline ID	OQA1	R1	OQA2	R2	OQA3	R3
AACAP 2012	3	No	3	No	4	Yes (mod)
American Academy of Paediatrics 2018	2	No	3	No	1	No
American Psychological Association 2015	3	No	2	No	3	No
Council for Choices in Healthcare Finland 2020	5	Yes (mod)	5	Yes	5	Yes (mod)
de Vries 2006	2	No	3	No	2	No
Endocrine Society 2009	3	No	4	No	4	Yes (mod)
Endocrine Society 2017	4	Yes (mod)	4	No	4	Yes (mod)
European Society for Sexual Medicine 2020	3	Yes (mod)	2	No	3	No
Fisher 2014	2	No	3	No	1	No
Health Policy Project 2015	2	No	1	No	2	No
Norwegian Directorate of Health 2020	3	No	3	Yes (mod)	4	Yes (mod)
Oliphant 2018	2	No	3	No	1	No
Pan American Health Organisation 2014	2	No	2	No	1	No
Royal Children's Hospital Melbourne 2018	3	No	3	No	2	No
Society for Adolescent Health and Medicine 2020	2	No	2	No	1	No
South African HIV Clinicians Society 2021	3	No	3	No	2	No
Strang 2018	3	Yes (mod)	2	No	2	No
Swedish National Board of Health & Welfare 2022	6	Yes (mod)	6	Yes	6	Yes
University California San Francisco 2016	3	No	2	No	3	No
WPATH 2012	3	Yes (mod)	3	No	2	No
WPATH 2022	3	Yes (mod)	3	No	3	No

OQA: Overall quality assessment - 1-7 where 1 is lowest possible score and 7 is the highest possible score

R: Recommend guideline for use - Possible responses are Yes, Yes with modifications (Yes (mod)), No

The numbers 1-3 refer to the three reviewers who appraised the guidelines

Abbreviations
AACAP – American Academy of Child & Adolescent Psychiatry
WPATH – World Professional Association for Transgender Health

EXHIBIT 87

OPEN ACCESS

Clinical guidelines for children and adolescents experiencing gender dysphoria or incongruence: a systematic review of recommendations (part 2)

Jo Taylor, Ruth Hall, Claire Heathcote, Catherine Elizabeth Hewitt, Trilby Langton, Lorna Fraser

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/archdischild-2023-326500).

Department of Health Sciences, University of York, York, UK

Correspondence to
Dr Jo Taylor, Department of Health Sciences, University of York, York, UK; dohs-gender-research@york.ac.uk

Received 26 October 2023
Accepted 15 December 2023

Linked

► http://dx.doi.org/10.1136/archdischild-2023-326347
► http://dx.doi.org/10.1136/archdischild-2023-326348
► http://dx.doi.org/10.1136/archdischild-2023-326112
► http://dx.doi.org/10.1136/archdischild-2023-326499
► http://dx.doi.org/10.1136/archdischild-2023-326669
► http://dx.doi.org/10.1136/archdischild-2023-326670
► http://dx.doi.org/10.1136/archdischild-2023-326760
► http://dx.doi.org/10.1136/archdischild-2023-326681

To cite: Taylor J, Hall R, Heathcote C, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2023-326500

ABSTRACT

Background Increasing numbers of children and adolescents experiencing gender dysphoria/incongruence are being referred to specialist gender services and there are various published guidelines outlining approaches to clinical care.

Aim To examine the recommendations about the management of children and/or adolescents (age 0-18) experiencing gender dysphoria/incongruence in published guidelines or clinical guidance. A separate paper examines the quality and development of guidelines.

Methods A systematic review and narrative synthesis. Databases (Medline, Embase, CINAHL, PsycINFO, Web of Science) were searched to April 2022 and web-based searches and contact with international experts continued to December 2022, with results assessed independently by two reviewers. The Appraisal of Guidelines for Research and Evaluation tool was used to examine guideline quality.

Results 23 guidelines/clinical guidance publications (1998–2022) were identified (4 international, 3 regional, 16 national). Guidelines describe a similar care pathway starting with psychosocial care for prepubertal children, puberty suppressants followed by hormones for eligible adolescents and surgical interventions as these adolescents enter adulthood. In general, there is consensus that adolescents should receive a multidisciplinary assessment, although clear guidance about the purpose or approach is lacking. There are differing recommendations about when and on what basis psychological and medical interventions should be offered. There is limited guidance about what psychological care should be provided, about the management of prepubertal children or those with a non-binary gender identity, nor about pathways between specialist gender services and other providers.

Conclusions Published guidance describes a similar care pathway; however, there is no current consensus about the purpose and process of assessment for children or adolescents with gender dysphoria/incongruence, or about when psychological or hormonal interventions should be offered and on what basis.

PROSPERO registration number CRD42021289659.

WHAT IS ALREADY KNOWN

⇒ Increasing numbers of children and adolescents are being referred to specialist gender services.
⇒ Several clinical guidelines exist to support the clinical care of children and adolescents with gender dysphoria/incongruence and their families.
⇒ There are divergent clinical approaches to the management of these children/adolescents and a need to synthesise guideline recommendations to explore areas of consensus, disagreement or uncertainty.

WHAT THIS STUDY ADDS

⇒ The clinical guidance identified describes a similar care pathway involving psychosocial care for prepubertal children followed by medical interventions for adolescents who meet certain criteria.
⇒ There is consensus that those requiring specialist gender care should receive a multidisciplinary assessment and be offered psychosocial support, although there is a lack of clarity about who should be involved in this and any differences for children and adolescents.
⇒ There are differing recommendations about when and on what basis psychological and hormone interventions should be offered, and limited guidance about prepubertal children or those with a non-binary gender identity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinicians should consider the diverging recommendations about when and on what basis psychosocial or hormone interventions should be offered to children and adolescents when working with this population. Detailed guidance to support psychological care is needed.

INTRODUCTION

The prevalence of gender dysphoria/incongruence in children and adolescents is currently unknown due to limited population-level data.[1 2] However, the number of referrals to paediatric gender services internationally has increased over the last 10-15 years.[2] These children and adolescents require timely, appropriate and evidence-based care. Numerous guidelines exist to inform healthcare provision for this population.[3 4] However, there remains debate about the most appropriate assessment and care pathways.[5]

Three systematic reviews have appraised clinical guidelines for transgender care.[3 4 6] They each focus on a subset: Dahlen *et al*[3] reviewed international

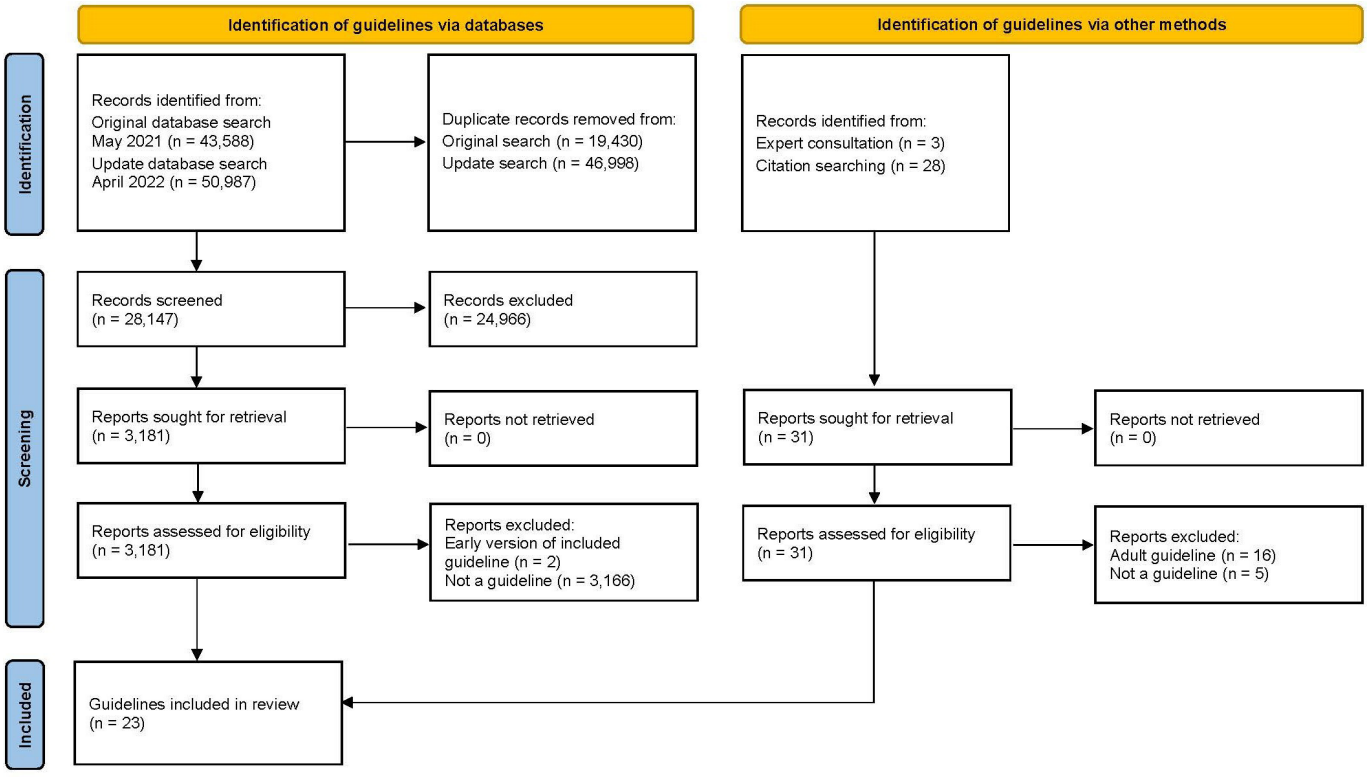


Figure 1 Study flow diagram.

guidelines, and Ziegler *et al*[4 6] focused on guidelines for use in primary care. This systematic review builds on these by appraising and synthesising all published clinical guidance that includes recommendations regarding the care of children/adolescents experiencing gender dysphoria/incongruence. The review is reported in two papers. The first describes the review methods and examines guideline quality and development.[7] This second paper provides a synthesis of recommendations.

METHODS

This review forms part of a linked series examining the epidemiology, care pathways, outcomes and experiences for children and adolescents experiencing gender dysphoria/incongruence (PROSPERO registration number CRD42021289659[8]).

To synthesise recommendations, we identified common areas of clinical care for which recommendations are given and worked systematically through guidance to extract and summarise recommendations pertaining to each topic. This enabled us to map recommendations as well as identify areas of consensus, uncertainty or disagreement. The full methods for this review are reported in the first paper.[7]

RESULTS

In total, 15 guidelines and 8 clinical guidance publications including at least one recommendation about the management of children/adolescents experiencing gender dysphoria/incongruence were identified (figure 1). The term guideline will be used in the synthesis.

Guidelines were published from 1998 to 2022. Four guidelines are international,[9–12] three regional (Europe,[13] Asia and the Pacific,[14] the Caribbean[15]) and others national (four US,[16–19] two Spain[20 21] and one from Australia,[22 23] Canada,[24] Denmark,[25] Finland,[26] Italy,[27] New Zealand,[28 29] Norway,[30] South Africa,[31 32] Sweden[33] and the UK[34]).

Nine guidelines are about management of children and/or adolescents experiencing gender dysphoria/incongruence.[11 19 20 22 24 26 27 33 34] One focuses on co-occurring autism spectrum condition (ASC) and gender dysphoria/incongruence.[12] Others cover broader populations (online supplemental table 1 and figure 2).

Guideline quality varies; the majority are of low to moderate quality. The development and recommendations of most guidelines were influenced by two international guidelines—version 7 of the World Professional Association for Transgender Health (WPATH) guideline published in 2012[35] (version 8 was published in 2022[9]), and the 2009[36] and 2017[10] versions of the Endocrine Society guideline. Details about this and guideline quality are reported in the first paper.

Guideline synthesis

The following sections summarise recommendations for key areas of practice identified (box 1). More guidelines focus on medical treatments than psychosocial care. The synthesis includes the latest version of guidelines and may not capture changes within guidelines over time.

Care models

Most guidelines recommend that a specialist multidisciplinary team of mental health professionals, endocrinologists and other professionals with expertise in gender and child development delivers assessment and care. Acknowledging different healthcare infrastructures, the WPATH guideline[9] and regional blueprints for Asia and the Pacific[14] and the Caribbean[15] recommend healthcare professionals involve relevant disciplines as an alternative to establishing multidisciplinary teams.

Six guidelines discuss the role of other services. The UK Royal College of Psychiatrist (RCPsych) guideline[34] recommends mental health services assess for gender dysphoria and

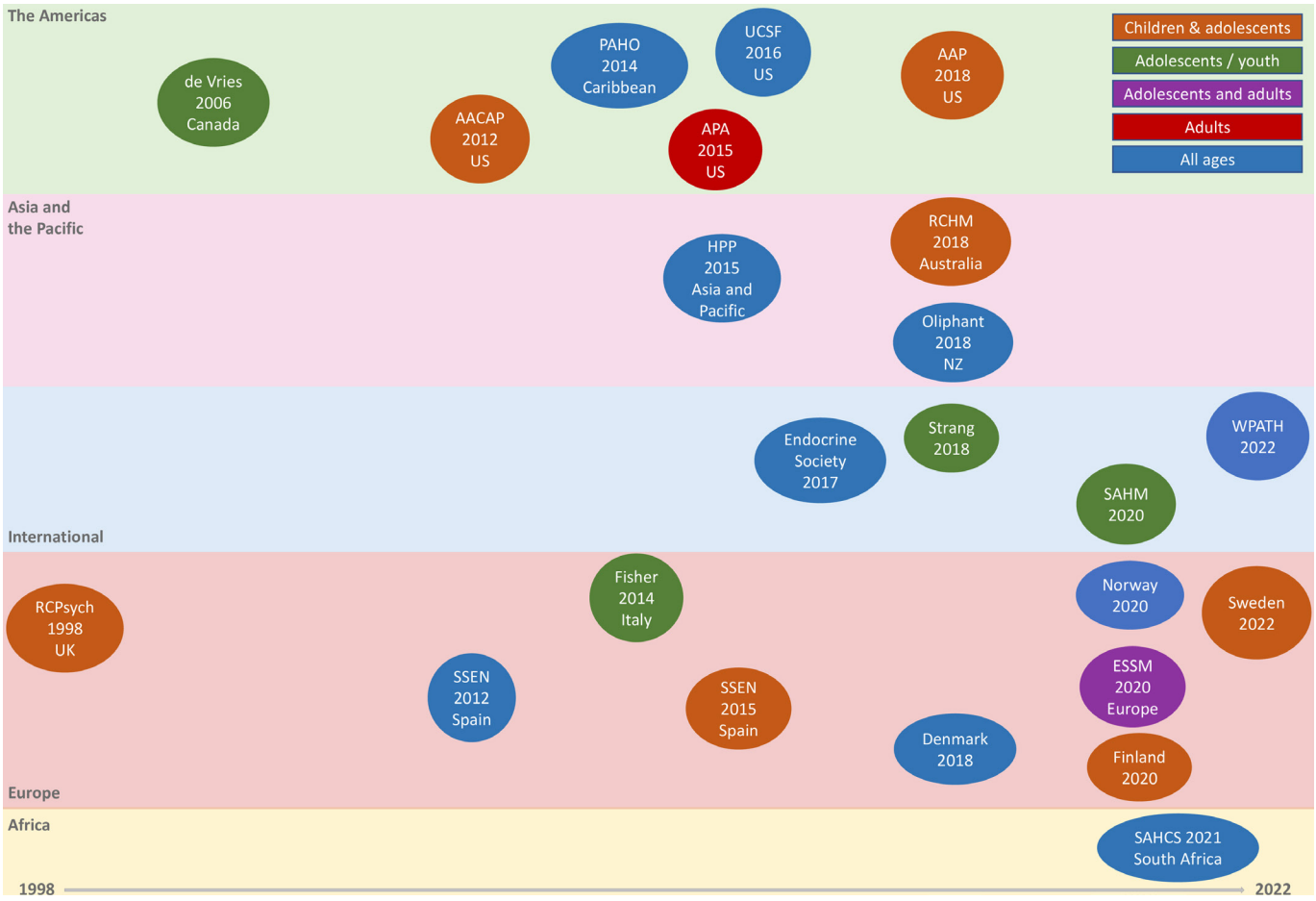


Figure 2 A timeline for the included guidelines by geographical region, country and target population. AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; APA, American Psychological Association; ESSM, European Society for Sexual Medicine; HPP, Health Policy Project; PAHO, Pan American Health Organisation; RCHM, Royal Children's Hospital Melbourne; RCPsych, UK Royal College of Psychiatrists; SAHCS, South African HIV Clinicians Society; SAHM, Society for Adolescent Health and Medicine; SSEN, Spanish Society of Endocrinology and Nutrition; UCSF, University California, San Francisco; WPATH, World Professional Association for Transgender Health.

co-occurring mental health difficulties. The University California, San Francisco guideline[16] states that paediatricians may provide care while recommending a role for mental health professionals. More recently, the Finnish,[26] Norwegian[30] and Swedish[33] guidelines recommend that local mental health services provide assessment and psychosocial interventions,

Box 1 Main practice areas in guidelines

- ⇒ Care models, principles and practices
- ⇒ Multidisciplinary team composition, roles, competencies and training
- ⇒ Assessment
- ⇒ Psychosocial care
- ⇒ Information, education and advocacy
- ⇒ Social transition
- ⇒ Puberty suppressant hormones
- ⇒ Feminising/Masculinising hormones
- ⇒ Surgical interventions
- ⇒ Fertility care
- ⇒ Other interventions (eg, voice therapy, hair removal)
- ⇒ Sexual health and functioning
- ⇒ Physical health and lifestyle

and the Finnish guideline describes multiple different pathways between local mental health and specialist gender services.[26] The Australian guideline outlines the roles for different professionals who might be involved in the assessment and/or care of a child/adolescent, although there is a lack of clarity about the referral pathways between local and specialist gender services. This is the only guideline that discusses transition to adult gender services, and recommends support for this.[22]

Most guidelines distinguish between care for prepubertal children and adolescents, recommending a phased approach. This begins with psychosocial support for children/adolescents and parents, followed by puberty suppressants and then hormones for adolescents, and surgical interventions in adulthood (figure 3). Assessment and psychoeducation are suggested along the pathway. Two guidelines[27 33] explicitly adopt the Dutch model (the earliest paediatric treatment protocol[37]), and most guidelines reflect this pathway. One of these, however, recommends that medical interventions occur under a research framework and modifies the original criteria for treatment.[33] Four guidelines propose an individualised approach to medical interventions, while still describing a phased approach.[16 22 28 31]

Care principles lack consensus and clarity about theoretical models or approaches. The following are referred to: informed consent model, a minority stress approach, a developmental

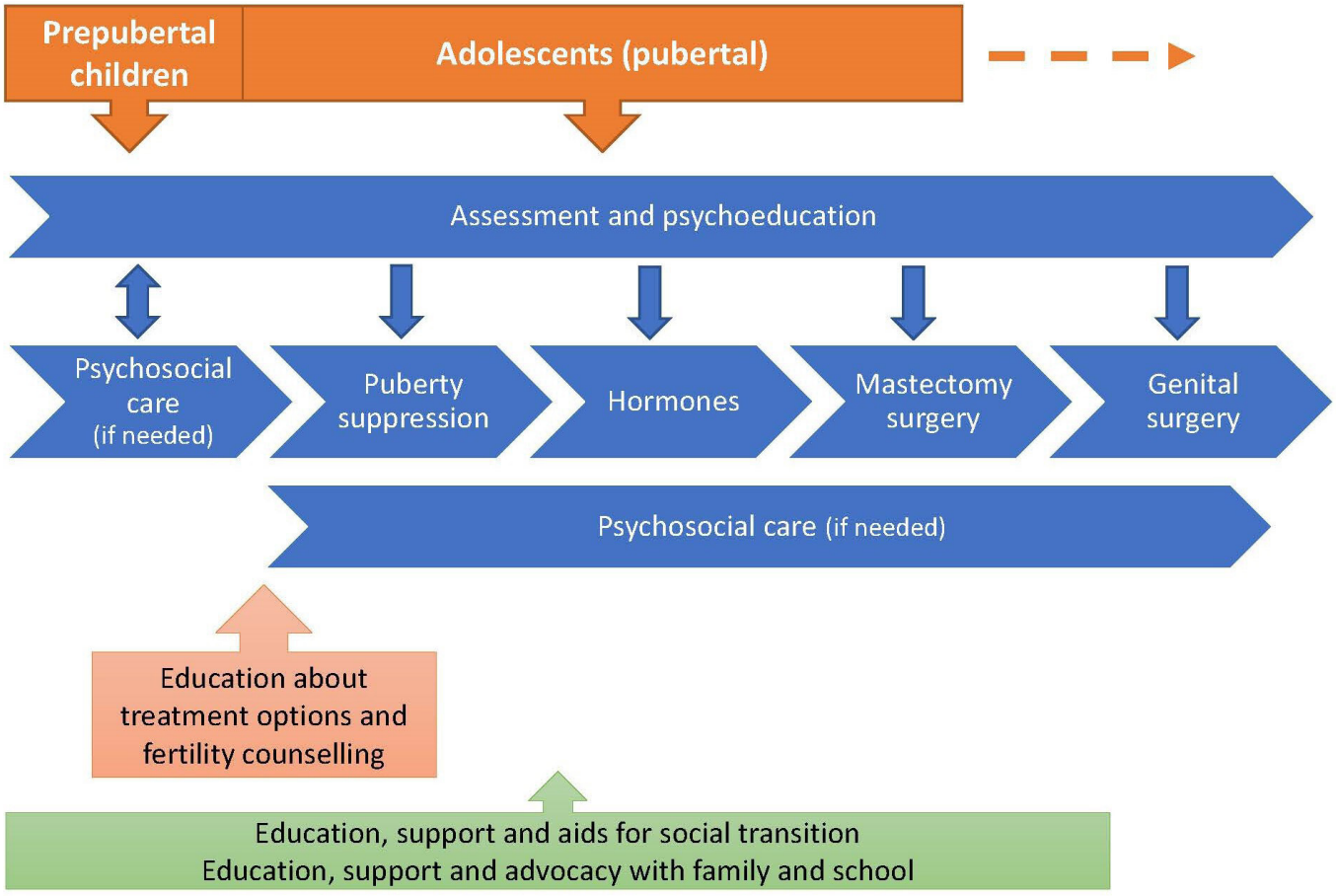


Figure 3 The phased pathway of assessment and care described across the guidelines.

approach and individualised or person-centred care. Sixteen guidelines use the term gender-affirming. Eight promote gender-affirming healthcare as a care principle,[9 11 16 18 19 22 28 31] defined as 'healthcare that is respectful and affirming of a person's unique sense of gender and provides support to identify and facilitate gender healthcare goals'.[28] The other eight use the term as a label for interventions like hormone treatments.[10 12–15 26 30 33]

Assessment

All guidelines recommend multidisciplinary assessment. Three types were identified: (1) comprehensive psychosocial assessment, (2) medical or 'readiness' assessment for adolescents seeking hormonal treatments and (3) diagnostic assessment for gender dysphoria/incongruence. Some guidelines integrate these, while others present them separately. In most guidelines, there is no distinct assessment section or recommendations. There is limited clarity about assessment purpose. Most cited reasons are to inform a care plan, or assess eligibility for hormone treatment. Although most guidelines describe different pathways for children and adolescents, only three provide separate guidance.[9 22 31] Five recent guidelines propose that prepubertal children only require assessment if gender-related psychosocial care is needed but provide limited detail about this.[9 22 26 28 30] Others propose all children be assessed. There is little consideration of how a psychosocial assessment might be different for children and adolescents.

Assessment domains

All guidelines recommend that discussion of gender development and identity forms part of assessment, however few provide detail. Several recommend assessing duration, severity, and persistence of gender dysphoria, and exploring different aspects including incongruence, distress, identity, expression, plans and future desires. Only four guidelines suggest formal measures to assess gender.[9 17 24 33] Three name specific measures, without a strong recommendation to use them (online supplemental table S2).[17 24 33] In the eight guidelines referring to a diagnostic classification system, four recommend the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[37] gender dysphoria classification,[17 24 27 33] three the International Classification of Diseases[38] gender incongruence[9 30 31] and four either.[10 21 22 34]

Sixteen guidelines suggest what else should be assessed (table 1).[9 10 13–15 17 18 22 24 25 27 28 30 31 33 34] Common domains include mental health, family functioning/support and psychosocial functioning. Less common domains include cognition/intellectual functioning, sexuality, sexual health, physical health and body image/satisfaction. The latter is discussed in seven guidelines[9 10 12 24 28 31 33] but only recommended for assessment in one.[24]

Five guidelines recommend assessing for neurodevelopment conditions. The guideline by Strang *et al* recommends those with gender dysphoria/incongruence be screened for ASC and vice versa.[12] The Swedish guideline recommends screening for ASC and attention deficit hyperactivity disorder.[33] The South African HIV Clinicians Society (SAHCS),[31] New Zealand[28] and WPATH[9] guidelines also recommend assessing for ASC. The guideline by

Table 1 Recommended assessment domains

Guideline ID	Gender	Body image	Mental health difficulties	Neurodiversity or ASC	Sexuality or sexual orientation	Sexual functioning or health	Psychosocial functioning	Cognitive functioning/ intelligence/ maturity	Family functioning or support	Physical health or conditions
American Academy of Child and Adolescent Psychiatry[17]	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	No
American Psychological Association[18]	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Danish Health Authority[25]	Yes	No	Yes	No	Yes	No	Yes	No	Yes	Yes
de Vries *et al*[24]	Yes	Yes	Yes	No	Yes*	Yes*	Yes	No	Yes	No
Endocrine Society[10]	Yes	No	Yes	No	Yes†	No	Yes	No	Yes	No
European Society for Sexual Medicine[13]	Yes	No	Yes	No	No	No	Yes	No	Yes	No
Health Policy Project[14]	Yes	No	Yes	No	Yes*	Yes*	Yes	No	Yes	Yes
Norwegian Directorate of Health[30]	Yes	No	Yes	No	Yes	No	Yes	No	Yes	Yes
Oliphant *et al*[28 29]	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	No
Pan American Health Organisation[15]	Yes	No	Yes	No	No	No	No	No	No	Yes
Royal Children's Hospital Melbourne[22 23]	Yes	No	Yes	No	No	No	Yes	Yes	Yes	No
The Royal College of Psychiatrists[34]	Yes	No	Yes	No	No	No	Yes	No	Yes	No
SIAMS-SIE-SIEDP-ONIG[27]	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	No
South African HIV Clinicians Society[31 32]	Yes	No	Yes	Yes	No	No	Yes	No	Yes	No
The Swedish National Board of Health and Welfare[33]	Yes	No‡	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
World Professional Association for Transgender Health[9]	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes

*HEEADSSS suggested as tool which includes sexuality.
†Assessment of psychosexual development.
‡Body image scale identified as useful tool.
ASC, autism spectrum condition; HEEADSSS, psychosocial assessment tool covering Home & Environment, Education & Education, Eating & Exercise, Activities, Drugs/Substances, Sexuality, Suicide/depression, Safety.

Strang *et al*,[12] and Swedish[33] and WPATH[9] guidelines suggest children with ASC may require extended assessment. There is a lack of guidance about what support might be indicated if both are present.

Assessment process

Recommendations regarding assessment process are sparse. Several guidelines suggest using multiple methods[9 24 27 33] and gathering information from multiple sources.[9 10 12 24 27 31 33] Nine guidelines describe a process involving multiple sessions with children/adolescents and/or parents.[9 12 14 15 19 24 27 31 33] One guideline suggests joint and separate sessions.[15] Four guidelines discuss confidentiality, with emphasis on giving the child/adolescent a safe and confidential environment and discussing limits of confidentiality.[9 17 31 33] The WPATH guideline recommends considering factors affecting accurate reporting by child/adolescent or caregiver(s).[9] Three guidelines outline when parental involvement may not be appropriate.[9 31 33] Three other guidelines identify confidentiality as an overall principle of care.[22 24 28]

Only the Swedish[33] and WPATH[9] guidelines contain detail on assessment process. Both recommend duration, structure and content be varied according to age, complexity and gender development. The Swedish guideline discusses benefits and risks of assessment, and recommends providing information about this.[33]

Psychosocial care

Psychosocial care for children and adolescents

All but two guidelines[11 20] describe psychosocial care as a key care component. Less consensus exists about approach, and there is limited guidance. There is little consideration of any differences in provision for prepubertal children versus adolescents. Guidelines use varying different terms, including psychosocial care, psychological care or psychotherapy, which are not defined. Most guidelines describe multiple aims with limited agreement. These range from supporting exploration of gender experiences and identity; improving psychosocial functioning; treating co-occurring mental health difficulties; facilitating healthy psychosexual development; alleviating gender-related distress/dysphoria; assisting families to create a gender-affirming environment; preparing/supporting social or medical transition and support to manage stigma or discrimination.

Most guidelines describe a needs-based approach and five recent guidelines state not all children or adolescents will require psychosocial care.[9 22 28 30 31] All but one of these[30] promote a model of gender-affirming healthcare and indicate that those with 'a stable gender identity' and 'supportive family and school environment' may not require psychosocial care. This recommendation marks a departure from earlier guidelines which describe psychosocial care as the mainstay of treatment, and the recent Finnish[26] and Swedish[33] guidelines which describe it as first-line treatment for childhood gender dysphoria/incongruence.

In around half of the guidelines, assessment and psychosocial care are presented as overlapping.[12–15 21 22 25 27 31 33 34] Only the European Society for Sexual Medicine (ESSM)[13] and Swedish[33] guidelines recommend psychosocial support for gender exploration during the assessment process. Other guidelines emphasise the importance of gender exploration, although there is a lack of definition and consensus, particularly regarding adolescents. For example, the ESSM[13] and Swedish[33] recommendations do not distinguish between children and adolescents. In contrast, the Australian[22] and WPATH[9] guidelines identify gender exploration for children as potentially useful whereas recommendations for adolescents focus on psychosocial support for social and/or medical transition. Several other guidelines adopt this approach, citing evidence that gender development is more fluid in childhood, that most children will not experience gender dysphoria/incongruence into adolescence and uncertainty about which children will have persistent dysphoria/incongruence.[10 14 16 18 34]

Most guidelines recommend co-occurring mental health difficulties are assessed and managed.[9 10 12–16 18 21 22 24–28 30 31 33 34] Only five consider how this might be integrated with psychological care for gender incongruence/dysphoria. The Finnish guideline recommends that local and specialist mental health services provide psychosocial support and any psychological care that is needed.[26] The early RCPsych guideline,[34] and the Swedish[33] and Danish[25] guidelines describe more of an integrated approach, although clarity and detail is lacking. The latter two recommend mental healthcare is provided outside the gender service if needed. The Australian guideline contains no explicit recommendation but describes different pathways depending on presentation.[22]

Several guidelines acknowledge additional challenges in caring for looked after children.[9 11 16 22 24 31] The Australian guideline suggests providing advocacy for these children and support for carers.[22]

Psychosocial support for parents

Seventeen guidelines discuss psychosocial support for parents.[9 13–19 21 22 24–26 28 30 31 33] While there is no consensus or clear purpose detailed, most highlight that children benefit from parental support in their gender development or care. There is no consensus about which interventions should be offered, and terms applied include counselling, supportive counselling, psychosocial support, support, education, psychoeducation, consultation and psychotherapy. Five guidelines recommend considering family therapy.[17–19 21 24] There is no consideration of how parental support may be different for those of prepubertal children versus adolescents.

Psychoeducation and advocacy

Most guidelines suggest providing education about gender development and identity to children/adolescents and families, although detailed guidance is lacking.[9 12–19 22 24 27 28 30 31 33] Several guidelines suggest peer support groups,[9 15 17 22 24 28 30 31 33] with a further two suggesting this for 'people' but not specifically children/adolescents.[14 18] Joint working, education and/or advocacy with schools and other services is recommended in 17 guidelines.[9 11 13–19 22 24 26 28 30 31 33 34]

Social transition

Eighteen guidelines discuss social transition.[9 10 12–19 21 22 24 28 30 31 33 34] Nearly all recommend providing information about benefits and risks of social transition, and psychosocial care for decision-making and during social transition, although detailed guidance is limited. Several guidelines recommend an educational and advocacy role with families, schools and other settings. Guidelines vary in whether recommendations refer to children and adolescents. For example, in the Australian,[22] South African[31] and WPATH[9] guidelines, recommendations are included in sections about children but not adolescents.

Two early guidelines[34 35] describe social transition decisions as ones requiring clinical judgement; others do not. The WPATH[9] and Swedish[33] guidelines discuss the limited evidence base regarding social transition, particularly for prepubertal children, and these and several others including the American

Psychological Association[18] and SAHCS[31] guidelines recommend framing social transition in a way that ensures children/adolescents feel free to reconsider or reconceptualise their gender feelings as they develop.

Six guidelines discuss items such as binders or packers for adolescents.[9 22 24 28 31 33] A further four include recommendations for 'people',[14–16 30] which may apply to adolescents. Most recommend education about risks and benefits and if necessary safe use. The Swedish guideline[33] recommends health services provide items to facilitate transition for adolescents after full assessment. The Norwegian guideline recommends this for 'people', which may apply to adolescents.[30]

Medical treatments

Medical treatments are not recommended for prepubertal children in any guideline.

For adolescents, most guidelines describe a phased approach starting with puberty suppression (specifically gonadotropin-releasing hormone analogues) before feminising/masculinising hormones (oestrogen or testosterone). The Swedish guideline is unique in recommending that hormone treatments be provided under a research framework and in exceptional cases until this is established.[33] The Finnish guideline, which describes medical treatments for adolescents as experimental due to the limited evidence-base, also recommends a cautious approach and mandates that medical treatments are only provided in two centralised research clinics which should collect data about the outcomes of treatment.[26] Three recent guidelines[9 30 31] use gender incongruence as the clinical indication for treatment,[38] others use gender dysphoria.[39]

Seven guidelines provide treatment protocols.[9 10 16 21 22 27 28] The Endocrine Society guideline[10] is the basis for others, resulting in similar recommendations regarding treatment contraindications, dosing, menstrual suppression and physical health risks and monitoring. Few guidelines address known treatment side effects and monitoring recommendations omit these.

Puberty suppression

Puberty suppressing treatments are discussed in all but one guideline.[34] Across guidelines there is ambiguity regarding treatment aims with various presented, including reducing gender-related distress/dysphoria, improving quality of life, allowing time for decision-making, supporting gender exploration or prolonging the diagnostic phase. Most guidelines emphasise full reversibility as a justification, while highlighting potential adverse effects on bone health, and uncertainty regarding cognitive development. Some guidelines discuss concerns about prolonged use, although few provide management suggestions. The Australian guideline[22] recommends vitamin D or early initiation of hormones as potential approaches.

Thirteen guidelines present eligibility criteria for puberty suppression.[9 10 13–15 20–22 24 25 27 28 33] Twelve recommend waiting until a child has achieved at least Tanner stage 2 of puberty, and the Swedish guideline recommends Tanner stage 3 to ensure adolescents experience more of puberty. This and the WPATH guideline discuss different options for treatment in early stage versus late-stage puberty.[9 33] Other common criteria are: presence of gender dysphoria (n=11) or incongruence (n=2), gender dysphoria has emerged or worsened at onset/progression of puberty (n=9), mental health difficulties are managed/unlikely to impact treatment (n=9), the adolescent has decision-making capacity (n=8), and parental consent (n=8). Several guidelines also require family/social support (n=6). Only two guidelines specify a minimum age (of 12 years).[20 33]

Masculinising/Feminising hormones

All but one guideline[34] discusses hormones for adolescents and eight provide eligibility criteria.[9 10 21 22 25 27 28 33] Common criteria are: presence of gender dysphoria (n=7) or incongruence (n=1) with most requiring persistence over time, capacity to consent (n=8) and that mental health difficulties are managed/unlikely to affect treatment (n=6). Several require parental consent (n=5) and/or family/social support (n=4). Most guidelines reference age 16 years as the typical starting point, although only five specify this as the minimum age.[20 21 27 30 33] Two of these require the adolescent to have lived experience in their gender identity, one from Spain published in 2012[21] and the Swedish guideline published in 2022.[33] One guideline recommends puberty suppression before initiating hormones.[24]

There are no recommendations about how to manage adolescents who, having started to medically transition wish to detransition (discontinue treatment and live as their birth-registered sex or retransition to an alternative gender[40]), although the Swedish[33] and WPATH[9] guidelines recommend supporting these adolescents.

Surgical treatments

Fourteen guidelines include recommendations about surgery. Six do not recommend surgery for adolescents.[21 24 26–28 34] Six do not recommend genital surgery but support mastectomy.[10 16 22 25 30 33] Only the Swedish guideline[33] includes minimum age criterion[17] for mastectomy if carried out under a research framework. The two remaining guidelines (WPATH[9] and SAHCS[31]), which also support surgery, include no restrictions for adolescents, although WPATH suggests phalloplasty be delayed until adulthood.

Nine guidelines offer no clear recommendations; three describe practice that includes chest surgery for adolescents,[14 15 19] three describe surgery as deferred until adulthood[12 17 20] and three contain no discussion.[11 13 18]

Fertility and sexual healthcare

Eighteen guidelines recommend providing information regarding the impact of hormones and surgery on fertility, and fertility preservation options with consensus that this should precede treatment initiation. Four of these guidelines,[9 10 22 33] published post-2017, explicitly require this for hormone treatments. Fertility counselling and preservation recommendations are lacking.

Few guidelines include recommendations about sexual healthcare and primarily discuss pregnancy-prevention and sexually transmitted diseases. The ESSM guideline seeks to address this gap by recommending psychosexual education about the effects on body satisfaction and sexual function before any interventions.[13] This is also recommended in the Swedish[33] and WPATH[9] guidelines.

Management of children/adolescents with non-binary gender identities

Fourteen guidelines recommend care that views gender as a spectrum.[9 11–13 16 18 19 22 24 26 28 30 31 33] Three guidelines explicitly discuss provision for those who identify as non-binary. The Swedish[33] and Norwegian[30] guidelines do not recommend hormone treatments due to lack of evidence. The Swedish guideline recommends non-binary children/adolescents receive psychosocial care.[33] Recommendations in the WPATH guideline are included in a separate chapter about non-binary people, which may apply to adolescents.[9]

DISCUSSION

This systematic review identified 23 clinical guidance publications (1998 to 2022), 9 focusing on management of children/adolescents

with gender dysphoria/incongruence.[11 19 20 22 24 26 27 33 34] The review identified areas on which there is agreement and areas of divergence and uncertainty with limited guidance on how to implement recommendations. Overall, guidelines describe a care pathway similar to the original Dutch protocol that involves psychosocial care for prepubertal children followed by hormonal interventions for adolescents who meet specific criteria, provided by a specialist multidisciplinary team.[41] This approach continues to dominate clinical guidance despite lack of high-quality evidence regarding treatments,[42–50] or exploring alternative care models.[5]

Although guidelines recommend similar treatments there are different recommendations about when hormone interventions should be offered and on what basis. The Dutch protocol required a diagnosis of gender dysphoria from early childhood that intensified during puberty as well as applying minimum age criterion for puberty suppressants and hormones.[37] Most subsequent guidance, influenced by WPATH version 7,[35] lacked minimum age criteria until the Swedish guideline re-introduced these.[33] The Swedish guideline additionally recommends adolescents are exposed to puberty until Tanner stage 3. The Swedish and Finnish guidelines require a diagnosis of gender dysphoria. In contrast, the South African,[31] Norwegian[30] and WPATH[9] guidelines specify gender incongruence as the treatment indication. The Finnish guideline, which views medical treatments for adolescents as experimental due to the limited evidence-base, recommends a cautious approach and the need for the centralised research clinics that provide these treatments to collect outcome data. The Swedish guideline recommends that these treatments are only provided under a research framework. This differs considerably to other guidance which identifies reversibility of puberty suppression as key justification for its use in practice, despite uncertainty about long-term effects.[45 48 51] A report by the Norwegian Healthcare Investigation Board[52] recommends a change in line with the cautious approach adopted by Sweden and Finland.[52]

Detailed guidance regarding assessment is lacking with no consensus about the aim or clinical approach, nor the necessity for assessment in prepubertal children. Although most guidance recommends assessing gender, mental health, psychosocial and family functioning, other domains vary. Few guidelines recommend exploring sexual orientation or assessing body image, despite these being identified as important factors.[1 18 53] Few recommend specific assessment tools, and those suggested have not been developed and/or validated for this population.[54–56]

Psychosocial care is recommended across guidelines, but detailed guidance is limited. Specifically lacking are recommendations regarding psychological care, how this overlaps with assessment, which children/adolescents receive it and how to manage co-occurring psychosocial concerns. There is a lack of clarity about how local mental health and gender services should work together. Such guidance may help reduce barriers to equitable and evidence-based care. However, limited research about psychosocial care for this population may prevent development of evidence-based guidance.[42–44]

There is uncertainty regarding management of specific groups highlighted in the literature, for example, those with non-binary identities, or those presenting in mid-adolescence without a long-standing history of gender incongruence.[57 58] The Dutch protocol was not developed for these groups,[37] and they may have different outcomes and needs. There is consensus among international experts that adolescents experiencing gender dysphoria/incongruence should be screened for ASC and those with co-occurring ASC may require extended assessment,[12] but detailed guidance is lacking.[12 59] Finally, there are no recommendations about the management of those who, having started to socially or medically transition, wish to desist, detransition or 're-transition'.[40]

Strengths and limitations

Strengths include a published protocol, robust search strategies and comprehensive narrative synthesis. Including no date restrictions enabled us to map the development of guidance in this area of practice and consider how recommendations have changed. However, including older guidelines may have shaped the synthesis and review conclusions. Some guidelines not published in English may not have been identified. As searches were conducted to April 2022, this review does not include more recently published guidance; as this is a rapidly evolving area this is a limitation.

CONCLUSIONS

Published guidance recommends a care pathway for children and adolescents experiencing gender dysphoria/incongruence for which there is limited evidence about benefits and risks, and long-term effects. Divergence of recommendations in recent guidelines suggest there is no current consensus about the purpose and process of assessment, or about when psychosocial care or hormonal interventions should be offered and on what basis.

Contributors LF and TL conceived the study. LF, TL, JT, RH, and CH contributed to the design of the review. JT, RH and CH conducted selection, extraction and synthesis. JT, CEH, RH, LF, and TL assisted with interpretation of synthesis. JT drafted the manuscript. All authors contributed to and reviewed the manuscript before submission. CEH accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was funded by NHS England to inform the Cass Review (Independent review of gender identity services for children and young people). The funder and Cass Review team had a role in commissioning the research programme but no role in the study conduct, interpretation or conclusion.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement Data sharing is not applicable as no datasets were generated and/or analysed for this study.

ORCID iDs
Jo Taylor http://orcid.org/0000-0001-5898-0900
Catherine Elizabeth Hewitt http://orcid.org/0000-0002-0415-3536

REFERENCES

1 Zucker KJ. Epidemiology of gender dysphoria and transgender identity. *Sex Health* 2017;14:404–11.
2 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender Dysphoria literature: 1) epidemiology. *PLOS Glob Public Health* 2022;2:e0000245.

3 Dahlen S, Connolly D, Arif I, *et al*. International clinical practice guidelines for gender minority/Trans people: systematic review and quality assessment. *BMJ Open* 2021;11:e048943.
4 Ziegler E, Charnish E, Carroll B, *et al*. A critical review of clinical practice guidelines for care of transgender and gender diverse children and youth for use by primary care practitioners. *Transgend Health* 2022;7:397–406.
5 Abbruzzese E, Levine SB, Mason JW. "The myth of "reliable research" in pediatric gender medicine: a critical evaluation of the Dutch studies-and research that has followed". *J Sex Marital Ther* 2023;49:673–99.
6 Ziegler E, Carroll B, Charnish E. Review and analysis of international Transgender adult primary care guidelines. *Transgend Health* 2021;6:139–47.
7 Hewitt CE, Taylor J, Hall R. A systematic review of clinical guidelines for children and adolescents with gender Incongruence or Dysphoria: part 1 – examination of development and quality. 2024. Available: https://doi.org/10.1136/archdischild-2023-326499
8 Fraser L, Hall R, Taylor J, *et al*. The epidemiology, management and outcomes of children with gender-related distress / gender Dysphoria: a systematic review; 2021. PROSPERO 2021 CRD42021289659.
9 Coleman E, Radix AE, Bouman WP, *et al*. Standards of care for the health of transgender and gender diverse people, version 8. *Int J Transgend Health* 2022;23(Suppl 1):S1–259.
10 Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-dysphoric/gender-Incongruent persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017;102:3869–903.
11 Society for Adolescent Health and Medicine. Promoting health equality and nondiscrimination for transgender and gender-diverse youth. *J Adolesc Health* 2020;66:761–5.
12 Strang JF, Meagher H, Kenworthy L, *et al*. Initial clinical guidelines for co-occurring autism spectrum disorder and gender dysphoria or incongruence in adolescents. *J Clin Child Adolesc Psychol* 2018;47:105–15.
13 T'Sjoen G, Arcelus J, De Vries ALC, *et al*. European society for sexual medicine position statement "assessment and hormonal management in adolescent and adult Trans people, with attention for sexual function and satisfaction. *J Sex Med* 2020;17:570–84.
14 Health Policy Project, Asia Pacific Transgender Network, United Nations Development Programme. *Blueprint for the Provision of Comprehensive Care for Trans People and Trans Communities in Asia and the Pacific*. Futures Group, Health Policy Project, 2015. Available: https://www.undp.org/asia-pacific/publications/blueprint-provision-comprehensive-care-trans-people-and-trans-communities-asia-and-pacific
15 Pan American Health Organisation, John Snow Inc, World Professional Association for Transgender Health. *Blueprint for the Provision of Comprehensive Care for Trans Persons and their Communities in the Caribbean and other Anglophone countries*. John Snow, Inc, 2014. Available: https://www.paho.org/en/node/50469
16 University of California San Francisco Gender Affirming Health Program. *Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People*. University of California San Francisco, 2016. Available: https://transcare.ucsf.edu/guidelines
17 Adelson SL, American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter on gay, lesbian, or bisexual sexual orientation, gender nonconformity, and gender discordance in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 2012;51:957–74.
18 American Psychological Association. Guidelines for psychological practice with transgender and gender Nonconforming people. *Am Psychol* 2015;70:832–64.
19 Rafferty J, Committee on Psychosocial Aspects of Child and Family Health, Committee on Adolescence, *et al*. Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. American academy of paediatrics (AAP). *Pediatrics* 2018;142:e20182162.
20 Antonio EI, Asenjo Araque N, Hurtado Murillo F, *et al*. Position statement: gender dysphoria in childhood and adolescence. working group on gender identity and sexual development of the Spanish society of endocrinology and nutrition (GIDSEEN). *Endocrinol Nutr* 2015;62:380–3.
21 Moreno-Pérez O, Esteva De Antonio I, Grupo de Identidad y Diferenciación Sexual de la SEEN (GIDSEEN). Clinical practice guidelines for assessment and treatment of transsexualism. SEEN identity and sexual differentiation group (GIDSEEN). *Endocrinol Nutr* 2012;59:367–82.
22 Telfer MM, Tollit MA, Pace CC, *et al*. Australian standards of care and treatment guidelines for transgender and gender diverse children and adolescents. *Med J Aust* 2018;209:132–6.
23 Telfer MM, Pang K, Pace C. Australian standards of care and Treatmentguidelines. for Trans and gender diverse children and adolescents. version 1.3. Theroyal children's hospital; 2020. Available: https://www.rch.org.au/uploadedFiles/Main/Content/adolescent-medicine/australian-standards-ofcare-and-treatment-guidelines-for-trans-and-gender-diverse-children-and-adolescents.pdf
24 de Vries AL, Cohen-Kettenis PT, Delemarre-Van de Waal H. Clinical management of gender dysphoria in adolescents. caring for transgender adolescents in BC: suggested guidelines. Transcend Transgender Support & Education Society and Vancouver Coastal Health's Transgender Health Program; 2006. Available: https://rainbowhealth.wpenginepowered.com/wp-content/uploads/2009/05/Guidelines-adolescent.pdf
25 Danish Health Authority. Guide on Healthcare related to gender identity. Danish Health Authority; 2018. Available: https://www.sst.dk/-/media/English/Publications/2018/Guide-on-healthcare-related-to-gender-identity.ashx?sc_lang=en&hash=0FF626604C50D5EED94852CA5D042A8E
26 Council for Choices in Healthcare in Finland. Medical treatment methods for Dysphoria associated with variations in gender identity in minors – recommendation. Council for Choices in Healthcare in Finland; 2020. Available: https://palveluvalikoima.fi/en/recommendations#genderidentity
27 Fisher AD, Ristori J, Bandini E, *et al*. Medical treatment in gender dysphoric adolescents endorsed by SIAMS-SIE-SIEDP-ONIG. *J Endocrinol Invest* 2014;37:675–87.
28 Oliphant J, Veale J, Macdonald J, *et al*. Guidelines for gender affirming healthcare for gender diverse and transgender children, young people and adults in Aotearoa, New Zealand. *N Z Med J* 2018;131:86–96.
29 Oliphant J, Veale J, Macdonald J, *et al*. Guidelines for gender affirming healthcare for gender diverse and transgender children, young people and adults in Aotearoa, New Zealand. Transgender Health Research Lab, University of Waikato; 2018. Available: https://researchcommons.waikato.ac.nz/handle/10289/12160
30 Norwegian Directorate of Health. Gender Incongruence: national professional guideline. Norwegian Directorate of Health; 2020. Available: https://www.helsedirektoratet.no/retningslinjer/kjonnsinkongruens
31 Tomson A, McLachlan C, Wattrus C, *et al*. Southern African HIV Clinicians' society gender-affirming Healthcare guideline for South Africa. *South Afr J HIV Med* 2021;22:1299.
32 Tomson A, McLachlan C, Wattrus C, *et al*. Southern African HIV Clinicians society gender-affirming Healthcare guideline for South Africa – expanded version. Southern African HIV Clinicians Society; 2021. Available: https://sahivsoc.org/Files/SAHCS%20GAHC%20guidelines-expanded%20version_Oct%202021(3).pdf
33 The Swedish National Board of Health and Welfare. Care of children and young people with gender Dysphoria - national knowledge support with recommendations for the profession and decision makers. The Swedish National Board of Health and Welfare 2022; 2022. Available: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-12-8302.pdf
34 The Royal College of Psychiatrists. Gender identity disorders in children and adolescents guidance for management, council report Cr63, January 1998. *Int J Transgend* 1998;2.
35 Coleman E, Bockting W, Botzer M, *et al*. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgenderism* 2012;13:165–232.
36 Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, *et al*. Endocrine treatment of transsexual persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2009;94:3132–54.
37 de Vries ALC, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the dutch approach. *J Homosex* 2012;59:301–20.
38 World Health Organisation. *ICD-11: International Classification of Diseases for Mortality and Morbidiy Statistics*.11th revision. 2022.
39 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*5th ed. Washington, DC: American Psychiatric Publishing, 2013.
40 Olson KR, Durwood L, Horton R, *et al*. Gender identity 5 years after social transition. *Pediatrics* 2022;150:e2021056082.
41 Biggs M. The dutch protocol for juvenile transsexuals: origins and evidence. *J Sex Marital Ther* 2023;49:348–68.
42 Lehmann K, Leavey G. Systematic review: psychological/psychosocial interventions for the families of gender diverse youth under 18 years old. *Clin Child Psychol Psychiatry* 2023;28:1160–74.
43 Catelan RF, Costa AB, Lisboa C de M. Psychological interventions for transgender persons: a scoping review. *Int J Sex Health* 2017;29:325–37.
44 Expósito-Campos P, Pérez-Fernández JI, Salaberria K. Empirically supported affirmative psychological interventions for transgender and non-binary youth and adults: a systematic review. *Clin Psychol Rev* 2023;100:102229.
45 Ludvigsson JF, Adolfsson J, Höistad M, *et al*. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatr* 2023;112:2279–92. 10.1111/apa.16791 Available: https://onlinelibrary.wiley.com/toc/16512227/112/11
46 Baker KE, Wilson LM, Sharma R, *et al*. Hormone therapy, mental health, and quality of life among transgender people: a systematic review. *J Endocr Soc* 2021;5:bvab011.
47 Pasternack I, Söderström I, Saijonkari M, *et al*. Medical approaches to treatment of dysphoria related to gender variations. A systematic review, Available: https://app.box.com/s/y9u791np8v9gsunwgpr2kqn8swd9vdtx
48 National Institute for Health and Care Excellence (NICE). Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender Dysphoria. NICE; 2020. Available: https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_GnRH-analogues_For-upload_Final.pdf
49 National Institute for Health and Care Excellence (NICE). Evidence review: gender-affirming hormones for children and adolescents with gender Dysphoria. NICE; 2020. Available: https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_Gender-affirming-hormones_For-upload_Final.pdf

50 Malpas J, Pellicane MJ, Glaeser E. Family-based interventions with transgender and gender expansive youth: systematic review and best practice recommendations. *Transgend Health* 2022;7:7–29.
51 Chew D, Anderson J, Williams K, *et al*. Hormonal treatment in young people with gender dysphoria: a systematic review. *Pediatrics* 2018;141:e20173742.
52 Norwegian Healthcare Investigation Board. Patient safety for children and young people with gender Incongruence. The National Commission of Inquiry for the Health and Care Service; 2023. Available: https://ukom.no/rapporter/pasientsikkerhet-for-barn-og-unge-med-kjonnsinkongruens/sammendrag
53 Verveen A, Kreukels BP, de Graaf NM, *et al*. Body image in children with gender incongruence. *Clin Child Psychol Psychiatry* 2021;26:839–54.
54 Bloom TM, Nguyen TP, Lami F, *et al*. Measurement tools for gender identity, gender expression, and gender dysphoria in transgender and gender-diverse children and adolescents: a systematic review. *Lancet Child Adolesc Health* 2021;5:582–8.
55 Bowman SJ, Casey LJ, McAloon J, *et al*. Assessing gender Dysphoria: A systematic review of patient-reported outcome measures. *Psychol Sex Orientation Gender Diver* 2022;9:398–409.
56 McGuire JK, Beek TF, Catalpa JM, *et al*. The genderqueer identity (GQI) scale: measurement and validation of four distinct subscales with trans and LGBQ clinical and community samples in two countries. *Int J Transgend* 2019;20:289–304.
57 Chew D, Tollit MA, Poulakis Z, *et al*. Youths with a non-binary gender identity: a review of their sociodemographic and clinical profile. *Lancet Child Adolesc Health* 2020;4:322–30.
58 Levine SB, Abbruzzese E. Current concerns about gender-affirming therapy in adolescents. *Curr Sex Health Rep* 2023;15:113–23.
59 Kallitsounaki A, Williams DM. Autism spectrum disorder and gender dysphoria/incongruence. a systematic literature review and meta-analysis. *J Autism Dev Disord* 2023;53:3103–17.

Supplementary Table S2 - Guideline characteristics*

Guideline ID, Year	Type of guideline	Country	Summary of guideline	Target audience	Population	Stated Aim	Produced by	Weblink	Version
American Academy of Child & Adolescent Psychiatry (AACAP) 2012 [22]	Practice Parameter	US	Sets out principles for practice but does not include specific treatment recommendations	Psychiatrists	Children and adolescents (includes sexual minority care as well)	To foster clinical competence in those caring for children and adolescents	American Academy of Child & Adolescent Psychiatry (AACAP)	https://doi.org/10.1016/j.jaac.2012.07.004	1
American Academy of Paediatrics (AAP) 2018 [23]	Policy Statement	US	Sets out nine recommendations regarding role of paediatricians but does not include specific treatment recommendations	Paediatrians	Children and adolescents	To provide suggestions for paediatric providers that are focused on promoting the health and positive development of youth that identity as transgender and gender diverse while eliminating discrimination and stigma	American Academy of Paediatrics	https://doi.org/10.1542/peds.2018-2162	1
American Psychological Association (APA) 2015 [24]	Guideline	US	Sets out 16 guidelines which are principles for psychological practice but within these are recommendations for assessment and psychological care	Psychologists	Adults (includes guideline specific to children and young people)	To assist psychologists in the provision of culturally competent, developmentally appropriate, and trans-affirmative psychological practice	American Psychological Association	https://www.apa.org/practice/guidelines/transgender.pdf	1
Council for Choices in Healthcare in (COHERE) Finland 2020 [35]	Guideline	Finland	National guideline focusing on medical research and treatment methods for the treatment of gender dysphoria	All healthcare providers	Minors (<18) - guidelines for adults and minors developed together but published separately	To provide a recommendation on medical treatment methods for dysphoria associated with variations in gender identity of minors	Council for Choices in Healthcare in Finland	https://palveluvalikoima.fi/en/recommendations#genderidentity	1
Danish Health Authority 2018 [36]	Guideline	Denmark	National guideline covering all aspects of care and broad recommendations	All healthcare providers	All (includes chapter on under 18s)	To ensure a high quality and equal access to healthcare related to gender identity in Denmark.	Danish Health Authority	https://www.sst.dk/-/media/English/Publications/2018/Guide-on-healthcare-related-to-gender-identity.ashx?sc_lang=en&hash=0FF626604C50D5EED94852CA5D042A8E	3
de Vries 2006 [37]	Guideline	Canada	Covers all aspects of care including assessment, psychosocial care and medical interventions	Health and social service professionals	Adolescents (not defined)	To provide professionals working with adolescents with gender-dysphoric feelings practical clinical guidelines for diagnosis and treatment.	Trans Care Project - initiative of Transcend Transgender Support & Education Society and Vancouver Coastal Health's Transgender Health Program	https://rainbowhealth.wpenginepowered.com/wp-content/uploads/2009/05/Guidelines-adolescent.pdf	1

Endocrine Society 2017 [25]	Guideline	International	Covers all aspects of hormone treatment and surgery, including assessment for these	Endocrinologists	All (includes sections on children and adolescents)	To make recommendations and suggestions, based on existing literature and clinical experience, that will enable treating physicians to maximize benefit and minimize risk when caring for individuals diagnosed with gender dysphoria/gender incongruence.	Endocrine Society	https://doi.org/10.1210/jc.2017-01658	2
European Society for Sexual Medicine (ESSM) 2020 [26]	Position statement	Europe	Covers assessment and hormone treatments with emphasis on sexual functioning - includes general principles and treatment recommendations	European sexologists and healthcare providers who encounter trans people in clinical practice.	Adolescents and Adults	To provide an up-to-date overview of clinical consensus statements on trans health care with attention for sexual function and satisfaction.	European Society for Sexual Medicine	https://doi.org/10.1016/j.jsxm.2020.01.012	1
Fisher 2014 [27]	Position Statement	Italy	Covers psychological support and medical intervention including specific recommendations regarding hormone treatments	All healthcare providers	Adolescents	To develop and subscribe Italian guidelines for treatment of gender dysphoria in adolescents, based on the ''Dutch Approach'', and in line with the Endocrine Society (ES), and the WPATH guidelines.	Fisher et al. (2014)	https://doi.org/10.1007/s40618-014-0077-6	1
Health Policy Project (HPP) 2015 [38]	Blueprint	Asia and the Pacific	Covers all aspects of policy affecting trans people and includes specific guidance about assessment, psychological care and medical care	Health providers, policymakers and governments	All (includes section on children and adolescents)	To improve access to competent primary and specialised care for trans people in Asia and the Pacific.	The Health Policy Project (HPP), Asia Pacific Transgender Network APTN), United Nations Development Programme (UNDP)	https://www.undp.org/asia-pacific/publications/blueprint-provision-comprehensive-care-trans-people-and-trans-communities-asia-and-pacific	1
Norwegian Directorate of Health 2020 [39]	Guideline	Norway	Naitonal guideline containing broad assessment and care recommendations and some criteria for medical treatments	Healthcare managers and staff working in general and specialist services	All (includes specific recommendations for children and young people)	To prepare recommendations on the treatment of gender dysphoria and gender incongruence, and to confirm the health services offered to people who experience gender incongruence.	Norwegian Directorate of Health	https://www.helsedirektoratet.no/retningslinjer/kjonnsinkongruens	1
Oliphant 2018 [28, 45]	Guidelines	New Zealand	Includes principles for care and covers all aspects of care and includes specific recommendations regarding hormone treatments	All healthcare providers	All (includes specific recommendations for children and young people)	To present guidance for the provision of gender affirming health care in Aotearoa, New Zealand, which is in step with current practice and international standards.	Oliphant et al. (2018)	https://nzmj.org.nz/journal/vol-131-no-1487/guidelines-for-gender-affirming-healthcare-for-gender-diverse-and-transgender-children-young-people-and-adults-in-aotearoa-new-z	2

Pan American Health Organisation (PAHO) 2014 [40]	Blueprint	The Caribbean	Covers all aspects of policy affecting trans people and includes specific guidance about assessment, psychological care and medical care	Health providers, programme planners and managers, policymakers, community leaders, and other stakeholders	All (includes section on children and adolescents)	To provide guidance on improving access to competent primary and specialized care for trans persons in the Latin American and Carribbean region	Pan American Health Organisation (PAHO), John Snow Inc. and WPATH are named as co-authors	https://www.paho.org/en/node/50469	2
Royal Children's Hospital Melbourne (RCHM) 2018 [29, 46]	Guidelines	Australia	Includes general principles and covers all aspects of care including specific recommendations regarding hormone treatments	All healthcare providers	Children and adolescents	To maximise quality care provision for trans and gender diverse children and adolescents across Australian	The Royal Children's Hospital, Melbourne	https://doi.org/10.5694/mja17.01044	1
Royal College of Psychiatrists (RCPsych) 1998 [30]	Guideline	UK	Covers psychological assessment and management and broad recommendations about medical treatments	Psychiatrists	Children and adolescents	Not reported	Royal College of Psychiatrists (UK)	http://web.archive.org/web/20070503090525/http://www.symposion.com/ijt/ijtc0402.htm	1
Society for Adolescent Health and Medicine (SAHM) 2020 [31]	Position Statement	International	Includes broad recommendations relating to care approach and model, and medical intervention - does not include specific treatment recommendations	All healthcare providers	Young people	Not reported	Society for Adolescent Health and Medicine	https://doi.org/10.1016/j.jadohealth.2020.03.016	1
South African HIV Clinicians Society (SAHCS) 2021 [41, 47]	Guideline	South Africa	Covers all aspects of care and treatment and includes detailed guidance on hormone treatments	All healthcare providers, particularly those working in a primary care setting, public or private	All (includes sections on children and adolescents)	To provide evidence-informed best practice recommendations to enable South African healthcare providers to offer quality, affirming services to transgender and gender diverse clients. The term 'client', for the purposes of this guideline, includes service users, patients and participants.	South African HIV Clinicians Society	https://doi.org/10.4102/sajhivmed.v22i1.1299	1
Spanish Society of Endocrinology and Nutrition (SSEN) 2012 [42]	Guideline	Spain	Covers assessment and treatment with main focus on hormone treatments	Not reported	All (includes section on children and adolescents)	To meet the need for implementing a coordinated action protocol for comprehensive health care for transgender people in the [Spanish] National Health System.	SSEN Identity and Sexual Differentiation Group (GIDSEEN)	https://doi.org/10.1016/j.endonu.2012.02.001	1

Spanish Society of Endocrinology and Nutrition (SSEN) 2015 [32]	Position Statement	Spain	Sets out broad recommendations for evaluation and treatment (no specific details)	All healthcare providers	Children and adolescents	To set out recommendations for evaluation and treatment of gender dysphoria in children and adolescents.	SSEN Working Group on Gender Identity and Sexual Development (GIDSEEN)	https://doi.org/10.1016/j.endonu.2015.03.004	1
Strang 2018 [33]	Guideline	International	Covers all aspects of care but does not include specific guidance on hormone treatments	Not reported	Adolescents (time of onset of puberty to age 19) with autism spectrum disorder and gender dysphoria	To develop initial clinical consensus guidelines for the care of adolescents with co-occuring autism spectrum disorder and gender non-conformity/gender dysphoria.	Strang et al. (2018)	https://doi.org/10.1080/15374416.2016.1228462	1
Swedish National Board of Health and Welfare 2022 [43]	Guideline	Sweden	National guideline covering all aspects of assessment and care including psychosocial care and hormone treatments	Health professionals in health care sector and decision-makers with responsibility for health care activities concerned	Children and adolescents	To contribute to good and equal care for children and young people with gender inequality and gender dysphoria.	Swedish National Board of Health and Welfare	https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-12-8302.pdf	2
University of California San Francisco (UCSF) 2016 [44]	Guideline	US	Covers all aspects of care including assessment, psychosocial care, medical and other interventions	All healthcare providers	All (includes chapter on children and adolescents)	To equip primary care providers and health systems with the tools and knowledge to meet the health care needs of their transgender and gender nonconforming patients.	Center of Excellence for Transgender Health, University of California, San Francisco (UCSF)	https://transcare.ucsf.edu/guidelines	2
World Professional Association for Transgender Health (WPATH) 2022 [34]	Guideline	International	Covers all aspects of assessment, care and treatment including specific recommendations regarding medical treatment	All healthcare providers	All (includes sections on children and adolescents)	To provide clinical guidance to assist transgender and gender diverse people in accessing safe and effective pathways to achieving lasting personal comfort with their gendered selves with the aim of optimizing overall physical health, psychological well-being, and self-fulfillment.	World Professional Association for Transgender Health (WPATH)	https://doi.org/10.1080/26895269.2022.2100644	8

* The terminology and language used by guidelines has been retained in this summary

Supplementary Table S1 - Guideline characteristics*

Guideline ID, Year	Type of guideline	Country	Summary of guideline	Target audience	Population	Stated Aim	Produced by	Weblink	Version
American Academy of Child & Adolescent Psychiatry (AACAP) 2012 [17]	Practice Parameter	US	Sets out principles for practice but does not include specific treatment recommendations	Psychiatrists	Children and adolescents (includes sexual minority care as well)	To foster clinical competence in those caring for children and adolescents	American Academy of Child & Adolescent Psychiatry (AACAP)	https://doi.org/10.1016/j.jaac.2012.07.004	1
American Academy of Paediatrics (AAP) 2018 [20]	Policy Statement	US	Sets out nine recommendations regarding role of paediatricians but does not include specific treatment recommendations	Paediatrians	Children and adolescents	To provide suggestions for paediatric providers that are focused on promoting the health and positive development of youth that identity as transgender and gender diverse while eliminating discrimination and stigma	American Academy of Paediatrics	https://doi.org/10.1542/peds.2018-2162	1
American Psychological Association (APA) 2015 [19]	Guideline	US	Sets out 16 guidelines which are principles for psychological practice but within these are recommendations for assessment and psychological care	Psychologists	Adults (includes guideline specific to children and young people)	To assist psychologists in the provision of culturally competent, developmentally appropriate, and trans-affirmative psychological practice	American Psychological Association	https://www.apa.org/practice/guidelines/transgender.pdf	1
Council for Choices in Healthcare in (COHERE) Finland 2020 [27]	Guideline	Finland	National guideline focusing on medical research and treatment methods for the treatment of gender dysphoria	All healthcare providers	Minors (<18) - guidelines for adults and minors developed together but published separately	To provide a recommendation on medical treatment methods for dysphoria associated with variations in gender identity of minors	Council for Choices in Healthcare in Finland	https://palveluvalikoima.fi/en/recommendations#genderidentity	1
Danish Health Authority 2018 [26]	Guideline	Denmark	National guideline covering all aspects of care and broad recommendations	All healthcare providers	All (includes chapter on under 18s)	To ensure a high quality and equal access to healthcare related to gender identity in Denmark.	Danish Health Authority	https://www.sst.dk/-/media/English/Publications/2018/Guide-on-healthcare-related-to-gender-identity.ashx?sc_lang=en&hash=0FF626604C50D5EED94852CA5D042A8E	3
de Vries 2006 [25]	Guideline	Canada	Covers all aspects of care including assessment, psychosocial care and medical interventions	Health and social service professionals	Adolescents (not defined)	To provide professionals working with adolescents with gender-dysphoric feelings practical clinical guidelines for diagnosis and treatment.	Trans Care Project - initiative of Transcend Transgender Support & Education Society and Vancouver Coastal Health's Transgender Health Program	https://rainbowhealth.wpenginepowered.com/wp-content/uploads/2009/05/Guidelines-adolescent.pdf	1

Endocrine Society 2017 [11]	Guideline	International	Covers all aspects of hormone treatment and surgery, including assessment for these	Endocrinologists	All (includes sections on children and adolescents)	To make recommendations and suggestions, based on existing literature and clinical experience, that will enable treating physicians to maximize benefit and minimize risk when caring for individuals diagnosed with gender dysphoria/gender incongruence.	Endocrine Society	https://doi.org/10.1210/jc.2017-01658	2
European Society for Sexual Medicine (ESSM) 2020 [14]	Position statement	Europe	Covers assessment and hormone treatments with emphasis on sexual functioning - includes general principles and treatment recommendations	European sexologists and healthcare providers who encounter trans people in clinical practice.	Adolescents and Adults	To provide an up-to-date overview of clinical consensus statements on trans health care with attention for sexual function and satisfaction.	European Society for Sexual Medicine	https://doi.org/10.1016/j.jsxm.2020.01.012	1
Fisher 2014 [28]	Position Statement	Italy	Covers psychological support and medical intervention including specific recommendations regarding hormone treatments	All healthcare providers	Adolescents	To develop and subscribe Italian guidelines for treatment of gender dysphoria in adolescents, based on the ''Dutch Approach'', and in line with the Endocrine Society (ES), and the WPATH guidelines.	Fisher et al. (2014)	https://doi.org/10.1007/s40618-014-0077-6	1
Health Policy Project (HPP) 2015 [15]	Blueprint	Asia and the Pacific	Covers all aspects of policy affecting trans people and includes specific guidance about assessment, psychological care and medical care	Health providers, policymakers and governments	All (includes section on children and adolescents)	To improve access to competent primary and specialised care for trans people in Asia and the Pacific.	The Health Policy Project (HPP), Asia Pacific Transgender Network APTN), United Nations Development Programme (UNDP)	https://www.undp.org/asia-pacific/publications/blueprint-provision-comprehensive-care-trans-people-and-trans-communities-asia-and-pacific	1
Norwegian Directorate of Health 2020 [31]	Guideline	Norway	Naitonal guideline containing broad assessment and care recommendations and some criteria for medical treatments	Healthcare managers and staff working in general and specialist services	All (includes specific recommendations for children and young people)	To prepare recommendations on the treatment of gender dysphoria and gender incongruence, and to confirm the health services offered to people who experience gender incongruence.	Norwegian Directorate of Health	https://www.helsedirektoratet.no/retningslinjer/kjonnsinkongruens	1
Oliphant 2018 [29, 30]	Guidelines	New Zealand	Includes principles for care and covers all aspects of care and includes specific recommendations regarding hormone treatments	All healthcare providers	All (includes specific recommendations for children and young people)	To present guidance for the provision of gender affirming health care in Aotearoa, New Zealand, which is in step with current practice and international standards.	Oliphant et al. (2018)	https://nzmj.org.nz/journal/vol-131-no-1487/guidelines-for-gender-affirming-healthcare-for-gender-diverse-and-transgender-children-young-people-and-adults-in-aotearoa-new-z	2

Pan American Health Organisation (PAHO) 2014 [16]	Blueprint	The Caribbean	Covers all aspects of policy affecting trans people and includes specific guidance about assessment, psychological care and medical care	Health providers, programme planners and managers, policymakers, community leaders, and other stakeholders	All (includes section on children and adolescents)	To provide guidance on improving access to competent primary and specialized care for trans persons in the Latin American and Carribbean region	Pan American Health Organisation (PAHO), John Snow Inc. and WPATH are named as co-authors	https://www.paho.org/en/node/50469	2
Royal Children's Hospital Melbourne (RCHM) 2018 [23, 24]	Guidelines	Australia	Includes general principles and covers all aspects of care including specific recommendations regarding hormone treatments	All healthcare providers	Children and adolescents	To maximise quality care provision for trans and gender diverse children and adolescents across Australian	The Royal Children's Hospital, Melbourne	https://doi.org/10.5694/mja17.01044	1
Royal College of Psychiatrists (RCPsych) 1998 [35]	Guideline	UK	Covers psychological assessment and management and broad recommendations about medical treatments	Psychiatrists	Children and adolescents	Not reported	Royal College of Psychiatrists (UK)	http://web.archive.org/web/20070503090525/http://www.symposion.com/ijt/ijtc0402.htm	1
Society for Adolescent Health and Medicine (SAHM) 2020 [12]	Position Statement	International	Includes broad recommendations relating to care approach and model, and medical intervention - does not include specific treatment recommendations	All healthcare providers	Young people	Not reported	Society for Adolescent Health and Medicine	https://doi.org/10.1016/j.jadohealth.2020.03.016	1
South African HIV Clinicians Society (SAHCS) 2021 [32, 33]	Guideline	South Africa	Covers all aspects of care and treatment and includes detailed guidance on hormone treatments	All healthcare providers, particularly those working in a primary care setting, public or private	All (includes sections on children and adolescents)	To provide evidence-informed best practice recommendations to enable South African healthcare providers to offer quality, affirming services to transgender and gender diverse clients. The term 'client', for the purposes of this guideline, includes service users, patients and participants.	South African HIV Clinicians Society	https://doi.org/10.4102/sajhivmed.v22i1.1299	1
Spanish Society of Endocrinology and Nutrition (SSEN) 2012 [22]	Guideline	Spain	Covers assessment and treatment with main focus on hormone treatments	Not reported	All (includes section on children and adolescents)	To meet the need for implementing a coordinated action protocol for comprehensive health care for transgender people in the [Spanish] National Health System.	SSEN Identity and Sexual Differentiation Group (GIDSEEN)	https://doi.org/10.1016/j.endonu.2012.02.001	1

Spanish Society of Endocrinology and Nutrition (SSEN) 2015 [21]	Position Statement	Spain	Sets out broad recommendations for evaluation and treatment (no specific details)	All healthcare providers	Children and adolescents	To set out recommendations for evaluation and treatment of gender dysphoria in children and adolescents.	SSEN Working Group on Gender Identity and Sexual Development (GIDSEEN)	https://doi.org/10.1016/j.endonu.2015.03.004	1
Strang 2018 [13]	Guideline	International	Covers all aspects of care but does not include specific guidance on hormone treatments	Not reported	Adolescents (time of onset of puberty to age 19) with autism spectrum disorder and gender dysphoria	To develop initial clinical consensus guidelines for the care of adolescents with co-occuring autism spectrum disorder and gender non-conformity/gender dysphoria.	Strang et al. (2018)	https://doi.org/10.1080/15374416.2016.1228462	1
Swedish National Board of Health and Welfare 2022 [34]	Guideline	Sweden	National guideline covering all aspects of assessment and care including psychosocial care and hormone treatments	Health professionals in health care sector and decision-makers with responsibility for health care activities concerned	Children and adolescents	To contribute to good and equal care for children and young people with gender inequality and gender dysphoria.	Swedish National Board of Health and Welfare	https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-12-8302.pdf	2
University of California San Francisco (UCSF) 2016 [17]	Guideline	US	Covers all aspects of care including assessment, psychosocial care, medical and other interventions	All healthcare providers	All (includes chapter on children and adolescents)	To equip primary care providers and health systems with the tools and knowledge to meet the health care needs of their transgender and gender nonconforming patients.	Center of Excellence for Transgender Health, University of California, San Francisco (UCSF)	https://transcare.ucsf.edu/guidelines	2
World Professional Association for Transgender Health (WPATH) 2022 [10]	Guideline	International	Covers all aspects of assessment, care and treatment including specific recommendations regarding medical treatment	All healthcare providers	All (includes sections on children and adolescents)	To provide clinical guidance to assist transgender and gender diverse people in accessing safe and effective pathways to achieving lasting personal comfort with their gendered selves with the aim of optimizing overall physical health, psychological well-being, and self-fulfillment.	World Professional Association for Transgender Health (WPATH)	https://doi.org/10.1080/26895269.2022.2100644	8

* The terminology and language used by guidelines has been retained in this summary

EXHIBIT 88

Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: a systematic review

Jo Taylor, Alex Mitchell, Ruth Hall, Claire Heathcote, Trilby Langton, Lorna Fraser, Catherine Elizabeth Hewitt

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/archdischild-2023-326669).

Department of Health Sciences, University of York, York, UK

Correspondence to
Dr Jo Taylor, Health Sciences, University of York, York, North Yorkshire, UK;
dohs-gender-research@york.ac.uk

Received 25 November 2023
Accepted 10 February 2024

Linked

► https://doi.org/10.1136/archdischild-2023-326112
► https://doi.org/10.1136/archdischild-2023-326347
► https://doi.org/10.1136/archdischild-2023-326348
► https://doi.org/10.1136/archdischild-2023-326500
► https://doi.org/10.1136/archdischild-2023-326499
► https://doi.org/10.1136/archdischild-2023-326760
► https://doi.org/10.1136/archdischild-2023-326670
► https://doi.org/10.1136/archdischild-2023-326681

To cite: Taylor J, Mitchell A, Hall R, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2023-326669

ABSTRACT

Background Treatment to suppress or lessen effects of puberty are outlined in clinical guidelines for adolescents experiencing gender dysphoria/incongruence. Robust evidence concerning risks and benefits is lacking and there is a need to aggregate evidence as new studies are published.

Aim To identify and synthesise studies assessing the outcomes of puberty suppression in adolescents experiencing gender dysphoria/incongruence.

Methods A systematic review and narrative synthesis. Database searches (Medline, Embase, CINAHL, PsycINFO, Web of Science) were performed in April 2022, with results assessed independently by two reviewers. An adapted version of the Newcastle-Ottawa Scale for cohort studies was used to appraise study quality. Only moderate-quality and high-quality studies were synthesised. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines were used.

Results 11 cohort, 8 cross-sectional and 31 pre-post studies were included (n=50). One cross-sectional study was high quality, 25 studies were moderate quality (including 5 cohort studies) and 24 were low quality. Synthesis of moderate-quality and high-quality studies showed consistent evidence demonstrating efficacy for suppressing puberty. Height increased in multiple studies, although not in line with expected growth. Multiple studies reported reductions in bone density during treatment. Limited and/or inconsistent evidence was found in relation to gender dysphoria, psychological and psychosocial health, body satisfaction, cardiometabolic risk, cognitive development and fertility.

Conclusions There is a lack of high-quality research assessing puberty suppression in adolescents experiencing gender dysphoria/incongruence. No conclusions can be drawn about the impact on gender dysphoria, mental and psychosocial health or cognitive development. Bone health and height may be compromised during treatment. More recent studies published since April 2022 until January 2024 also support the conclusions of this review.

PROSPERO registration number CRD42021289659.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Increasing numbers of children and adolescents experiencing gender dysphoria/incongruence are being referred to specialist gender services.
⇒ National and international guidelines have changed over time and outline that medications to suppress puberty can be considered for adolescents experiencing gender dysphoria/incongruence.
⇒ Several systematic reviews report a limited evidence base for these treatments, and uncertainty about the benefits, risks and long-term effects.

WHAT THIS STUDY ADDS

⇒ No high-quality studies were identified that used an appropriate study design to assess the outcomes of puberty suppression in adolescents experiencing gender dysphoria/incongruence.
⇒ There is insufficient and/or inconsistent evidence about the effects of puberty suppression on gender-related outcomes, mental and psychosocial health, cognitive development, cardiometabolic risk, and fertility.
⇒ There is consistent moderate-quality evidence, although from mainly pre-post studies, that bone density and height may be compromised during treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, POLICY OR PRACTICE

⇒ There is a lack of high-quality evidence to support the use of puberty suppression in adolescents experiencing gender dysphoria/incongruence, and large well-designed research is needed.

INTRODUCTION

Over the last 10-15 years, increasing numbers of children and adolescents experiencing gender dysphoria/incongruence are being referred to specialist paediatric gender services.[1 2]

Gender dysphoria/incongruence in childhood is associated with high rates of co-occurring mental health and psychosocial difficulties, which can affect health and well-being.[3] Clinical guidelines recommend psychosocial care to alleviate gender-related distress and any co-occurring difficulties. For pubertal adolescents, medications to suppress or lessen effects of puberty are also outlined. Gonadotropin-releasing hormone analogues (GnRH-a) are used as first-line treatment, although other drugs with anti-androgenic properties including progestins and spironolactone are used in this population.[4 5] The effects differ depending on

whether they are initiated in early puberty or mid-puberty, as well as the type of intervention used, with GnRH-a suppressing puberty when started early or suspending further progression when initiated in mid-puberty, and anti-androgens instead blocking specific downstream effects of sex hormones.[4]

Rationales for puberty suppression in the Dutch treatment protocol, which has informed practice internationally, were to alleviate worsening gender dysphoria, allow time for gender exploration, and pause development of secondary sex characteristics to make passing in the desired gender role easier.[6] Practice guidelines propose other indications for puberty suppression, including allowing time and/or capacity for decision-making about masculinising or feminising hormone interventions, and improving quality of life.[4 7 8]

Criteria in early treatment protocols for puberty suppression specified adolescents be at least age 12 years, at Tanner stage 2 in puberty, experienced gender dysphoria in childhood which persisted and intensified during puberty and met criteria for diagnosis of gender dysphoria.[6] It was also expected that any psychosocial difficulties that could interfere with treatment were managed.[6] The World Professional Association for Transgender Health standards of care[4] and other practice guidelines[5 8 9] have broadened these criteria, for example, removing minimum age. However, other recent guidelines have taken a more cautious approach and restricted inclusion criteria in response to uncertainties in the evidence base.[7 10]

Systematic reviews have consistently found mainly low-quality evidence, limited data on key outcomes or long-term follow-up.[11–16] These reviews report that while puberty suppression may offer some benefit, there are concerns about the impact on bone health, and uncertainty regarding cognitive development, psychosocial outcomes and cardiometabolic health. They conclude there is insufficient evidence to support clinical recommendations.

The proliferation of research in this area and lack of evidence to support practice means there is an ongoing need to aggregate evidence. This systematic review aims to synthesise evidence published to April 2022 that reports outcomes of puberty suppression in adolescents experiencing gender dysphoria/incongruence.

METHODS

The review forms part of a linked series examining the epidemiology, care pathways, outcomes and experiences for children and adolescents experiencing gender dysphoria/incongruence and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] The protocol was registered on PROSPERO (CRD42021289659.[18]

Search strategy

A single search strategy was used to identify studies comprising two combined concepts: 'children', which included all terms for children and adolescents and 'gender dysphoria', which included associated terms such as gender-related distress and gender incongruence, and gender identity terms including transgender, gender diverse and non-binary.

MEDLINE (online supplemental table S1), EMBASE and PsycINFO through OVID, CINAHL Complete through EBSCO, and Web of Science (Social Science Citation Index) were searched (13–23 May 2021 and updated on 27 April 2022).

Reference lists of included studies and relevant systematic reviews were assessed for inclusion.[11–16 19 20]

Table 1 Inclusion and exclusion criteria

Population	Children and/or adolescents aged 0–18 years experiencing gender dysphoria, gender incongruence or referral to a gender identity service. Studies of adults or a mixed population of adolescents and adults where treatment was initiated in childhood (<18 years).
Intervention	GnRH-a, progestins and other anti-androgens used to suppress puberty or part of puberty (eg, menstrual suppression).
Comparator	Any or none.
Outcomes	Expected or desired physiological effects, side effects, gender dysphoria or other gender-related outcomes, mental/psychological health, physical health, psychosocial outcomes, cognitive outcomes, fertility.
Study design	Clinical trials, cohort studies, case-control studies, cross-sectional studies, pre-post single-group design studies or service evaluations that provided treatment outcome data. Case studies and case series were excluded.
Publication	Studies published in the English language in a peer-reviewed journal. Conference abstracts were excluded.

GnRH-a, gonadotropin-releasing hormone analogues.

Inclusion criteria

The review included published research that reported outcomes of interventions used to suppress puberty for children and/or adolescents experiencing gender dysphoria/incongruence (table 1).

Selection process

The results of database and other searches were uploaded to Covidence[21] and screened independently by two reviewers. Full texts of potentially relevant articles were retrieved and reviewed against inclusion criteria by two reviewers independently. Disagreements were resolved through discussion and inclusion of a third reviewer.

Data extraction

Data on study characteristics, methods and reported outcomes were extracted into prepiloted data extraction templates by one reviewer and second-checked by another.

Study quality

Critical appraisal was undertaken by two reviewers independently, with consensus reached through discussion and involvement of a third reviewer where necessary.

Quality was assessed using a modified version (online supplemental file 1) of the Newcastle-Ottawa Scale for cohort studies, a validated scale of eight items covering three domains: selection, comparability and outcome.[22] Scale modification included not scoring certain question(s) for cross-sectional and single-group designs, or particular outcomes; specification of key confounders to assess comparability of cohorts; guidance regarding sufficiency of follow-up and use of numerical scores for items and overall (maximum score 9 for cohorts, 8 for pre-post and cross-sectional studies with comparator). Total scores were calculated as percentages to account for different total scores (≤50% low quality, >50%–75% moderate quality, >75% high quality).

Synthesis

Narrative synthesis methods were used because of heterogeneity in study design, intervention, comparator, outcome and measurement. Due to high risk of bias in low-quality studies, these were excluded from the synthesis.

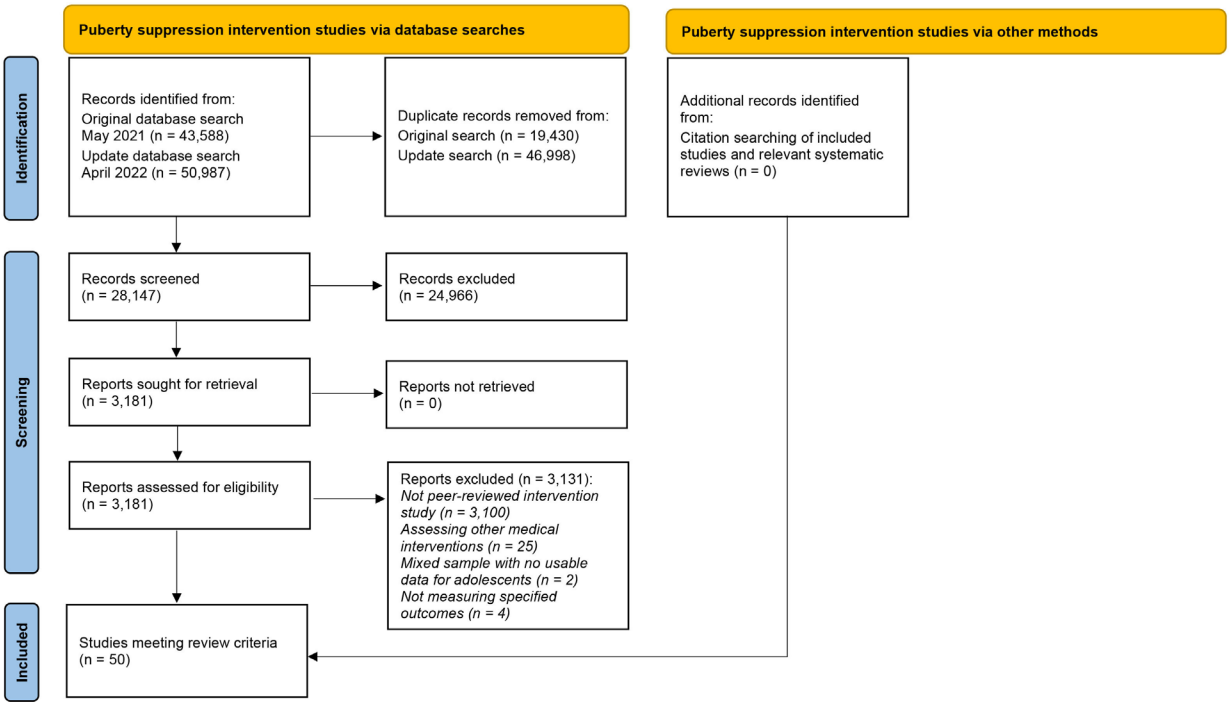


Figure 1 Study flow diagram.

When synthesising results by outcome domains, care was taken to differentiate between different study designs, comparators and interventions. Where possible, potential differences in effects by birth-registered sex, treatment duration or treatment in early puberty versus late puberty were examined.

RESULTS

The database search yielded 28 147 records, 3181 of which were identified as potentially relevant for the linked systematic reviews and full texts reviewed. From these, 50 studies met inclusion criteria for this review (figure 1).

Study characteristics

Studies were published from 2006 to 2022 with the majority published in 2020–2022 (n=29). Studies were conducted in the Netherlands (n=17),[23–39] the US (n=15),[40–54] the UK (n=6),[55–60] Canada (n=4),[61–64] three in Belgium[65–67] and Israel[68–70] and one in Brazil[71] and Germany[72] (online supplemental table S2).

The 50 studies included 11 cohorts comparing adolescents experiencing gender dysphoria/incongruence receiving puberty suppression with a comparator,[35 39–42 45 49 50 52 56 72] 8 cross-sectional with a comparator[23 33 37 47 51 53 60 71] and 31 pre-post single group studies.[24–32 34 36 38 43 44 46 48 54 55 57–59 61–70] More than half of studies (n=29) used retrospective chart review.

All but 4 studies selected adolescents experiencing gender dysphoria/incongruence from specialist gender or endocrinology services: 43 from single services (in Belgium, Israel, the Netherlands and the UK these were large regional or national services) and 3 from multiple US services.[48–50] The other four included three US studies (national survey recruiting via community settings,[53] clinical and community settings,[51] US Military Healthcare Data Repository[54]) and a study from Brazil recruiting via Facebook.[71]

Overall, studies included 10 673 participants: 9404 were adolescents experiencing gender dysphoria/incongruence (4702 received puberty suppression, 4702 did not) and 1269 other comparators. Comparator groups included adolescents or adults experiencing gender dysphoria/incongruence who had not received puberty suppression,[35 39 40 42 51–53 60 71 72] untreated adolescents not experiencing gender dysphoria/incongruence,[36 47 50] both of these comparators[23 33 37 56] or adolescents receiving treatment for a different medical reason.[41 45 49]

Most studies (n=39) assessed GnRH-a. In one, some participants received GnRH-a and some (birth-registered males) spironolactone.[62] In another, GnRH-a or progestins/anti-androgens were used but numbers taking each were not reported.[40] Among the other 11 studies, 5 assessed effects of progestins (cyproterone acetate,[66 67] lynestrenol,[65 66] medroxyprogesterone[44] and levonorgestrel-releasing intrauterine system[41]) as alternatives to GnRH-a,[41 44 65–67] 1 assessed bicalutamide[46] and 5 did not specify.[43 52–54 71]

Of the 50 studies, 29 reported outcomes for feminising or masculinising hormones as well as for puberty suppression, either by including a mixed sample of those receiving the two different interventions or by assessing those who progressed to hormones following puberty suppression.

The most frequently measured outcomes were puberty suppression (n=30) and physical health outcomes (n=27) (figure 2, online supplemental table S3). Gender-related outcomes and body image were measured in five and four studies, respectively. Psychological health was measured in 13 studies, psychosocial in 9 studies and cognitive/neurodevelopmental outcomes in 3 studies. Side effects were reported in six, bone health in nine, and one study measured fertility.

Study quality

One cross-sectional study was rated high quality,[37] 25 moderate quality[23 24 29–32 34–36 39 48–51 54–59 64 65 67–69] and 24 low quality.[25–28 33 38 40–47 52 53 60–63 66 70–72] Of the 11 cohort studies, which were the only studies to include a comparator and assess outcomes over time, only 5 were rated moderate quality (figure 2, online supplemental table S4).[35 39 49 50 56]

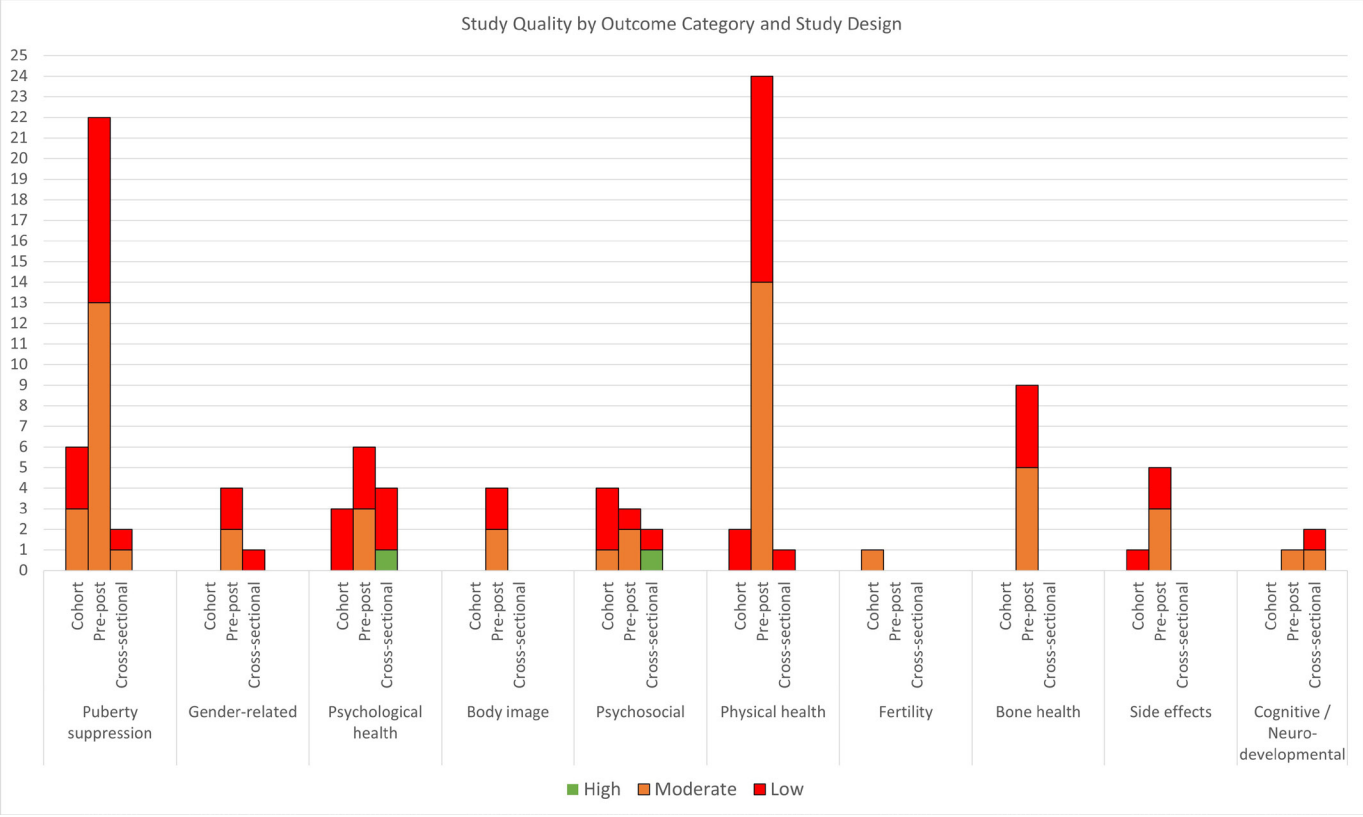


Figure 2 Outcome categories by study quality and design.

In most studies, there were concerns about sample representativeness due to single site recruitment, inclusion of a selected group and/or poor reporting of the eligible population. In studies including a comparator, most did not report or control for key differences between groups and only four used matched controls.[23 33 41 47] Most studies presented results for birth-registered males and females separately or controlled for this. Few studies controlled for age or Tanner stage or co-interventions that could influence outcomes.

Overall, studies used appropriate methods to ascertain exposure and assess outcomes. Adequacy of follow-up was evident in 18 studies, with multiple studies not reporting treatment duration, including participants receiving treatment at baseline, and not aligning follow-up with treatment initiation. Missing data at follow-up/analysis or poor reporting of this affected many studies.

Four studies did not report separate outcome data for adolescents receiving puberty suppression or masculinising/feminising hormones.[39 54 60 71] Two of these were of moderate quality and not included in the synthesis,[39 54] one of which was the only study to assess fertility outcomes.[39] One moderate-quality study assessed amplitude of click-evoked otoacoustic emissions.[23] This was excluded from the synthesis on the basis of not being clinically relevant.

Synthesis of outcomes

Gender dysphoria and body satisfaction

Two pre-post studies measured gender dysphoria and body satisfaction (with primary and secondary sex or neutral body characteristics) and reported no change before and after receiving treatment[24 55] (table 2).

Psychological health

One cross-sectional[37] and two pre-post studies[24 55] measured symptoms of depression (n=1), anxiety (n=1), anger (n=1), internalising and externalising symptoms (n=3), suicide and/or self-harm (n=2) and psychological functioning (n=2).

Three studies assessed internalising and externalising symptoms with one reporting improvements in both (pre-post[24]), one improvement in internalising but not externalising symptoms when compared with adolescents under assessment by a gender service (cross-sectional[37]) and one observed no change in either (pre-post).[55]

For other psychological outcomes, there was either a single study, or two studies showing inconsistent results, with studies reporting either a small to moderate significant improvement or no change (table 2).

Psychosocial outcomes

One cohort[56] and two pre-post[24 55] studies measured psychosocial functioning, one pre-post study assessed quality of life[55] and one cross-sectional study measured peer-relations (table 2).[37]

For psychosocial functioning, both pre-post studies reported no clinically significant change at follow-up.[24 55] The cohort study compared adolescents who were not immediately eligible for puberty suppression and received psychological support only, and adolescents who additionally received GnRH-a after 6 months.[56] Improvements were seen in both groups after 6 months of psychological support. This improvement was maintained over time for those receiving psychological support only. For those receiving GnRH-a, further improvements were observed at 12 and 18 months. At 18 months, psychosocial functioning in this group was considerably higher than in those still waiting for puberty suppression, and similar to adolescents not

Table 2 Gender-related, body image, psychological, psychosocial, and cognitive/neurodevelopmental outcomes

Study	Country	Study design	Study quality	Treated sample	Comparator	Intervention	Outcome (measure)	Follow-up specific to outcome	Summary of study results
Gender-related outcomes									
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	N/A	GnRH-a	Gender dysphoria (UGDS)	12 m, 24 m	No change over time.
de Vries *et al*[24]	The Netherlands	Pre-post	Moderate	70 (37 brf, 33 brm)	N/A	GnRH-a	Gender dysphoria (UGDS)	Before CSH start (range 0.4–5.1 y)	No change.
Body image									
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	N/A	GnRH-a	Satisfaction with primary or secondary sex, or neutral body characteristics (BIS)	12 m, 24 m, 36 m	No change over time.
de Vries *et al*[24]	The Netherlands	Pre-post	Moderate	70 (37 brf, 33 brm)	N/A	GnRH-a	Satisfaction with primary or secondary sex, or neutral body characteristics (BIS)	Before CSH start (range 0.4–5.1 y)	No change.
Psychological health									
Depression									
de Vries *et al*[24]	The Netherlands	Pre-post	Moderate	70 (37 brf, 33 brm)	N/A	GnRH-a	Depressive symptoms (BDI)	Before CSH start (range 0.4–5.1 y)	Reduction in depressive symptoms.
Anxiety									
de Vries *et al*[24]	The Netherlands	Pre-post	Moderate	70 (37 brf, 33 brm)	N/A	GnRH-a	Anxiety symptoms (STAI)	Before CSH start (range 0.4–5.1 y)	No change in anxiety symptoms.
Internalising problems									
van der Miesen *et al*[37]	The Netherlands	Cross-sectional	High	178 (110 brf, 68 brm)	272+651 no GD	GnRH-a	Internalising problems (YSR)	N/A	Fewer problems in those treated compared with not treated. Scores in treated brm similar to cisgender brm, and scores in treated brf lower than cisgender brf.
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	N/A	GnRH-a	Internalising problems (CBCL/YSR)	12 m, 24 m, 36 m	No change over time.
de Vries *et al*[24]	The Netherlands	Pre-post	Moderate	70 (37 brf, 33 brm)	N/A	GnRH-a	Internalising problems (CBCL/YSR)	Before CSH start (range 0.4–5.1 y)	Small decrease (improvement).
Externalising problems									
van der Miesen *et al*[37]	The Netherlands	Cross-sectional	High	178 (110 brf, 68 brm)	272+651 no GD	GnRH-a	Externalising problems (YSR)	N/A	No difference between groups.
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	N/A	GnRH-a	Externalising problems (CBCL/YSR)	12 m, 24 m, 36 m	No change over time.
de Vries *et al*[24]	The Netherlands	Pre-post	Moderate	70 (37 brf, 33 brm)	N/A	GnRH-a	Externalising problems (CBCL/YSR)	Before CSH start (range 0.4–5.1 y)	Small decrease (improvement).
Psychological functioning/psychopathology									
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	N/A	GnRH-a	Psychological functioning (total CBCL/YSR)	12 m, 24 m, 36 m	No change over time.
de Vries *et al*[24]	The Netherlands	Pre-post	Moderate	70 (37 brf, 33 brm)	N/A	GnRH-a	Psychological functioning (total CBCL/YSR)	Before CSH start (range 0.4–5.1 y)	Small decrease (improvement).
Suicidality/Self-harm									
van der Miesen *et al*[37]	The Netherlands	Cross-sectional	High	178 (110 brf, 68 brm)	272+651 no GD	GnRH-a	Self-harm/suicidality (YSR item 18 and 91)	N/A	Less self-harm/suicidality in those treated, although similar to group with no GD.

Continued

Table 2 Continued

Study	Country	Study design	Study quality	Treated sample	Comparator	Intervention	Outcome (measure)	Follow-up specific to outcome	Summary of study results
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	N/A	GnRH-a	Self-harm/suicidality (YSR item 18 and 91)	12 m, 24 m, 36 m	No change over time.
Other									
de Vries *et al*[24]	The Netherlands	Pre-post	Moderate	70 (37 brf, 33 brm)	N/A	GnRH-a	Anger (STAXI)	Before CSH start (range 0.4–5.1 y)	No change.
Psychosocial outcomes									
Psychosocial functioning									
Costa *et al*[56]	UK	Cohort	Moderate	60 (brm:brf ratio 1:1.7)	61+169 no GD	GnRH-a	Psychosocial functioning (CGAS)	6 m, 12 m, 18 m (GnRH-a initiated at 6 m)	Both groups improved after 6 m and 12 m of psychological care. At 18 m, treated group improved further, untreated remained the same.
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	N/A	GnRH-a	Psychosocial functioning (CGAS)	12 m, 24 m, 36 m	No change over time.
de Vries *et al*[24]	The Netherlands	Pre-post	Moderate	70 (37 brf, 33 brm)	N/A	GnRH-a	Psychosocial functioning (CGAS)	Before CSH start (range 0.4–5.1 y)	No clinically significant change.
Quality of life									
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	N/A	GnRH-a	Quality of life (Kidscreen-52)	12 m, 24 m	No change over time.
Peer-relations									
van der Miesen *et al*[37]	The Netherlands	Cross-sectional	High	178 (110 brf, 68 brm)	272+651 no GD	GnRH-a	Poor peer-relations (YSR items 25, 38 and 48)	N/A	Fewer problems in those treated, but more compared with adolescents with no GD.
Cognitive/neurodevelopmental outcomes									
Strang *et al*[51]	UK	Cross-sectional	Moderate	14 (brs not reported)	58+52 CSH	GnRH-a	Executive functioning (BRIEF Global Executive Composite)	N/A	No change in those treated with puberty suppression for <1 year. Worse functioning in those treated for longer (although some may have been taking CSH).
Russell *et al*[59]	UK	Pre-post	Moderate	95 (57 brf, 38 brm)	N/A	GnRH-a	Features of autism spectrum condition (SRS)	12 m	No change.

BDI, Beck's Depression Inventory; BIS, Body Image Scale; brf, birth-registered females; BRIEF, Behaviour Rating Inventory of Executive Function; brm, birth-registered males; CBCL, Child Behaviour Checklist; CGAS, Children's Global Assessment Scale; CSH, cross-sex hormones; GD, gender dysphoria; GnRH-a, gonadotropin-Releasing Hormone analogues; m, months; N/A, not applicable; SRS, Social Responsiveness Scale; STAI, State-Trait Anxiety Inventory; STAXI, State-Trait Anger Expression Inventory; UGDS, Utrecht Gender Dysphoria Scale; y, years; YSR, youth self-report.

experiencing gender dysphoria/incongruence. However, there were considerably fewer participants included at final follow-up.

There was no change in quality of life pre-post,[55] and treated adolescents had better peer-relations compared with adolescents under assessment at a gender service but poorer peer-relations than adolescents not experiencing gender dysphoria/incongruence.[37]

Cognitive/neurodevelopmental outcomes

One cross-sectional study measured executive functioning and found no difference between adolescents who were treated for <1 year compared with those not treated, but worse executive functioning in those treated for >1 year compared with those not treated.[51] A pre-post study found no differences in features typically associated with autism spectrum condition after treatment (table 2).[59]

Physical health outcomes

Bone health

Five studies found decreases in bone mineral apparent density and z-scores pre-post treatment; however, absolute measures generally remained stable or increased/decreased slightly.[29 32 34 55 58] Results were similar across birth-registered males and females.[29 32 55 58] One study considered timing of treatment, and found similar decreases among those starting GnRH-a in early or late puberty (table 3).[32]

Cardiometabolic health

Twelve pre-post studies measured body mass index (BMI), and in 10 studies there was no evidence of a clinically significant change in BMI and/or BMI SD score.[29 30 32 34 55 57 65 67–69] In one study, BMI increased for birth-registered males but not females.[58] Another study found BMI increased for birth-registered females who started GnRH-a in early puberty or mid-puberty, and birth-registered males in early puberty.[36]

Three studies assessed cholesterol markers, one after GnRH-a (no changes),[34] one after cyproterone acetate (decrease in high-density lipoprotein (HDL) and triglycerides)[67] and one after lynestrenol (decrease in HDL, increase in low-density lipoprotein).[65] Three studies assessing GnRH-a reported blood pressure: two found similar systolic and diastolic blood pressure before and after treatment,[34 68] and one found a non-clinically significant increase in diastolic but not systolic blood pressure.[69] Two studies measured markers of diabetes (fasting glucose, HbA1c and/or insulin) and noted no changes.[65 67]

Other physiological parameters

Five pre-post studies assessed other parameters from blood tests undertaken at baseline and follow-up,[30 31 34 65 67] three in those treated with GnRH-a,[30 31 34] one lynestrenol[65] and one cyproterone acetate.[67] Measurements included haemoglobin count (n=3), haematocrit percentage (n=3), creatinine (n=4), aspartate aminotransferase (n=3), alanine aminotransferase (n=3), γ-glutamyl transferase (n=1), alkaline phosphatase (n=2), prolactin (n=2), free thyroxin (n=3), thyroid-stimulating hormone (n=3), sex hormone binding globulin (n=3), vitamin D levels (n=1), dehydroepiandrosterone sulfate (n=3) and androstenedione (n=2). For most outcomes, no changes were reported. Where there were changes, these were not consistent in direction across studies.

One pre-post study assessing GnRH-a reported QTc prolongation,[64] and found no change in mean QTc, with no participants outside normal range.

Side effects

A cohort study of GnRH-a reported side effects including mild headaches or hot flushes (~20%) and moderate/severe headaches or hot flushes, mild fatigue, mood swings, weight gain and sleep problems (<10%) (table 3).[55]

Two studies assessed other medications and reported headaches and hot flushes as common and an increase in acne in a sample of birth-registered females receiving lynestrenol,[65] and complaints of fatigue in birth-registered males receiving cyproterone acetate.[67]

Puberty suppression

Hormone levels

Hormone levels were reported in nine studies of GnRH-a (two cohort,[49 50] seven pre-post[30 34 36 48 55 68 69]), two in birth-registered females,[34 69] one in birth-registered males[68] and six including both (table 4).[30 36 48–50 55]

Five studies reported decreases in luteinising hormone, follicle-stimulating hormone, oestradiol and testosterone after receiving GnRH-a.[30 34 48 68 69] Another study, which reported luteinising and follicle-stimulating hormones, also found decreases in both pre-post.[55] One study reported that where baseline levels were high due to puberty starting, decreases were reported in testosterone and oestradiol.[36] One cohort study reporting pre-post data found smaller decreases in luteinising hormone, follicle-stimulating hormone, oestradiol and testosterone compared with other studies; however, it included a younger population, some of who were likely prepubertal.[50] The other cohort study included a comparator of adolescents with precocious puberty and found similar decreases in luteinising hormone and oestradiol.[49]

One pre-post study of lynestrenol (birth-registered females) found a decrease in luteinising hormones but not follicle-stimulating hormone, oestradiol or testosterone.[65] One study of cyproterone acetate (birth-registered males) found no changes in luteinising hormone, follicle-stimulating hormone or oestradiol, but a decrease in total testosterone.[67]

Pubertal progression

Puberty development was reported in four studies (two cohort, two pre-post).[30 35 49 67] One only included birth-registered males,[67] and three included both birth-registered males and females.[30 35 49]

A cohort study assessing GnRH-a reported clinical pubertal escape in 2/21 adolescents treated for gender dysphoria/incongruence, in the form of breast enlargement or testicular enlargement together with deepening of voice, compared with no children treated for precocious puberty.[49] A pre-post study reported a decrease in testicular volume in birth-registered males, but unclear results with regard to breast development in birth-registered females (most started treatment at Tanner stage 4–5).[30] A pre-post study of birth-registered males using cyproterone acetate reported decreases in facial shaving and spontaneous erections.[67]

A cohort study assessed whether secondary sex characteristics differed depending on receipt or timing of GnRH-a, and whether this affected which surgical interventions/techniques were later used.[35] The study found breast size was smallest in birth-registered females who received GnRH-a in Tanner stage 2/3 and largest in untreated participants. Those treated early in puberty were less likely to require a mastectomy and when surgery was required it was less burdensome. In birth-registered males, penile length was greater in those who received GnRH-a

Table 3 Physical health outcomes and side effects

Study	Country	Study design	Study quality	Treated sample	Intervention	Outcome (measure)	Follow-up specific to outcome	Summary of study results
Physical health outcomes								
Bone health								
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	GnRH-a	BMD and BMC (hip, lumbar, spine). Absolute values and z-scores	12 m, 24 m, 36 m	Between baseline and 12 months, there was an increase in absolute measures of bone health, but z-scores decreased.
Joseph *et al*[58]	UK	Pre-post	Moderate	70 (39 brf, 31 brm)	GnRH-a	BMD, BMAD. Absolute values and z-scores	12 m, 24 m, 36 m	Absolute measures of bone health remained constant, but z-scores decreased.
Klink *et al*[29]	The Netherlands	Pre-post	Moderate	34 (19 brf, 15 brm)	GnRH-a	aBMD and BMAD (absolute, z-scores using natal sex)	Before CSH start (mean 1.3 y for brm, 1.5 y for brf, range 0.25–5.2 y)	Absolute measures of bone health remained constant, but z-scores decreased.
Schagen *et al*[32]	The Netherlands	Pre-post	Moderate	121 (70 brf, 51 brm)	GnRH-a	aBMD and BMAD (absolute, z-scores using natal sex), serum bone markers	24 m	Absolute measures of bone health increased, but z-scores decreased (decreases similar in groups who started GnRH-a in early puberty and mid-puberty).
Stoffers *et al*[34]	The Netherlands	Pre-post	Moderate	62 brf	GnRH-a	BMD, BMAD (absolute, z-scores using natal sex)	Before CSH start (median 8 m, range 3–39)	Absolute measures of bone health and z-scores decreased.
BMI								
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	GnRH-a	BMI z-score (reference population for age and natal sex)	12 m, 24 m, 36 m	No evidence for change in BMI z-score.
Ghelani *et al*[57]	UK	Pre-post	Moderate	36 (25 brf, 11 brm)	GnRH-a	BMI SD score (reference sex unspecified)	6 m, 12 m	No evidence for change in BMI SD score.
Joseph *et al*[58]	UK	Pre-post	Moderate	70 (39 brf, 31 brm)	GnRH-a	BMI	12 m, 24 m, 36 m	BMI increased over time in birth-registered males.
Klink *et al*[29]	The Netherlands	Pre-post	Moderate	34 (19 brf, 15 brm)	GnRH-a	BMI and BMI SD score (in reference to natal sex)	Before CSH start (mean 1.3 y for brm, 1.5 y for brf, range 0.25–5.2 y)	BMI and BMI SD score remained the same.
Perl *et al*[69]	Israel	Pre-post	Moderate	15 brf	GnRH-a	BMI and BMI SD score (reference sex unspecified)	Single (end of GnRH-a, mean 3 m SD 1)	No evidence for clinically significant change in BMI or BMI SD score.
Perl *et al*[68]	Israel	Pre-post	Moderate	19 brm	GnRH-a	BMI and BMI SD score (reference sex unspecified)	Single (end of GnRH-a, mean 9 m SD 6)	No evidence for change in BMI or BMI SD score.
Schagen *et al*[30]	The Netherlands	Pre-post	Moderate	116 (67 brf, 49 brm)	GnRH-a	BMI and BMI SD score (reference sex used unspecified)	12 m, 24 m, 36 m	No evidence for clinically significant change in BMI or BMI SD score.
Schagen *et al*[32]	The Netherlands	Pre-post	Moderate	121 (70 brf, 51 brm)	GnRH-a	BMI	24 m	No evidence for change in BMI.
Stoffers *et al*[34]	The Netherlands	Pre-post	Moderate	62 brf	GnRH-a	BMI and BMI SD score (reference unspecified)	Before CSH start (median 8 m, range 3–39)	No evidence for change in BMI or SD score.
Tack *et al*[65]	Belgium	Pre-post	Moderate	38 brf	Lynestrenol	BMI and BMI SD score (reference population for natal sex)	6 m, 12 m	No evidence for change in BMI or BMI SD score.
Tack *et al*[67]	Belgium	Pre-post	Moderate	27 brm	Cyproterone acetate	BMI and BMI SD score (in reference to natal sex)	6 m, 12 m	No evidence for change in BMI SD score.
van der Loos *et al*[36]	The Netherlands	Pre-post	Moderate	322 (106 brm, 216 brf)	GnRH-a	BMI	Before CSH start (mean follow-up between 0.9 and 3.9 y)	BMI increased for brf who started in early puberty and mid-puberty. For brm, BMI there was an increase in the early puberty group. No change in the late-puberty group.
Blood pressure								
Perl *et al*[69]	Israel	Pre-post	Moderate	15 brf	GnRH-a	Systolic and diastolic blood pressure	Single (end of GnRH-a, mean 3 m SD 1)	Systolic blood pressure remained the same, whereas diastolic blood pressure increased, although not clinically significant.

Continued

Table 3 Continued

Study	Country	Study design	Study quality	Treated sample	Intervention	Outcome (measure)	Follow-up specific to outcome	Summary of study results
Perl *et al*[68]	Israel	Pre-post	Moderate	19 brm	GnRH-a	Systolic and diastolic blood pressure	Single (end of GnRH-a, mean 9 m SD 6)	Systolic and diastolic blood pressure remained the same.
Stoffers *et al*[34]	The Netherlands	Pre-post	Moderate	62 brf	GnRH-a	Systolic and diastolic blood pressure	Before CSH start (median 8 m, range 3–39)	Systolic and diastolic blood pressure remained the same.
Metabolic measures								
Stoffers *et al*[34]	The Netherlands	Pre-post	Moderate	62 brf	GnRH-a	Total cholesterol, HDL, LDL, triglycerides	Before CSH start (median 8 m, range 3–39)	No evidence for a change in any measure.
Tack *et al*[65]	Belgium	Pre-post	Moderate	38 brf	Lynestrenol	Total cholesterol, triglycerides, HDL, LDL, fasting insulin, HbA1c	6 m, 12 m	No evidence for a change in any measure, except for a decrease in HDL and increase in LDL.
Tack *et al*[67]	Belgium	Pre-post	Moderate	27 brm	Cyproterone acetate	Triglycerides, total cholesterol, HDL, LDL, HbA1c, glucose, insulin	6 m, 12 m	There was a decrease in HDL and triglycerides.
Other physical parameters								
Schagen *et al*[30]	The Netherlands	Pre-post	Moderate	116 (67 brf, 49 brm)	GnRH-a	ALT, AST, ALP, γ-glutamyl transferase, creatinine	3 m, 6 m, 12 m	There was a decrease in alkaline phosphate (both sexes) and creatinine (brf only). No changes were reported in AST, γ-glutamyl and ALT (narrative—no data).
Stoffers *et al*[34]	The Netherlands	Pre-post	Moderate	62 brf	GnRH-a	SHBG, TSH, prolactin, free thyroxine, DHEAS, A4, haemoglobin, haematocrit, creatinine, ALP, vitamin D, ureum	Before CSH start (median 8 m, range 3–39)	There was an increase in vitamin D levels and a decrease in prolactin levels—no change for other measures.
Tack *et al*[65]	Belgium	Pre-post	Moderate	38 brf	Lynestrenol	Haemoglobin, haematocrit, creatinine, ALT, AST, TSH, free thyroxine, anti-Müllerian hormone, SHBG	6 m, 12 m	There were increases in haemoglobin and haematocrit and a decrease in SHBG. Increases in free thyroxine levels, creatinine and ALT were reported.
Tack *et al*[67]	Belgium	Pre-post	Moderate	27 brm	Cyproterone acetate	DHEAS, haemoglobin, haematocrit, creatinine, AST, ALT, prolactin, TSH, free thyroxine, SHBG	6 m, 12 m	There was an increase in prolactin and free thyroxine levels, and a decrease in haemoglobin and haematocrit. No change in other measures.
Schagen *et al*[31]	The Netherlands	Pre-post	Moderate	127 (73 brf, 54 brm)	GnRH-a	DHEAS and A4	12 m, 24 m	DHEAS increased in brf and increased slightly in brm. A4 decreased in brf and remained constant in brm.
Waldner *et al*[64]	Canada	Pre-post	Moderate	33 (23 brf, 10 brm)	GnRH-a	Proportion with clinically significant QTc prolongation (defined as QTc >460 ms)	Single (>6 weeks after initiation of treatment)	There was no change in the mean QTc over time. At follow-up, no participants were in the clinical range >(460 ms). Just under 25% had a QTc between 440 and 460 ms.
Side effects								
Carmichael *et al*[65]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	GnRH-a	Patient-reported side effects	12 m, 24 m, 36 m	Mild headaches or hot flushes common (~20%). Moderate/Severe headaches or hot flushes, mild fatigue, mood swings, weight gain, sleep problems less common (<10%).
Tack *et al*[65]	Belgium	Pre-post	Moderate	38 brf	Lynestrenol	Patient-reported side effects	6 m, 12 m	Headaches and hot flushes were common, reported increase in acne and metrorrhagia was also reported—no numbers given.
Tack *et al*[67]	Belgium	Pre-post	Moderate	27 brm	Cyproterone acetate	Patient-reported side effects	6 m, 12 m	Complaints of fatigue in 37% and emotionality in ~10%.

A4, androstenedione; aBMD, areal bone mineral density; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; brf, birth-registered females; brm, birth-registered males; CSH, cross-sex hormones; DHEAS, dehydroepiandrosterone sulfate; GnRH-a, gonadotropin-releasing hormone analogues; HBA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; m, months; QTc, heart-rate corrected QT interval; SHBG, sex hormone binding globulin; TSH, thyroid-stimulating hormone; y, years.

Table 4 Puberty suppression outcomes

Study	Country	Study design	Study quality	Treated sample	Comparator	Intervention	Outcome (measure)	Follow-up specific to outcome	Summary of study results
Hormone levels									
Pine-Twaddell *et al*[49]	USA	Cohort	Moderate	42 (22 brf, 20 brm)	7 with central precocious puberty	GnRH-a	Testosterone, oestradiol, LH	Single (range 17–65 m)	LH decreased to similar levels at follow-up in both groups. Oestradiol decreased in brf in both groups.
Schulmeister *et al*[50]	USA	Cohort	Moderate	55 (29 brf, 26 brm)	226 no GD	GnRH-a	Testosterone, oestradiol, LH, FSH	6 m, 12 m	For brf, all decreased at follow-up. Decreases were smaller in brm, but with larger decreases in upper limit of the IQR.
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	N/A	GnRH-a	Testosterone, oestradiol, LH, FSH	12 m, 24 m, 36 m	Decreases in LH and FSH observed over time. Oestradiol and testosterone not reported (full suppression reported).
Olson-Kennedy *et al*[48]	USA	Pre-post	Moderate	66 (34 brf, 32 brm)	N/A	GnRH-a	Testosterone, oestradiol, LH, FSH	Single (range 2–12 m)	Decreases reported in all outcomes.
Perl *et al*[69]	Israel	Pre-post	Moderate	15 brf	N/A	GnRH-a	Testosterone, oestradiol, LH, FSH	Single (end of GnRH-a, mean 3 m SD 1)	Decreases reported in all outcomes.
Perl *et al*[68]	Israel	Pre-post	Moderate	19 brm	N/A	GnRH-a	Testosterone, oestradiol, LH, FSH	Single (end of GnRH-a, mean 9 m SD 6)	Decreases reported in all outcomes.
Schagen *et al*[30]	The Netherlands	Pre-post	Moderate	116 (67 brf, 49 brm)	N/A	GnRH-a	Testosterone, oestradiol, LH, FSH	3 m, 6 m, 12 m	Decreases reported in all outcomes.
Stoffers *et al*[34]	The Netherlands	Pre-post	Moderate	62 brf	N/A	GnRH-a	Testosterone, oestradiol, LH, FSH	Before CSH start (median 8 m, range 3–39)	Decreases reported in all outcomes.
Tack *et al*[65]	Belgium	Pre-post	Moderate	38 brf	N/A	Lynestrenol	Testosterone (total, free), oestradiol, LF, FSH	6 m, 12 m	A decrease was reported in LH, but no change was observed in FSH, oestradiol or testosterone.
Tack *et al*[67]	Belgium	Pre-post	Moderate	27 brm	N/A	Cyproterone acetate	Testosterone (total, free), oestradiol, LF, FSH	6 m, 12 m	No changes were reported in hormone levels, except for a decrease in total testosterone.
van der Loos *et al*[36]	The Netherlands	Pre-post	Moderate	322 (106 brm, 216 brf)	N/A	GnRH-a	Testosterone, oestradiol	Before CSH start (mean follow-up 0.9, 3.1 and 3.9 y)*	Where baseline levels were high due to puberty starting, decreases reported in all outcomes.
Pubertal progression									
Pine-Twaddell *et al*[49]	USA	Cohort	Moderate	42 (22 brf, 20 brm)	7 CPP	GnRH-a	Tanner stage progression (physical examination)	Single (range 17–65 m)	Clinical pubertal escape was reported in 2/21 participants (breast enlargement in one case and in another case testicular enlargement and voice change).
van de Grift *et al*[35]	The Netherlands	Cohort	Moderate	200 (134 brf, 66 brm)	100	GnRH-a	Breast and genital characteristics (clinical examination)	At initiation of surgery (after CSH)	Tanner stage 2/3 treatment resulted in smaller breast size in brf and lower average penile length and fewer testes descended in brm, compared with Tanner stage 4/5 or no GnRH-a.
van de Grift *et al*[35]	The Netherlands	Cohort	Moderate	200 (134 brf, 66 brm)	100	GnRH-a	Needs for future surgery (clinical examination, surgery performed)	At initiation of surgery (after CSH)	Tanner stage 2/3 treatment resulted in need for fewer and less burdensome mastectomies in brf, but more genital surgery in brm, compared with Tanner stage 4/5 or no treatment.
Schagen *et al*[30]	The Netherlands	Pre-post	Moderate	116 (67 brf, 49 brm)	N/A	GnRH-a	Tanner stage by physical examination	3 m, 6 m, 12 m, 24 m	In brm, testicular volume decreased for 43/49 participants during GnRH-a treatment. Results unclear for brf, most of who started treatment in Tanner stage 4/5.
Tack *et al*[67]	Belgium	Pre-post	Moderate	27 brm	N/A	Cyproterone acetate	Puberty development (physical changes)	6 m, 12 m	>50% brm reported decreased facial shaving. Some reported decreased spontaneous erections (numbers not reported). Breast development noted in ~30% of brf.
Menstrual suppression									
Pine-Twaddell *et al*[49]	USA	Cohort	Moderate	42 (22 brf, 20 brm)	7 CPP	GnRH-a	Suppression of menstruation	Single (range 17–65 m)	No participants in the intervention group reported pubertal escape in the form of menstruation or spotting.
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	N/A	GnRH-a	Suppression of menstruation	12 m, 24 m, 36 m	All birth-registered females reported amenorrhoea in the 3 months after starting GnRH-a treatment.
Schagen *et al*[30]	The Netherlands	Pre-post	Moderate	116 (67 brf, 49 brm)	N/A	GnRH-a	Suppression of menstruation	12 m	All birth-registered females who had started menses experienced full suppression.

Continued

Table 4 Continued

Study	Country	Study design	Study quality	Treated sample	Comparator	Intervention	Outcome (measure)	Follow-up specific to outcome	Summary of study results
Height/Growth									
Schulmeister *et al*[50]	USA	Cohort	Moderate	55 (29 brf, 26 brm)	226 no GD	GnRH-a	Height velocity	6 m, 12 m	After controlling for mid-age, height velocity in participants using GnRH-a was similar to the cisgender comparison.
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	N/A	GnRH-a	Height z-score	12 m, 24 m, 36 m	No change in height z-score over time.
Ghelani *et al*[57]	UK	Pre-post	Moderate	36 (25 brf, 11 brm)	N/A	GnRH-a	Height SD score (reference sex unspecified)	6 m, 12 m	Decrease over time observed in height SD score for brm. No change observed in brf.
Joseph *et al*[58]	UK	Pre-post	Moderate	70 (39 brf, 31 brm)	N/A	GnRH-a	Height	12 m, 24 m, 36 m	Height increased over time for both brm and brf.
Klink *et al*[29]	The Netherlands	Pre-post	Moderate	34 (19 brf, 15 brm)	N/A	GnRH-a	Height and height SD score (reference to natal sex)	Before CSH start (mean 1.3 y for brm, 1.5 y for brf, range 0.25–5.2 y)	Height increased for both brm and brf. Height SD score decreased for brm but not for brf.
Schagen *et al*[30]	The Netherlands	Pre-post	Moderate	116 (67 brf, 49 brm)	N/A	GnRH-a	Height and height SD score (reference sex unspecified)	12 m	Height increased for both brm and brf. Height SD score decreased for both brm and brf.
Schagen *et al*[32]	The Netherlands	Pre-post	Moderate	121 (70 brf, 51 brm)	N/A	GnRH-a	Height	24 m	Height increased.
Stoffers *et al*[34]	The Netherlands	Pre-post	Moderate	62 brf	N/A	GnRH-a	Height, height SD score (reference to natal sex and affirmed gender)	Before CSH start (median 8 m, range 3–39)	No substantial change in average height. Height SD score decreased against male reference population, and no change against female reference population.
Tack *et al*[65]	Belgium	Pre-post	Moderate	38 brf	N/A	Lynestrenol	Height	6 m, 12 m	Height increased over time.
Tack *et al*[67]	Belgium	Pre-post	Moderate	27 brm	N/A	Cyproterone acetate	Height SD score (reference using natal sex)	6 m, 12 m	Height SD score decreased over time.
van der Loos *et al*[36]	The Netherlands	Pre-post	Moderate	322 (106 brm, 216 brf)	N/A	GnRH-a	Height	Before CSH start (mean follow-up 0.9, 3.1 and 3.9 y)*	Height increased in the early puberty and mid-puberty groups.
Body composition									
Ghelani *et al*[57]	UK	Pre-post	Moderate	36 (11 brm, 25 brf)	N/A	GnRH-a	Body composition (lean mass SD score). Reference sex unspecified	6 m, 12 m	In both sexes, the lean mass SD score decreased over time.
Schagen *et al*[30]	The Netherlands	Pre-post	Moderate	116 (67 brf, 49 brm)	N/A	GnRH-a	Body composition (lean body mass percentage)	12 m	In both sexes, lean body mass percentage decreased.
Schagen *et al*[30]	The Netherlands	Pre-post	Moderate	116 (67 brf, 49 brm)	N/A	GnRH-a	Body composition (fat percentage)	12 m	In both sexes, fat percentage increased.
Bone geometry									
van der Loos *et al*[36]	The Netherlands	Pre-post	Moderate	322 (106 brm, 216 brf)	N/A	GnRH-a	Subperiosteal width and endocortical diameter of hip bone	Before CSH start (mean follow-up 0.9, 3.1 and 3.9 y)*	In brm, both measures increased in early puberty and mid-puberty groups. In brf, both increased in the early puberty group only. No change in late-puberty group for either.

*Sample divided into three groups, those starting GnRH-a in early puberty, mid-puberty and late puberty. Mean follow-up presented for each group, respectively.
brf, birth-registered females; brm, birth-registered males; CSH, cross-sex hormones; FSH, follicle-stimulating hormone; GD, gender dysphoria; GnRH-a, gonadotropin-releasing hormone analogues; LH, luteinising hormone; m, months; N/A, not applicable; y, years.

at Tanner stage 4/5 compared with Tanner stage 2/3, and greatest in untreated participants.[35] Those who received GnRH-a early required more invasive vaginoplasty techniques than those who received it later or not at all.

Menstrual suppression

Three studies (one cohort, two pre-post) measured menstrual suppression in birth-registered females, and found full suppression at follow-up,[30 49 55] which was similar to the effect seen in those with precocious puberty in the cohort study.[49]

Height/Growth

Eleven studies (1 cohort,[50] 10 pre-post[29 30 32 34 36 55 57 58 65 67]) reported height, nine after GnRH-a,[29 30 32 34 36 50 55 57 58] one lynestrenol[65] and one cyproterone acetate.[67] The cohort study found a similar height velocity between the GnRH-a group and adolescent controls.[50] Six studies reported height Z or SD score[29 30 34 55 57 67] with two studies finding no change,[34 55] two a decrease for birth-registered males but not females,[29 57] one a decrease across birth-registered males and females[30] and one a decrease in birth-registered males with cyproterone acetate.[67] Absolute measures of height generally increased slightly or remained the same.[29 30 32 34 36 58 65 67]

Body composition

Two studies reported changes in body composition pre-post,[30 57] reporting a significant decrease in lean mass SD score[57] and percentage[30] in males and females. One also measured body fat percentage and reported significant increases in both groups.[30]

Bone geometry

One pre-post study measured the subperiosteal width and endocortical diameter of the hip bone and found that in birth-registered males these increased in those starting GnRH-a in early puberty and mid-puberty, but only in the early puberty group for birth-registered females.[36]

DISCUSSION

This systematic review identified 50 studies reporting outcomes relating to puberty suppression in adolescents experiencing gender dysphoria/incongruence. No high-quality studies using an appropriate design were identified, and only four measured gender dysphoria as an outcome. Only 5 of the 11 cohort studies, which were the only studies to compare groups over time, were rated as moderate quality.[35 40 49 50 56]

There was evidence from multiple mainly pre-post studies that puberty suppression exerts its expected physiological effect, as previously demonstrated in children with precocious puberty.[73] In adolescents experiencing gender dysphoria/incongruence, puberty suppression is initiated at different stages of puberty,[74] and two studies found that the effects on secondary sex characteristics may vary depending on whether treatment is initiated in early puberty versus mid-puberty, with potentially different outcomes for birth-registered males and females.[30 35] Multiple studies also found that bone density is compromised during puberty suppression, and gains in height may lag behind that seen in other adolescents. High-quality research is needed to confirm these findings; however, these potential risks should be explained to adolescents considering puberty suppression.

These findings add to other systematic reviews in concluding there is insufficient and/or inconsistent evidence about the effects of puberty suppression on gender dysphoria, body satisfaction, psychological and psychosocial health, cognitive development, cardiometabolic risk and fertility.[11–16] Regarding psychological health, one recent systematic review[14] reported some evidence of benefit while others have not. The results in this review found no consistent evidence of benefit. Inclusion of only moderate-quality to high-quality studies may explain this difference, as 8 of the 12 studies reporting psychological outcomes were rated as low-quality.

The lack of representativeness of samples and comparability of selected control groups were key concerns across studies. Only one study attempted to compare puberty suppression with psychosocial care, which is the only other treatment offered for gender dysphoria/incongruence in childhood, and this included a small sample, limited analyses, and little detail about the intervention.[56] Other studies lacked information about any psychological care provided to participants, and in studies that included a comparator there was limited information about any differences between groups. Large, well-designed studies with appropriate comparators that enable long-term outcomes of puberty suppression to be measured are needed.

Many studies reported effects of both puberty suppressants and hormones used in later adolescence for feminisation/masculinisation. In adolescents, GnRH-a often continues during hormone treatment,[74] or for adolescents who do not receive puberty suppression, GnRH-a or other anti-androgens may be offered at initiation of hormones.[66] This makes long-term follow-up of puberty suppression difficult to assess, including any differences between the types of interventions that are offered and when these are initiated, and the few studies reporting long-term outcomes either did not control for this or reported overall effects for both interventions. Although recent studies suggest nearly all adolescents who receive puberty suppression go on to feminising/masculinising hormones,[74–76] research is still needed to assess whether suppression will have any lasting effects for those who do not. Aggregation of studies reporting proportions of adolescents who progress to hormones and reasons for discontinuation would also offer useful insights.

Included studies assessed different outcomes across various outcome domains and employed multiple different measures. Agreement about the primary aim and related core outcomes of puberty suppression in this population would help to ensure studies measure key outcomes and facilitate future aggregation of evidence. Expert consensus recommendations to guide the methods and domains for assessing the neurodevelopmental effects of puberty suppression have been developed[77]; however, there is currently no agreement across other outcome domains.

Strengths and limitations

Strengths include a published protocol with robust search strategies, use of PRISMA guidelines and comprehensive synthesis of moderate and high quality studies. Poor reporting across studies may have resulted in moderate-quality studies being rated low-quality and excluded from synthesis. As searches were conducted up to April 2022, this review does not include more recently published studies. However, the findings are in line with previous reviews despite the inclusion of numerous additional studies. In an update of the National Institute for Health and Care Excellence evidence review of GnRH-a performed in April 2023,[78] nine additional studies were identified, two of which they felt might materially affect their conclusions.[72 74] One was already included in this review,[72] and the other examined treatment trajectories which was not an outcome of interest.[74]

Of other studies that we are aware have been published since April 2022 until January 2024, very few used a cohort design or an appropriate comparator and were of a similar low quality to moderate quality as the studies summarised in this review. Of those likely to contribute new data for synthesis, five examined physical growth and development,[79–83] one cardiometabolic health[84] and one psychological health.[85] The latter, a study from the US, found that adolescents who received puberty suppression before assessment for masculinising or feminising hormones had fewer symptoms of depression, anxiety, stress and suicidal thoughts compared with those who had not received puberty suppression. A sensitivity analysis found similar results, although no difference in suicidal thoughts.[85] Adding this study would provide no further clarity about whether puberty suppression improves psychological health due to the inconsistency of results between studies, and the limited high-quality research measuring these outcomes.

Two studies from the Netherlands found that height growth and bone maturation both decelerated during GnRH-a treatment,[80 81] and a third assessing only bone health found the same.[83] A Belgian study found stable height growth in birth-registered females but deceleration in birth-registered males.[82] These studies add strength to the conclusion that bone health and adult height may be compromised during GnRH-a, although like in previous studies the participants went on to receive masculinising or feminising hormones, and therefore the long-term outcomes of puberty suppression alone were not possible to determine.

Another new study, also from the Netherlands, assessed changes in body composition.[79] This found that in both birth-registered males and females lean mass z-scores decreased during puberty suppression and fat mass z-scores increased, although the rate and duration of change differed by birth-registered sex. These changes were also found in the two studies synthesised,[30 57] but as all three included no comparator uncertainty continues about the effect of puberty suppression on body composition.

A large study of adults in the US examined whether receipt of hormone interventions during adolescence was associated with cardiometabolic-related diagnoses, and for GnRH-a found no statistically significant differences for any diagnosis.[84] However, the study uses a retrospective cross-sectional design and is the only study to have examined cardiometabolic diagnoses, so no conclusions can be drawn about these outcomes.

To our knowledge, there are no additional moderate-quality or high-quality studies that have measured psychosocial or fertility outcomes, and only a single study assessing cognitive effects which measured a different outcome (white matter microstructure) to those included in this review.[86]

Conclusions

There are no high-quality studies using an appropriate study design that assess outcomes of puberty suppression in adolescents experiencing gender dysphoria/incongruence. No conclusions can be drawn about the effect on gender-related outcomes, psychological and psychosocial health, cognitive development or fertility. Bone health and height may be compromised during treatment. High-quality research and agreement on the core outcomes of puberty suppression are needed.

Contributors LF, CEH, RH, TL and JT contributed to the conception of this review. RH, CEH, CH, AM and JT contributed to screening and selection. AM and JT completed data extraction. CEH, RH, AM and JT contributed to critical appraisal. CEH, AM and JT completed the synthesis and drafted the manuscript. All authors contributed to interpretation and reviewed and approved the manuscript prior to submission. CEH accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was funded by NHS England to inform the Cass Review (Independent review of gender identity services for children and young people). The funder and Cass Review team had a role in commissioning the research programme but no role in the study conduct, interpretation or conclusion.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

ORCID iDs
Jo Taylor http://orcid.org/0000-0001-5898-0900
Catherine Elizabeth Hewitt http://orcid.org/0000-0002-0415-3536

REFERENCES

1 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender Dysphoria literature: 1) epidemiology. *PLOS Glob Public Health* 2022;2:e0000245.
2 Kaltiala R, Bergman H, Carmichael P, *et al*. Time trends in referrals to child and adolescent gender identity services: a study in four Nordic countries and in the UK. *Nord J Psychiatry* 2020;74:40–4.
3 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender Dysphoria literature: 2) mental health. *PLOS Glob Public Health* 2022;2:e0000426.
4 Coleman E, Radix AE, Bouman WP, *et al*. Standards of care for the health of transgender and gender diverse people, version 8. *Int J Transgend Health* 2022;23:S1–259.
5 Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-Dysphoric/gender-Incongruent persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017;102:3869–903.
6 de Vries ALC, Cohen-Kettenis PT. Clinical management of gender Dysphoria in children and adolescents: the Dutch approach. *J Homosex* 2012;59:301–20.
7 The Swedish National Board of Health and Welfare. Care of children and young people with gender Dysphoria - national knowledge support with recommendations for the profession and decision makers. 2022. Available: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-12-8302.pdf
8 Telfer MM, Tollit MA, Pace CC, *et al*. Australian standards of care and treatment guidelines for transgender and gender diverse children and adolescents. *Med J Aust* 2018;209:132–6.
9 University of California San Francisco Gender Affirming Health Program. *Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People*. University of California San Francisco, 2016. Available: https://transcare.ucsf.edu/guidelines
10 Medical treatment methods for Dysphoria associated with variations in gender identity in minors – recommendation. 2020. Available: https://palveluvalikoima.fi/en/recommendations#genderidentity
11 National Institute for Health and Care Excellence (NICE). Evidence review: gonadotrophin releasing hormone analogues for children and adolescents with gender Dysphoria. 2020. Available: https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_GnRH-analogues_For-upload_Final.pdf
12 Pasternack I, Söderström I, Saijonkari M, *et al*. Medical approaches to treatment of Dysphoria related to gender variations. A systematic review. 2019. Available: https://app.box.com/s/y9u791np8v9gsunwgpr2kqn8swd9vdtx
13 Ludvigsson JF, Adolfsson J, Höistad M, *et al*. A systematic review of hormone treatment for children with gender Dysphoria and recommendations for research.

Acta Paediatrica 2023;112:2279–92. 10.1111/apa.16791 Available: https://onlinelibrary.wiley.com/toc/16512227/112/11
14 Baker KE, Wilson LM, Sharma R, *et al*. Hormone therapy, mental health, and quality of life among transgender people: a systematic review. *J Endocr Soc* 2021;5:bvab011.
15 Chew D, Anderson J, Williams K, *et al*. Hormonal treatment in young people with gender Dysphoria: a systematic review. *Pediatrics* 2018;141:e20173742.
16 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender Dysphoria literature: 3) treatment. *PLOS Glob Public Health* 2023;3:e0001478.
17 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
18 Fraser L, Hall R, Taylor J, *et al*. The epidemiology, management and outcomes of children with gender-related distress/gender Dysphoria: a systematic review. PROSPERO 2021 Crd42021289659. 2021. Available: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021289659
19 Wilson LM, Baker KE, Sharma R, *et al*. Effects of Antiandrogens on prolactin levels among transgender women on estrogen therapy: a systematic review. *Int J Transgend Health* 2020;21:391–402.
20 Ramos GGF, Mengai ACS, Daltro CAT, *et al*. Systematic review: puberty suppression with GnrH analogues in adolescents with gender incongruity. *J Endocrinol Invest* 2021;44:1151–8.
21 Veritas Health Innovation. *Covidence systematic review software*. Melbourne, Australia: Veritas Health Innovation, 2023.
22 Wells G, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2021. Available: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
23 Burke SM, van Heesewijk JO, Menks WM, *et al*. Postnatal effects of sex hormones on click-evoked Otoacoustic emissions: a study of adolescents with gender Dysphoria. *Arch Sex Behav* 2020;49:455–65.
24 de Vries ALC, Steensma TD, Doreleijers TAH, *et al*. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med* 2011;8:2276–83.
25 de Vries ALC, McGuire JK, Steensma TD, *et al*. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics* 2014;134:696–704.
26 Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur j Endocrinol* 2006;155:S131–7.
27 Klaver M, de Mutsert R, Wiepjes CM, *et al*. Early hormonal treatment affects body composition and body shape in young transgender adolescents. *J Sex Med* 2018;15:251–60.
28 Klaver M, de Mutsert R, van der Loos MATC, *et al*. Hormonal treatment and cardiovascular risk profile in transgender adolescents. *Pediatrics* 2020;145:e20190741.
29 Klink D, Caris M, Heijboer A, *et al*. Bone mass in young adulthood following Gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender Dysphoria. *J Clin Endocrinol Metab* 2015;100:E270–5.
30 Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA, *et al*. Efficacy and safety of Gonadotropin-releasing hormone agonist treatment to suppress puberty in gender Dysphoric adolescents. *J Sex Med* 2016;13:1125–32.
31 Schagen SEE, Lustenhouwer P, Cohen-Kettenis PT, *et al*. Changes in adrenal androgens during puberty suppression and gender-affirming hormone treatment in adolescents with gender Dysphoria. *J Sex Med* 2018;15:1357–63.
32 Schagen SEE, Wouters FM, Cohen-Kettenis PT, *et al*. Bone development in transgender adolescents treated with GnrH analogues and subsequent gender-affirming hormones. *J Clin Endocrinol Metab* 2020;105:e4252–63.
33 Staphorsius AS, Kreukels BPC, Cohen-Kettenis PT, *et al*. Puberty suppression and executive functioning: an fMRI-study in adolescents with gender Dysphoria. *Psychoneuroendocrinology* 2015;56:190–9.
34 Stoffers IE, de Vries MC, Hannema SE. Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender Dysphoria. *J Sex Med* 2019;16:1459–68.
35 van de Grift TC, van Gelder ZJ, Mullender MG, *et al*. Timing of puberty suppression and surgical options for transgender youth. *Pediatrics* 2020;146:e20193653.
36 van der Loos MA, Hellinga I, Vlot MC, *et al*. Development of hip bone geometry during gender-affirming hormone therapy in transgender adolescents resembles that of the experienced gender when pubertal suspension is started in early puberty. *J Bone Miner Res* 2021;36:931–41.
37 van der Miesen AIR, Steensma TD, de Vries ALC, *et al*. Psychological functioning in transgender adolescents before and after gender-affirmative care compared with Cisgender general population peers. *J Adolesc Health* 2020;66:699–704.
38 Vlot MC, Klink DT, den Heijer M, *et al*. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in Transgender adolescents. *Bone* 2017;95:11–9.
39 de Nie I, Mulder CL, Meißner A, *et al*. Histological study on the influence of puberty suppression and hormonal treatment on developing germ cells in Transgender women. *Hum Reprod* 2022;37:297–308.
40 Achille C, Taggart T, Eaton NR, *et al*. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of Transgender youths: preliminary results. *Int J Pediatr Endocrinol* 2020;2020:8.
41 Akgul S, Bonny AE, Ford N, *et al*. Experiences of gender minority youth with the Intrauterine system. *J Adolesc Health* 2019;65:32–8.
42 Grimstad FW, Knoll MM, Jacobson JD. Oxandrolone use in Trans-masculine youth appears to increase adult height: preliminary evidence. *LGBT Health* 2021;8:300–6.
43 Kuper LE, Stewart S, Preston S, *et al*. Body dissatisfaction and mental health outcomes of youth on gender-affirming hormone therapy. *Pediatrics* 2020;145:e20193006.
44 Lynch MM, Khandheria MM, Meyer WJ. Retrospective study of the management of childhood and adolescent gender identity disorder using Medroxyprogesterone acetate. *Int J Transgenderism* 2015;16:201–8.
45 Mejia-Otero JD, White P, Lopez X. Effectiveness of puberty suppression with Gonadotropin-releasing hormone agonists in Transgender youth. *Transgend Health* 2021;6:31–5.
46 Neyman A, Fuqua JS, Eugster EA. Bicalutamide as an androgen blocker with secondary effect of promoting Feminization in male-to-female Transgender adolescents. *J Adolesc Health* 2019;64:544–6.
47 Nokoff NJ, Scarbro SL, Moreau KL, *et al*. Body composition and markers of Cardiometabolic health in Transgender youth on Gonadotropin-releasing hormone agonists. *Transgend Health* 2021;6:111–9.
48 Olson-Kennedy J, Streeter LH, Garofalo R, *et al*. Histrelin implants for suppression of puberty in youth with gender Dysphoria: A comparison of 50 Mcg/day (Vantas) and 65 Mcg/day (Supprelinla). *Transgend Health* 2021;6:36–42.
49 Pine-Twaddell E, Newfield RS, Marinkovic M. Extended use of Histrelin implant in pediatric patients. *Transgend Health* 2023;8:264–72.
50 Schulmeister C, Millington K, Kaufman M, *et al*. Growth in Transgender/gender-diverse youth in the first year of treatment with Gonadotropin-releasing hormone agonists. *J Adolesc Health* 2022;70:108–13.
51 Strang JF, Chen D, Nelson E, *et al*. Transgender youth executive functioning: relationships with anxiety symptoms, autism spectrum disorder, and gender-affirming medical treatment status. *Child Psychiatry Hum Dev* 2022;53:1252–65.
52 Tordoff DM, Wanta JW, Collin A, *et al*. Mental health outcomes in Transgender and Nonbinary youths receiving gender-affirming care. *JAMA Netw Open* 2022;5:e220978.
53 Turban JL, King D, Carswell JM, *et al*. Pubertal suppression for Transgender youth and risk of suicidal Ideation. *Pediatrics* 2020;145:e20191725.
54 Hisle-Gorman E, Schvey NA, Adirim TA, *et al*. Mental Healthcare utilization of Transgender youth before and after affirming treatment. *J Sex Med* 2021;18:1444–54.
55 Carmichael P, Butler G, Masic U, *et al*. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender Dysphoria in the UK. *PLoS One* 2021;16:e0243894.
56 Costa R, Dunsford M, Skagerberg E, *et al*. Psychological support, puberty suppression, and Psychosocial functioning in adolescents with gender Dysphoria. *J Sex Med* 2015;12:2206–14.
57 Ghelani R, Lim C, Brain C, *et al*. Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender Dysphoria. *J Pediatr Endocrinol Metab* 2020;33:107–12.
58 Joseph T, Ting J, Butler G. The effect of Gnrh analogue treatment on bone mineral density in young adolescents with gender Dysphoria: findings from a large national cohort. *J Pediatr Endocrinol Metab* 2019;32:1077–81.
59 Russell I, Pearson B, Masic U. A longitudinal study of features associated with autism spectrum in clinic referred, gender diverse adolescents Accessing puberty suppression treatment. *J Autism Dev Disord* 2021;51:2068–76.
60 Arcelus J, Claes L, Witcomb GL, *et al*. Risk factors for non-suicidal self-injury among Trans youth. *J Sex Med* 2016;13:402–12.
61 Chiniara LN, Bonifacio HJ, Palmert MR. Characteristics of adolescents referred to a gender clinic: are youth seen now different from those in initial reports? *Horm Res Paediatr* 2018;89:434–41.
62 Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender Dysphoria in Vancouver. *J Pediatr* 2014;164:906–11.
63 Navabi B, Tang K, Khatchadourian K, *et al*. Pubertal suppression, bone mass, and body composition in youth with gender Dysphoria. *Pediatrics* 2021;148:e2020039339.
64 Waldner RC, Doulla M, Atallah J, *et al*. Leuprolide acetate and QTc interval in gender-diverse youth. *Transgend Health* 2023;8:84–8.
65 Tack LJW, Craen M, Dhondt K, *et al*. Consecutive Lynestrenol and cross-sex hormone treatment in biological female adolescents with gender Dysphoria: a retrospective analysis. *Biol Sex Differ* 2016;7:14.
66 Tack LJW, Craen M, Lapauw B, *et al*. Proandrogenic and Antiandrogenic Progestins in Transgender youth: differential effects on body composition and bone metabolism. *J Clin Endocrinol Metab* 2018;103:2147–56.
67 Tack LJW, Heyse R, Craen M, *et al*. Consecutive cyproterone acetate and estradiol treatment in late-pubertal Transgender female adolescents. *J Sex Med* 2017;14:747–57.
68 Perl L, Elkon-Tamir E, Segev-Becker A, *et al*. Blood pressure Dynamics after pubertal suppression with Gonadotropin-releasing hormone analogs followed by estradiol treatment in Transgender female adolescents: a pilot study. *J Pediatr Endocrinol Metab* 2021;34:741–5.

69 Perl L, Segev-Becker A, Israeli G, *et al*. Blood pressure Dynamics after pubertal suppression with Gonadotropin-releasing hormone analogs followed by testosterone treatment in Transgender male adolescents: A pilot study. *LGBT Health* 2020;7:340–4.
70 Segev-Becker A, Israeli G, Elkon-Tamir E, *et al*. Children and adolescents with gender Dysphoria in Israel: increasing referral and fertility preservation rates. *Endocr Pract* 2020;26:423–8.
71 Fontanari AMV, Vilanova F, Schneider MA, *et al*. Gender affirmation is associated with Transgender and gender Nonbinary youth mental health improvement. *LGBT Health* 2020;7:237–47.
72 Becker-Hebly I, Fahrenkrug S, Campion F, *et al*. Psychosocial health in adolescents and young adults with gender Dysphoria before and after gender-affirming medical interventions: a descriptive study from the Hamburg gender identity service. *Eur Child Adolesc Psychiatry* 2021;30:1755–67.
73 Luo X, Liang Y, Hou L, *et al*. Long-term efficacy and safety of Gonadotropin-releasing hormone analog treatment in children with idiopathic central precocious puberty: A systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 2021;94:786–96.
74 van der Loos MATC, Klink DT, Hannema SE, *et al*. Children and adolescents in the Amsterdam cohort of gender Dysphoria: trends in Diagnostic- and treatment Trajectories during the first 20 years of the Dutch protocol. *J Sex Med* 2023;20:398–409.
75 Masic U, Butler G, Carruthers P, *et al*. Trajectories of Transgender adolescents referred for endocrine intervention in England. *Arch Dis Child* 2022;107:1012–7.
76 van der Loos MATC, Hannema SE, Klink DT, *et al*. Continuation of gender-affirming hormones in Transgender people starting puberty suppression in adolescence: a cohort study in the Netherlands. *Lancet Child Adolesc Health* 2022;6:869–75.
77 Chen D, Strang JF, Kolbuck VD, *et al*. Consensus parameter: research Methodologies to evaluate neurodevelopmental effects of pubertal suppression in Transgender youth. *Transgend Health* 2020;5:246–57.
78 NHS England. URN 1927 literature surveillance report. 2023. Available: https://www.engage.england.nhs.uk/consultation/puberty-suppressing-hormones/user_uploads/literature-surveillace-report-on-gnrh-analogues-for-children-and-adolescents-with-gender-dysphoria-may-2023.pdf
79 Boogers LS, Reijtenbagh SJP, Wiepjes CM, *et al*. Time course of body composition changes in Transgender adolescents during puberty suppression and sex hormone treatment. *J Clin Endocrinol Metab* 2023;21:21.
80 Boogers LS, Wiepjes CM, Klink DT, *et al*. Transgender girls grow tall: adult height is unaffected by Gnrh analogue and estradiol treatment. *J Clin Endocrinol Metab* 2022;107:e3805–15.
81 Willemsen LA, Boogers LS, Wiepjes CM, *et al*. Just as tall on testosterone; a neutral to positive effect on adult height of Gnrha and testosterone in Trans boys. J Clin Endocrinol Metab 2023;108:414–21.
82 Ciancia S, Klink D, Craen M, *et al*. Early puberty suppression and gender-affirming hormones do not alter final height in Transgender adolescents. *Eur J Endocrinol* 2023;189:396–401.
83 van der Loos MATC, Vlot MC, Klink DT, *et al*. Bone mineral density in Transgender adolescents treated with puberty suppression and subsequent gender-affirming hormones. *JAMA Pediatr* 2023;177:1332.
84 Valentine A, Davis S, Furniss A, *et al*. Multicenter analysis of Cardiometabolic-related diagnoses in Transgender and gender-diverse youth: A Pedsnet study. *J Clin Endocrinol Metab* 2022;107:e4004–14.
85 McGregor K, McKenna JL, Williams CR, *et al*. Association of pubertal blockade at Tanner 2/3 with Psychosocial benefits in Transgender and gender diverse youth at hormone readiness assessment. *J Adolesc Health* 2023;12:S1054-139X(23)00560-8.
86 van Heesewijk J, Steenwijk MD, Kreukels BPC, *et al*. Alterations in the inferior Fronto-occipital Fasciculus - a specific neural correlate of gender Incongruence? *Psychol Med* 2023;53:3461–70.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (Adapted cohort study scale)

Adapted from Wells G, Shea B, O'Connell D, et al. (2021) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Selection

1) Representativeness of the paediatric gender dysphoric group

Score 1 if:
a) truly representative of the average child or adolescent with gender dysphoria / incongruence, e.g., nationally representative community sample, population-based medical database, national gender service, multiple gender services covering different localities

Score 0.5 if:
b) somewhat representative of the average child or adolescent with gender dysphoria / incongruence, e.g., single gender service (in a country where there are several), locality representative community sample

Score 0 if:
c) a selected group of users e.g., convenience sample, self-selection, sub-sample due to data availability
or
d) no description of the derivation of the cohort

Q1. TIP: If paper does not include information on sample size / representativeness / response rate in relation to eligible clinic population, score 0 as we must assume it is a selected group of users.

Q1. NOTE: When scoring take into consideration that puberty blockers are not available to pre-pubertal children and cross-sex hormones not until mid-adolescence, therefore an adolescent sample would be representative of those seeking medical treatment for gender dysphoria.

2) Selection of the non-exposed group

Score 1 if:
a) drawn from the same community as the exposed group

Score 0.5 if:
b) drawn from a different source that is comparable e.g., population norms for all adolescents or matched cisgender controls where outcome is expected to be the same for both groups such as BMI or adult height

Score 0 if:
c) drawn from a different source that is not comparable e.g., cisgender population for studies measuring psychosocial outcomes
or
d) no description of the derivation of the non-exposed cohort

Score N/A if:
e) single group study (e.g., pre-post treatment design)

Q2. TIP: Some studies include two plus comparator groups – score 1 if all appropriate, score 0.5 if mix of comparable and non-comparable, and score 0 if none are comparable.

3) Ascertainment of exposure (medical treatment for gender dysphoria)
Score 1 if:
a) secure record, e.g., clinic or medical records
or
b) structured interview

Score 0 if:
c) written self-report
or
d) no description

Q3. TIP: Use of medical records can be inferred from methods reporting overall, e.g., if sample eligibility was based on medical records and this includes treatment, or if detailed treatment information provided from medical records.

4) Demonstration that outcome of interest was not present at start of study
Score 1 if:
a) yes

Score 0 if:
b) no

Score N/A if:
c) study is measuring an outcome such as quality of life or severity of anxiety for which there would be an intrinsic value for each participant at any time during the study

Comparability

5) Comparability of cohorts based on the design (e.g., matched controls, inclusion criteria) or analysis (e.g., propensity score matching, regression analysis)

PART A
Score 1 if:
a) study controls for [age OR puberty stage] AND [natal sex OR gender]

Score 0.5 if:
b) one (but not both) of the above confounders is controlled for
or
c) other important sociodemographic confounders are controlled for, e.g., family support for studies measuring mental health / psychosocial outcomes

Score 0 if:
d) study does not control for important sociodemographic confounders

PART B
Score 1 if:
a) study controls for co-interventions expected to affect the outcome(s), e.g., psychosocial support, psychiatric medication, use of other medication likely to alter outcome (e.g., contraceptive pill),

other aid or intervention designed to address gender dysphoria or to modify body (e.g., social transition, binders, voice therapy)
or
b) there are no co-interventions that are expected to affect the outcome(s)

Score 0.5 if:
c) at least one (but not all) of the important co-intervention confounders are controlled for

Score 0 if:
d) study does not control for important co-intervention confounders

Q5. TIP (from manual): Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.
This question needs to be answered for single group studies (i.e., how do these studies control for potential demographic and treatment confounders that occur between baseline and follow-up).

Outcome

6) Assessment of outcome
Score 1 if:
a) validated scale or standardised assessment tool/method
or
b) record linkage, e.g., medical/clinic/administrative records

Score 0.5 if:
c) combination of validated / standardised and non-validated / unstandardised assessment methods

Score 0 if:
d) self-report
or
e) no description

7) Was follow-up long enough for outcomes to occur?
Score 1 if:
a) follow-up is sufficient for all reported outcomes

Guidance on follow-up:
For puberty suppressants follow-up should be at least 3 months to assess desired / expected effect, gender dysphoria / incongruence or psychosocial outcomes.

For cross-sex hormones follow-up should be at least 6 months to assess desired / expected effect, gender dysphoria / incongruence, or psychosocial outcomes.

For both treatments, follow-up should be at least 3 months to assess safety, side-effects or cardiometabolic risk; and at least 12 months for cognitive development, bone health or fertility.

Score 0.5 if:
b) follow-up is sufficient for some outcomes but not others, e.g., studies that examine multiple outcomes requiring different follow-up
or

c) follow-up is sufficient for some participants but not others, e.g., where follow-up or treatment duration varies between participants

Score 0 if:
d) follow-up is not sufficient
or
e) no clear description, e.g., follow-up duration unclear

Score N/A if:
f) cross-sectional design (i.e., no follow-up)

8) Adequacy of follow up of cohorts
Score 1 if:
a) complete follow up or all subjects accounted for in analysis of outcomes
or
b) subjects lost to follow up or outcome analyses unlikely to introduce bias - small number lost (≤10%) or description provided of those lost justifies that there is no potential bias due to loss to follow-up

Score 0.5 if:
c) there are multiple sufficient follow-up timepoints (based on Q7) and follow-up is adequate for some but not others, e.g., all retained at 12 months but considerable attrition at 24 months

Score 0 if:
c) follow up / analysis rate < 90% and no description of those lost
or
d) no statement

TOTAL SCORING
Cohort studies – total score = 8
Pre-post single group studies – total score = 7 (Q2 not relevant)
Cross-sectional studies with comparators – total score = 7 (Q7 not relevant)

Any study for which Q4 is relevant, total score would be as above plus 1

Low: ≤ 50%
Moderate: >50 to 75%
High – > 75%

Supplementary Table S1: Final search strategy for Ovid MEDLINE

1 exp Child/ or Child Behavior/ or Child Health/ or Child Welfare/ or Psychology, Child/ or Child Psychiatry/ or Child Health Services/ or Child Development/ (1984459)
2 Minors/ (2638)
3 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or emerging adult$).ti,ab,kf,jn. (1862660)
4 (young$ adj (people$ or person$1 or adult$ or man$1 or men$1 or woman$ or women$ or male$1 or female$1)).ti,ab,kf,jn. (224878)
5 pediatrics/ (55388)
6 (pediatric$ or paediatric$ or peadiatric$).ti,ab,kf,jn. (543516)
7 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Psychology, Adolescent/ or Adolescent Psychiatry/ or Adolescent Health Services/ or Adolescent Medicine/ or Adolescent Development/ (2088552)
8 Puberty/ (13562)
9 (adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or underage$ or under-age$).ti,ab,kf,jn. (522801)
10 Schools/ or Schools, Nursery/ (42221)
11 exp Child Day Care Centers/ or Child Care/ (11287)
12 (school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1).ti,ab,kf,jn. (356157)
13 or/1-12 (4333601)
14 Gender Dysphoria/ (581)
15 "Sexual and Gender Disorders"/ (79)
16 Transsexualism/ (3895)
17 Transgender Persons/ (3835)
18 Health Services for Transgender Persons/ (152)
19 exp Sex Reassignment Procedures/ (969)
20 "Sexual and Gender Minorities"/ (4924)
21 ((gender$ and dysphori$) or (gender$ adj5 incongru$) or sexual dysphori$).ti,ab,kf. (1784)
22 (gender$ adj (disorder$ or identi$)).ti,ab,kf. or (gender identity/ and dysphori$.ti,ab,kf.) (4568)
23 (GID or GIDS or GIDC or GIDCS).ti,ab,kf. (456)
24 (gender$ adj5 (confusion or confused or questioning or distress$ or discomfort)).ti,ab,kf. (980)
25 (gender$ adj5 (minority or minorities)).ti,ab,kf. (1593)
26 (gender$ adj5 (variant$ or variance$ or nonconform$ or non-conform$ or diverse or diversity or atypical$)).ti,ab,kf. (3409)
27 (non-binary or nonbinary or enby or genderqueer or gender-queer or neutrois).ti,ab,kf. (796)
28 (agender$ or genderless$ or gender-less$ or genderfree or gender-free or ungender$ or un-gender$ or non-gender$ or nongender$ or bigender$ or bi-gender$ or dual gender$ or dualgender$ or demi-gender$ or demigender$ or genderfluid$ or gender-fluid$ or trigender$ or tri-gender$).ti,ab,kf. (315)
29 two spirit$.ti,ab,kf. (84)
30 (trans adj3 (female$ or feminin$ or woman$ or women$ or male$1 or man or mans or men or mens or masculin$ or person$1 or peopl$ or population$ or individual$)).ti,ab,kf. (1362)
31 (transgend$ or trans-gend$ or transex$ or transsex$ or trans-sex$ or transfemale$ or transfeminin$ or transwom$ or transmale$ or transman$ or transmasculin$ or transmen$ or transperson$ or transpeopl$ or transpopulation$ or transindividual$).ti,ab,kf. (10832)

32 (trans adj3 identi$).ti,ab,kf. or (gender identity/ and trans.ti,ab,kf.) or (trans and dysphori$).ti,ab,kf. (1447)
33 (crossgender$ or cross-gender$ or crossex$ or crosssex$ or cross-sex$).ti,ab,kf. (836)
34 ((sex or gender$) adj3 (reassign$ or re-assign$ or affirm$ or confirm$ or transition$)).ti,ab,kf. (3963)
35 ((gender$ or sex) adj (change or changes or changing or changed)).ti,ab,kf. (825)
36 (detransition$ or de-transition$ or desister$ or de-sister$).ti,ab,kf. (134)
37 ((desist$ or persist$) adj5 (transition$ or trans or dysphori$)).ti,ab,kf. (823)
38 or/14-37 (28731)
39 (trans and (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ti. (339)
40 (trans adj5 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ab,kf. (397)
41 (transchild$ or transminor$ or transboy$ or transgirl$ or transkid or transkids or transyoung$ or transyouth$ or transteen$ or transtween$ or transadoles$ or transjuvenil$).ti,ab,kf. (15)
42 13 and 38 (9819)
43 39 or 40 or 41 or 42 (10343)
44 exp animals/ not humans/ (4823832)
45 (editorial or news or comment or case reports).pt. or case report.ti. (3692318)
46 43 not (44 or 45) (9429)
47 limit 46 to english language (9029)

Key to Ovid symbols and commands:

$	Unlimited right-hand truncation symbol
$N	Limited right-hand truncation - restricts the number of characters following the word to N
ti,ab,kf,	Searches are restricted to the Title (ti), Abstract (ab), Keyword Heading Word (kf) fields
.jn	Searches are restricted to the Journal name field
adj	Retrieves records that contain terms next to each other (in the shown order)
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-12	Combines sets 1 to 12 using OR

Supplementary table S2 - Study characteristics

Study ID	Country	Relevant study aim*	Setting	Population*	Primary sample (size (age; birth-registered sex**))	Puberty suppressant hormones	Cross-sex hormones	Intervention	GnRHa	Progestins	Others	Comparator	Comparator category	Other control group (size (age; gender))	Study design	Study follow-up	Data collection period
Cohort																	
Achille 2020	US	To examine the associations of endocrine intervention with depression and quality of life scores over time in transgender youths	Paediatric endocrine department for gender dysphoria	Children and adolescents age 9-25 years referred to the department for gender dysphoria	50 (mean age 16.2 (SD 2.2); 33 birth-registered females, 17 birth-registered males)	Yes	Yes	Puberty suppressants and/or cross-sex hormones	Yes	Yes	Yes	Participants who had received nothing at all or only cross sex-hormones.	Non-exposed individuals from primary sample	N/A	Prospective cohort study	Baseline and two follow-ups at ~6-monthly intervals (time-points not linked to treatment initiation)	Questionnaires completed between Dec 2013 to Dec 2018
Akgul 2019	US	To evaluate the experience of menstruating gender minority youth with the levonorgestrel-releasing intrauterine system (LNG-IUS) as a method of menstrual suppression	Adolescent division at a children's hospital	Gender minority youth age 12-22 who self-selected LNG-IUS for menstrual suppression	30 (20 matched with controls: mean age 16.6 range 13-19; 19 transgender, 1 agender; 10 unmatched mean age 14.9 range 13-17; 1 transgender, 8 agender, 1 gender fluid)	Yes	No	Levonorgestrel-releasing intrauterine system (LNG-IUS)	No	Yes	No	Adolescents receiving the same intervention for non-contraceptive reasons matched for age and time of insertion.	Other control group	20 girls (mean age 16.9 (SD 1.5))	Retrospective cohort study	Baseline, and all follow-up contacts during study period (period not specified - treatment duration range 1-32 months)	Selected intervention between Jun 2014 to Jan 2018
Becker-Hebly 2020	Germany	To describe how dimensions of psychosocial health are distributed among different intervention groups of adolescents with a gender dysphoria diagnosis before and after treatment	Gender identity service for children and adolescents	Young people age 11 and over who were seeking and eligible for medication interventions	75 (mean age at baseline 15.56 range 11-18; 64 birth-registered female, 11 birth-registered male)	Yes	Yes	GnRHa; cross-sex hormones and GnRHa; cross-sex hormones and surgery	Yes	No	No	No hormone treatment	Non-exposed individuals from primary sample	N/A	Retrospective cohort study	Baseline (at intake) and single follow-up (follow-up ranged 13 to 38 months after baseline, mean 21.4 months - not linked to treatment start)	Clinical entry Sep 2013 to Jun 2017 (follow-up to Mar 2018)
Costa 2015	UK	To assess the global functioning of adolescents with gender dysphoria after psychological support and puberty suppression	Paediatric gender identity service	Adolescents referred to the service who completed the diagnostic procedure	201 (mean age 15.52 range 12-17; birth-registered male / female ratio = 1:1.6)	Yes	No	Psychological support and puberty suppressants (GnRHa)	Yes	No	No	Sample of adolescents without observed psychological/ psychiatric symptoms (recruited via paediatric mental health services)	Non-exposed individuals from primary sample; Other control group	n=169	Prospective cohort study	Baseline and 6, 12 and 18 month follow-up	Referred between 2010 and 2014
de Nie 2022	Netherlands	To evaluate the influence of puberty suppression and/or gender affirming hormonal treatment on exocrine testicular function in transgender women	Center for Gender Dysphoria for all ages	Transgender women who underwent bilateral orchiectomy combined with vaginoplasty	214 (mean age at time of surgery 29.6 years SD 12.4)	Yes	Yes	Puberty suppressants and/or cross-sex hormones initiated in adolescence	Yes	Yes	No	Hormones initiated in adulthood	Individuals from primary sample receiving hormones in adulthood	N/A	Retrospective cohort study	Single time-point	Underwent surgery from 2006 to 2019
Grimstad 2021b	US	To identify the impact of oxandrolone in the presence or absence of GnRHa on adult height in trans-masculine youth	Multi-disciplinary gender clinic at paediatric medical centre	Sex assigned female at birth and diagnosis of gender dysphoria and whose final adult heights were available	154 (mean age of referral 15.7 SD 1.9)	Yes	Yes	Oxandrolone with or without GnRHa; Testosterone with or without GnRHa; GnRHa only; Progesterone only	Yes	No	No	No hormone therapy	Non-exposed individuals from primary sample	N/A	Retrospective cohort study	All heights available in the medical record were collected up to adult height	Seen between 2013 and 2018 (data collected to 2020)
Mejia-Otero 2021	US	To analyse the effectiveness of GnRHa in suppressing the hypothalamic-pituitary gonadal axis in transgender adolescents	Gender clinic for youth at children's hospital	Transgender youth treated with GnRHa for puberty suppression who had undergone blood tests at baseline and 2-12 months after treatment	30 (mean age 13.0 SD 2.1; 17 birth-registered male, 13 birth-registered female)	Yes	No	GnRHa	Yes	No	No	Children with central precocious puberty treated with GnRHa	Other control group	(21 girls, mean age 6.3 (SD 2.3); 9 boys, mean age 9.6 (SD 1.0))	Retrospective cohort study	Baseline and single follow-up (mean 5.2 months SD 1.9 in transgender group, 5.9 months SD 2.9 in controls)	Seen between Jan 2014 and Jun 2018
Pine-Twaddell 2022	US	To present retrospective data on clinical and biochemical outcomes of extended Histrelin implant use in adolescents with gender dysphoria	Two paediatric centres	Patients with gender dysphoria with Histrelin implant in place for 17 months or longer	42 (mean age at presentation 11.6 SD 2.4; 22 birth-registered female, 20 birth-registered male)	Yes	No	Histrelin implant (GnRHa)	Yes	No	No	Children with central precocious puberty with Histrelin implant	Other control group	n=7	Retrospective cohort study	Baseline and single follow-up (17 to 65 months post-insertion)	Seen between Jan 2010 and Dec 2020
Schulmeister 2022	US	To quantify the growth of transgender and gender diverse youth starting GnRHa therapy	Four children's hospital-based gender specialty clinics	Transgender and gender diverse youth initiating GnRHa treatment for puberty suppression (included if treatment duration 10-14 months)	55 (mean age at GnRHa start 11.5 range 9.0-14.5; 26 birth-registered male, 29 birth-registered female)	Yes	No	GnRHa	Yes	No	No	Prepubertal adolescents presumed not to have gender dysphoria not receiving hormone treatment	Other control group	226 (mean 11.0 (SD 2.8); 118 males, 108 females)	Prospective cohort study	Baseline, 6 and 12 month follow-up	Recruited between Jul 2016 and Sep 2018
Tordoff 2022	US	To investigate whether initiation of puberty blockers and gender-affirming hormones is associated with changes in depression, anxiety, and suicidality in transgender and nonbinary youths	Urban multidisciplinary children's gender clinic	Transgender and nonbinary adolescents and young adults who completed the initial clinic appointment	104 (mean age 15.8 range 13-20; 63 trans males, 27 trans females, 10 nonbinary / fluid, 4 don't know)	Yes	Yes	Puberty suppressants and cross-sex hormones	Not stated	Not stated	Not stated	No hormone treatment	Non-exposed individuals from primary sample	N/A	Prospective cohort study	Baseline (initial appointment), 3, 6 and 12 month follow-up (follow-up timepoints not linked to initiation of medical intervention)	Initial appointment from Aug 2017 to Jun 2018
van de Grift 2020	Netherlands	To describe the development of sex characteristics in a transgender adolescent cohort of early and later-initiated puberty suppressant treatement compared with young adults without treatment	Patients were identified using local registries (single centre)	Adolescents with gender dysphoria who initiated and continued puberty suppression treatment, and were less than age 18 at initiation	300 (mean age at start of puberty suppressants 15 SD 2.0; 184 birth-registered female, 116 birth-registered male)	Yes	Yes	Puberty suppressants and cross-sex hormones	Yes	No	No	No puberty suppressants	Non-exposed individuals from primary sample	N/A	Retrospective cohort study	Baseline, and follow-ups at initiation of cross-sex hormones	Sought treatment from 2006 to 2013 (data collected until 2018)
Pre-post																	
Carmichael 2021	UK	To evaluate the benefits and risks for physical and mental health and wellbeing of mid-pubertal suppression in adolescents with gender dysphoria	Paediatric gender identity service	12-15 year olds with persistent and severe gender dysphoria who requested and were eligible for puberty suppressants	44 (median age at consent 13.6 years; 25 birth-registered male, 19 birth-registered female)	Yes	No	GnRHa (monotherapy) together with psychosocial support and therapy	Yes	No	No	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline and 12, 24 and 36 month follow-up	Recruited Apr 2011 to Apr 2014 (commenced GnRHa between Jun 2011 and Apr 2015)
Chiniara 2018	Canada	To examine characteristics, including mental health comorbidities, among adolescents presenting to a transgender clinic and to compare these data to previous reports.	Specialist gender service based in children's hospital	12-18 year olds with gender dysphoria who desired pubertal suppression or cross-gender hormones	115 (no information on characteristics provided)	Yes	Yes	GnRHa and cross-sex hormones	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and single-follow-up (average 3.8 months (SD 1.9) after treatment)	Initial visit between January 2014 and June 2016
de Vries 2011	Netherlands	To compare psychological functioning and gender dysphoria before and after puberty suppression in gender dysphoric adolescents	Center for Gender Dysphoria for all ages	Adolescents with gender identity disorder who were prescribed GnRHa to suppress puberty	70 (mean age at assessment 13.7 years SD 1.9; 33 birth-registered male, 37 birth-registered female)	Yes	No	Puberty suppressants (GnRHa)	Yes	No	No	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline and single follow-up before initiation of cross-sex hormones	Received treatment between 2000 and 2008
de Vries 2014	Netherlands	To investigate whether gender dysphoric youth improve over time with medical intervention consisting of puberty suppressants followed by cross-sex hormones and gender reassignment surgery	Center for Gender Dysphoria for all ages	Young adults who had received puberty suppressants followed by cross-sex hormones and gender reassignment surgery	55 (mean age at GnRHa intiation 14.8 range 11.5–18.5; 22 birth-registered male, 33 birth-registered female)	Yes	Yes	Puberty suppression followed cross-sex hormones and surgery	Yes	No	No	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline and follow-ups at intiation of cross-sex hormones	Referred between 2000 and 2008 (follow-up between 2008 and 2012)
Delemarre-van de Waal 2006	Netherlands	To investigate the efficacy and safety of GnRHa treatment in adolescents with gender dysphoria	Center for Gender Dysphoria for all ages	Adolescents receiving GnRHa under the Dutch protocol for 2 years or longer	21 (age not reported; 11 birth-registered female, 10 birth-registered male)	Yes	Yes	GnRHa and cross-sex hormones	Yes	No	No	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline, 12 months and 24 months for some outcomes, and 24 months for others	Not reported
Ghelani 2020	UK	To observe the effect of suddenly withdrawing sex hormones on the body composition in late-pubertal adolescents with gender dysphoria using GnRH analogues	Paediatric gender identity service	Late and post-pubertal individuals aged 15–17 with gender dysphoria receiving GnRHa for at least 12 months	36 (11 birth-registered male mean age 16.4, 25 birth-registered female mean age 16.6)	Yes	No	Puberty suppressants (GnRHa - Triptorelin)	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, 6 and 12 month follow-up	Treated between 2013 and 2015
Hisle-Gorman 2021	US	To examine mental health and psychotropic medication use among transgender adolescents following gender-affirming pharmaceutical care (secondary aim of sub-group of primary sample)	Military Healthcare Data Repository	Transgender military dependent youth who received care for gender dysphoria before age 18	963 (median age study start 12 IQR 10-14; 300 birth-registered male, 663 birth-registered female)	Yes	Yes	Puberty suppressants or cross-sex hormones	Not stated	Not stated	Not stated	No comparator	No comparator	N/A	Retrospective pre-post single group study	All available data before and after initiation of treatment (followed for mean 1.5 years [IQR 0.8-2.8] after start of treatment)	Received care between Oct 2010 and Sep 2018
Joseph 2019	UK	To investigate whether there are any clinically significant changes in bone mineral density and bone mineral apparent density in adolescents with gender dysphoria who are taking GnRHa	Gender identity service for children and adolescents / national endocrine clinic	Adolescents age 12-14 years referred to Early Intervention programme and offered GnRHa treatment	70 (31 birth-registered male mean age at scan 1 13.0 SD 1.1 and 39 birth-registered female average age at scan 1 12.9 SD 1.0)	Yes	No	GnRHa	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, and ~12 months, ~24 months, and ~36 months follow-up	Referred from 2011 to 2016
Khatchadourian 2014	Canada	To describe patient characteristics at presentation, treatment, and response to treatment in youth with gender dysphoria	Children's gender programme	Youth with a diagnosis of gender dysphoria and achieved at least Tanner stage 2	84 (median age at first visit 16.8 range 11.4-22.5; 45 birth-registered female, 37 birth-registered male)	Yes	Yes	GnRHa, spironolactone, cross-sex hormones, surgery	Yes	No	Yes	No comparator	No comparator	N/A	Retrospective pre-post single group study	All relevant clinic notes (follow-up ranged from 0.0 to 11.3 years)	Seen from Jan 1998 to Dec 2011
Klaver 2018	Netherlands	To examine the change in body shape and composition in transgender adolescents receiving hormone treatments	Center for Gender Dysphoria for all ages	All persons who started hormone treatment before 18 years old and had undergone x-rays and medical checkups to adulthood	192 (71 birth-registered male mean age at start of GnRHa 14.5 SD 1.8, 121 birth-registered female mean age 15.3 SD 2.0)	Yes	Yes	GnRHa followed by cross-sex hormones	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and follow-ups at addition of cross-sex hormones	Started treatment between 1998 and 2014
Klaver 2020	Netherlands	To investigate cardiovascular risk factors, and assess obesity and dyslipidemia prevalence in transgender adolescents receiving hormone treatments	Center for Gender Dysphoria for all ages	All persons who started hormone treatment before 18 years old and had undergone x-rays and medical checkups to adulthood	192 (71 birth-registered male mean age at start of GnRHa 14.6 SD 1.8, 121 birth-registered female mean age 15.2 SD 2.0)	Yes	Yes	GnRHa followed by cross-sex hormones	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and follow-ups at addition of cross-sex hormones	Diagnosed with gender dysphoria from 1998 to Dec 2015
Klink 2015	Netherlands	To assess peak bone mass in young adults with gender dysphoria who had been treated with GnRHa and cross-sex hormones during their pubertal years	Tertiary referral center	At least 21 years, gonadectomy had taken place, and data on bone development at start of GnRHa treatment, at start of cross-sex hormone therapy, and at the age of 22 years were available	34 (15 birth-registered male mean age at start of GnRHa 14.9 SD 1.9, 19 birth-registered female mean age at start of GnRHa 15.0 SD 2.0)	Yes	Yes	GnRHa followed by cross-sex hormones followed by gonadectomy	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Follow-ups at addition of cross-sex hormones.	Received gonadectomy from Jun 1998 to Aug 2012
Kuper 2020	US	To examine how transgender youth body dissatisfaction, depression, and anxiety symptoms change over the first year of receiving gender-affirming hormone therapy	Multi-disciplinary programme	Youth who received gender-affirming hormone therapy	n = 148 (mean age 14.9 range 9-18; 55 birth-registered male, 94 birth-registered female)	Yes	Yes	GnRHa and cross-sex hormones	Not stated	Not stated	Not stated	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline (initial assessment) and 12 month follow-up (mean 14.9 months, range 11-18 months)	Initial assessments between Aug 2014 and Mar 2018
Lynch 2015	US	To determine the efficacy and safety of medroxyprogesterone to suppress puberty sex steroids in adolescents with gender dysphoria	Gender identity clinic	Adolescents with gender identity disorder less than age 19 who were treated with medroxyprogesterone	14 (age range at evaluation 9 to 18; 7 birth-registered male, 7 birth-registered female)	Yes	No	Medroxyprogesterone	No	Yes	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and relevant data from clinic follow-up at 1 and 6-monthly intervals (duration of follow-up not reported)	Seen from Oct 1995 to Mar 2013

Navabi 2021	Canada	To examine the effects of GnRHa on bone health and body composition among youth with gender dysphoria, including the role of Vitamin D	Endocrine diversity clinic children's hospital	Adolescents with gender dysphoria age <18, with at least 1 baseline dual-energy radiograph absorptiometry assessment	172 (119 birth-registered female mean age 15.2 SD 1.8, 51 birth-registered male mean age 15.4 SD 2.0, 2 nonbinary)	Yes	No	GnRHa	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and single follow-up (median 352.5 median days after GnRHa initiation, range 188-676 days)	Seen from Jan 2006 to Apr 2017 (data collection to Jan 2019)
Neyman 2019	US	To describe the novel use of androgen receptor blocker bicalutamide in transgender youth as an alternative to GnRHa	Paediatric endocrine clinic at children's hospital	Male to female adolescents with gender dysphoria treated with bicalutamide	23 (median age 16 at start of treatment range 12.0-18.2)	Yes	No	Puberty suppressants (Bicalutamide)	No	No	Yes	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and two follow-ups (first follow-up ranged 2.17 to 8.0 months, second 10.9 to 13.3 months)	Treated between 2013 and 2018
Olson-Kennedy 2021	US	To determine if Vantas and SupprelinLA are effective in suppressing the hypothalamic-pituitary-gonadal axis in early-to-mid pubertal youth with gender dysphoria	Four specialist gender services based in children's hospitals	Youth with gender dysphoria who were prescribed and adminstered GnRHa implant at Tanner stage 2-3	66 (mean age of insertion 11.3 range 9-15 years; 34 birth-registered female, 32 birth-registered male)	Yes	No	Vantas and SupprelinLA (GnRHa histrelin implants)	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and single follow-up (2-12 months after treatment)	Not reported
Perl 2020	Israel	To examine blood pressure changes in transgender male adolescents treated with GnRHa alone and after the addition of testosterone	Gender dysphoria clinic at children's hospital	Transgender male adolescents who were treated solely with GnRHa for at least 2 months	15 (mean age at intiation of GnRHa 14.4 SD 1.0)	Yes	Yes	GnRHa followed by addition of testosterone	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, and follow-ups at end of GnRHa treatment (average 3 months SD 1), initiation of testosterone mean 4 months (SD 2)	Sought care between 2013 and 2018
Perl 2021	Israel	To examine blood pressure changes in transgender female adolescents treated with GnRHa alone and after the addition of estradiol	Gender dysphoria clinic at children's hospital	Transgender female adolescents who were treated solely with GnRHa for at least 2 months	19 (mean age at initiation of GnRHa 15.7 SD 1.6)	Yes	Yes	GnRHa and estradiol	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, and follow-ups at end of GnRHa treatment (mean 9 months SD 6), initiation of estradiol	Sought care between 2013 and 2020
Russell 2021	UK	To investigate whether features of autism change over time for gender diverse adolescents after accessing GnRHa alongside psychosocial support	Paediatric Gender Identity Development Service	Gender diverse young people who were offered GnRHa	95 (mean age at consent for treatment 13.6 range 9.9-15.9; 38 birth-registered male, 57 birth-registered female)	Yes	No	Puberty suppressants (GnRHa)	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and 12 month follow-up (plus / minus 3 months)	Data included for participants meeting inclusion criteria up to March 2020
Schagen 2016	Netherlands	To evaluate the efficacy and safety of GnRHa treatment to suppress puberty in gender dysphoric adolescents	Center for Gender Dysphoria for all ages	Gender dysphoric adolescents treated with triptorelin (GnRHa) for at least 3 months	116 (49 birth-registered male median age 13.6 range 11.6-17.9, 67 birth-registered female median age 14.2 range 11.1 to 18.6)	Yes	No	GnRHa (triptorelin)	Yes	No	No	No comparator	No comparator	N/A	Prospective pre-post single group study	12 months	Seen from 1998 to 2009
Schagen 2018	Netherlands	To assess the effects of GnRHa treatment and gender-affirming hormone treatment on adrenal androgen levels in adolescents with gender dysphoria	Center for Gender Dysphoria for all ages	Adolescents with gender identity disorder who fulfilled criteria for treatment according to Endocrine Society guideline	127 (73 birth-registered female mean age at GnRHa start 14.3 range 11.5-18.6, 54 birth-registered male age 14.0 range 11.6 to 17.9)	Yes	Yes	GnRHa treatment followed by GnRHa combined with estradiol or testosterone	Yes	No	No	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline and 6 monthly follow-up to 4 years	Treated between 1998 and 2009
Schagen 2020	Netherlands	To describe bone mass development in adolescents with gender dysphoria treated with GnRHa, subsequently combined with gender-affirming hormones	Center for Gender Dysphoria for all ages	Adolescents with gender identity disorder who fulfilled criteria for treatment according to existing guidelines	121 (51 birth-registered male mean age 14.1 SD 1.7, 70 birth-registered female mean age 14.5 SD 2.0)	Yes	Yes	GnRHa treatment followed by GnRHa combined with estradiol or testosterone	Yes	No	No	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline and 12-monthly follow-up to 5 years	Treated between 1998 and 2009
Segev-Becker 2020	Israel	To describe patient characteristics at presentation, management, and fertility preservation among a cohort of children with gender dysphoria	Multidisciplinary paediatric gender dysphoria clinic	All patients younger than 18 years who began GnRHa treatment	106 (median age at referral 15.5 range 4.6-18 years)	Yes	Yes	GnRHa followed by cross-sex hormones	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	All relevant data following initiation of treatment (follow-up period not reported)	Referred from Mar 2013 to Dec 2018
Stoffers 2019	Netherlands	To investigate the efficacy and safety of testosterone treatment in transgender adolescents	Clinic (no other information provided)	Adolescents diagnosed with gender dysphoria who hard started GnRHa and had subsequently received testosterone for more than 6 months	62 (median age at GnRHa initiation 16.5 range 11.8-18.0)	Yes	Yes	GnRHa followed by testosterone	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	The median duration of follow-up was 12 months (range 5-33 months).	Received treatment between Nov 2010 and Aug 2018
Tack 2016	Belgium	To analyse the impact of consecutive treatment with Lynestrenol monotherapy and in combination with testosterone on physical characteristics, safety, metabolic parameters, and hormone levels in gender dysphoric adolescent transboys	Multi-disciplinary child gender team	Gender dysphoric transmale adolescents who received Lynestrenol for at least 6 months	38 (mean age at start of treatment 15 years 10 months)	Yes	Yes	Lynestrenol - androgonic progestin (puberty suppressant) only, and in combination with testosterone	No	Yes	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, 6 and 12 months follow-up with Lynestrenol	Treated from 2010 until Sep 2015
Tack 2017	Belgium	To assess the side effects and biochemical changes of Cyproterone acetate alone and in combination with estrogen in adolescent trans-girls	Multi-disciplinary child gender team	Transgirls with gender dysphoria who received Cyproterone acetate for at least 6 months	27 (mean age at start of treatment 16 years 6 months)	Yes	Yes	Cyproterone acetate (puberty suppressant) only, and in combination with estrogen	No	Yes	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, 6 and 12 month follow-up with Cyproterone	Treated from 2008 to Oct 2016
Tack 2018	Belgium	To study prospectively the evolution of body composition and bone mass in late-pubertal trans adolescents using the proandrogenic or antiandrogenic progestins Lynestrenol and Cyproterone acetate, respectively	Multi-disciplinary child gender team	Gender dysphoric late-pubertal (Tanner stage 4) adolescents treated with Lynestrenol or Cyproterone acetate	65 (44 birth-registered female mean age at treatment initiation 16.2 SD 1.05, 21 birth-registered male mean age 16.3 SD 1.21)	Yes	No	Proandrogenic or antiandrogenic progestins Lynestrenol and Cyproterone acetate (puberty suppressants)	No	Yes	No	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline and single follow-up prior to addition of cross-sex hormones	Treated between Mar 2011 and Jan 2017
van der Loos 2021	Netherlands	To investigate changes in bone geometry among transgender adolescents using GnRHa and gender-affirming hormones	Center for Gender Dysphoria for all ages	Transgender adolescents treated with GnRHa and subsequent gender-affirming hormones before the age of 18 years, min. duration 6 months GnRHa, and for whom DXA scans were available	322 (106 birth-registered male median age 13.1 to 15.5 for sub-groups at GnRHa start, 216 birth-registered female median age 11.9 to 15.7 for subgroups at GnRHa)	Yes	Yes	GnRHa and cross-sex hormones	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, and follow-up at addition of cross-sex hormones	Visited clinic between 1972 and Dec 2018
Vlot 2017	Netherlands	To investigate the effect of GnRHa and cross-sex hormone treatment on bone turnover markers and bone mineral apparent density in transgender adolescents	Center for Gender Dysphoria for all ages	Adolescents diagnosed with gender dysphoria who were treated with GnRHa and cross-sex hormone treatment, with available outcome data	70 (28 birth-registered male median age at GnRHa start 13.5 range 11.5-18.3, 42 birth-registered female median age 15.1 range 11.7-18.6)	Yes	Yes	GnRHa and cross-sex hormones	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, and follow-ups at addition of cross-sex hormones	Started treatment between 2001 and 2011
Waldner 2022	Canada	To determine the proportion of gender diverse youth who had QTc prolongation while on leuprolide acetate therapy	Children's hospital paediatric endocrinology gender clinic	Youth age 9-18 years receiving leuprolide acetate therapy with completed ECG after initiation	33 (mean age 13.7 SD 2.1; 23 birth-registered female, 10 birth-registered male)	Yes	No	GnRHa (leuprolide acetate)	Yes	No	No	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and single follow-up (at least 6 weeks after initation of treatment)	Treatment started between Jul 2018 and Dec 2019
Cross-sectional																		
Arcelus 2016	UK	To explore prevalence of non-suicidal self-injury (NSSI) in young trans people and to identify what factors can predict this	National gender clinic for adults (age 17+)	All individuals below the age of 25 years old who were referred for and offered an assessment	268 (mean age 19.9 SD 2.17; 121 birth-registered female, 136 birth-registered male, 11 no answer)	Yes	Yes	GnRNa or cross-sex hormones	Yes	No	No	No hormone treatment	Non-exposed individuals from primary sample	N/A	Cross-sectional study	Single time-point (initial assessment after referral to service)	Referred between Nov 2012 to June 2015
Burke 2020	Netherlands	To investigate whether hormonal interventions in adolescents diagnosed with gender dysphoria affect their click-evoked otoacoustic emissions compared to age- and sex-matched controls	Center for Gender Dysphoria for all ages	Children and adolescents diagnosed with gender dysphoria	105 (62 birth-registered female mean age 15.6 range 10.3-20.3, 43 birth-registered male mean age 15.9 range 11-20)	Yes	Yes	GnRHa; cross-sex hormones and GnRHa	Yes	No	No	No hormone treatment; Age- and sex-matched controls divided into early, mid- and late-adolescent groups.	Non-exposed individuals from primary sample; Other control group	Early (13 boys, mean 12.8 (SD 1.9); 15 girls, 12.2 (1.7)); mid- (18 boys, 13.9 (1.9); 10 girls, 15.1 (1.8)); late-adolescent (20 boys, 17.1 (0.8); 21 girls, 17.9 (0.4))	Cross-sectional study with controls	Single time-point	Not reported
Fontanari 2020	Brazil	To evaluate the impact of each domain of gender affirmation (social, legal, and medical/surgical) on the mental health of transgender and gender nonbinary youth.	Facebook	Transgender boys, transgender girls, and gender nonbinary Brazilian youth, age 16 to 24 years	350 (mean age 18.61 (CI 95% 18.34–18.88; 149 transgender boys, 85 transgender girls, 116 gender nonbinary)	Yes	Yes	Hormone therapy'; 'any hormone or surgical treatment'	Not stated	Not stated	Not stated	No hormone therapy; no hormone or surgical treatment	Non-exposed individuals from primary sample	N/A	Cross-sectional study	Single time-point	Recruitment Feb to Apr 2018
Nokoff 2021	US	To evaluate insulin sensitivity and body composition among transgender adolescents receiving GnRHa compared with adolescents not experiencing gender dysphoria	Centre for gender diversity at children's hospital	Transgender youth treated with GnRHa for at least 3 months	17 (9 birth-registered male mean age 13.8 SD 1.7, 8 birth-registered female mean age 13.7 SD 1.2)	Yes	No	GnRHa	Yes	No	No	Adolescents assumed not to have gender dysphoria matched on age, BMI and sex assigned at birth	Other control group	(14 girls, mean age 13.9 (SD 1.7); 17 boys, mean age 13.9 (SD 0.9))	Cross-sectional study with controls	Single time-point (GnRHa treatment duration birth-registered females mean 20.9 months range 17.5 to 70.4, males mean 11.3 months range 4.7 to 24.2)	Recruited from 2016 to 2019
Staphorsius 2015	Netherlands	To determine whether the performance on the Tower of London task, a commonly used Executive Function task, was altered in adolescents with gender dysphoria when treated with GnRHa	Center for Gender Dysphoria for all ages	Adolescents who were diagnosed with gender identity disorder (at least 12 years old)	40 (22 birth-registered female mean age 15.8 SD 1.9, 18 birth-registered male mean age 15.1 SD 2.4)	Yes	No	GnRHa treated	Yes	No	No	Untreated adolescents with gender dysphoria; age-matched controls (siblings or friends)	Non-exposed individuals from primary sample; Other control group	(24 girls, mean age 14.4 (SD 1.8); 21 boys, mean age 14.9 (SD 1.5))	Cross-sectional study with controls	Single time-point	Not reported
Strang 2022	US	To explore the relationship between gender-affirming medical intervention status (i.e., pubertal suppression, gender-affirming hormones) and executive functioning in adolescents with gender dysphoria / incongruence	Community, gender services, gender and neurodiversity programme	Transgender youth age 11-21 enrolled in a study of cognition, mental health and neurodevelopment (all met criteria for gender dysphoria)	124 (mean age 16.67 range 11.65-21.56, 82 birth-registered female, 42 birth-registered male)	Yes	Yes	Puberty suppressants and cross-sex hormones	Yes	No	No	No hormone treatment	Non-exposed individuals from primary sample	N/A	Cross-sectional study	Single time-point	Enrolled in study between 2018 and 2020
Turban 2020	US	To examine associations between access to pubertal suppression during adolescence and mental health outcomes in transgender adults	Community	Transgender adults age 18 to 36 who reside in the US who reported ever desiring pubertal suppression	3,494 (mean age 23.4 SD 5.0; 1913 birth-registered female, 1,581 birth-registered male)	Yes	No	Puberty suppressants	Not stated	Not stated	Not stated	No puberty suppressants	Non-exposed individuals from primary sample	N/A	Cross-sectional study	Single time-point	Data collected Aug to Sep 2015
van der Miesen 2020	Netherlands	To compare transgender adolescents before and after gender-affirmative care with a sample of non-clinical age-equivalent adolescents (with no gender dysphoria) on psychological well-being	Center for Gender Dysphoria for all ages	Adolescents who were referred to the clinic and who completed the assessment process	450 (272 in assessment: mean age 14.47 SD 2.18 years, 116 birth-registered male, 156 birth-registered female; 178 taking GnRHa: mean age 16.75 SD 1.24, 68 birth-registered male, 110 birth-registered female)	Yes	No	Puberty suppressants	Yes	No	No	No puberty suppressants; Dutch high school adolescents.	Non-exposed individuals from primary sample; Other control group	651 (mean 15.39 (SD 1.36); 346 males, 305 females)	Cross-sectional study with controls	Single time-point (no treatment group assessed at referral, puberty suppressant group assessed before initiation of cross-sex hormones)	Referred between 2012 and 2015

* For study aim and population, terminology from primary study is retained
** Where birth-registered sex is not reported in the study, gender identity is provided

Supplementary table S3 - Reported study outcomes and measures

Study ID	Puberty suppression	Side effects	Gender-related	Body image	Psychological	Psychosocial	Physical health	Bone health	Fertility	Cognition/ neuro-developmental	Other	Outcomes (measures)
Cohort												
Achille 2020	No	No	No	No	Yes	Yes	No	No	No	No	No	Depression (Patient Health Questionnaire-9 modifed for teens (PHQ-9), Center for Epidemiologic Studies Depression Scale - Revised (CESD-R)); quality of life (Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (QLES-Q-SF))
Akgul 2019	Yes	Yes	No	No	No	Yes	Yes	No	No	No	No	Menstrual distress (presence); need for hormonal medication; presence of dysmenorrhea; removal; complications / side effects; menstrual bleeding
Becker-Hebly 2020	No	No	No	No	Yes	Yes	No	No	No	No	No	Psychological functioning (Youth Self Report (YSR) for age 11-18 and Adult Self Report (ASR) for 18+); Global functioning (Children's Global Assessment Scale (CGAS); Health-related quality of life (Kidscreen-27 for age 11-18 and SF (short form)-8 for 18+)
Costa 2015	No	No	No	No	No	Yes	No	No	No	No	No	Gender dysphoria (UGDS); psychosocial functioning (CGAS)
de Nie 2022	No	No	No	No	No	No	No	No	Yes	No	No	Exocrine testicular function (Spermatogenesis (Johnsen score), germ cell type (ratio of most advanced germ cell types)); Fertility preservation
Grimstad 2021b	Yes	No	No	No	No	No	Yes	No	No	No	No	Anthropometrics (adult height); skeletal maturation (Delta bone age)
Mejia-Otero 2021	Yes	No	No	No	No	No	No	No	No	No	No	Hormone levels (LH,FSH, testosterone, estradiol)
Pine-Twaddell 2022	Yes	No	No	No	No	No	No	No	No	No	No	Pubertal suppression or progression (hormone levels (testosterone, estradiol, LH), lack of Tanner stage progression on physical exam), menstruation; Safety (presence of complications related to removal or replacement)
Schulmeister 2022	Yes	No	No	No	No	No	No	No	No	No	No	Anthropometric (height velocity); hormone levels (LH, FSH, estradiol, testosterone)
Tordoff 2022	No	No	No	No	Yes	No	No	No	No	No	No	Depression (PHQ-9); Anxiety (GAD-7); Self-harm or suicidal thoughts over previous 2 weeks (PHQ-9 question 9)
van de Grift 2020	Yes	No	No	No	No	No	No	No	No	No	No	Anthropometrics (height, weight, BMI); puberty development (Tanner staging, breast and genital characteristics - clinical exam); surgical requirements for sex re-assignment
Pre-post												
Carmichael 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Bone health (bone mineral density (BMD) and content (BMC) - hip, lumbar, spine); hormone levels (LH, FSH, testosterone, estrogen); menstruation; anthropometrics (height, weight, BMI); adverse events / side effects (patient reported); psychological functioning (Child Behavior Checklist (CBCL), YSR); suicidality / self-harm (item 18, 91 from CBCL/YSR); quality of life (Kidscreen-52); body image (Body Image Scale (BIS)); gender dysphoria (Utrecht Gender Dysphoria Scale (UGDS)); psychosocial functioning (CGAS)
Chiniara 2018	Yes	No	Yes	No	Yes	No	No	No	No	No	No	Depression (BDI II)); anxiety (MASC2); gender dysphoria (UGDS); hormone levels (LH, FSH, oestradiol, testosterone); menstruation; pubertal progression
de Vries 2011	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Behavioral and emotional problems (CBCL and YSR); depressive symptoms (Beck Depression Inventory (BDI)); anxiety and anger (State-Trait Anxiety Inventory (STAI) and State-Trait Anger Expression Inventory (STAXI)); general functioning (CGAS); gender dysphoria (UGDS); body satisfaction (BIS)
de Vries 2014	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Behavioral and emotional problems (CBCL and YSR); depressive symptoms (BDI); anxiety and anger (STAI); global functioning (CGAS); gender dysphoria (UGDS); body image (BIS); well-being (own questionnaire; Satisfaction with Life Scale (SWLS); Subjective Happiness Scale (SHS)); quality of life (World Health Organization Quality of Life Brief Version (WHOQOL-BREF))
Delemarre-van de Waal 2006	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Puberty development (Tanner stage, skeletal age - left hand); anthropometrics (height, weight, sitting height, hip / waist circumference); bone density (whole body, hip, lumbar spine); body composition (fat mass percentage, lean body mass); carbohydrate and lipid metabolism (fasting glucose, insulin, cholesterol, HDL, LDL); hormone levels (gonadotrophins and sex hormones)
Ghelani 2020	Yes	No	No	No	No	No	Yes	No	No	No	No	Body composition (lean mass Sd score - Tanita body composition analysis); anthropometrics (height, weight, BMI)
Hisle-Gorman 2021	No	No	No	No	Yes	No	No	No	No	No	No	Mental health care visits (number of visits, diagnosis sub-category); psychotropic medications (type)
Joseph 2019	Yes	No	No	No	No	No	Yes	Yes	No	No	No	bone health (BMD, bone mineral apparent density (BMAD)); height, weight BMI
Khatchadourian 2014	No	Yes	No	No	No	No	Yes	No	No	No	No	Side effects (patient reported); Safety for antiandrogens (electrolyte and urea/creatinine levels)
Klaver 2018	Yes	No	No	No	No	No	Yes	No	No	No	No	Body shape (anthropometrics) (waist-hip ratio, body weight, waist/hip circumference, body height, BMI); body composition (whole-body and regional-body fat, total lean body mass, total body mass)
Klaver 2020	Yes	No	No	No	No	No	Yes	No	No	No	No	Anthropometrics (body height, body weight, BMI, waist/hip circumference); cardiovascular risk (blood pressure, glucose, insulin, homeostatic model assessment for insulin resistance (HOMA-IR), lipid values (total cholesterol, HDL, LDL, triglycerides), prevalence of obesity and dyslipidemia)
Klink 2015	Yes	No	No	No	No	No	Yes	Yes	No	No	No	bone health (BMD, BMAD); height, weight, BMI
Kuper 2020	No	No	No	Yes	Yes	No	No	No	No	No	No	Body dissatisfaction (BIS); depression (Quick Inventory of Depressive Symptoms (QIDS) - self- and clinician report); Anxiety (SCARED); suicidality (suicidal ideation, suicide attempt); suidality and self-harm (passive ideation, suicide attempt, NSSI); mental health treatment (psychiatric medication, therapy, support group)

Lynch 2015	Yes	No	No	No	No	No	Yes	No	No	No	No	Hormone levels (testosterone); Side effects
Navabi 2021	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Bone health (areal bone mineral density (aBMD) (lumbar spine, left total hip, total body less head), BMC); anthropometrics (height, weight, BMI); body composition (lean body mass, total body fat, regional fat mass ratios, fat distribution); Vitamin D status (to assess efficacy of vitamin D supplementation)
Neyman 2019	Yes	Yes	No	No	No	No	Yes	No	No	No	No	Breast development; liver function tests; estrodial and testosterone levels (no outcomes reported in methods)
Olson-Kennedy 2021	Yes	No	No	No	No	No	No	No	No	No	No	Hormone levels (total testosterone, estradiol, LH, FSH)
Perl 2020	Yes	No	No	No	No	No	Yes	No	No	No	No	Changes in weight status (BMI); Changes in blood pressure (systolic and diastolic); puberty development (hypothalamic–pituitary–gonadal axis suppression); hormone levels (tesosterone; estradiol, LH, FSH)
Perl 2021	Yes	No	No	No	No	No	Yes	No	No	No	No	Changes in weight status (BMI); Changes in blood pressure (systolic and diastolic); puberty development (hypothalamic–pituitary–gonadal axis suppression); hormone levels (tesosterone; estradiol, LH, FSH)
Russell 2021	No	No	No	No	No	No	No	No	No	Yes	No	Features of autism spectrum disorder (ASD) using the Social Responsiveness Scale 2 (SRS-2) School Age Form
Schagen 2016	Yes	No	No	No	No	No	Yes	No	No	No	No	Puberty development (Tanner stage by physical exam); body composition (fat percentage and lean body mass percentage); hormone levels (LH, FSH, testosterone, estradiol); safety (ALT, AST, alkaline phosphate, γ-glutamyl transferase, creatinine); Height, weight. BMI
Schagen 2018	No	No	No	No	No	No	Yes	No	No	No	No	adrenal androgen levels (dehydropepiandrosterone (DHEAS), androstenedione); testosterone levels
Schagen 2020	Yes	No	No	No	No	No	Yes	Yes	No	No	No	bone health (BMAD (whole body, hip, lumbar spine), serum bone markers); BMI, height, weight
Segev-Becker 2020	No	No	No	No	No	No	Yes	No	No	No	No	Side effects related to medical treatment (from medical record)
Stoffers 2019	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Anthropometrics (height, weight, BMI); blood pressure; hormone levels (FSH, LH, testosterone, estradiol, SHBG); safety (creatinine, ALP, total cholesterol, HDL, LDL, triglycerides, thyroid stimulating hormone, prolactin, free thyroxine, DHEAS, hemoglobin, hematocrit, androstenedione and vitamin D); bone health (BMD at lumbar spine, left neck, right hip, BMAD for spine and left neck)
Tack 2016	Yes	Yes	No	No	No	No	Yes	No	No	No	No	Anthropometry (height, weight, BMI); Blood pressure; Side effects (acne, hirsutism, patient-reported); Safety (complete complete blood count, electrolytes, liver and renal function, fasting glucose, HbA1c, insulin, lipid metabolism); hormone levels (thyroid stimulating hormone, anti-Müllerian hormone, free thyroxin, LH, FSH, estradiol, total and free testosterone, SHBG)
Tack 2017	Yes	Yes	No	No	No	No	Yes	No	No	No	No	Puberty development (physical changes); Side effects (patient-reported); Anthropometry (height, weight, BMI); Safety (hemoglobin, hematocrit, creatinine, AST, ALT, triglycerides, total cholesterol, HDL, LDL, DHEAS, prolactin); Hormone levels (thyroid stimulating hormone, free thyroxin, LH, FSH, estradiol, total and free testosterone, SHBG)
Tack 2018	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Antropometrics (weight, height, waist/hip circumference and ratio, BMI); body composition (total body minus head (total, lean, fast mass, body fat percentage, muscle area; Grip strength); bone health (BMC, aBMD, BMD, bone geometry, polar strength strain index); hormone levels (total testosterone, estradiol, testosterone:estradiol ratio, SHBG, LH, FSH); Safety (calcium/creatinine levels, serum 25-OH Vitamin D, parathyroid hormone, serum C-terminal telopeptide, procollagen type 1 N-terminal propeptide)
van der Loos 2021	Yes	No	No	No	No	No	Yes	No	No	No	No	Bone geometry (subperiosteal width (SPW) and endocortical diameter (ED)); hormone levels (testosterone, estradiol); anthropometrics (height, BMI)
Vlot 2017	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Anthropometrics (height, weight); Tanner stage (clinician assessed, bone age); bone turnover markers (P1NP (Procollagen type 1 N propeptide), osteocalcin, ICTP (Cross-linked carboxyterminal telopeptide of type I collagen)); bone health (BMD, BMAD for lumbar spine and femoral neck)
Waldner 2022	No	No	No	No	No	No	Yes	No	No	No	No	Proportion of adolescents with clinically significant QTc prolongation (defined as QTc >460 milliseconds)
Cross-sectional												
Arcelus 2016	No	No	No	No	Yes	No	No	No	No	No	No	Psychopathology (Symptom Checklist 90 Revised)
Burke 2020	Yes	No	No	No	No	No	No	No	No	No	No	Click-Evoked Otoacoustic Emissions
Fontanari 2020	No	No	Yes	No	Yes	No	No	No	No	No	No	Anxiety (Overall Anxiety Severity and Impairment Scale (OASIS)); depressive symptoms (Modified Depression Scale (MDS)); gender distress (Gender Distress Scale (GDS)); gender positivity (Gender Positivity Scale (GPS))
Nokoff 2021	Yes	No	No	No	No	No	Yes	No	No	No	No	Insulin sensitivity (fasted serum/plasma blood samples - glucose, insulin, HbA1c; leptin); Lipids (total cholesterol, triglycerides, HDL, LDL); Safety (AST, ALT, hematrocit; blood pressure); hormone levels (LH, FSH, SHBG, testosterone, estradiol, free androgen index); body composition (total body fat, fat mass, lean tissue, lean mass); anthropometrics (BMI)
Staphorsius 2015	No	No	No	No	No	No	No	No	No	Yes	No	Executive functioning (Tower of London experiment via fMRI - performance, task load, typical / atypical sex differentiation)
Strang 2022	No	No	No	No	No	No	No	No	No	Yes	No	Executive functioning problems (Behavior Rating Inventory of Executive Function (BRIEF- 2; Adult BRIEF) - primary outcome BRIEF Global Executive Composite (GEC), subscales - inhibition, cognitive flexibility, updating/working memory)
Turban 2020	No	No	No	No	Yes	Yes	No	No	No	No	No	Severe psychological distress in month before survey (defined as score of 13+ on Kessler-6 Psychological Distress Scale (K6+)); Binge drinking in month before survey (defined as 5+ standard alcoholic drinks on single occasion; Life-time illicit drug use; Suicidality (ideation, ideation with plan during year prior; attempt requiring hospitalisation in year prior, lifetime ideation and attempts)
van der Miesen 2020	No	No	No	No	Yes	Yes	No	No	No	No	No	Emotional and behavioral problem (YSR); Self-harm/suicidality (YSR items 18 and 91) ; Poor peer relations (YSR items 25, 38 and 48)

Supplementary table S4 - Critical appraisal summary by question

Study ID	Study design	NOS total score	NOS Q1 representative of population	NOS Q1 score	NOS Q8 adequacy of follow-up	NOS Q8 score	NOS Q3 Ascertainment of treatment exposure	NOS Q3 score	NOS Q2 Selection of non-exposed group	NOS Q2 score	NOS Q5 comparability of cohorts (part 1 - controls for key demographics; part 2 - controls for co-interventions)	NOS Q5 part 1 score	NOS Q5b part 2 score	NOS Q7 follow-up duration	NOS Q7 score	NOS Q6 assessment of outcome	NOS Q6 score	NOS Q4 Demonstration that outcome of interest not present at study start	NOS Q4 score
Cohort																			
Achille 2020	Prospective cohort study	4	States that vast majority of eligible population entered study, but no values or percentages provided. Recruited from single clinic.	0	116 participants entered study - 50 who completed questionnaires reported on. No information on those lost to follow-up.	0	Information in paper provides confidence that clinic data used.	1	Participants who had received puberty blockers were compared to participants who've received nothing at all or only cross sex-hormones.	1	Controlled for outcome at baseline, psychiatric medication and psychotherapy. Separate analysis by gender. Did not control for age or report differences between groups. Did not control for either hormone treatment.	0.5	0.5	Follow-up not linked to treatment duration. Exposure to treatment at any time used as variable - not duration.	0	Validated scales designed for self-completion.	1	N/A	
Akgul 2019	Retrospective cohort study	3	Ten out of thirty participants excluded due to not being able to be matched with controls.	0	For most outcomes, no information given on follow-up rates. For the satisfaction outcome, the follow-up rate was less than 90%.	0	Procedure codes for LNG-IUS insertion used in medical records.	1	Matched with adolescents who received the 52 mg LNG-IUS primarily for noncontraceptive purposes (seen at the same subspecialty clinic by many of the same providers).	0.5	Participants were matched on age. Only participants assigned female at birth were included. Unadjusted analyses were used.	1	0	Insufficient information given to assess follow-up duration.	0	Mixture of clinical record data and Likert scales to measure satisfaction.	0.5	N/A	
Becker-Hebly 2020	Retrospective cohort study	3	434 children seen by clinic, 204 with baseline data and eligible, and invited to take part. Large proportion not included. Single clinic.	0	Response rate for follow-up 37% (n=75).	0	Self-reported treatment path then controlled via clinicians' reports.	1	Those not treated with hormones from same clinic sample.	1	Did not control for gender / sex, other treatments or outcome at baseline. Used age-adjusted population norms to compare outcomes. Did not control for distribution in intervention group.	0	0	Treatment started after baseline but duration and start of treatment not reported or included in analysis.	0	Validated scales - combination of self-report and clinician-report.	1	N/A	
Costa 2015	Prospective cohort study	5.5	National clinic. Included all eligible adolescents.	1	None lost at 12 months, around half lost at 18 months - reasons not reported	0.5	Information in paper provides confidence that clinic data used.	1	Drawn from same source; plus comparison to adolescents without observed psychological / psychiatric symptoms.	1	Split analysis by delayed eligible and immediately eligible, presented some analysis re: natal sex differences but main analysis didn't control for this.	0	0	Sufficient follow-up period - 12 month follow-up was reported as 6 months of puberty suppression.	1	Validated measures used.	1	N/A	
de Nie 2022	Retrospective cohort study	5	Single clinic population - only those who underwent bilateral orchiectomy combined with vaginoplasty were eligible - random sample taken for study.	0	Of the 263 sampled, 49 were then excluded due to no tissue being stored or no testicular parenchyma on slides.	1	Authors state data was collected from medical records.	1	Adults presenting to the same clinic who underwent bilateral orchiectomy combined with vaginoplasty.	0.5	Study participants are birth-registered males only, groups are split by puberty stage (Tanner stage 2-3; Tanner stage 4-5; Adult). Study does not control for use of medications such as contraceptive pill.	1	0	Information on follow-up period not explicitly given. Indications some participants would have had a duration of medical treatment longer than 12 months.	0.5	Detailed information on sample testing given.	1	N/A	
Grimstad 2021b	Retrospective cohort study	3.5	Single-clinic population, very small number excluded due to incomplete height data (6/195 eligible patients).	0.5	Only those with complete height data were included, those had not reached adult height by the end of the study were excluded.	0.5	Data obtained from medical records.	1	Drawn from same source.	1	Only participants who were assigned a female sex at birth were included. Unadjusted analyses were carried out.	0.5	0	No information provided on time between start of treatment and measurement of final height.	0	Height measured in triplicate at each clinic visit. Participants were defined as growing if they demonstrated a growth velocity of 0.5cm per year.	0	N/A	
Mejia-Otero 2021	Retrospective cohort study	4	Single-clinic - only included patients who had undergone blood tests at baseline and 2-12 months. No information on number excluded.	0	Only those with blood test data were included.	1	Retrospective review of medical records.	1	Adolescents with central precocious puberty. Substantial differences between groups in age and sex.	0	Separate analyses for males and females were carried out. Unadjusted analyses were used.	0.5	0	Mean time between onset of therapy and follow-up was 5.9 months (SD2.9). Patients were eligible if they'd had a blood test 2-12 months after starting treatment.	0.5	Retrospective review of medical records.	1	N/A	
Pine-Twaddell 2022	Retrospective cohort study	5	Two clinics. Participants without follow-up data were excluded.	0	Only participants with follow-up data were included.	1	Data was extracted from medical records.	1	Patients with central precocious puberty were selected from the same study clinics as the exposed group.	0.5	Separate analyses were carried out for males and females. No other covariates were adjusted for.	0.5	0	Baseline and single follow-up (17 to 65 months post-insertion).	1	All relevant study data were retrieved retrospectively from medical records.	1	N/A	
Schulmeister 2022	Prospective cohort study	5	Four large clinics in the US (different localities). Aimed to recruit all treated. No information given on consent rates, exclusions.	0.5	12 participants excluded from analysis due to not having a documented height at between 10-12 months of GnRHa treatment.	0	Information given on whether participant received implant or injection - medical records used.	1	Prepubertal adolescents (presumed not to have GD) not receiving hormonal intervention was drawn from the Bone Mineral Density in Childhood Study.	0.5	Analyses comparing exposed group to non-exposed group, stratified by sex and controlled for age. Other important covariates such as BMI, ethnicity and baseline hormones were used as covariates.	1	0	Follow-up carried out between 10-14 months post-treatment.	1	Anthropometric and laboratory data collected during clinical care were abstracted from the medical record.	1	N/A	
Tordoff 2022	Prospective cohort study	3.5	Single-clinic study. 30% of eligible patients did not take part.	0	Follow-up rates less than 90% at each follow-up timepoint.	0	Data on puberty suppression collected via self-report.	0	Drawn from same source as exposed population.	1	Gender, but not sex was controlled for as a confounder. Ethnicity was also controlled for. The analysis controlled for receipt of mental health therapy.	0.5	0.5	3, 6, 9, 12 month - follow-up not linked to treatment initiation but some participants with sufficient follow-up	0.5	Collected via validated scales.	1	N/A	
van de Grift 2020	Retrospective cohort study	5	Single-clinic study. Patients lost to follow-up (n=68) were excluded.	0	Only participants with complete follow-up data were included.	1	Registry and patient record data collection used.	1	Drawn from same source as exposed group.	1	Males and females were analysed separately. Unadjusted analyses were used.	0.5	0	Initiation of different therapies in treatment protocol indicate most participants followed up for considerable duration.	0.5	Data collected as part of routine clinical practice.	1	N/A	
Pre-post																			
Carmichael 2021	Prospective pre-post single group study	4.5	Included sequentially eligible from single clinic. 44 out of 48 who discussed the study took part.	0.5	Very few lost to 12 month follow-up. However, around half lost at 24 months.	0.5	Recruitment to study was for treatment in clinic - medical records data.	1	N/A		Sex / gender, puberty status at baseline controlled for in some analyses of continuous variable outcomes but not others. Co-interventions not controlled for.	0.5	0	Sufficient follow-up period.	1	Validated measures for psychosocial / mental health; validated approaches for physiologic measures.	1	N/A	
Chiniara 2018	Retrospective pre-post single group study	3.5	Single-clinic study, 15/218 excluded due to missing data.	0.5	Low follow-up rates reported.	0	Retrospective review of medical records.	1	N/A		Separate analyses were conducted by sex.	0.5	0	Repeat hormonal levels measured after 3.8 ± 1.9 months of initiation of GnRH-a therapy	0.5	Validated scales and clinical record data used.	1	N/A	
de Vries 2011	Prospective pre-post single group study	4	National clinic. 111 prescribed GnRHa. Participants first 70 adolescents who subsequently started hormones. Unclear who excluded were.	0.5	Not all 70 provided data. Response across questionnaires: CBCL, YSR: 54; BDI, TPI, STAI, CGAS, and UGS: 41; BIS: 57.	0	Information presented on start of treatment - medical records data.	1	N/A		Sex was controlled for. Study does not control for age/puberty stage or co-interventions.	0.5	0	Time between start of GnRHa and follow-up ranged between 0.42 and 5.06 years.	1	Validated measures used.	1	N/A	
de Vries 2014	Prospective pre-post single group study	3.5	National clinic. 111 prescribed GnRHa. 70 participants approached one-year post-surgery - 55 took part. Large proportion of eligible population missing.	0	Only participants with data at all waves were included. Numbers: CGAS 32, BDI 32, TPI 32, STAI 32, CBCL-ABCL 40, YSR-ASR 43. UGDS 33, BIS 45.	0	Information presented on start of treatment - medical records data.	1	N/A		Separate analyses were conducted by sex, and age was adjusted for.	1	0	Final follow-up took place one year after surgery.	1	All validated scales except 'self-constructed' objective measure of wellbeing.	0.5	N/A	
Delemarre-van de Waal 2006	Prospective pre-post single group study	2.5	Single clinic, inadequate information on response rates given.	0	Inadequate information on follow-up given.	0	Follow-up protocol integrated into clinical practice - medical records data.	1	N/A		No adjustment made for age, sex, co-interventions or sociodemographic confounders.	0	0	Participants were treated for two years or longer.	1	Clinical measurements presented, but no information given on how this information was obtained.	0.5	N/A	
Ghelani 2020	Retrospective pre-post single group study	4.5	National clinic. Only those with complete data included and excluded some based on confounding lifestyle factors such as anorexia or bodybuilding.	0	Only those with complete data were included.	1	Data was collected as part of routine clinical practice - medical records data.	1	N/A		Seprate analyses carried out by sex. No adjustment made for age or co-interventions or sociodemographic confounders.	0.5	0	Follow-up was from treatment and up until 12 months.	1	Whole-body impedance measured using Tanita Body Composition Analyser. SDS for lean mass - UK reference data. Height, weight and BMI SDS - UK90 data.	1	N/A	
Hisle-Gorman 2021	Retrospective pre-post single group study	4	All eligible participants were included from the Military Health System.	0.5	No information given on missing data.	0	Obtained from pharmacy records.	1	N/A		Analyses adjusted for age and sex. Some important covariates such as parental rank adjusted for.	1	0	Median follow-up post-treatment was 1.5 years (IQR 0.7 to 2.7).	0.5	Outcome data collected from Military Healthcare Data Repository.	1	N/A	
Joseph 2019	Retrospective pre-post single group study	5	National clinic, participants without complete data were excluded, with no information given on how many were excluded.	0.5	Only those with complete data were included in the study.	1	Data was collected as part of routine clinical practice.	1	N/A		Separate analyses were carried out for sex. No other covariates were adjusted for.	0.5	0	All participants were followed up for at least one year post starting GnRHA treatment.	1	Assessed as part of clinical practice.	1	N/A	
Khatchadourian 2014	Retrospective pre-post single group study	3	Single-clinic study, included all patients.	0.5	No information given on missing data.	0	Data obtained from clinical records.	1	N/A		Descriptive summaries were presented separately for males and females.	0.5	0	No information given on time between start of treatment and assesment of outcomes.	0	Clinical outcomes assessed as part of routine medical care.	1	N/A	
Klaver 2018	Retrospective pre-post single group study	3	Single-clinic study, participants without whole-body DXA excluded (n=5). 66 participants excluded on different treatment protocol - reason unclear.	0	No information given on follow-up rates.	0	Data collected from medical records.	1	N/A		Analyses were carried out separately for sex. No other covariates were adjusted for.	0.5	0	Duration of GnRHA monotherapy median 2.1 years (IQR 1.0-2.8) for birth-registered males and median 1.0 (0.5-2.9) for birth-registered females.	0.5	Collected from medical records.	1	N/A	
Klaver 2020	Retrospective pre-post single group study	3.5	Single-clinic study. Excluded those without whole-body DXA and with no consultation in early adulthood. No numbers reported.	0	No information given on follow-up timepoint.	0	Data collected from medical records.	1	N/A		Separate analyses were carried out for males and females. No other covariates were adjusted for.	0.5	0	At addition of cross sex hormones - sufficient follow-up indicated by age at starting this.	1	Collected from medical records.	1	N/A	
Klink 2015	Retrospective pre-post single group study	4	Single-clinic study. Only included participants with data available at each timepoint. Number of patients excluded not reported.	0	High follow-up rates at final timepoint.	1	Detailed information on timing of treatment given.	1	N/A		Separate analyses were carried out for males and females. No other covariates were adjusted for.	0.5	0	At addition of cross sex hormones - sufficient follow-up for most participants but not all.	0.5	Collected from medical records.	1	N/A	
Kuper 2020	Prospective pre-post single group study	2.5	Single-clinic study that excluded 22/209 patients due to missing follow-up.	0.5	Despite those with follow-up data being excluded, less than 90% of participants included in analysis of each outcome.	0	Clinician data were entered into a research database.	1	N/A		Hypothesis testing (not separately by age or sex). Regression controlling for demographic and treatment variables planned, but no correlations found between change scores and demographic/treatment variables.	0	0	No information given on time between start of puberty suppresion and follow-up.	0	Validated scales used.	1	N/A	
Lynch 2015	Retrospective pre-post single group study	2.5	Single-clinic study, not enough information given to ascertain proportion of eligible patients included in study.	0	Study makes reference to participants being lost to follow-up, but does not present information on follow-up rates.	0	Clinical data extracted from medical records.	1	N/A		Narrative summary presented.	0	0	Baseline and relevant data from clinic follow-up at 1 and 6-monthly intervals (duration of follow-up not reported)	0.5	Extracted from medical records.	1	N/A	
Navabi 2021	Retrospective pre-post single group study	3	Single-clinic study. Only participants with at least one DXA measurement were included.	0	Considerable number not included in analysis.	0	Retrospective review of medical records.	1	N/A		Separate analyses carried out for males and females. Unadjusted analyses used.	0.5	0	Baseline and single follow-up (median 352.5 median days after GnRHa initiation, range 188-676 days)	0.5	Outcomes collected via DXA.	1	N/A	
Neyman 2019	Retrospective pre-post single group study	3	Single-clinic study. No information given on eligibility.	0	Less than 90% follow-up for some outcomes.	0	Collected from medical records.	1	N/A		Narrative summary presented. Only birth-registered males were included.	0.5	0	Time between baseline and first follow-up ranged from 2.18 to 8 months.	0.5	Extracted from medical records.	1	N/A	
Olson-Kennedy 2021	Retrospective pre-post single group study	4	Small number of clinics. Participants excluded if they did not have data before and after histrelin implant placement. No information provided.	0	Only one participants excluded from one analysis.	1	Charts of existing patients who had a histrelin implant in place were reviewed.	1	N/A		Stratified analyses by sex were carried out. No other covariates were adjusted for.	0.5	0	Baseline and single follow-up (2-12 months after treatment)	0.5	Abstracted from the medical record and from the larger study data pool.	1	N/A	
Peri 2020	Retrospective pre-post single group study	5	Participants ecruited from a national clinic, only 3 participants were excluded due to missing BP data.	1	Those with missing data were excluded from the study.	1	Medical records data used to identify those on treatment.	1	N/A		Only birth-registered females were included in the study. No information is given on adjustment for baseline variables.	0.5	0	Baseline, and follow-ups at end of GnRHa treatment (average 3 months SD 1).	0.5	Most measures extracted from medical records. BP measured during clinic visit using Welch Allyn Vital Signs Monitor VSM 300 (Welch Allyn, Inc., Beaverton, OR)	1	N/A	

Perl 2021	Retrospective pre-post single group study	5	Participants were recruited from national clinic, only 1 participant was excluded due to missing BP data.	1	Those with missing data were excluded from the study.	1	Data extracted from medical records.	1	N/A		Only birth-registered males were included in the study. Unadjusted analyses were used.	0.5	0	Baseline, and follow-ups at end of GnRHa treatment (mean 9 months SD 6).	0.5	Most measures extracted from medical records. BP measured during clinic visit using Welch Allyn Vital Signs Monitor VSM 300 (Welch Allyn, Inc., Beaverton, OR)	1	N/A	
Russell 2021	Retrospective pre-post single group study	5	Two national clinics. Participants with incomplete outcome data were excluded (27/122).	0.5	Only participants with complete outcome data were included.	1	Details on GnRHa consent given.	1	N/A		The analysis adjusted for sex. No other covariates were adjusted for.	0.5	0	Baseline and 12 month follow-up (plus / minus 3 months)	1	Validated scale used.	1	N/A	
Schagen 2016	Prospective pre-post single group study	4.5	National clinic. All eligible.	1	Low follow-up rates reported.	0	Participants excluded baised on treatment duration and receipt of medication, which implies access to medical records.	1	N/A		Separate analyses carried out for males and females. Unadjusted analyses used.	0.5	0	Baseline, and 3, 6, 12, 24 and 36 months	1	Detailed information given on laboratory investigations and use DXA provided.	1	N/A	
Schagen 2018	Prospective pre-post single group study	4	National clinic. No information on consent rates but selected from all eligible.	0.5	No information given on follow-up rates.	0	Details on duration of treatment provided.	1	N/A		Separate analyses carried out for males and females. No other covariates were adjusted for.	0.5	0	Analyses used data up to two years post-treatment.	1	Detailed information given on laboratory investigations.	1	N/A	
Schagen 2020	Prospective pre-post single group study	5	National clinic. Small number excluded due to DXA scans not being available at the start of GnRHa.	1	No information given on missing data rates at follow-up.	0	Detailed treatment protocol provided.	1	N/A		Analyses adjusted for pubertal stage and sex. No other covariates were adjusted for.	1	0	Analyses presented up to 36 months of treatment.	1	Dual-energy x-ray absorptiometry (DXA) using Hologic QDR 4500. Markers of bone formation and resorption used fasting blood samples, drawn on day of DXA.	1	N/A	
Segev-Becker 2020	Retrospective pre-post single group study	3	National clinic. Consecutive participants recruited.	1	No information given on follow-up rates.	0	Information on treatment delivery presented.	1	N/A		Some but not all descriptive summaries stratified by gender/sex. Participants were split into pre-pubertal and pubertal groups.	0	0	No information given on follow-up period.	0	Data collected retrospectively from clinical records.	1	N/A	
Stoffers 2019	Retrospective pre-post single group study	4	Single-clinic study. Only 2/64 participants declined to participate.	0.5	High rates of follow-up at 6 months post-treatment, but low rates at 12 and 24 months post-treatment.	0.5	Information provides confidence that medical data were used.	1	N/A		Only birth-registered females were included. Unadjusted analyses were used.	0.5	0	The median duration of follow-up was 12 months (range 5-33 months).	0.5	Data collected via chart review.	1	N/A	
Tack 2016	Retrospective pre-post single group study	4	Single-centre study in country with three clinics. Small number (5 out of 43) excluded due to missing laboratory data.	0.5	No information given on follow-up rates at each timepoint.	0	Information provides confidence that medical data were used.	1	N/A		Only birth-registered female adolescents were included. Unadjusted analyses were used.	0.5	0	Data collected 6 and 12 months after start of lynestrenol,	1	Data collected as part of clinical follow-up.	1	N/A	
Tack 2017	Retrospective pre-post single group study	4.5	Single-centre study in country with three clinics. All those who received CA for at least 6 months during study period were included.	1	No information given on follow-up rates at each timepoint.	0	Information provided on age at start of treatment - medical records data.	1	N/A		Only birth-registered males were included in the study. Unadjusted analyses were used.	0.5	0	Baseline, 6 and 12 month follow-up with Cyproterone acetate.	1	Data collected as part of clinical follow-up.	1	N/A	
Tack 2018	Prospective pre-post single group study	3	Single-centre study in a country with three clinics. No information on eligibility or consent rates.	0	No information given on follow-up rates at each timepoint.	0	Mean age at start of treatment given - medical records data.	1	N/A		Separate analyses were carried out for males and females. Unadjusted analyses were used.	0.5	0	The mean time interval between both examinations was 11.64 (4 to 40) months in birth-registered females and 10.57 (5 to 31) months in birth-registered males.	0.5	Detailed information on assessment of outcomes provided.	1	N/A	
van der Loos 2021	Retrospective pre-post single group study	4.5	Single-clinic study. 123 excluded due to DXA not being available.	0	Only participants who had a DXA were included.	1	Information presented on start of treatment - medical records data.	1			Separate analyses were carried out for males and females. Analyses were stratified by puberty stage.	1	0	Some participants received GnRHA alone for less than one year.	0.5	Detailed information on DXA testing given.	1	N/A	
Vlot 2017	Retrospective pre-post single group study	3.5	Single-clinic study. A large number of eligible participants were excluded due to incomplete data.	0	Data indicates that more than 10% were missing data for outcomes.	0	Data collection took place at point of treatment.	1	N/A		Analysis stratified on sex and bone age. Unadjusted analyses were used.	1	0	Age ranges given at each timepoint indicate follow-up sufficient for some patients.	0.5	Detailed information on DXA testing provided.	1	N/A	
Waldner 2022	Retrospective pre-post single group study	4.5	15 out of 48 patients excluded due to incomplete data.	0	Only participants with complete data were included.	1	Retrospective chart review of medical records.	1	N/A		The mean post-Lupron QTc was presented separately for patients assigned male and assigned female at birth.	0.5	0	Stated that time between baseline and follow-up was at least 6 weeks, but no further information given.	0	Assessed as part of clinical practice.	1	Table 3 shows QTc range was 384-454ms.	1
Cross-sectional																							
Arcelus 2016	Cross-sectional study with controls	3.5	299 eligible patients - 31 did not answer questions regarding NSSI and were excluded. National clinic.	1	More than 10% excluded from analysis - no information provided on those or explanation.	0	Self-reported data on treatments received prior to assessment at adult clinic.	0	Those not treated with hormones from same clinic sample.	1	Controlled for gender, self-esteem, transphobia, interpersonal problems, social support.	0.5	0	N/A		Validated assessment tools used.	1	N/A	
Burke 2020	Cross-sectional study with controls	5	Single clinic population - no information provided about recruitment and response, or number of eligible individuals.	0	All participants included in analysis.	1	Clinic data used to select / categorise treatment groups.	1	Two control groups - treatment naive adolescents from same source and adolescent controls, which were appropriate for examining this outcome.	1	Controlled for puberty stage / age, sex assigned at birth but no other treatments. Cross-sectional so no baseline control.	1	0	N/A		Standard assessment - equipment and procedure explained in full - same applied to all participants (treatments and controls).	1	N/A	
Fontanari 2020	Cross-sectional study with controls	3	Self-selecting survey.	0	All participants who completed survey were included in the analysis.	1	Self-report.	0	Non-exposed group from same survey sample.	1	No adjustment made for age, sex, co-interventions or sociodemographic confounders.	0	0	N/A		Validated scales used.	1	N/A	
Nokoff 2021	Cross-sectional study with controls	3.5	Single-clinic study. No information provided on consent rate.	0	All participants included in analysis according to table data.	1	No information provided on ascertainment of treatment exposure.	0	Adolescents from Colorado RESistance to InSulin in Type 1 ANd Type 2 diabetes (RESISTANT) study and the Health Influences in Puberty (HIP) study.	0.5	Separate analyses were carried out for sex, and analyses matched on age. Analyses also matched on BMI.	1	0	N/A		Body composition measured using DXA and detailed information on laboratory assays provided.	1	N/A	
Staphorsius 2015	Cross-sectional study with controls	2.5	Single-clinic study. No information given on consent rates.	0	Considerable number removed from analysis.	0	Information on treatment delivery presented.	1	Self-selective sample from friends and siblings of participants with GD.	0	ANOVA was used to examine differences in accuracy and reaction time. An analysis using ANCOVA examined the effect of IQ on group differences.	0.5	0	N/A		The Tower of London Test was used. Detailed information is provided fMRI analysis.	1	N/A	
Strang 2022	Cross-sectional study with controls	4	Shared study protocol in two locations. No information given on consent rates.	0	Only those with complete report forms were included.	1	Collected through parent and self-report, and only verified when dates not fully recalled by families.	0	Drawn from same population as exposed group.	1	Analyses adjusted for assigned sex and age. Membership in the puberty suppression group included those who had ever taken it, including those in current receipt and those who were now taking cross-sex hormones.	1	0	N/A		Validated scales and evaluations used.	1	N/A	
Turban 2020	Cross-sectional study with controls	3	National survey covering all 50 states in collaboration with 400+ lesbian, gay, bisexual and transgender organisations.	1	No information given on number of participants excluded from analyses due to missing data.	0	Self-reported by participants.	0	Drawn from same population as exposed group.	1	Age and sex were not adjusted for. Education level, employment status, and total household income were adjusted for.	0.5	0	N/A		One validated scale used, the rest appear to be bespoke for the study.	0.5	N/A	
van der Miesen 2020	Cross-sectional study with controls	5.5	Nearly all patients included from a national service.	1	Only participants who completed the questionnaire were included.	1	Questionnaires were completed during clinical assessments.	1	Group with GD who had not received puberty suppressants drawn from same source as exposed group.	1	An analysis controling for gender and age confirmed the group effects.	1	0	N/A		A validated scale was used (YSR). An ad hoc peer relations scale was created using 3 items of the YSR.	0.5	N/A	

EXHIBIT 89

Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: a systematic review

Jo Taylor , Alex Mitchell, Ruth Hall, Trilby Langton, Lorna Fraser, Catherine Elizabeth Hewitt

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/archdischild-2023-326670).

Department of Health Sciences, University of York, York, YO10 5DD, UK

Correspondence to
Dr Jo Taylor, Department of Health Sciences, University of York, York, YO10 5DD, UK; dohs-gender-research@york.ac.uk

Received 30 November 2023
Accepted 16 February 2024

Linked

► https://doi.org/10.1136/archdischild-2023-326112
► https://doi.org/10.1136/archdischild-2023-326347
► https://doi.org/10.1136/archdischild-2023-326348
► https://doi.org/10.1136/archdischild-2023-326500
► https://doi.org/10.1136/archdischild-2023-326499
► https://doi.org/10.1136/archdischild-2023-326760
► https://doi.org/10.1136/archdischild-2023-326681
► https://doi.org/10.1136/archdischild-2023-326669

To cite: Taylor J, Mitchell A, Hall R, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2023-326670

ABSTRACT

Background Clinical guidelines outline the use of hormones for masculinisation/feminisation in adolescents experiencing gender dysphoria or incongruence. Robust evidence concerning risks and benefits is lacking. There is a need to aggregate evidence as research becomes available.

Aim Identify and synthesise studies assessing the outcomes of hormones for masculinisation/feminisation in adolescents experiencing gender dysphoria/incongruence.

Methods Systematic review and narrative synthesis. Database searches (MEDLINE, Embase, CINAHL, PsycINFO, Web of Science) were performed in April 2022, with results assessed independently by two reviewers. An adapted version of the Newcastle-Ottawa Scale for Cohort Studies was used to assess study quality. Moderate- and high-quality studies were synthesised.

Results 12 cohort, 9 cross-sectional and 32 pre–post studies were included (n=53). One cohort study was high-quality. Other studies were moderate (n=33) and low-quality (n=19). Synthesis of high and moderate-quality studies showed consistent evidence demonstrating induction of puberty, although with varying feminising/masculinising effects. There was limited evidence regarding gender dysphoria, body satisfaction, psychosocial and cognitive outcomes, and fertility. Evidence from mainly pre–post studies with 12-month follow-up showed improvements in psychological outcomes. Inconsistent results were observed for height/growth, bone health and cardiometabolic effects. Most studies included adolescents who received puberty suppression, making it difficult to determine the effects of hormones alone.

Conclusions There is a lack of high-quality research assessing the use of hormones in adolescents experiencing gender dysphoria/incongruence. Moderate-quality evidence suggests mental health may be improved during treatment, but robust study is still required. For other outcomes, no conclusions can be drawn. More recent studies published since April 2022 until January 2024 also support the conclusions of this review.

PROSPERO registration number: CRD42021289659.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Increasing numbers of children and adolescents experiencing gender dysphoria/incongruence are being referred to specialist gender services.
⇒ National and international guidelines outline the use of hormones for masculinisation or feminisation in adolescents experiencing gender dysphoria/incongruence.
⇒ Several systematic reviews report a limited evidence base for initiating these treatments during adolescence, and uncertainty about benefits, risks and long-term effects.

WHAT THIS STUDY ADDS

⇒ There is a lack of high-quality research assessing the outcomes of hormones for masculinisation or feminisation in adolescents experiencing gender dysphoria/incongruence.
⇒ There is limited or inconsistent evidence regarding gender dysphoria, body satisfaction, psychosocial and cognitive outcomes, fertility, height/growth, bone health and cardiometabolic effects.
⇒ There is moderate-quality evidence from mainly pre–post studies that hormone treatment may in the short-term improve psychological health.

HOW THIS STUDY MIGHT AFFECT RESEARCH, POLICY OR PRACTICE

⇒ There is a lack of high-quality evidence to support the initiation of hormones for masculinisation or feminisation in adolescents experiencing gender dysphoria/incongruence. Agreement on core outcomes and high-quality research are needed.

INTRODUCTION

Over the last 10-15 years, there has been a rise in the number of children and adolescents being referred to specialist paediatric gender services.[1 2] Clinical guidelines for managing gender dysphoria/incongruence recommend assessment and psychosocial care to alleviate gender-related distress and any co-occurring difficulties. For pubertal adolescents, medications to suppress puberty in early to mid-adolescence followed by hormones that induce feminisation/masculinisation are outlined in what is described as a staged model of care. These interventions, often referred to as cross-sex hormones or gender-affirming hormones, comprise testosterone for birth-registered females and oestrogen for birth-registered males, which is sometimes given in combination with gonadotropin-releasing

hormone analogues (GnRH-a), progestins, or other medications with anti-androgenic properties.[3 4]

In early treatment protocols and clinical guidelines, treatments for feminisation/masculinisation were offered from age 16, and mainly in adulthood.[5 6] Over the last decade, guidelines have broadened these criteria, for example, removing minimum age[4 7 8] and making changes to the requirement of a diagnosis of gender dysphoria (Diagnostic and Statistical Manual of Mental Disorders 5th edition, DSM-5), being replaced by gender incongruence (International Classification of Diseases 11th revision, ICD-11).[3] In a study of 1766 children and adolescents receiving care at a national gender service in the Netherlands (1997–2018), 202 birth-registered males and 454 birth-registered females received hormones at a median age of 16.0 (IQR 15.5–17.1) and 16.7 (16.0–17.5), respectively.[9] In the UK, the mean age of consent for treatment was 17.3 (SD 0.1).[10]

Robust evidence concerning the risks and benefits of initiating hormones during adolescence is lacking. Several systematic reviews have found mainly low-quality or limited evidence.[11–20] Due to the proliferation of research in this area, there is a need to update systematic reviews as evidence becomes available. This systematic review aims to synthesise evidence published up to April 2022 that reports outcomes of feminising/masculinising hormones in adolescents experiencing gender dysphoria/incongruence.

METHODS

The review forms part of a linked series examining the epidemiology, care pathways, outcomes and experiences of children and adolescents experiencing gender dysphoria/incongruence and is reported according to Preferred Reporting Items for Systematic review and Meta-Analysis guidelines.[21] The protocol was registered on PROSPERO (CRD42021289659).[22]

Search strategy

A single search strategy was used to identify studies comprising two combined concepts: 'children', which included all terms for children and adolescents; and 'gender dysphoria', which included associated terms such as gender-related distress and gender incongruence, and gender identity terms including transgender, gender diverse and non-binary.

MEDLINE (online supplemental table S1), Embase and PsycINFO through OVID, CINAHL Complete through EBSCO and Web of Science (Social Science Citation Index) were searched (13–23 May 2021; updated 27 April 2022).

Reference lists of included studies and relevant systematic reviews were assessed.[11–20]

Inclusion criteria

The review included published research that reported outcomes of hormones used for masculinisation/feminisation in adolescents experiencing gender dysphoria/incongruence (table 1).

Selection process

Results of all searches were uploaded to Covidence[23] and screened independently by two reviewers. Full texts of potentially relevant articles were reviewed against inclusion criteria by two reviewers independently. Disagreements were resolved through discussion or by a third reviewer.

Table 1 Inclusion and exclusion criteria

Population	Children and/or adolescents aged 0–18 experiencing gender dysphoria, gender incongruence or referral to a gender identity service. Studies of adults or a mixed population of adolescents and adults where treatment was initiated in adolescence (<18).
Intervention	Masculinising or feminising hormone treatments.
Comparator	Any or none.
Outcomes	Pubertal development, side effects, gender dysphoria or other gender-related outcomes, psychological health, physical health, psychosocial outcomes, cognitive outcomes, fertility.
Study design	Clinical trials, cohort studies, case–control studies, cross-sectional studies, pre–post single-group design studies or service evaluations that provided treatment outcome data. Case studies and case series were excluded.
Publication	Studies published in the English language in a peer-reviewed journal. Conference abstracts were excluded.

Data extraction

Data on study characteristics, methods and outcomes were extracted into pre-piloted data extraction templates by one reviewer and second-checked by another.

Study quality

Critical appraisal was undertaken by two reviewers independently, with consensus reached through discussion or involvement of a third reviewer.

Quality was assessed using a modified version (online supplemental file 1) of the Newcastle-Ottawa Scale for cohort studies, a validated scale of eight items covering three domains: selection, comparability and outcome.[24] Scale modification included not scoring certain question(s) for cross-sectional or single-group designs, or particular outcomes; specification of key confounders to assess comparability of cohorts; guidance regarding sufficiency of follow-up; and use of numerical scores for items and overall (maximum score 9 for cohorts, 8 for pre–post and cross-sectional studies with a comparator). Total scores are presented as percentages to account for different total scores (≤50% low, >50–75% moderate, >75% high quality).

Synthesis

Narrative synthesis methods were used because of heterogeneity in study design, intervention, comparator, outcome and measurement. Low-quality studies were excluded from the synthesis due to the high risk of bias. For studies that reported outcomes for both puberty suppression and hormones, only the findings relating to hormones were synthesised.

Outcomes were grouped into distinct and clinically meaningful categories for synthesis, based on what had been measured across the studies in addition to the a priori categories informing the review. Care was taken to differentiate between different study designs, comparators and interventions. Where possible, potential differences by birth-registered sex, and treatment duration/initiation were examined.

RESULTS

Database searches yielded 28 147 records, 3181 of which were identified as potentially relevant for the linked systematic reviews, and full texts reviewed. From these, 53 studies met the inclusion criteria for this review (figure 1).

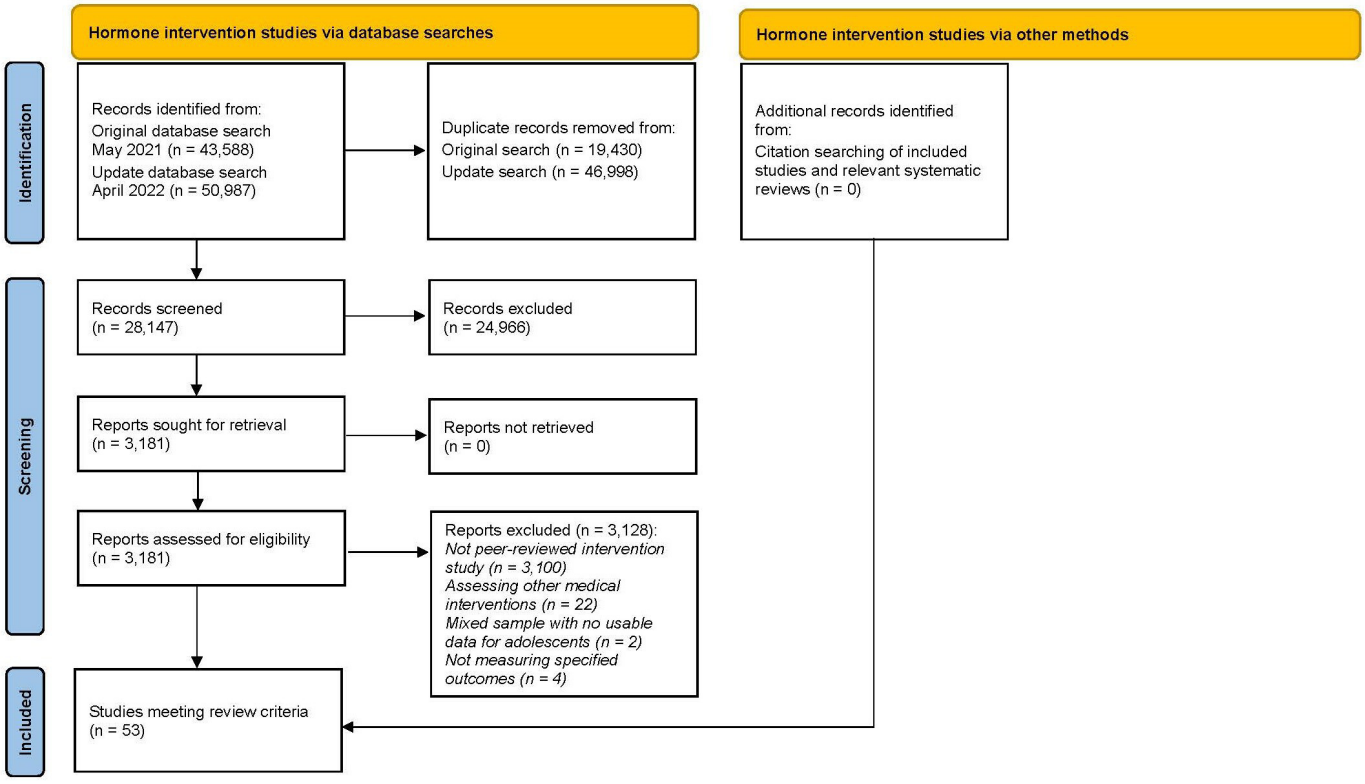


Figure 1 Study flow diagram.

Study characteristics

Studies were published from 2006 to 2022 (with 60% from 2020 to 2022 (n=32)), and conducted in the Netherlands (n=17),[25–41] US (n=24),[42–65] Israel (n=3),[66–68] Belgium (n=2),[69 70] Canada (n=2)[71 72] and one in Brazil,[73] Finland,[74] Germany,[75] Spain[76] and the UK[77] (online supplemental table S2).

Of the 53 studies, 12 were cohorts comparing adolescents experiencing gender dysphoria/incongruence receiving hormones with a comparator,[34 37–39 42 43 46 49 54 64 75 76] 9 cross-sectional with comparator[25 45 50 51 57 60 65 73 77] and 32 pre–post designs.[26–33 35 36 40 41 44 47 48 52 53 55 56 58 59 61–63 66–72 74] Over half of the studies (n=30) used retrospective chart review.

All but five studies recruited adolescents experiencing gender dysphoria/incongruence from specialist gender or endocrinology services: 46 from single clinics (in Belgium, Israel, Netherlands and the UK these were large regional/national services), and 2 from multiple US clinics. Of the remaining five, four were US studies (national survey recruiting via community settings,[65] clinical and community settings,[45] social media platforms,[50] US Military Healthcare Data Repository[47]). The final study from Brazil recruited via Facebook.[73]

Overall, the studies included 40 906 participants, of which 22 192 were adolescents experiencing gender dysphoria/incongruence (8164 received hormone treatments and 14 028 did not), and 18 714 comparators. Comparator groups included adolescents who had either not received hormones or received it in adulthood[34 39 42 43 45 46 49–51 65 73 75 78]; adolescents not experiencing gender dysphoria/incongruence[37 38 57 60 64 76]; both comparators[25]; or studies comparing those receiving hormones alone with those receiving it in combination with GnRH-a/progestins/anti-androgens.[54]

The most frequently reported outcomes were physical health outcomes (n=29) and puberty development (n=25) (figure 2, online supplemental table S3). Side effects, bone health and fertility were measured in six, five and one study, respectively. Psychological health was measured in 15 studies, psychosocial in 7 and cognitive/neurodevelopmental outcomes in 4. Gender-related outcomes and body image were each measured in three studies.

Study quality

One cohort study measuring side effects only was rated as high-quality,[54] 33 were moderate[25 30–41 45 47 48 50–53 55 56 59–63 66 67 69 70 74 76] and 19 low.[26–29 42–44 46 49 57 58 64 65 68 71–73 75 77] Of the 12 cohort studies, (the only studies to include a comparator group and assess outcomes over time), 6 were rated as high or moderate quality (figure 2, online supplemental table S4).[34 37–39 54 76]

In most studies, there were concerns about the representativeness of the population due to single-site recruitment, selective inclusion and/or poor reporting of the eligible population. In the 21 studies including a comparator, most did not report or control for key differences between groups, and only 6 used matched controls.[25 37 38 60 64 76] Most studies presented results separately by birth-registered sex or controlled for this, but few controlled for age, Tanner stage or co-interventions.

Overall, studies used appropriate methods to ascertain exposure and assess outcomes. Follow-up was adequate in 22 studies, with others not reporting clear information, or follow-up varying between participants or not linked to treatment initiation. Missing data at follow-up/analysis or poor reporting of this affected many studies.

Three studies did not report separate outcomes for adolescents receiving puberty suppression or hormones (one was moderate quality and excluded from synthesis).[47 73 77] One moderate-quality study assessing the amplitude of click-evoked otoacoustic emissions was excluded from the synthesis due to not being clinically relevant.[25]

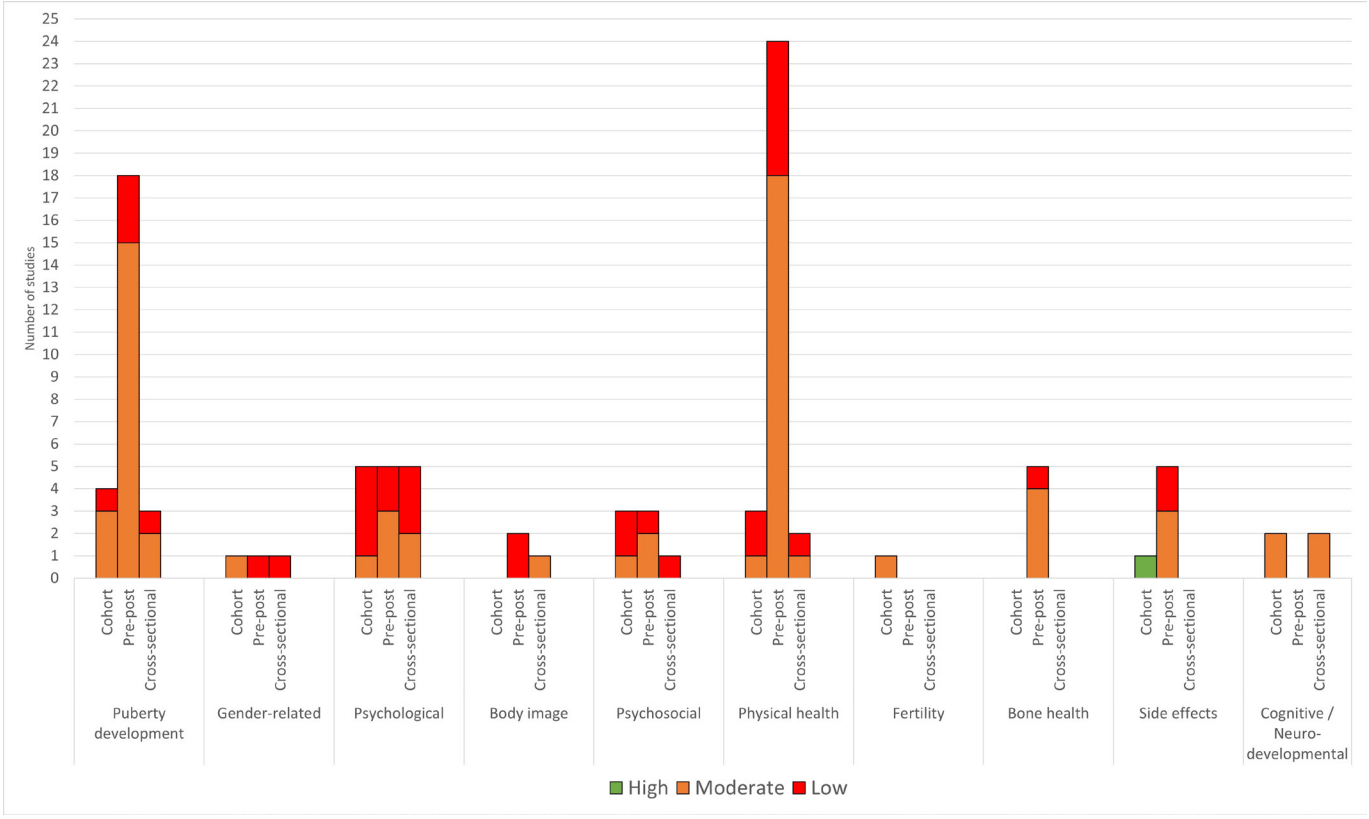


Figure 2 Outcome categories by study quality and design.

Synthesis of outcomes

Gender dysphoria and body satisfaction

One cohort study measured gender dysphoria pre–post, and reported a reduction in dysphoria with no participants in clinical range at follow-up.[76] One cross-sectional study measured body satisfaction in birth-registered females and reported lower dissatisfaction in those receiving hormone treatment compared with those who had not[51] (online supplemental table S5).

Psychological health

Five studies (one cohort,[76] two pre–post[48 74] and two cross-sectional[50 51]) measured psychological health. In four studies, participants had received hormones for ~12 months at follow-up. One cross-sectional study did not report treatment duration.[50] Reported outcomes were depression (n=4), anxiety (n=3), suicide and/or self-harm (n=4), need for specialist-level psychiatric treatment for different mental health difficulties (n=1) and internalising and externalising symptoms (n=1) (online supplemental table S5).

Studies found a reduction in depression and anxiety at follow-up (cohort[76]) and for birth-registered females receiving hormones compared with females not receiving hormones (cross-sectional[51]), but levels were higher when compared with adolescents not experiencing gender dysphoria/incongruence (cohort[76]). Lower treatment needs for depression and anxiety were reported after treatment in a pre–post study.[74] A cross-sectional study reported lower levels of depression in adolescents who had received hormones compared with those who had wanted hormones but had not received them.[50]

A pre–post study found no changes in treatment need for conduct problems, psychotic symptoms/psychosis, substance abuse, autism spectrum condition, attention-deficit hyperactivity disorder or eating disorders,[74] but two pre–post studies found a reduction in treatment needs for (or lower levels of) suicidality/self-harm.[48 74] Two cross-sectional studies found conflicting results: those receiving hormones were less likely to have seriously considered/attempted suicide compared with adolescents not receiving hormones,[50] and in birth-registered females there was no difference between groups.[51]

One cohort study reported a significant decrease in total psychological difficulties and scores for hyperactivity, emotional and conduct problems, with fewer participants in borderline and abnormal ranges at follow-up.[76] Compared with adolescents not experiencing gender dysphoria/incongruence, psychological difficulties were higher at baseline but similar at follow-up.

Psychosocial functioning

A cohort study reported no change in family functioning or peer problems but more peer problems when compared with adolescents not experiencing gender dysphoria/incongruence.[76] A small improvement was reported in prosocial skills. A pre–post study measured peer relations, living arrangements, school/work participation, romantic involvement and competence in managing everyday matters, with the only changes being a decrease in participants living with parents/guardians at follow-up and a small decrease in normative peer relationships.[74] A pre–post study reported an increase in well-being after receipt of hormones[48] (online supplemental table S5).

Cognitive outcomes

Two cohort studies of birth-registered females assessed whether exogenous testosterone-induced changes reflect sex-based differences in brain activity. One study measured visuospatial working memory, and found no difference in performance between those treated and female and male controls not experiencing gender

dysphoria/incongruence, but did observe stronger frontal and parietal activation at follow-up in male controls and those treated.[38] The second study measured amygdala activation, observing slightly more rightward lateralisation following treatment, and similar lateralisation in those treated compared with female and male controls who did not change.[37]

Amygdala activation was also assessed in a cross-sectional study of birth-registered females, finding greater activation and increased connectivity between the amygdala and prefrontal cortex in those receiving hormones compared with those who had not.[51]

A cross-sectional study found those receiving hormones had better executive functioning, cognitive flexibility and working memory compared with a group not receiving hormones[45] (online supplemental table S5).

Physical health outcomes

Bone health

Four pre–post studies[30 32 33 36] measured bone health. Two reported an increase at follow-up in absolute measures of bone density and SD scores[32 33] (one included birth-registered females only[33]), and two reported no change in these and/or bone biomarkers, although these included small samples[30 36] (online supplemental table S6).

Cardiometabolic health

Body mass index (BMI) and/or a standardised measure (BMI SD/z score or percentile) was reported in 16 studies (1 cohort,[34] 14 pre–post[30 33 35 40 53 55 56 61–63 66 67 69 70] and 1 cross-sectional[60]), showing no change overall but some inconsistencies (online supplemental table S6).

For birth-registered males, one study reported an increase in SD score,[30] one a decrease[40] and two no change.[66 70] All reported no clinically significant change in BMI.[30 40 66 70] Four studies only reported BMI: three found no change[53 56 62] and one reported an increase for participants starting GnRH-a in early puberty prior to initiating hormones.[35]

For birth-registered females, two studies reported an increase in SD score[30 69] and four no change.[33 55 63 67] All but one of these, which found an increase in BMI as well as SD score,[69] reported no change in BMI.[33 55 63 67] Five studies only reported BMI: four found no change,[53 56 61 62] and one an increase in the early puberty group.[35]

A cross-sectional study of both sexes found no difference in BMI percentile between those receiving hormones compared with controls,[60] and a single cohort study found those who started hormones earlier had a lower BMI (although not clinically significant) than those who started treatment later.[34]

Seven pre–post studies assessed cholesterol markers: three reported a decrease in high-density lipoprotein (HDL),[33 53 55] one an increase[62 70] and three no change.[61 69 70] A cross-sectional study found that birth-registered females receiving hormones had lower HDL than controls, whereas birth-registered males had higher HDL than controls.[60]

Eight pre–post studies measured blood pressure[33 40 53 61 62 66 67] and one hypertension,[55] all reported no clinically significant change. One cross-sectional study found similar blood pressure in adolescents receiving hormones compared with adolescents not experiencing gender dysphoria/incongruence.[60]

Six studies measured HbA1c (glycated haemoglobin),[33 40 53 60 69 70] four glucose levels,[60 62 69 70] three fasting insulin[60 69 70] and two homeostatic model assessment (HOMA) index.[60 69] One cross-sectional study reported differences between birth-registered males and controls in the inverse of fasting insulin (lower) and HOMA insulin resistance (higher) compared with controls.[60] No changes were reported by other studies.

Other parameters

Twelve studies assessed other physiological parameters obtained from blood tests (11 pre–post[31 33 40 41 53 55 56 61 62 69 70] and one cross-sectional[60]; (online supplemental table S6)): dehydroepiandrosterone sulfate (n=3), androstenedione (n=2), creatinine (n=6), estimated glomerular filtration rate (n=1), prolactin (n=5), alanine transaminase (n=8), aspartate transaminase (n=8), g-glutamyl transferase (n=1), haematocrit (n=7), serum urea nitrogen (n=1), haemoglobin (n=7), potassium (n=1), vitamin D (n=1), thyroid stimulating hormone (n=3), free thyroxin (n=3), anti-Müllerian hormone (n=1), alkaline phosphatase (n=2), sex hormone binding globulin (n=4), free androgen index (n=1) and urea (n=1). For most outcomes there were no changes pre–post or differences between groups; where there were changes results were inconsistent.

One pre–post study found no occurrence of thrombosis after masculinising/feminising hormones.[59]

Pubertal development

Hormone levels

Fifteen studies measured hormone levels (2 cohort,[37 38] 12 pre–post[33 35 40 53 55 59 61 62 66 67 69 70] and 1 cross-sectional[60]), 7 studies in birth-registered females,[33 37 38 55 61 67 69] 3 in birth-registered males[40 66 70] and 5 both (online supplemental table 7).[35 53 59 60 62]

All pre–post studies and a cohort reporting pre–post data found increased/heightened testosterone and oestradiol in birth-registered females and males, respectively.[33 35 40 53 55 59 61 62 66 67 69 70] Three studies (two cohort and one cross-sectional) found testosterone levels in birth-registered females receiving hormones were higher than female controls but lower than male controls.[37 38 60] The cross-sectional study reported similar oestradiol levels in birth-registered males receiving hormones and female controls, and higher levels compared with male controls.[60] Luteinising and follicle-stimulating hormones remained constant or decreased slightly.[33 40 60 66 67 69 70]

In birth-registered females, three studies reported increases in oestradiol,[33 35 67] two no change[53 69] and three reported decreases[55 61 62] (with varying follow-up across studies). In birth-registered males, one study reported no change in testosterone,[66] four a decrease[35 53 62 70] and one observed higher testosterone levels compared with female but lower compared with male controls.[60]

Induced pubertal progression

Four pre–post studies with at least 12 months follow-up measured pubertal development,[33 36 40 70] and three Tanner breast stage (online supplemental table 7).[36 40 70] Two observed an increase in breast volume in birth-registered males after hormones,[40 70] although objectively breast volume was small,[70] and another reported no change in breast volume in birth-registered females.[36] One study of birth-registered females reported an increase in facial, abdominal, chest and extremities hair, and voice deepening in all participants at follow-up.[33] Another reported no change in Tanner genital stage in birth-registered males,[36] and no change in Tanner pubic hair stage for both.[36]

Menstrual suppression

Three pre–post studies reported suppression in most participants (online supplemental table 7): 85% cessation after 6 months,[61] 80% no breakthrough bleeding at 12 months[52] and nearly all reported suppression on 200 mg of subcutaneous testosterone, although just over half reported suppression on 140 mg (median follow-up 1.9 years).[55]

Height/growth

One cohort[34] and six pre–post studies[30 33 35 36 40 70] reported height and/or height SD score, showing mixed results (online supplementary material S7).

For birth-registered males, two studies reported an increase in height SD score[30 70] and one no change.[40] Three studies reported an increase in absolute height.[30 36 40] An increase was observed in height SD when using affirmed-gender references.[40]

For birth-registered females, two studies reported no change in height SD score,[30 33] and three reported an increase in absolute height.[30 33 36]

One study reported that birth-registered females who received hormones earlier and for longer, were taller than those who started treatment later. There was no difference for birth-registered males.[34] All participants in the study had first received puberty suppression. A second study found that for both sexes, the average height at follow-up was higher in those who started hormone treatment earlier.[35]

Body composition/shape

Birth-registered females receiving testosterone had lower body fat percentage and fat mass, and higher lean tissue percentage and lean mass than female controls not experiencing gender dysphoria/incongruence, and the converse compared with males controls.[60] Higher body fat percentage and fat mass and lower lean tissue percentage were seen for birth-registered males compared with male controls, and the converse compared with females controls (online supplemental table 7).

A pre–post study in birth-registered males reported no change in fat mass after 2 years of treatment, but at 3 years it was higher compared with baseline (online supplemental table 7). Both fat percentage and lean body mass percentage remained the same.[40] The same study reported a decrease in absolute and SD score for waist–hip ratio (compared with reference data for males and females), a decrease in SD score but no absolute change in waist circumference, and no change in SD score but an absolute increase in hip circumference.[40]

Bone age and geometry

Two pre–post studies measured bone age and reported an increase after treatment (online supplementary material S7).[36 40] In birth-registered males who started GnRH-a in mid-puberty or late-puberty prior to initiating hormones, there was an increase in subperiosteal width and endocortical diameter, but not in those who started this treatment in early puberty.[35] For birth-registered females, there was no evidence of change.

Fertility

One cohort study measured fertility in birth-registered males by comparing orchiectomy specimens of those who started hormone treatment at Tanner stage 2/3, 4/5 or in adulthood, with all adolescents first receiving puberty suppression (online supplemantary table S6).[39] Mature spermatozoa were only encountered in those who started this treatment at Tanner stage 4 or higher. Immature germ cells were present in all those treated in early puberty. Duration of hormone treatment did not influence study outcomes.

Side effects

Four studies reported side effects (one cohort[54] and three pre–post[55 69 70]). Three studies of birth-registered females reported an increase in acne at follow-up.[54 55 69] One study also reported mood changes, elevated red blood markers and increased appetite as common, with headaches, hot flashes, fatigue and hair loss less commonly reported.[54] One study reported a slight increase in metrorrhagia after adding testosterone following <6 months of lynestrenol.[69]

Breast tenderness was commonly reported in two studies of birth-registered males,[54 70] with less common reports of increased liver enzymes and oestradiol levels above the normal limit,[54 70] and mood swings and increased appetite frequently reported.[70] The cohort study reported similar side effect profiles in those receiving GnRH-a concurrently with hormones and those receiving hormones alone.[54]

DISCUSSION

This systematic review identified 53 studies reporting outcomes for feminising/masculinising hormones for adolescents experiencing gender dysphoria/incongruence. Only 6 of the 12 cohort studies were rated as high or moderate quality.[34 37–39 54 76]

There was evidence from multiple studies that exogenous hormones increase hormone levels and to varying degrees induce pubertal development, with potential differences depending on birth-registered sex and timing of treatment. Inconsistent results were found for height/growth, bone health and cardiometabolic health. There was insufficient evidence regarding changes to gender dysphoria, body satisfaction, psychosocial and cognitive outcomes, or fertility (no study assessed fertility in birth-registered females). These findings add to other systematic reviews in concluding there is insufficient and/or inconsistent evidence about the risks and benefits of hormone interventions in this population.[11–20]

Regarding psychological health, evidence from mainly pre–post studies suggests hormones are associated with improvements in depression, anxiety and other mental health difficulties after 12 months of treatment, although there were inconsistencies regarding suicidality and/or self-harm, with three of four studies reporting an improvement and one no change. Concerns about study representativeness and comparability of control groups (where used) mean these findings must be interpreted with caution. Well-designed robust studies that control for key confounding factors with longer-term follow-up are needed.

Over half of the studies reported the effects of both puberty suppression and hormones. In adolescents, GnRH-a often continues during hormone treatment.[9] For adolescents who do not first receive puberty suppression, GnRH-a or another anti-androgenic treatment may be offered at the initiation of hormones although the reasons for this are unclear.[79] Although recent studies suggest most adolescents who proceed with hormones will receive puberty suppression before this,[9 10 80] research that robustly compares outcomes for adolescents on this treatment pathway versus receiving hormones alone is needed, especially given recent studies suggesting the effect on secondary sex characteristics and fertility may be different.[34 39]

Agreement about core aims and outcomes for hormone interventions for adolescents would facilitate future aggregation of evidence. Included studies assessed multiple different outcomes across various domains. The rationale for cognitive outcomes

varied, with some studies primarily focusing on sex-based differences presumed from wider research.[81] Few studies examined whether hormones influence cognitive development in adolescence, which is identified as a key area of uncertainty.

Clinicians should ensure that adolescents considering hormone interventions are fully informed about the potential risks and benefits including side-effects, and the lack of high-quality evidence regarding these. In response to their own evidence review, the Swedish National Board of Health and Welfare now recommends that hormone treatments should only be provided under a research framework, a key aim for which is to develop a stronger evidence base.[82] As they point out, this approach is common practice in other clinical specialties, where to receive treatments for which the benefits and risks are uncertain, patients must take part in research.

Strengths and limitations

Strengths include a published protocol with robust search strategies, and comprehensive synthesis of high-quality and moderate-quality studies. Poor study reporting may have resulted in moderate-quality studies being rated as low-quality and excluded from the synthesis. As searches were conducted to April 2022 this review does not include more recently published studies. However, this review draws similar conclusions to other reviews despite including numerous additional studies. Of other studies published since April 2022 until January 2024, very few used a cohort design or an appropriate comparator and were of similar low-quality to moderate-quality. Of those likely to contribute new data to the synthesis, five focused on bone health and growth,[83–87] one on cardiometabolic risk[88] and two assessed psychological health,[89 90] one of which also assessed life satisfaction and congruence with gender identity and appearance,[89] and the other additionally assessed body image and sex-typed brain activity.[90]

All three studies assessing bone health examined changes over time for participants treated with GnRH-a followed by hormones and found, overall, that after hormone treatment, bone mineral density scores were in line with expected maturation, despite a deceleration during GnRH-a treatment.[83 86 87] Two of these studies also found that height growth was not affected following hormone treatment,[84 87] and this was found in a third study as well.[85] The increasing number of studies assessing bone health and height growth potentially indicate that following hormone treatment, bone health is in line with expected maturation and height growth is not affected. However, there remains uncertainty about these outcomes due to the lack of high-quality studies that use a longitudinal design and appropriate comparator with longer-term follow-up.

A single new study assessed changes in body composition.[83] It found an increase in lean body mass z-scores and a decrease in fat mass z-scores during the first year of treatment in birth-registered females, which remained stable over 3 years of treatment. For birth-registered males, there was a slight decrease in lean mass z-scores in the first year which remained stable over time, but little change in fat mass z-scores. This study adds to the limited evidence base for body composition, but no conclusions can be drawn due to the inconsistency in results across studies.

One study examined whether receipt of hormone interventions was associated with cardiometabolic-related diagnoses and found that certain diagnoses were more likely in birth-registered females receiving testosterone, suggesting that cardiometabolic health may be compromised in this group.[88] However, it is the only study that has examined diagnoses rather than cardiometabolic markers, and it used a cross-sectional design, therefore no conclusions can be drawn about these outcomes.

Two studies measured psychological health.[89 90] They both found lower levels of anxiety and depression for birth-registered females, in one study during 2 years after hormone initiation,[89] and in the other when compared with those not receiving hormones,[90] which also found lower levels of suicidality in those receiving hormones but no difference for internalising symptoms.[90] Overall, no differences for birth-registered males were observed for the same outcomes in both studies, although one study found that for both sexes, taking hormones for longer durations was associated with fewer depression and suicidality symptoms, with a stronger association between longer duration and lower suicidality in birth-registered males.[90] These studies add to the moderate-quality evidence that hormone treatment may improve psychological health, although robust research with long-term follow-up is still needed.

A single study assessing outcomes during the 2 years after hormone initiation found that scores for gender congruence and life satisfaction increased, but there were differences by birth-registered sex and timing of hormone initiation.[89] Lastly, a single cross-sectional study explored body image and sex-typed brain activity.[90] It found body image satisfaction was higher in those receiving hormones compared with those not receiving hormones and those taking hormones for longer durations. In terms of sex-typed brain activity, analysis of amygdala-vmPFC (ventromedial prefrontal cortex) coupling found greater coupling in those receiving hormones. However, as there is still limited evidence about the effect of hormones on gender-related, psychosocial and cognitive outcomes, no further conclusions can be drawn.

CONCLUSIONS

There is a lack of high-quality research assessing the outcomes of hormone interventions in adolescents experiencing gender dysphoria/incongruence, and few studies that undertake long-term follow-up. No conclusions can be drawn about the effect on gender-related outcomes, body satisfaction, psychosocial health, cognitive development or fertility. Uncertainty remains about the outcomes for height/growth, cardiometabolic and bone health. There is suggestive evidence from mainly pre–post studies that hormone treatment may improve psychological health although robust research with long-term follow-up is needed.

Contributors LF, RH, TL and JT contributed to the conception of this review. RH, CEH, AM and JT contributed to screening and selection. AM and JT completed data extraction. CEH, RH, AM and JT contributed to critical appraisal. CEH, AM and JT completed the synthesis and drafted the manuscript. All authors contributed to the interpretation, and reviewed and approved the manuscript. CEH accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was funded by NHS England to inform the Cass Review (Independent review of gender identity services for children and young people). The funder and Cass Review team had a role in commissioning the research programme but no role in the study conduct, interpretation or conclusion.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement Data sharing is not applicable as no datasets were generated and/or analysed for this study.

ORCID iDs
Jo Taylor http://orcid.org/0000-0001-5898-0900
Catherine Elizabeth Hewitt http://orcid.org/0000-0002-0415-3536

REFERENCES

1 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender dysphoria literature: 1) epidemiology. *PLOS Glob Public Health* 2022;2:e0000245.
2 Kaltiala R, Bergman H, Carmichael P, *et al*. Time trends in referrals to child and adolescent gender identity services: a study in four Nordic countries and in the UK. *Nord J Psychiatry* 2020;74:40–4.
3 Coleman E, Radix AE, Bouman WP, *et al*. Standards of care for the health of transgender and gender diverse people, version 8. *Int J Transgend Health* 2022;23:S1–259.
4 Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017;102:3869–903.
5 Biggs M. The Dutch protocol for juvenile transsexuals: origins and evidence. *J Sex Marital Ther* 2023;49:348–68.
6 de Vries ALC, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the Dutch approach. *J Homosex* 2012;59:301–20.
7 Telfer MM, Tollit MA, Pace CC, *et al*. Australian standards of care and treatment guidelines for transgender and gender diverse children and adolescents. *Med J Aust* 2018;209:132–6.
8 University of California San Francisco Gender Affirming Health Program. Guidelines for the primary and gender-affirming care of transgender and gender nonbinary people. University of California San Francisco; 2016. Available: https://transcare.ucsf.edu/guidelines
9 van der Loos MATC, Klink DT, Hannema SE, *et al*. Children and adolescents in the Amsterdam cohort of gender dysphoria: trends in diagnostic- and treatment trajectories during the first 20 years of the Dutch protocol. *J Sex Med* 2023;20:398–409.
10 Masic U, Butler G, Carruthers P, *et al*. Trajectories of transgender adolescents referred for endocrine intervention in England. *Arch Dis Child* 2022;107:1012–7.
11 Pasternack I, Söderström I, Saijonkari M, *et al*. Medical approaches to treatment of dysphoria related to gender variations. A systematic review. 2019. Available: https://app.box.com/s/y9u791np8v9gsunwgpr2kqn8swd9vdtx
12 Ludvigsson JF, Adolfsson J, Höistad M, *et al*. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatr* 2023;112:2279–92.
13 Baker KE, Wilson LM, Sharma R, *et al*. Hormone therapy, mental health, and quality of life among transgender people: a systematic review. *J Endocr Soc* 2021;5:bvab011.
14 Chew D, Anderson J, Williams K, *et al*. Hormonal treatment in young people with gender dysphoria: a systematic review. *Pediatrics* 2018;141:e20173742.
15 National Institute for Health and Care Excellence (NICE). Evidence review: gender-affirming hormones for children and adolescents with gender dysphoria [NICE]. 2020. Available: https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_Gender-affirming-hormones_For-upload_Final.pdf
16 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS Glob Public Health* 2023;3:e0001478.
17 Wilson LM, Baker KE, Sharma R, *et al*. Effects of antiandrogens on prolactin levels among transgender women on estrogen therapy: a systematic review. *Int J Transgend Health* 2020;21:391–402.
18 Singh-Ospina N, Maraka S, Rodriguez-Gutierrez R, *et al*. Effect of sex steroids on the bone health of transgender individuals: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2017;102:3904–13.
19 Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, *et al*. Sex steroids and cardiovascular outcomes in transgender individuals: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2017;102:3914–23.
20 Karalexi MA, Georgakis MK, Dimitriou NG, *et al*. Gender-affirming hormone treatment and cognitive function in transgender young adults: a systematic review and meta-analysis. *Psychoneuroendocrinology* 2020;119.
21 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
22 Fraser L, Hall R, Taylor J, *et al*. The epidemiology, management and outcomes of children with gender-related distress / gender dysphoria: a systematic review. PROSPERO 2021 CRD42021289659. 2021. Available: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021289659
23 Veritas Health Innovation. Covidence systematic review software. Melbourne, Australia Veritas Health Innovation; 2023.
24 Wells G, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2021. Available: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
25 Burke SM, van Heesewijk JO, Menks WM, *et al*. Postnatal effects of sex hormones on click-evoked otoacoustic emissions: a study of adolescents with gender dysphoria. *Arch Sex Behav* 2020;49:455–65.
26 de Vries ALC, McGuire JK, Steensma TD, *et al*. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics* 2014;134:696–704.
27 Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur j Endocrinol* 2006;155:S131–7.
28 Klaver M, de Mutsert R, Wiepjes CM, *et al*. Early hormonal treatment affects body composition and body shape in young transgender adolescents. *J Sex Med* 2018;15:251–60.
29 Klaver M, de Mutsert R, van der Loos MATC, *et al*. Hormonal treatment and cardiovascular risk profile in transgender adolescents. *Pediatrics* 2020;145:e20190741.
30 Klink D, Caris M, Heijboer A, *et al*. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab* 2015;100:E270–5.
31 Schagen SEE, Lustenhouwer P, Cohen-Kettenis PT, *et al*. Changes in adrenal androgens during puberty suppression and gender-affirming hormone treatment in adolescents with gender dysphoria. *J Sex Med* 2018;15:1357–63.
32 Schagen SEE, Wouters FM, Cohen-Kettenis PT, *et al*. Bone development in transgender adolescents treated with GnRH analogues and subsequent gender-affirming hormones. *J Clin Endocrinol Metab* 2020;105:e4252–63.
33 Stoffers IE, de Vries MC, Hannema SE. Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. *J Sex Med* 2019;16:1459–68.
34 van de Grift TC, van Gelder ZJ, Mullender MG, *et al*. Timing of puberty suppression and surgical options for transgender youth. *Pediatrics* 2020;146:e20193653.
35 van der Loos MA, Hellinga I, Vlot MC, *et al*. Development of hip bone geometry during gender-affirming hormone therapy in transgender adolescents resembles that of the experienced gender when pubertal suspension is started in early puberty. *J Bone Miner Res* 2021;36:931–41.
36 Vlot MC, Klink DT, den Heijer M, *et al*. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone* 2017;95:11–9.
37 Beking T, Burke SM, Geuze RH, *et al*. Testosterone effects on functional amygdala lateralization: a study in adolescent transgender boys and cisgender boys and girls. *Psychoneuroendocrinology* 2020;111.
38 Burke SM, Kreukels BPC, Cohen-Kettenis PT, *et al*. Male-typical visuospatial functioning in gynephilic girls with gender dysphoria - organizational and activational effects of testosterone. *J Psychiatry Neurosci* 2016;41:395–404.
39 de Nie I, Mulder CL, Meißner A, *et al*. Histological study on the influence of puberty suppression and hormonal treatment on developing germ cells in transgender women. *Hum Reprod* 2022;37:297–308.
40 Hannema SE, Schagen SEE, Cohen-Kettenis PT, *et al*. Efficacy and safety of pubertal induction using 17Beta-estradiol in transgirls. *J Clin Endocrinol Metab* 2017;102:2356–63.
41 Madsen MC, van Dijk D, Wiepjes CM, *et al*. Erythrocytosis in a large cohort of trans men using testosterone: a long-term follow-up study on prevalence. *J Clin Endocrinol Metab* 2021;106:1710–7.
42 Achille C, Taggart T, Eaton NR, *et al*. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. *Int J Pediatr Endocrinol* 2020;2020:8.
43 Grimstad FW, Knoll MM, Jacobson JD. Oxandrolone use in trans-masculine youth appears to increase adult height: preliminary evidence. *LGBT Health* 2021;8:300–6.
44 Kuper LE, Stewart S, Preston S, *et al*. Body dissatisfaction and mental health outcomes of youth on gender-affirming hormone therapy. *Pediatrics* 2020;145:e20193006.
45 Strang JF, Chen D, Nelson E, *et al*. Transgender youth executive functioning: relationships with anxiety symptoms, autism spectrum disorder, and gender-affirming medical treatment status. *Child Psychiatry Hum Dev* 2022;53:1252–65.
46 Tordoff DM, Wanta JW, Collin A, *et al*. Mental health outcomes in Transgender and Nonbinary youths receiving gender-affirming care. *JAMA Netw Open* 2022;5:e220978.
47 Hisle-Gorman E, Schvey NA, Adirim TA, *et al*. Mental healthcare utilization of transgender youth before and after affirming treatment. *J Sex Med* 2021;18:1444–54.
48 Allen LR, Watson LB, Egan AM, *et al*. Well-being and suicidality among transgender youth after gender-affirming hormones. *Clin Pract Pediatr Psychol* 2019;7:302–11.

49 Cantu AL, Moyer DN, Connelly KJ, *et al*. Changes in anxiety and depression from intake to first follow-up among transgender youth in a pediatric endocrinology clinic. *Transgend Health* 2020;5:196–200.
50 Green AE, DeChants JP, Price MN, *et al*. Association of gender-affirming hormone therapy with depression, thoughts of suicide, and attempted suicide among transgender and nonbinary youth. *J Adolesc Health* 2022;70:643–9.
51 Grannis C, Leibowitz SF, Gahn S, *et al*. Testosterone treatment, internalizing symptoms, and body image dissatisfaction in transgender boys. *Psychoneuroendocrinology* 2021;132.
52 Grimstad F, Kremen J, Shim J, *et al*. Breakthrough bleeding in transgender and gender diverse adolescents and young adults on long-term testosterone. *J Pediatr Adolesc Gynecol* 2021;34:706–16.
53 Jarin J, Pine-Twaddell E, Trotman G, *et al*. Cross-sex hormones and metabolic parameters in adolescents with gender dysphoria. *Pediatrics* 2017;139:e20163173.
54 Jensen RK, Jensen JK, Simons LK, *et al*. Effect of concurrent gonadotropin-releasing hormone agonist treatment on dose and side effects of gender-affirming hormone therapy in adolescent transgender patients. *Transgend Health* 2019;4:300–3.
55 Laurenzano SE, Newfield RS, Lee E, *et al*. Subcutaneous testosterone is effective and safe as gender-affirming hormone therapy in transmasculine and gender-diverse adolescents and young adults: a single center's 8-year experience. *Transgend Health* 2021;6:343–52.
56 Millington K, Barrera E, Daga A, *et al*. The effect of gender-affirming hormone treatment on serum creatinine in transgender and gender-diverse youth: implications for estimating GFR. *Pediatr Nephrol* 2022;37:2141–50.
57 Millington K, Chan YM. Lipoprotein subtypes after testosterone therapy in transmasculine adolescents. *J Clin Lipidol* 2021;15:840–4.
58 Millington K, Liu E, Chan YM. The utility of potassium monitoring in gender-diverse adolescents taking spironolactone. *J Endocr Soc* 2019;3:1031–8.
59 Mullins ES, Geer R, Metcalf M, *et al*. Thrombosis risk in transgender adolescents receiving gender-affirming hormone therapy. *Pediatrics* 2021;147:e2020023549.
60 Nokoff NJ, Scarbro SL, Moreau KL, *et al*. Body composition and markers of cardiometabolic health in transgender youth compared with cisgender youth. *J Clin Endocrinol Metab* 2020;105:e704–14.
61 Olson J, Schrager SM, Clark LF, *et al*. Subcutaneous testosterone: an effective delivery mechanism for masculinizing young transgender men. *LGBT Health* 2014;1:165–7.
62 Olson-Kennedy J, Okonta V, Clark LF, *et al*. Physiologic response to gender-affirming hormones among transgender youth. *J Adolesc Health* 2018;62:397–401.
63 Sequeira GM, Kidd K, El Nokali NE, *et al*. Early effects of testosterone initiation on body mass index in transmasculine adolescents. *J Adolesc Health* 2019;65:818–20.
64 Valentine A, Nokoff N, Bonny A, *et al*. Cardiometabolic parameters among transgender adolescent males on testosterone therapy and body mass index-matched cisgender females. *Transgend Health* 2021;6:369–73.
65 Turban JL, King D, Kobe J, *et al*. Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. *PLoS One* 2022;17:e0261039.
66 Perl L, Elkon-Tamir E, Segev-Becker A, *et al*. Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogs followed by estradiol treatment in transgender female adolescents: a pilot study. *J Pediatr Endocrinol Metab* 2021;34:741–5.
67 Perl L, Segev-Becker A, Israeli G, *et al*. Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogs followed by testosterone treatment in transgender male adolescents: a pilot study. *LGBT Health* 2020;7:340–4.
68 Segev-Becker A, Israeli G, Elkon-Tamir E, *et al*. Children and adolescents with gender dysphoria in Israel: increasing referral and fertility preservation rates. *Endocrine Practice* 2020;26:423–8.
69 Tack LJW, Craen M, Dhondt K, *et al*. Consecutive lynestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: a retrospective analysis. *Biol Sex Differ* 2016;7:14.
70 Tack LJW, Heyse R, Craen M, *et al*. Consecutive cyproterone acetate and estradiol treatment in late-pubertal transgender female adolescents. *J Sex Med* 2017;14:747–57.
71 Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. *J Pediatr* 2014;164:906–11.
72 Chiniara LN, Bonifacio HJ, Palmert MR. Characteristics of adolescents referred to a gender clinic: are youth seen now different from those in initial reports *Horm Res Paediatr* 2018;89:434–41.
73 Fontanari AMV, Vilanova F, Schneider MA, *et al*. Gender affirmation is associated with transgender and gender nonbinary youth mental health improvement. *LGBT Health* 2020;7:237–47.
74 Kaltiala R, Heino E, Työläjärvi M, *et al*. Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. *Nordic Journal of Psychiatry* 2020;74:213–9.
75 Becker-Hebly I, Fahrenkrug S, Campion F, *et al*. Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: a descriptive study from the Hamburg gender identity service. *Eur Child Adolesc Psychiatry* 2021;30:1755–67.
76 López de Lara D, Pérez Rodríguez O, Cuellar Flores I, *et al*. Psychosocial assessment in transgender adolescents [Psychosocial assessment in transgender adolescents]. *Anales de Pediatría (English Edition)* 2020;93:41–8.
77 Arcelus J, Claes L, Witcomb GL, *et al*. Risk factors for non-suicidal self-injury among trans youth. *J Sex Med* 2016;13:402–12.
78 Arcelus J, Bouman WP, Van Den Noortgate W, *et al*. Systematic review and meta-analysis of prevalence studies in transsexualism. *Eur Psychiatr* 2015;30:807–15.
79 Tack LJW, Craen M, Lapauw B, *et al*. Proandrogenic and antiandrogenic progestins in transgender youth: differential effects on body composition and bone metabolism. *J Clin Endocrinol Metab* 2018;103:2147–56.
80 van der Loos M, Hannema SE, Klink DT, *et al*. Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: a cohort study in the Netherlands. *Lancet Child Adolesc Health* 2022;6:869–75.
81 Eliot L, Ahmed A, Khan H, *et al*. Dump the "Dimorphism": comprehensive synthesis of human brain studies reveals few male-female differences beyond size. *Neurosci Biobehav Rev* 2021;125:667–97.
82 The Swedish National Board of Health and Welfare. Care of children and young people with gender dysphoria - national knowledge support with recommendations for the profession and decision makers [The Swedish National Board of Health and Welfare]. 2022. Available: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-12-8302.pdf
83 Boogers LS, Reijtenbagh SJP, Wiepjes CM, *et al*. Time course of body composition changes in transgender adolescents during puberty suppression and sex hormone treatment. *J Clin Endocrinol Metab* 2023;21:21.
84 Boogers LS, Wiepjes CM, Klink DT, *et al*. Transgender girls grow tall: adult height is unaffected by GnRH analogue and estradiol treatment. *J Clin Endocrinol Metab* 2022;107:e3805–15.
85 Ciancia S, Klink D, Craen M, *et al*. Early puberty suppression and gender-affirming hormones do not alter final height in transgender adolescents. *Eur J Endocrinol* 2023;189:396–401.
86 van der Loos MATC, Vlot MC, Klink DT, *et al*. Bone mineral density in transgender adolescents treated with puberty suppression and subsequent gender-affirming hormones. *JAMA Pediatr* 2023;177:1332–41.
87 Willemsen LA, Boogers LS, Wiepjes CM, *et al*. Just as tall on testosterone; a neutral to positive effect on adult height of GnRHa and testosterone in trans boys. *J Clin Endocrinol Metab* 2023;108:414–21.
88 Valentine A, Davis S, Furniss A, *et al*. Multicenter analysis of cardiometabolic-related diagnoses in transgender and gender-diverse youth: a PEDSnet study. *J Clin Endocrinol Metab* 2022;107:e4004–14.
89 Chen D, Berona J, Chan Y-M, *et al*. Psychosocial functioning in transgender youth after 2 years of hormones. *N Engl J Med* 2023;388:240–50.
90 Grannis C, Mattson WI, Leibowitz SF, *et al*. Expanding upon the relationship between gender-affirming hormone therapy, neural connectivity, mental health, and body image dissatisfaction. *Psychoneuroendocrinology* 2023;156.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (Adapted cohort study scale)

Adapted from Wells G, Shea B, O'Connell D, et al. (2021) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Selection

1) Representativeness of the paediatric gender dysphoric group

Score 1 if:
a) truly representative of the average child or adolescent with gender dysphoria / incongruence, e.g., nationally representative community sample, population-based medical database, national gender service, multiple gender services covering different localities

Score 0.5 if:
b) somewhat representative of the average child or adolescent with gender dysphoria / incongruence, e.g., single gender service (in a country where there are several), locality representative community sample

Score 0 if:
c) a selected group of users e.g., convenience sample, self-selection, sub-sample due to data availability
or
d) no description of the derivation of the cohort

Q1. TIP: If paper does not include information on sample size / representativeness / response rate in relation to eligible clinic population, score 0 as we must assume it is a selected group of users.

Q1. NOTE: When scoring take into consideration that puberty blockers are not available to pre-pubertal children and cross-sex hormones not until mid-adolescence, therefore an adolescent sample would be representative of those seeking medical treatment for gender dysphoria.

2) Selection of the non-exposed group

Score 1 if:
a) drawn from the same community as the exposed group

Score 0.5 if:
b) drawn from a different source that is comparable e.g., population norms for all adolescents or matched cisgender controls where outcome is expected to be the same for both groups such as BMI or adult height

Score 0 if:
c) drawn from a different source that is not comparable e.g., cisgender population for studies measuring psychosocial outcomes
or
d) no description of the derivation of the non-exposed cohort

Score N/A if:
e) single group study (e.g., pre-post treatment design)

Q2. TIP: Some studies include two plus comparator groups – score 1 if all appropriate, score 0.5 if mix of comparable and non-comparable, and score 0 if none are comparable.

3) Ascertainment of exposure (medical treatment for gender dysphoria)
Score 1 if:
a) secure record, e.g., clinic or medical records
or
b) structured interview

Score 0 if:
c) written self-report
or
d) no description

Q3. TIP: Use of medical records can be inferred from methods reporting overall, e.g., if sample eligibility was based on medical records and this includes treatment, or if detailed treatment information provided from medical records.

4) Demonstration that outcome of interest was not present at start of study
Score 1 if:
a) yes

Score 0 if:
b) no

Score N/A if:
c) study is measuring an outcome such as quality of life or severity of anxiety for which there would be an intrinsic value for each participant at any time during the study

Comparability

5) Comparability of cohorts based on the design (e.g., matched controls, inclusion criteria) or analysis (e.g., propensity score matching, regression analysis)

PART A
Score 1 if:
a) study controls for [age OR puberty stage] AND [natal sex OR gender]

Score 0.5 if:
b) one (but not both) of the above confounders is controlled for
or
c) other important sociodemographic confounders are controlled for, e.g., family support for studies measuring mental health / psychosocial outcomes

Score 0 if:
d) study does not control for important sociodemographic confounders

PART B
Score 1 if:
a) study controls for co-interventions expected to affect the outcome(s), e.g., psychosocial support, psychiatric medication, use of other medication likely to alter outcome (e.g., contraceptive pill),

other aid or intervention designed to address gender dysphoria or to modify body (e.g., social transition, binders, voice therapy)
or
b) there are no co-interventions that are expected to affect the outcome(s)

Score 0.5 if:
c) at least one (but not all) of the important co-intervention confounders are controlled for

Score 0 if:
d) study does not control for important co-intervention confounders

Q5. TIP (from manual): Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.
This question needs to be answered for single group studies (i.e., how do these studies control for potential demographic and treatment confounders that occur between baseline and follow-up).

Outcome

6) Assessment of outcome
Score 1 if:
a) validated scale or standardised assessment tool/method
or
b) record linkage, e.g., medical/clinic/administrative records

Score 0.5 if:
c) combination of validated / standardised and non-validated / unstandardised assessment methods

Score 0 if:
d) self-report
or
e) no description

7) Was follow-up long enough for outcomes to occur?
Score 1 if:
a) follow-up is sufficient for all reported outcomes

Guidance on follow-up:
For puberty suppressants follow-up should be at least 3 months to assess desired / expected effect, gender dysphoria / incongruence or psychosocial outcomes.

For cross-sex hormones follow-up should be at least 6 months to assess desired / expected effect, gender dysphoria / incongruence, or psychosocial outcomes.

For both treatments, follow-up should be at least 3 months to assess safety, side-effects or cardiometabolic risk; and at least 12 months for cognitive development, bone health or fertility.

Score 0.5 if:
b) follow-up is sufficient for some outcomes but not others, e.g., studies that examine multiple outcomes requiring different follow-up
or

c) follow-up is sufficient for some participants but not others, e.g., where follow-up or treatment duration varies between participants

Score 0 if:
d) follow-up is not sufficient
or
e) no clear description, e.g., follow-up duration unclear

Score N/A if:
f) cross-sectional design (i.e., no follow-up)

8) Adequacy of follow up of cohorts
Score 1 if:
a) complete follow up or all subjects accounted for in analysis of outcomes
or
b) subjects lost to follow up or outcome analyses unlikely to introduce bias - small number lost (≤10%) or description provided of those lost justifies that there is no potential bias due to loss to follow-up

Score 0.5 if:
c) there are multiple sufficient follow-up timepoints (based on Q7) and follow-up is adequate for some but not others, e.g., all retained at 12 months but considerable attrition at 24 months

Score 0 if:
c) follow up / analysis rate < 90% and no description of those lost
or
d) no statement

TOTAL SCORING
Cohort studies – total score = 8
Pre-post single group studies – total score = 7 (Q2 not relevant)
Cross-sectional studies with comparators – total score = 7 (Q7 not relevant)

Any study for which Q4 is relevant, total score would be as above plus 1

Low: ≤ 50%
Moderate: >50 to 75%
High – >75%

Supplementary Table S1: Final search strategy for Ovid MEDLINE

1 exp Child/ or Child Behavior/ or Child Health/ or Child Welfare/ or Psychology, Child/ or Child Psychiatry/ or Child Health Services/ or Child Development/ (1984459)
2 Minors/ (2638)
3 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or emerging adult$).ti,ab,kf,jn. (1862660)
4 (young$ adj (people$ or person$1 or adult$ or man$1 or men$1 or woman$ or women$ or male$1 or female$1)).ti,ab,kf,jn. (224878)
5 pediatrics/ (55388)
6 (pediatric$ or paediatric$ or peadiatric$).ti,ab,kf,jn. (543516)
7 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Psychology, Adolescent/ or Adolescent Psychiatry/ or Adolescent Health Services/ or Adolescent Medicine/ or Adolescent Development/ (2088552)
8 Puberty/ (13562)
9 (adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or underage$ or under-age$).ti,ab,kf,jn. (522801)
10 Schools/ or Schools, Nursery/ (42221)
11 exp Child Day Care Centers/ or Child Care/ (11287)
12 (school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1).ti,ab,kf,jn. (356157)
13 or/1-12 (4333601)
14 Gender Dysphoria/ (581)
15 "Sexual and Gender Disorders"/ (79)
16 Transsexualism/ (3895)
17 Transgender Persons/ (3835)
18 Health Services for Transgender Persons/ (152)
19 exp Sex Reassignment Procedures/ (969)
20 "Sexual and Gender Minorities"/ (4924)
21 ((gender$ and dysphori$) or (gender$ adj5 incongru$) or sexual dysphori$).ti,ab,kf. (1784)
22 (gender$ adj (disorder$ or identi$)).ti,ab,kf. or (gender identity/ and dysphori$.ti,ab,kf.) (4568)
23 (GID or GIDS or GIDC or GIDCS).ti,ab,kf. (456)
24 (gender$ adj5 (confusion or confused or questioning or distress$ or discomfort)).ti,ab,kf. (980)
25 (gender$ adj5 (minority or minorities)).ti,ab,kf. (1593)
26 (gender$ adj5 (variant$ or variance$ or nonconform$ or non-conform$ or diverse or diversity or atypical$)).ti,ab,kf. (3409)
27 (non-binary or nonbinary or enby or genderqueer or gender-queer or neutrois).ti,ab,kf. (796)
28 (agender$ or genderless$ or gender-less$ or genderfree or gender-free or ungender$ or un-gender$ or non-gender$ or nongender$ or bigender$ or bi-gender$ or dual gender$ or dualgender$ or demi-gender$ or demigender$ or genderfluid$ or gender-fluid$ or trigender$ or tri-gender$).ti,ab,kf. (315)

29 two spirit$.ti,ab,kf. (84)
30 (trans adj3 (female$ or feminin$ or woman$ or women$ or male$1 or man or mans or men or mens or masculin$ or person$1 or peopl$ or population$ or individual$)).ti,ab,kf. (1362)
31 (transgend$ or trans-gend$ or transex$ or transsex$ or trans-sex$ or transfemale$ or transfeminin$ or transwom$ or transmale$ or transman$ or transmasculin$ or transmen$ or transperson$ or transpeopl$ or transpopulation$ or transindividual$).ti,ab,kf. (10832)
32 (trans adj3 identi$).ti,ab,kf. or (gender identity/ and trans.ti,ab,kf.) or (trans and dysphori$).ti,ab,kf. (1447)
33 (crossgender$ or cross-gender$ or crossex$ or crosssex$ or cross-sex$).ti,ab,kf. (836)
34 ((sex or gender$) adj3 (reassign$ or re-assign$ or affirm$ or confirm$ or transition$)).ti,ab,kf. (3963)
35 ((gender$ or sex) adj (change or changes or changing or changed)).ti,ab,kf. (825)
36 (detransition$ or de-transition$ or desister$ or de-sister$).ti,ab,kf. (134)
37 ((desist$ or persist$) adj5 (transition$ or trans or dysphori$)).ti,ab,kf. (823)
38 or/14-37 (28731)
39 (trans and (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ti. (339)
40 (trans adj5 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ab,kf. (397)
41 (transchild$ or transminor$ or transboy$ or transgirl$ or transkid or transkids or transyoung$ or transyouth$ or transteen$ or transtween$ or transadoles$ or transjuvenil$).ti,ab,kf. (15)
42 13 and 38 (9819)
43 39 or 40 or 41 or 42 (10343)
44 exp animals/ not humans/ (4823832)
45 (editorial or news or comment or case reports).pt. or case report.ti. (3692318)
46 43 not (44 or 45) (9429)
47 limit 46 to english language (9029)

Key to Ovid symbols and commands:
$ Unlimited right-hand truncation symbol
$N Limited right-hand truncation - restricts the number of characters following the word to N

ti,ab,kf,	Searches are restricted to the Title (ti), Abstract (ab), Keyword Heading Word (kf) fields
.jn	Searches are restricted to the Journal name field
adj	Retrieves records that contain terms next to each other (in the shown order)
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-12	Combines sets 1 to 12 using OR

Supplementary Table 2 - Study characteristics

Study ID	Country	Relevant study aim*	Setting	Population*	Primary sample (size (age; gender))	Hormones	Reports data on puberty suppression	Intervention	Comparator	Comparator category	Other control group (size (age; gender))	Study design	Study follow-up	Data collection period
Cohort														
Achille 2020	US	To examine the associations of endocrine intervention with depression and quality of life scores over time in transgender youths	Paediatric endocrine department for gender dysphoria	Children and adolescents age 9-25 years referred to the department for gender dysphoria	50 (mean age 16.2 (SD 2.2); 33 brf, 17 brm)	Yes	Yes	Puberty suppressants and/or cross-sex hormones	Participants who had received nothing at all or only puberty suppressants	Non-exposed individuals from primary sample	N/A	Prospective cohort study	Baseline and two follow-ups at ~6-monthly intervals (time-points not linked to treatment initiation)	Questionnaires completed between Dec 2013 to Dec 2018
Becker-Hebly 2020	Germany	To describe how dimensions of psychosocial health are distributed among different intervention groups of adolescents with a gender dysphoria diagnosis before and after treatment	Gender identity service for children and adolescents	Young people age 11 and over who were seeking and eligible for medication interventions	75 (mean age at baseline 15.56 range 11-18; 64 brf, 11 brm)	Yes	Yes	GnRHa; cross-sex hormones and GnRHa; cross-sex hormones and surgery	No hormone treatment	Non-exposed individuals from primary sample	N/A	Retrospective cohort study	Baseline (at intake) and single follow-up (follow-up ranged 13 to 38 months after baseline, mean 21.4 months - not linked to treatment start)	Clinical entry Sep 2013 to Jun 2017 (follow-up to Mar 2018)
Beking 2020	Netherlands	To investigate the effect of testosterone treatment in trans boys on functional lateralization of the amygdala and compare this with cisgender male and female control groups	Center for Gender Dysphoria for all ages	Birth-registered females with gender dysphoria who had received puberty suppressants and were starting testosterone treatment	21 (mean age 16.1 SD 0.7)	Yes	No	Testosterone	Two age-matched control groups presumed no GD recruited from schools and friends of treated participants	Other control group	(20 boys, mean 15.9 (SD 0.6); 21 girls, mean 16.4 (SD 1.0))	Prospective cohort study	Baseline and single follow-up (on average 10 months after baseline, treatment duration range 5.6-14.8 months, mean average 9.8)	Not reported
Burke 2016	Netherlands	To investigate whether adolescent girls with gender dysphoria, before and after testosterone treatment, would show male- or female-typical brain activity during a mental rotation task	Center for Gender Dysphoria for all ages	Adolescent birth-registered females with gender dysphoria who had been gender dysphoric since childhood and had received puberty suppressants	21 (mean age 16.1 years SD 0.8)	Yes	No	Testosterone	Two age-matched control groups presumed no GD	Other control group	(21 girls, mean age 16.3 (SD 1.0); 20 boys, mean age 15.9 (SD 0.6))	Prospective cohort study	Baseline and single follow-up (on average 10 months after baseline, treatment duration range 6-15 months, average 10)	Not reported
Cantu 2020	US	To examine changes in anxiety, depression and suicidality in young people receiving gender-affirming care	Paediatric gender clinic	Transgender and gender-nonconforming youth seeking gender-affirming care ages 11-18 who attended an initial visit and one follow-up and completed distress measures at both visits	80 (mean age 15.1 SD 1.8; 15 affirmed gender female, 58 affirmed gender male, 7 non-binary)	Yes	Yes	Puberty suppressants; cross-sex hormones (with or without puberty suppressants)	No hormone treatment	Non-exposed individuals from primary sample	N/A	Retrospective cohort study	Baseline (initial appointment) and single follow-up (average 4 months after baseline, range < 1 to 11 months)	Initial appointment Sep 2017 to Jun 2019
de Nie 2022	Netherlands	To evaluate the influence of puberty suppression and/or gender affirming hormonal treatment on exocrine testicular function in transgender women	Center for Gender Dysphoria for all ages	Transgender women who underwent bilateral orchiectomy combined with vaginoplasty	214 (mean age at time of surgery 29.6 years SD 12.4)	Yes	Yes	Puberty suppressants and/or cross-sex hormones intiated in adolescence	Hormones initiated in adulthood	Individuals from primary sample receiving hormones in adulthood	N/A	Retrospective cohort study	Single time-point	Underwent surgery from 2006 to 2019
Grimstad 2021b	US	To identify the impact of oxandrolone in the presence or absence of GnRHa on adult height in trans-masculine youth	Multi-disciplinary gender identity clinic at paediatric medical centre	Sex assigned female at birth and diagnosis of gender dysphoria and whose final adult heights were available	154 (mean age of referral 15.7 SD 1.9)	Yes	Yes	Oxandrolone with or without GnRHa; Testosterone with or without GnRHa; GnRHa only; Progesterone only	No hormone therapy	Non-exposed individuals from primary sample	N/A	Retrospective cohort study	All heights available in the medical record were collected up to adult height	Seen between 2013 and 2018 (data collected to 2020)
Jensen 2019	US	To determine whether dosages of gender-affirming hormones in transgender adolescents taking GnRHa differ from those not taking GnRHa, and identify the frequency of associated side effects	Paediatric gender clinic	Patients who started or were currently receiving gender-affirming hormone therapy	85 (62 brf: median age at CSH+GnRHa 15.0 range 13.7-16.5, at CSH only 16.9 range 13.4-22.1; 23 brm: median age at CSH+GnRHa 14.9 range 14.1-15.7, CSH only 16.7 range 14.4-18.2)	Yes	No	Cross-sex hormones with GnRHa	Cross-sex hormones without GnRHa	Individuals from primary sample receiving hormones in combination with another medication	N/A	Retrospective cohort study	Relevant data from medical record (follow-up ranged from 6.4 to 53.0 months)	Treatment started before Mar 2016 (data extracted to Jan 2018)
Lopez de Lara 2020	Spain	To evaluate the psychosocial status of paediatric patients with gender incongruity and to establish the impact on this after one-year of cross hormonal therapy	Paediatric endocrinology clinic	Adolescents age 14-18 with gender incongruity, at Tanner stage 2 or higher	23 (mean age 16; 16 brf, 7 brm)	Yes	No	Cross-sex hormones	Age, ethnicity and socio-economically matched controls presumed no GD	Other control group	30 (mean age 16 (range 14-18); 12 females, males)	Prospective cohort study	Baseline and 12 month follow-up	Attended clinic during 2018 and 2019
Tordoff 2022	US	To investigate whether initiation of puberty blockers and gender-affirming hormones is associated with changes in depression, anxiety, and suicidality in transgender and nonbinary youths	Urban multidisciplinary children's gender clinic	Transgender and nonbinary adolescents and young adults who completed the initial clinic appointment	104 (mean age 15.8 range 13-20; 63 trans males, 27 trans females, 10 nonbinary / fluid, 4 don't know)	Yes	Yes	Puberty suppressants and cross-sex hormones	No hormone treatment	Non-exposed individuals from primary sample	N/A	Prospective cohort study	Baseline (initial appointment), 3, 6 and 12 month follow-up (follow-up timepoints not linked to initiation of medical intervention)	Initial appointment from Aug 2017 to Jun 2018
Valentine 2021	US	To examine changes in BMI and lipids in transgender youth on testosterone therapy compared to cisgender females	Multidisciplinary gender identity programme at a large pediatric centre	Transgender males age 14-21 on testosterone therapy with available follow-up data	42 (mean age 16.6 SD 1.3)	Yes	No	Testosterone	BMI-matched female adolescents presumed no GD	Other control group	82 (mean age 15.5 (SD 1.8))	Retrospective cohort study	Baseline and available short- and long-term follow-up data (average short-term 4.9 months range 0.5-17.7, long-term 10.8 months range 2.6–25.7)	Treated from 2014 to 2018
van de Grift 2020	Netherlands	To describe the development of sex characteristics in a transgender adolescent cohort of early and later-initiated puberty suppressant treatment compared with young adults without treatment	Patients were identified using local registries (single centre)	Adolescents with gender dysphoria who initiated and continued puberty suppression treatment, and were less than age 18 at initiation	300 (mean age at start of puberty suppressants 15 SD 2.0; 184 brf, 116 brm)	Yes	Yes	Puberty suppressants and cross-sex hormones	No puberty suppressants prior to hormones	Non-exposed individuals from primary sample	N/A	Retrospective cohort study	Baseline, and follow-ups at initiation of cross-sex hormones, and initiation of surgery	Sought treatment from 2006 to 2013 (data collected until 2018)
Pre-post														
Allen 2019	US	To evaluate the effectiveness of gender-affirming hormones for improving psychological well-being and decreasing suicidality among transgender youth	Gender identity clinic at a large children's hospital	Young people age 13-20 years who were treated with gender-affirming hormones for at least 3 months	47 (mean age at treatment initiation 16.50; 33 brf, 14 brm)	Yes	No	Cross-sex hormones (with and without previous GnRHa)	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and single follow-up (at least 3 months after start of treatment - treatment duration ranged 113-1016 days, mean 349)	Presented to clinic between 2015 and 2018
Chiniara 2018	Canada	To examine characteristics, including mental health comorbidities, among adolescents presenting to a transgender clinic and to compare these data to previous reports.	Specialist gender service based in children's hospital	12-18 year olds with gender dysphoria who desired pubertal suppression or cross-gender hormones	75 (no information on characteristics provided)	Yes	Yes	GnRHa and cross-sex hormones	No comparator	No comparator	N/A	Retrospective pre-post single group study	Follow-up at 4.7 ± 3.7 months after starting gender-affirming hormones	Recruited Apr 2011 to Apr 2014 (commenced GnRHa between Jun 2011 and Apr 2015)
de Vries 2014	Netherlands	To investigate whether gender dysphoric youth improve over time with medical intervention consisting of puberty suppressants followed by cross-sex hormones and gender reassignment surgery	Center for Gender Dysphoria for all ages	Young adults who had received puberty suppressants followed by cross-sex hormones and gender reassignment surgery	55 (mean age at GnRHa intiation 14.8 range 11.5–18.5; 22 brm, 33 brf)	Yes	Yes	Puberty suppression followed cross-sex hormones and surgery	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline and follow-ups at intiation of cross-sex hormones, and 1 year after surgery	Referred between 2000 and 2008 (follow-up between 2008 and 2012)
Delemarre-van de Waal 2006	Netherlands	To investigate the efficacy and safety of GnRHa treatment in adolescents with gender dysphoria	Center for Gender Dysphoria for all ages	Adolescents receiving GnRHa under the Dutch protocol for 2 years or longer	21 (age not reported; 11 brf, 10 brm)	Yes	Yes	GnRHa and cross-sex hormones	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline, 12 months and 24 months for some outcomes, and 24 months for others	Not reported
Grimstad 2021a	US	To evaluate breakthrough bleeding in trangender adolescents receiving testosterone treatment	Gender service at children's hospital	Sex assigned female at birth with functional uterus and ovaries present at start of testosterone treatment, received treatment for 12 months plus	232 (age 13-28 years, mean age 16.3)	Yes	No	Testosterone	No comparator	No comparator	N/A	Retrospective pre-post single group study	All outcome data available in the medical record after 12 months of testosterone treatment (duration of follow-up varied)	Seen between 2010 and 2020
Hannema 2017	Netherlands	To evaluate the efficacy and safety of estrogen treatment for pubertal induction in transgirls	Center for Gender Dysphoria for all ages	Birth-registered males diagnosed with gender dysphoria and treated with estrogen for 12 months or longer	28 (median age 16.0 range 13.9-18.9)	Yes	No	Estrogen	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline, and 12, 24 and 36 month follow-up	Seen between 1998 and 2009
Hisle-Gorman 2021	US	To examine mental health and psychotropic medication use among transgender adolescents following gender-affirming pharmaceutical care (secondary aim of sub-group of primary sample)	Military Healthcare Data Repository	Transgender military dependent youth who received care for gender dysphoria before age 18	963 (median age study start 12 IQR 10-14; 300 brm, 663 brf)	Yes	Yes	Puberty suppressants or cross-sex hormones	No comparator	No comparator	N/A	Retrospective pre-post single group study	All available data before and after initiation of treatment (followed for mean 1.5 years [IQR 0.8-2.8] after start of treatment)	Received care between Oct 2010 and Sep 2018

Jarin 2017	US	To identify patterns in metabolic and cardiovascular parameters in transgender adolescents receiving cross-sex hormones	Four medical centers / hospitals (two paediatric)	Adolescents age 14-25 diagnosed with gender dysphoria and receiving cross-sex hormones	116 (72 brf mean age 16 range 13-22, 44 brm mean age 18 range 14-25)	Yes	No	Cross-sex hormones	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, and 1-3 months, 4-6 months, and 6 plus months follow-up	Seen in clinics between 2008 and 2014
Kaltiala 2020	Finland	To assess how adolescent development progresses and psychosocial functioning changes among transexual adolescents after starting cross-sex hormone treatment	Gender identity unit for minors	Adolescents diagnosed with transexualism who were offered cross-sex hormones (referred before age 18)	52 (mean age 18.1 at diagnosis, range 15.2 - 19.9 years; 11 brm, 41 brf)	Yes	No	Cross-sex hormones	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline (during initial assessment) and 12 months follow-up (during real-life phase)	Offered treatment between 2011 and 2017
Khatchadourian 2014	Canada	To describe patient characteristics at presentation, treatment, and response to treatment in youth with gender dysphoria	Children's gender identity programme	Youth with a diagnosis of gender dysphoria and achieved at least Tanner stage 2	84 (median age at first visit 16.8 range 11.4-22.5; 45 brf, 37 brm)	Yes	Yes	GnRHa, spironolactone, cross-sex hormones, surgery	No comparator	No comparator	N/A	Retrospective pre-post single group study	All relevant clinic notes (follow-up ranged from 0.0 to 11.3 years)	Seen from Jan 1998 to Dec 2011
Klaver 2018	Netherlands	To examine the change in body shape and composition in transgender adolescents receiving hormone treatments	Center for Gender Dysphoria for all ages	All persons who started hormone treatment before 18 years old and had undergone x-rays and medical checkups to adulthood	192 (71 brm mean age at start of GnRHa 14.5 SD 1.8, 121 brf mean age 15.3 SD 2.0)	Yes	Yes	GnRHa followed by cross-sex hormones	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and follow-ups at addition of cross-sex hormones, and 22 years of age	Started treatment between 1998 and 2014
Klaver 2020	Netherlands	To investigate cardiovascular risk factors, and assess obesity and dyslipidemia prevalence in transgender adolescents receiving hormone treatments	Center for Gender Dysphoria for all ages	All persons who started hormone treatment before 18 years old and had undergone x-rays and medical checkups to adulthood	192 (71 brm mean age at start of GnRHa 14.6 SD 1.8, 121 brf mean age 15.2 SD 2.0)	Yes	Yes	GnRHa followed by cross-sex hormones	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and follow-ups at addition of cross-sex hormones, and 22 years of age	Diagnosed with gender dysphoria from 1998 to Dec 2015
Klink 2015	Netherlands	To assess peak bone mass in young adults with gender dysphoria who had been treated with GnRHa and cross-sex hormones during their pubertal years	Tertiary referral center	At least 21 years, gonadectomy had taken place, and data on bone development at start of GnRHa treatment, at start of cross-sex hormone therapy, and at the age of 22 years were available	34 (15 brm mean age at start of GnRHa 14.9 SD 1.9, 19 brf mean age at start of GnRHa 15.0 SD 2.0)	Yes	Yes	GnRHa followed by cross-sex hormones followed by gonadectomy	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and follow-ups at addition of cross-sex hormones, and 22 years of age	Received gonadectomy from Jun 1998 to Aug 2012
Kuper 2020	US	To examine how transgender youth body dissatisfaction, depression, and anxiety symptoms change over the first year of receiving gender-affirming hormone therapy	Multi-disciplinary programme	Youth who received gender-affirming hormone therapy	n = 148 (mean age 14.9 range 9-18; 55 brm, 94 brf)	Yes	Yes	GnRHa and cross-sex hormones	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline (initial assessment) and 12 month follow-up (mean 14.9 months, range 11-18 months)	Initial assessments between Aug 2014 and Mar 2018
Laurenzano 2021	US	To assess the effectiveness and safety of subcutaneous testosterone in achieving recommended testosterone levels and cessation of menses in transmasculine and gender-diverse adolescents	Gender management clinic for children and adolescents (not explicitly stated)	Transmasculine and gender diverse youth who started subcutaneuous testosterone at age 13-19 and received it for > 6 months	119 (mean age at presentation 16.0; transmale 110, nonbinary 3, other 6)	Yes	No	Subcutaneuos testosterone	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and follow-up to most recent data available (median follow-up 1.9 years range 6 months to 5.5 years)	Received treatment between Aug 2012 and Feb 2020
Madsen 2021	Netherlands	To study the prevalence and determinants in the development of erythrocytosis in trans men on testosterone therapy	Center for Gender Dysphoria for all ages	Trans men who started testosterone and had at least one follow-up visit and laboratory results	1073 (mean age at initiation of treatment 22.5, IQR 18.4-31.8)	Yes	No	Testosterone	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and regular follow-up data up to 20 years (follow-up varied in terms of frequency and length)	Seen between 1972 and 2015 (data collection Jan 2004 to Dec 2018)
Millington 2019	US	To assess prevalence of hyperkalemia in gender-diverse adolescents taking spironolactone for gender transition	Gender Management Service Programme at children's hospital	Adolescents prescribed spironolactone for gender transition	85 (mean age 16.6 SD 1.7; 82 female gender identity, 3 nonbinary gender identity)	Yes	No	Spironolactone	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline and follow-up of all measures recorded during treatment (up to 7 years, variation in follow-up period not reported, median no. of measures 3 (range 1-10))	Seen from 2007 to 2017
Millington 2022	US	To examine changes in serum creatinine during gender affirming hormone treatment in transgender and gender diverse youth	Four specialist gender services based in children's hospitals	Transgender and gender diverse adolescents prior to initiation of gender-affirming treatment with no prior GnRHa treatment	286 (92 brm median age 17.3 IQR 16.2-18.6, 194 brf median age 16.2 IQR 15.1-17.5)	Yes	No	Testosterone, estrodial (with or without spironolactone)	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline, and 6, 12, 18 and 24 month follow-up	Recruitment Jul 2016 to Sep 2018
Mullins 2021	US	To examine thrombosis and thrombosis risk factors among an exclusively adolescent and young adult transgender population receiving gender-affirming hormone therapy	Pediatric hospital-associated gender identity clinic	Age 13 to 24 at initiation of gender-affirming hormone treatment	611 (median age at presentation to clinic 17.0 IQR 16.0-19.0; 428 brf, 183 brm)	Yes	No	Testosterone, estrogen	No comparator	No comparator	N/A	Retrospective pre-post single group study	All relevant data before and during treatment (estrogen median treatment duration 554 days IQR 283-1037, testosterone 577 days IQR 283-923)	Seen from Jul 2013 to Mar 2019
Olson 2014	US	To determine if subcutaneous delivery of testosterone resulted in menstrual cessation and the normal male ranges of serum testosterone in female-to-male transgender youth	Large, gender identity youth-specialized multidisciplinary clinic	Transgender males age 12 to 24 receiving testosterone cypionate via subcutaneous injections for masculinization	36 (mean age 18.7 SD 2.6)	Yes	No	Subcutaneuos testosterone	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline and 6 month follow-up	Recruited from 2011 to 2012
Olson-Kennedy 2018	US	To examine the physiologic impact of gender-affirming hormones in a cohort of adolescents with gender dysphoria	Large, gender identity youth-specialized multidisciplinary clinic	Transgender youth age 12-24 with gender dysphoria who wished to undergo phenotypic gender transition	59 (mean age 18 range 12-23; 34 brf, 25 brm)	Yes	No	Cross-sex hormones	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline and 24 month follow-up (range 21-31 months)	Presented for care between Feb 2011 and Jun 2013
Perl 2020	Israel	To examine blood pressure changes in transgender male adolescents treated with GnRHa alone and after the addition of testosterone	Gender dysphoria clinic at children's hospital	Transgender male adolescents who were treated solely with GnRHa for at least 2 months	15 (mean age at intiation of GnRHa 14.4 SD 1.0)	Yes	Yes	GnRHa followed by addition of testosterone	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, and follow-ups at end of GnRHa treatment (average 3 months SD 1), initiation of testosterone, and mean 4 months (SD 2) after starting testosterone	Sought care between 2013 and 2018
Perl 2021	Israel	To examine blood pressure changes in transgender female adolescents treated with GnRHa alone and after the addition of estradiol	Gender dysphoria clinic at children's hospital	Transgender female adolescents who were treated solely with GnRHa for at least 2 months	19 (mean age at initiation of GnRHa 15.7 SD 1.6)	Yes	Yes	GnRHa and estradiol	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, and follow-ups at end of GnRHa treatment (mean 9 months SD 6), initiation of estradiol, and 18.5 months (mean) after estradiol (range 3-63 months)	Sought care between 2013 and 2020
Schagen 2018	Netherlands	To assess the effects of GnRHa treatment and gender-affirming hormone treatment on adrenal androgen levels in adolescents with gender dysphoria	Center for Gender Dysphoria for all ages	Adolescents with gender identity disorder who fulfilled criteria for treatment according to Endocrine Society guideline	127 (73 brf mean age at GnRHa start 14.3 range 11.5-18.6, 54 brm age 14.0 range 11.6 to 17.9)	Yes	Yes	GnRHa treatment followed by GnRHa combined with estradiol or testosterone	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline and 6 monthly follow-up to 4 years	Treated between 1998 and 2009
Schagen 2020	Netherlands	To describe bone mass development in adolescents with gender dysphoria treated with GnRHa, subsequently combined with gender-affirming hormones	Center for Gender Dysphoria for all ages	Adolescents with gender identity disorder who fulfilled criteria for treatment according to existing guidelines	121 (51 brm mean age 14.1 SD 1.7, 70 brf mean age 14.5 SD 2.0)	Yes	Yes	GnRHa treatment followed by GnRHa combined with estradiol or testosterone	No comparator	No comparator	N/A	Prospective pre-post single group study	Baseline and 12-monthly follow-up to 5 years	Treated between 1998 and 2009
Segev-Becker 2020	Israel	To describe patient characteristics at presentation, management, and fertility preservation among a cohort of children with gender dysphoria	Multidisciplinary paediatric gender dysphoria clinic	All patients younger than 18 years who began GnRHa treatment	106 (median age at referral 15.5 range 4.6-18 years)	Yes	Yes	GnRHa followed by cross-sex hormones	No comparator	No comparator	N/A	Retrospective pre-post single group study	All relevant data following initiation of treatment (follow-up period not reported)	Referred from Mar 2013 to Dec 2018
Sequeira 2019	US	To determine the effect of testosterone on body mass index (BMI) z-score in transmasculine adolescents at 6 and 12 months after initiation	Adolescent medicine clinic at large children's hospital	Transmasculine adolescents age 13 to 19 who received testosterone	46 (mean age not reported - criteria range 13-19)	Yes	No	Testosterone	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, 6 and 12 month follow-up	Seen between Sep 2014 and May 2017

Stoffers 2019	Netherlands	To investigate the efficacy and safety of testosterone treatment in transgender adolescents	Clinic (no other information provided)	Adolescents diagnosed with gender dysphoria who hard started GnRHa and had subsequently received testosterone for more than 6 months	62 (median age at GnRHa initiation 16.5 range 11.8-18.0)	Yes	Yes	GnRHa followed by testosterone	No comparator	No comparator	N/A	Retrospective pre-post single group study	Median duration of follow-up 12 months (range 5-33 months).	Received treatment between Nov 2010 and Aug 2018
Tack 2016	Belgium	To analyse impact of consecutive treatment with Lynestrenol in combination with testosterone on physical characteristics, safety, metabolic parameters, and hormone levels in gender dysphoric adolescent transboys	Multi-disciplinary child gender team	Gender dysphoric transmale adolescents who received Lynestrenol for at least 6 months	38 (mean age at start of treatment 15 years 10 months)	Yes	Yes	Lynestrenol - androgonic progestin (puberty suppressant) only, and in combination with testosterone	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, 6 and 12 months follow-up with Lynestrenol plus testosterone	Treated from 2010 until Sep 2015
Tack 2017	Belgium	To assess the side effects and biochemical changes of Cyproterone acetate alone and in combination with estrogen in adolescent trans-girls	Multi-disciplinary child gender team	Transgirls with gender dysphoria who received Cyproterone acetate for at least 6 months	27 (mean age at start of treatment 16 years 6 months)	Yes	Yes	Cyproterone acetate (puberty suppressant) only, and in combination with estrogen	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline, 6 and 12 month follow-up with Cyproterone acetate plus estrogen	Treated from 2008 to Oct 2016
van der Loos 2021	Netherlands	To investigate changes in bone geometry among transgender adolescents using GnRHa and gender-affirming hormones	Center for Gender Dysphoria for all ages	Transgender adolescents treated with GnRHa and subsequent gender-affirming hormones before the age of 18 years, min. duration 6 months GnRHa, and for whom DXA scans were available	322 (106 brm median age 13.1 to 15.5 for sub-groups at GnRHa start, 216 brf median age 11.9 to 15.7 for subgroups at GnRHa)	Yes	Yes	GnRHa and cross-sex hormones	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline (start of GnRHa), and follow-ups at addition of cross-sex hormones, and ≥2 years after cross-sex hormones (median 3.1 4.3 years across six sub-groups)	Visited clinic between 1972 and Dec 2018
Vlot 2017	Netherlands	To investigate the effect of GnRHa and cross-sex hormone treatment on bone turnover markers and bone mineral apparent density in transgender adolescents	Center for Gender Dysphoria for all ages	Adolescents diagnosed with gender dysphoria who were treated with GnRHa and cross-sex hormone treatment, with available outcome data	70 (28 brm median age at GnRHa start 13.5 range 11.5-18.3, 42 brf median age 15.1 range 11.7-18.6)	Yes	Yes	GnRHa and cross-sex hormones	No comparator	No comparator	N/A	Retrospective pre-post single group study	Baseline (start of GnRHa), and follow-ups at addition of cross-sex hormones, and 24 months after cross-sex hormones	Started treatment between 2001 and 2011
Cross-sectional														
Arcelus 2016	UK	To explore prevalence of non-suicidal self-injury (NSSI) in young trans people and to identify what factors can predict this	National gender clinic for adults (age 17+)	All individuals below the age of 25 years old who were referred for and offered an assessment	268 (mean age 19.9 SD 2.17; 121 brf, 136 brm, 11 no answer)	Yes	Yes	GnRNa or cross-sex hormones	No hormone treatment	Non-exposed individuals from primary sample	N/A	Cross-sectional study with controls	Single time-point (initial assessment after referral to service)	Referred between Nov 2012 to June 2015
Burke 2020	Netherlands	To investigate whether hormonal interventions in adolescents diagnosed with gender dysphoria affect their click-evoked otoacoustic emissions compared to age- and sex-matched controls	Center for Gender Dysphoria for all ages	Children and adolescents diagnosed with gender dysphoria	105 (62 brf mean age 15.6 range 10.3-20.3, 43 brm mean age 15.9 range 11-20)	Yes	Yes	GnRHa; cross-sex hormones and GnRHa	No hormone treatment; Age- and sex-matched controls divided into early, mid- and late-adolescent groups.	Non-exposed individuals from primary sample; Other control group	Early (13 boys, mean age 12.8 (SD 1.9); 15 girls, 12.2 (1.7)); mid- (18 boys, 13.9 (1.9); 10 girls, 15.1 (1.8)); late-adolescent (20 boys, 17.1 (0.8); 21 girls, 17.9 (0.4))	Cross-sectional study with controls	Single time-point	Not reported
Fontanari 2020	Brazil	To evaluate the impact of each domain of gender affirmation (social, legal, and medical/surgical) on the mental health of transgender and gender nonbinary youth.	Facebook	Transgender boys, transgender girls, and gender nonbinary Brazilian youth, age 16 to 24 years	350 (mean age 18.61 (CI 95% 18.34–18.88; 149 transgender boys, 85 transgender girls, 116 gender nonbinary)	Yes	Yes	Hormone therapy'; 'any hormone or surgical treatment'	No hormone therapy; no hormone or surgical treatment	Non-exposed individuals from primary sample	N/A	Cross-sectional study with controls	Single time-point	Recruitment Feb to Apr 2018
Grannis 2021	US	To assess the effect of testosterone treatment on internalizing symptoms, body image dissatisfaction, and activation patterns within the amygdala-prefrontal cortex circuit in transgender adolescent boys	Gender development clinic at a large children's hospital	Adolescent transgender boys age 9-21 with a diagnosis of gender dysphoria receiving gender affirming medical care	47 (22 treated: mean age 17.03 SD 1.24; 25 untreated mean age 15.75 SD 1.47)	Yes	No	Testosterone	No testosterone	Non-exposed individuals from primary sample	N/A	Cross-sectional study with controls	Single time-point (around 1 year after treatment)	Recruited Dec 2018 to Mar 2020
Green 2022	US	To examine associations among access to gender-affirming hormone therapy with depression, thoughts of suicide, and attempted suicide among transgender and nonbinary youth	Community	Transgender or non-binary youth age 13-24 who reside in the US	11,914 (average age received GAHT 17.62, average age not received GAHT 17.30; transgender male 29%, transgender female 8%, nonbinary 63%)	Yes	No	Gender-affirming hormones	No hormones but wants to take them; no hormones and does not want to take them	Non-exposed individuals from primary sample	N/A	Cross-sectional study with controls	Single time-point	Data collected from Oct to Dec 2020
Millington 2021b	US	To examine lipoprotein subtype profiles in transmasculine adolescents treated with testosterone	Children's hospital (biobank)	Transmasculine adolescents age 12 to 23 treated with testosterone	17 (median age 18.4 IQR 17.6-19.5)	Yes	No	Testosterone	Two adolesecent control groups (male and female) presumed no GD	Other control group	32 girls, mean age 17.6 (IQR 17.1-18.5); 33 boys, mean age 17.8 (IQR 17.0-19.4))	Cross-sectional study with controls	Single time-point (duration of treatment mean 1.2 months range 0.33 to 3.3 years)	Samples collected between Jan 2017 and Aug 2020
Nokoff 2020	US	To evaluate insulin sensitivity and body composition among transgender adolescents receiving cross-sex hormones compared with cisgender adolescents	Centre for gender diversity at children's hospital	Transgender adolescents (up to age 21) on either testosterone or estradiol for at least 3 months	35 (21 brf mean age 17.0 SD 1.4, 14 brm mean age 16.3 SD 1.4)	Yes	No	Testosterone, estradiol	Adolescents presumed no GD (matched on pubertal stage and BMI for brf, and age and BMI for brm	Other control group	Controls for brf: 42 girls, mean age 15.2 (SD 1.9); 19 boys, 15.3 (SD 1.6) Controls for brm: 23 girls, 15.9 (SD 1.4); 24 boys, 15.7 (SD 1.4)	Cross-sectional study with controls	Single time-point (testosterone mean duration 11.2 SD 5.9 months, estradiol mean duration 12.3 SD 9.9 months)	Recruited from 2016 to 2018
Strang 2022	US	To explore the relationship between gender-affirming medical intervention status (i.e., pubertal suppression, gender-affirming hormones) and executive functioning in transgender youth	Community, gender services, gender and neurodiversity programme	Transgender youth age 11-21 enrolled in a study of cognition, mental health and neurodevelopment (all met criteria for gender dysphoria)	124 (mean age 16.67 range 11.65-21.56, female 41, male 81, non-binary 2)	Yes	Yes	Testosterone or estrogen (with or without puberty suppression)	No hormone treatment	Non-exposed individuals from primary sample	N/A	Cross-sectional study with controls	Single time-point	Enrolled in study between 2018 and 2020
Turban 2022	US	To examine associations between recalled access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults	Community	Transgender adults age 18 plus who reside in the US who reported ever desiring gender-affirming hormones	21,598 (accessed CSH: age 14-15 median age 21 IQR 18-35; age 16-17 median 19 IQR 18-22), age 18+ median 31 IQR 25-45, no access age not reported; 11,346 brf, 10,252 brm)	Yes	No	Cross-sex hormones	No cross-sex hormones; cross-sex hormones in adulthood	Non-exposed individuals from primary sample; Individuals from primary sample receiving hormones in adulthood	N/A	Cross-sectional study with controls	Single time-point	Data collected Aug to Sep 2015

Abbreviations: BMI -body mass index; brf - birth-registered female; brm - birth-registered male; CSH - cross-sex hormones; GD - gender dysphoria; GnRHa - Gonadotropin-releasing hormone analogue; NSSI - non-suicidal self-injury;
* Terminology used in original paper retained for these columns to accurately reflect study aim and population selected

Supplementary Table 3 - Outcomes reported by included studies

Study ID	Pubertal development	Side effects	Gender-related outcomes	Body image	Psychological health	Psychosocial outcomes	Physical health	Bone health	Fertility	Cognitive/neuro-developmental	Other	Outcomes (measures)
Cohort												
Achille 2020	No	No	No	No	Yes	Yes	No	No	No	No	No	Depression (Patient Health Questionnaire-9 modifed for teens (PHQ-9), Center for Epidemiologic Studies Depression Scale - Revised (CESD-R)); quality of life (Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (QLES-Q-SF))
Becker-Hebly 2020	No	No	No	No	Yes	Yes	No	No	No	No	No	Psychological functioning (Youth Self Report (YSR) for age 11-18 and Adult Self Report (ASR) for 18+); Global functioning (Children's Global Assessment Scale (CGAS); Health-related quality of life (Kidscreen-27 for age 11-18 and SF (short form)-8 for 18+)
Beking 2020	Yes	No	No	No	No	No	No	No	No	Yes	No	Lateralization index of the amygdala (during an emotional face matching task with angry and fearful faces - fMRI); hormone levels (testosterone - not explicitly identified as an outcome);
Burke 2016	Yes	No	No	No	No	No	No	No	No	Yes	No	Visuospatial working memory (brain activation pattern by sex, performance - mental rotation task - fMRI); hormone levels (testosterone - not explicitly identified as an outcome)
Cantu 2020	No	No	No	No	Yes	No	No	No	No	No	No	Depression (PHQ-9); Suicidality (item 9 on PHQ-9); Anxiety (Generalised Anxiety Disorder Assessment (GAD-7))
de Nie 2022	No	No	No	No	No	No	No	No	Yes	No	No	Exocrine testicular function (Spermatogenesis (Johnsen score), germ cell type (ratio of most advanced germ cell types)); Fertility preservation
Grimstad 2021b	Yes	No	No	No	No	No	Yes	No	No	No	No	Anthropometrics (adult height); skeletal maturation (Delta bone age)
Jensen 2019	No	Yes	No	No	No	No	No	No	No	No	No	Reported side effects (identified based on those recorded by care team physicians in narrative portions of electronic patient notes); required dose (ending dose of treatment)
Lopez de Lara 2020	No	No	Yes	No	Yes	Yes	No	No	No	No	No	Severity of gender dysphoria (UGDS); Patient strengths and difficulties (Strengths and Difficulties Questionnaire (SDQ)); Level of anxiety (STAI); Mood (BDI); family functioning (Family apgar test)
Tordoff 2022	No	No	No	No	Yes	No	No	No	No	No	No	Depression (PHQ-9); Anxiety (GAD-7); Self-harm or suicidal thoughts over previous 2 weeks (PHQ-9 question 9)
Valentine 2021	No	No	No	No	No	No	Yes	No	No	No	No	Anthropometrics (BMI); Metabolic parameters (lipid profile - total cholesterol, LDL-C, HDL, triglycerides)
van de Grift 2020	Yes	No	No	No	No	No	Yes	No	No	No	No	Anthropometrics (height, weight, BMI, waist/hip circumference); puberty development (Tanner staging, breast and genital characteristics - clinical exam); surgical requirements for sex re-assignment
Pre-post												
Allen 2019	No	No	No	No	Yes	Yes	No	No	No	No	No	Suicidality (Ask Suicide-Screening Questions (ASQ) instrument); Well-being (General Well-Being Scale (GWBS of the Pediatric Quality of Life Inventory)
Chiniara 2018	No	No	No	No	No	No	Yes	No	No	No	No	Safety (AST, ALT, total cholesterol, HDL, LDL, triglycerides, glucose, HbA1c, hemoglobin, red blood cell count, hematocrit, insulin)
de Vries 2014	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Behavioral and emotional problems (CBCL and YSR); depressive symptoms (BDI); anxiety and anger (STAI); global functioning (CGAS); gender dysphoria (UGDS); body image (BIS); well-being (own questionnaire; Satisfaction with Life Scale (SWLS); Subjective Happiness Scale (SHS)); quality of life (World Health Organization Quality of Life Brief Version (WHOQOL-BREF))
Delemarre-van de Waal 2006	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Puberty development (Tanner stage, skeletal age - left hand); anthropometrics (height, weight, sitting height, hip / waist circumference); bone density (whole body, hip, lumbar spine); body composition (fat mass percentage, lean body mass); cardio-metabolic measures (fasting glucose, insulin, cholesterol, HDL, LDL); hormone levels (gonadotrophins, sex hormones)
Grimstad 2021a	Yes	No	No	No	No	No	No	No	No	No	No	Menstruation (presence of, and risk factors for, breakthrough bleeding)
Hannema 2017	Yes	No	No	No	No	No	Yes	No	No	No	No	Puberty development (Tanner stage, bone age); anthropometrics (weight, height, sitting height, waist/hip circumference/ratio, BMI); hormone levels (LH, FSH, testosterone, estradiol); safety (blood pressure, prolactin, ALT, AST, alkaline phosphatase, γ-glutamyl tranferase, creatinine, HbA1c, hematocrit); body composition (fat mass, fat percentage, lean body mass percentage)
Hisle-Gorman 2021	No	No	No	No	Yes	No	No	No	No	No	No	Mental health care visits (number of visits, diagnosis sub-category); psychotropic medications (type)
Jarin 2017	Yes	No	No	No	No	No	Yes	No	No	No	No	Anthropometrics (height, weight, BMI); Safety (blood pressure, lipids (total cholesterol, LDL, HDL, triglycerides, triglyceride:HDL ratio), AST, ALT, hemoglobin, hematocrit, HbA1c, prolactin, serum urea nitrogen, creatinine); hormone levels (testosterone, estradiol)
Kaltiala 2020	No	No	No	No	Yes	Yes	No	No	No	No	No	Adolescent development (living arrangements, peer relationships, school / work participation, romantic involvement, competence in managing everyday matters); need for specialist level psychiatric treatment (depression, anxiety, suicidality/self-harm, conduct problems, psychotic symptoms, substance abuse, autism, attention deficit hyperactivity disorder, eating disorder)
Khatchadourian 2014	No	Yes	No	No	No	No	Yes	No	No	No	No	Side effects (patient reported); Safety for antiandrogens (electrolyte and urea/creatinine levels)

Klaver 2018	Yes	No	No	No	No	No	Yes	No	No	No	No	Body shape (anthropometrics) (waist-hip ratio, body weight, waist/hip circumference, body height, BMI); body composition (whole-body and regional-body fat, total lean body mass, total body mass)
Klaver 2020	Yes	No	No	No	No	No	Yes	No	No	No	No	Anthropometrics (body height, body weight, BMI, waist/hip circumference); cardiovascular risk (blood pressure, glucose, insulin, homeostatic model assessment for insulin resistance (HOMA-IR), lipid values (total cholesterol, HDL, LDL, triglycerides), prevalence of obesity and dyslipidemia)
Klink 2015	Yes	No	No	No	No	No	Yes	Yes	No	No	No	bone health (BMD, BMAD); height, weight, BMI
Kuper 2020	No	No	No	Yes	Yes	No	No	No	No	No	No	Body dissatisfaction (BIS); depression (Quick Inventory of Depressive Symptoms (QIDS) - self- and clinician report); Anxiety (SCARED); suicidality (suicidal ideation, suicide attempt); suidality and self-harm (passive ideation, suicide attempt, NSSI); mental health treatment (psychiatric medication, therapy, support group)
Laurenzano 2021	Yes	Yes	No	No	No	No	Yes	No	No	No	No	side effects (injection site reaction, acne); hormone levels (total and free testosterone, estradiol); menstruation (time to cessation); safety (hematocrit, AST, ALT, blood pressure (hypertension), lipids (total cholesterol, LDL, HDL, triglycerides)); anthropometrics (BMI)
Madsen 2021	No	No	No	No	No	No	Yes	No	No	No	No	Erythrocytosis (hematocrit levels); hormone levels
Millington 2019	No	No	No	No	No	No	Yes	No	No	No	No	Incidence of hyperkalemia (serum potassium concentration >5.0 mmol/L; relationship between potassium levels and treatment dose and duration
Millington 2022	No	No	No	No	No	No	Yes	No	No	No	No	Kidney function (serum creatinine, estimated glomerular filtration rate (eGFR)); BMI
Mullins 2021	Yes	No	No	No	No	No	Yes	No	No	No	No	Incidence of arterial or venous thrombosis during treatment. Testosterone and estradiol levels.
Olson 2014	Yes	No	No	No	No	No	Yes	No	No	No	No	Menstrual cessation; hormone levels (testosterone (free and total levels), estradiol); anthropometrics (BMI); safety (blood pressure; hemoglobin, ALT, AST, non-fasting total cholesterol)
Olson-Kennedy 2018	Yes	No	No	No	No	No	Yes	No	No	No	No	Safety (total cholesterol, HDL, triglycerides, AST, ALT, potassium, prolactin, hemoglobin, glucose, blood pressure); anthropometrics (BMI); hormone levels (estradiol, testosterone free and total)
Perl 2020	Yes	No	No	No	No	No	Yes	No	No	No	No	Changes in weight status (BMI); Changes in blood pressure (systolic and diastolic); puberty development (hypothalamic–pituitary–gonadal axis suppression); hormone levels (tesosterone; estradiol, LH, FSH)
Perl 2021	Yes	No	No	No	No	No	Yes	No	No	No	No	Changes in weight status (BMI); Changes in blood pressure (systolic and diastolic); puberty development (hypothalamic–pituitary–gonadal axis suppression); hormone levels (testosterone; estradiol, LH, FSH)
Schagen 2018	No	No	No	No	No	No	Yes	No	No	No	No	adrenal androgen levels (dehydropepiandrosterone (DHEAS), androstenedione)
Schagen 2020	No	No	No	No	No	No	No	Yes	No	No	No	bone health (BMAD (whole body, hip, lumbar spine), serum bone markers)
Segev-Becker 2020	No	Yes	No	No	No	No	No	No	No	No	No	Side effects related to medical treatment (from medical record)
Sequeira 2019	No	No	No	No	No	No	Yes	No	No	No	No	BMI
Stoffers 2019	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Puberty development (acne, hair growth / shaving, voice lowering, menses); anthropometrics (height, weight, BMI); blood pressure; hormone levels (FSH, LH, testosterone, estradiol, SHBG); safety (Creatinine, ALP, total cholesterol, HDL, LDL, triglycerides, hemoglobin, hematocrit, vitamin D, DHEAS, androstenedione); bone health (BMD at lumbar spine, left neck, right hip, BMAD for spine and left neck)
Tack 2016	Yes	Yes	No	No	No	No	Yes	No	No	No	No	Anthropometry (height, weight, BMI); Side effects (acne, hirsutism, patient-reported); Safety (Hemoglobin, hematocrit, electrolytes, creatinine, AST, ALT, total cholesterol, triglycerides, HDL, LDL, hemoglobin andfasting insulin); hormone levels (thyroid stimulating hormone, anti-Müllerian hormone, free thyroxin, LH, FSH, estradiol, total and free testosterone, SHBG)
Tack 2017	Yes	Yes	No	No	No	No	Yes	No	No	No	No	Puberty development (physical changes); Side effects (patient-reported); Anthropometry (height, weight, BMI); Safety (hemoglobin, hematocrit, creatinine, AST, ALT, triglycerides, total cholesterol, HDL, LDL, DHEAS, prolactin); Hormone levels (thyroid stimulating hormone, free thyroxin, LH, FSH, estradiol, total and free testosterone, SHBG, free androgen index)
van der Loos 2021	Yes	No	No	No	No	No	Yes	No	No	No	No	Bone geometry (subperiosteal width (SPW) and endocortical diameter (ED)); hormone levels (testosterone, estradiol); anthropometrics (height, BMI)
Vlot 2017	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Anthropometrics (height, weight); Tanner stage (clinician assessed, bone age); bone turnover markers (P1NP (Procollagen type 1 N propeptide), osteocalcin, ICTP (Cross-linked carboxyterminal telopeptide of type I collagen)); bone health (BMD, BMAD for lumbar spine and femoral neck)
Cross-sectional												
Arcelus 2016	No	No	No	No	Yes	No	No	No	No	No	No	Psychopathology (Symptom Checklist 90 Revised)
Burke 2020	Yes	No	No	No	No	No	No	No	No	No	No	Click-Evoked Otoacoustic Emissions

Fontanari 2020	No	No	Yes	No	Yes	No	No	No	No	No	No	Anxiety (Overall Anxiety Severity and Impairment Scale (OASIS)); depressive symptoms (Modified Depression Scale (MDS)); gender distress (Gender Distress Scale (GDS)); gender positivity (Gender Positivity Scale (GPS))
Grannis 2021	No	No	No	Yes	Yes	No	No	No	No	Yes	No	Generalized anxiety symptoms (Screen for Child Anxiety Related Emotional Disorders (SCARED)); social anxiety (Liebowitz Social Anxiety Scale (LSAS)); depression (Children's Depression Inventory (CDI)); suicidality/non-suicidal self-injury (Suicidal Behaviors Questionnaire - Revised (SBQ-R)); body image dissatisfaction (BIS); amygdala activation (face processing task with functional MRI)
Green 2022	No	No	No	No	Yes	No	No	No	No	No	No	Depression (PHQ-2, score 3+ coded as depression); Suicidality (considered suicide in last year, if yes how many attempts in last year (dichotomised as 0 or 1+))
Millington 2021b	Yes	No	No	No	No	No	Yes	No	No	No	No	Cardiovascular risk (HDL, HDL-C, LDL, LDL-C, triglyceride-rich lipoprotein (TRL)); testosterone levels
Nokoff 2020	Yes	No	No	No	No	No	Yes	No	No	No	No	Insulin sensitivity (glucose, insulin, HbA1c; leptin); Lipids (total cholesterol, triglycerides, HDL, LDL); Safety (AST, ALT); hormone levels (LH, FSH, SHBG, testosterone, estradiol, free androgen index); body composition (total body fat, fat mass, lean tissue, lean mass); anthropometrics (BMI); blood pressure
Strang 2022	No	No	No	No	No	No	No	No	No	Yes	No	Executive functioning problems (Behavior Rating Inventory of Executive Function (BRIEF- 2; Adult BRIEF) - primary outcome BRIEF Global Executive Composite (GEC), subscales - inhibition, cognitive flexibility, updating/working memory)
Turban 2022	No	No	No	No	Yes	Yes	No	No	No	No	No	Severe psychological distress in month before survey (defined as score of 13+ on K6+); Binge drinking in month before survey (defined as 5+ standard alcoholic drinks on single occasion; Life-time illicit drug use; Suicidality (ideation during year prior; attempt requiring hospitalisation in year prior)

Supplementary Table 4 - Critical appraisal scores for included studies

Study ID	Study design	NOS total score	NOS Q1 representative of population	NOS Q1 score	NOS Q8 adequacy of follow-up	NOS Q8 score	NOS Q3 Ascertainment of treatment exposure	NOS Q3 score	NOS Q2 Selection of non-exposed group	NOS Q2 score	NOS Q5 comparability of cohorts	NOS Q5 part 1	NOS Q5 part 2	NOS Q7 follow-up duration	NOS Q7 score	NOS Q6 assessment of outcome	NOS Q6 score	NOS Q4 Demonstration outcome of interest not present at start	NOS Q4 score
Cohort																			
Achille 2020	Prospective cohort study	4	States that vast majority of eligible population entered the study, but no values or indication of what this means given. Recruited from single clinic.	0	116 participants entered study - 50 who completed questionnaires reported on. No information on those lost to follow-up.	0	Information in paper provides confidence that clinic data used.	1	Participants who had received either nothing at all or only puberty blockers.	1	Controlled for outcome at baseline, psychiatric medication and psychotherapy. Separate analysis by gender. Did not control for age. Did not control for prior receipt of pubertal suppression.	0.5	0.5	Follow-up not linked to treatment duration. Exposure to treatment at any time used as variable - not duration	0	Validated scales designed for self-completion.	1	N/A	
Becker-Hebly 2020	Retrospective cohort study	3	204 eligible and invited to take part. Large proportion not included. Single clinic.	0	Response rate for follow-up 37% (n=75).	0	Self-reported treatment path then controlled via clinicians' reports.	1	Those not treated with hormones from same clinic sample.	1	Did not control for gender / sex, other treatments or outcome at baseline. Used age-adjusted population norms to compare outcomes. Did not control for distribution in intervention group.	0	0	Treatment started after baseline but duration and start of treatment not reported or included in analysis	0	Validated scales - combination of self-report and clinician-report.	1	N/A	
Beking 2020	Prospective cohort study	5	Single clinic population but recruitment / response not described so no way of knowing what proportion of clinic population were included.	0	All treated participated at follow-up (4 of 41 controls dropped out before follow-up).	1	Clinic data on treatment reported.	1	Male and female controls presumed to not experience gender incongruence.	0.5	Controlled for testosterone levels and handedness (identified as confounders). Controlled for session effect in analysis (baseline). Matched for age and birth-registered sex.	1	0	Mean duration treatment / follow-up 9.8 months (sufficient for some)	0.5	Independent assessment using validated method.	1	N/A	
Burke 2016	Prospective cohort study	5	Single clinic population and recruitment / response not described. No way of knowing what proportion of clinic population were included.	0	All 21 girls with gender dysphoria followed-up (5 of 41 controls dropped out between sessions).	1	Clinic data on treatment reported.	1	Male and female controls presumed to not experience gender incongruence.	0.5	Controlled for testosterone levels and IQ (identified as confounder). Controlled for session effect in analysis (baseline). Matched for age and birth-registered sex.	1	0	Mean duration treatment / follow-up 10 months (sufficient for some)	0.5	Independent assessment using validated method.	1	N/A	
Cantu 2020	Retrospective cohort study	4	Single clinic population - likely to be a selected sample because participation depends on data availability. No information provided on numbers.	0	Participation depended on outcome data being available for analysis so all followed up. Two did not provide GAD-7 data.	1	Clinic data used to categorise treatment groups.	1	Drawn from same source as exposed participants.	1	Nothing reported about potential confounders being controlled for in the analysis.	0	0	Follow-up not linked to treatment - exposure to treatment occurred between baseline and follow-up	0	Validated measures for depression and anxiety used. Suicidality outcome not included in analysis on treatment differences.	1	N/A	
de Nie 2022	Retrospective cohort study	5	Single clinic population - only those who underwent bilateral orchiectomy combined with vaginoplasty were eligible - random sample taken.	0	Of the 263 sampled, 49 were then excluded due to no tissue being stored or no testicular parenchyma on slides. Not likely to influence results.	1	Authors state data was collected from medical records.	1	Adults presenting to the same clinic who underwent bilateral orchiectomy combined with vaginoplasty.	0.5	Study participants are birth-registered males only, groups are split by puberty stage (Tanner stage 2-3; Tanner stage 4-5; Adult). Study does not control for use of medications such as contraceptive pill.	1	0	Information on follow-up not explicit - indications follow-up sufficient for some participants (12 months plus)	0.5	Detailed information on sample testing given.	1	N/A	
Grimstad 2021b	Retrospective cohort study	3.5	Single-clinic population, very small number excluded due to incomplete height data (6/195 eligible patients).	0.5	Only those with complete height data were included, those had not reached adult height by the end of the study were excluded.	0.5	Data obtained from medical records.	1	Drawn from same source as exposed participants.	1	Only participants who were assigned female sex at birth were included. Unadjusted analyses were carried out.	0.5	0	No information provided on time between start of treatment and measurement of final height	0	Height measured in triplicate at clinic visits. Participants defined as growing if demonstrated growth velocity of 0.5cm per year. Parental height used - unclear how outcome data were calculated.	0	N/A	
Jensen 2019	Retrospective cohort study	6	Single-clinic study, one participant excluded due to non-binary gender identification and two participants excluded from analysis.	0.5	No loss to follow-up.	1	Data extracted from medical records.	1	Drawn from same source as exposed participants.	1	Separate analyses were carried out for sex. No other covariates were adjusted for.	0.5	0	Median duration and range of duration of hormone treatment and follow-up indicates sufficiency	1	Extracted from medical records.	1	N/A	
Lopez de Lara 2020	Prospective cohort study	4.5	No information given on the number eligible or the response rate.	0	Table 3 indicates all participants were successfully followed up.	1	Treatment data from clinic records used.	1	Controls presumed to not experience gender incongruence matched on age, ethnicity and socio-economic status. Outcomes are psychosocial.	0	The non-exposed group was matched on age, however men and women were analysed together. No other covariates were controlled for.	0.5	0	Follow up was carried a year after initiation of treatment	1	Validates scales were used.	1	N/A	
Tordoff 2022	Prospective cohort study	3.5	Single-clinic study. 30% of eligible patients did not take part.	0	Follow-up rates less than 90% at each follow-up timepoint.	0	Data on hormone use was collected via self-report.	0	Drawn from same source as exposed population.	1	Gender but not sex was controlled for as confounder. Ethnicity was also controlled for. The analysis controlled for receipt of mental health therapy.	0.5	0.5	3, 6, 9, 12 month - follow-up not linked to treatment initiation but some participants with sufficient follow-up	0.5	Collected via validated scales.	1	N/A	
Valentine 2021	Retrospective cohort study	3.5	Single-clinic study. Nearly 20% excluded due to only being seen twice.	0	Only patients who had been seen twice were included, although only 28 had lipid panels and 18 pre- and post-testosterone.	0	Information obtained from primary care database.	1	Females presumed to not experience gender incongruence drawn from a primary care database.	0.5	Only birth-registered females were included. Unadjusted analyses were used.	0.5	0	Average total follow-up 10.8 months (range 2.6 - 25.7), therefore sufficient for some but not all.	0.5	Data collected at clinical visits.	1	N/A	
van de Grift 2020	Retrospective cohort study	5	Single-clinic study. Patients lost to follow-up (n=68) were excluded.	0	Only participants with complete follow-up data were included.	1	Registry and patient record data collection used.	1	Drawn from same source as exposed group.	1	Separate analyses were carried out for males and females.	0.5	0	Initiation of different therapies in treatment protocol indicate follow-up sufficient for most but not all	0.5	Data collected as part of routine clinical practice.	1	N/A	
Pre-post																			
Allen 2019	Retrospective pre-post single group study	4	Required pre- and post-treatment data to be available. States that around half of eligible youth did not have pre-test data so were not included. Single clinic.	0	Only those with data available at both time-points were included.	1	Clinic data on treatment reported.	1	N/A		Controlled for treatment duration and outcome at baseline (ANCOVA). Separate analysis by birth-registered sex.	0.5	0	At least 3 months and treatment duration mean 349 days. Potentially not all participants sufficient.	0.5	Questionnaires administered by mental health professional as part of clinical care assessment. Validated scales used.	1	N/A	
Chiniara 2018	Retrospective pre-post single group study	3.5	Single-clinic study, 15/218 excluded due to missing data.	0.5	Low follow-up rates reported.	0	Retrospective review of medical records.	1	N/A		Separate analyses were conducted by sex.	0.5	0	Repeat hormonal levels measured after 4.7 (SD 3.7) months of hormone therapy - sufficient for some not all	0.5	Validated scales and clinical record data used.	1	N/A	
de Vries 2014	Prospective pre-post single group study	3.5	National clinic. 111 prescribed GnRHa. 70 participants approached one-year post-surgery, 55 took part. Large proportion of eligible population now missing.	0	Not all 70 provided data (some questionnaires added partway through). Response rate: CBCL, YSR: 54; BDI, TPI, STAI, CGAS, and UGS: 41; BIS: 57.	0	Information presented on start of treatment - medical records data.	1	N/A		Separate analyses were conducted by sex, and age was adjusted for.	1	0	Final follow-up takes place one year after surgery	1	All validated scales except 'self-constructed' objective measure of wellbeing.	0.5	N/A	
Delemarre-van de Waal 2006	Prospective pre-post single group study	1.5	Single clinic, inadequate information on response rates given.	0	Inadequate information on follow-up given.	0	Follow-up protocol integrated into clinical practice.	1	N/A		No adjustment made for age, sex, co-interventions or socio-demographic confounders.	0	0	Insufficient information provided on duration of follow-up	0	Clinical measurements presented, but no information given on how this information was obtained.	0.5	N/A	
Grimstad 2021a	Retrospective pre-post single group study	4.5	Single-site clinic. Inclusion based on medical charts explicitly documenting occurrence or absence of breakthrough bleeding, for which 5 were excluded.	0.5	Only those with complete outcome data were included.	1	Data collected from medical records.	1	N/A		Unadjusted analyses used.	0	0	Breakthrough bleeding measured up to 12 months following start of treatment	1	Breakthrough bleeding recorded on medical records.	1	N/A	
Hannema 2017	Prospective pre-post single group study	4	Single-clinic population. Participants were invited to participate but no information is given on response rates.	0	Complete data available at earlier timepoints but attrition at later timepoints.	0.5	Data obtained from medical records.	1	N/A		The study only included birth-registered males. Unadjusted analyses were used.	0.5	0	Participants had been treated for at least 12 months	1	Detailed information given on physical, laboratory and radiological investigations.	1	N/A	
Hisle-Gorman 2021	Retrospective pre-post single group study	4	All eligible participants were included from the Military Health System.	0.5	No information given on missing data.	0	Obtained from pharmacy records.	1	N/A		Analyses adjusted for age and sex. Some important covariates such as parental rank adjusted for.	1	0	Median follow-up post-treatment was 1.5 years (IQR 0.7 to 2.7) - potentially not sufficient for all participants	0.5	Outcome data collected from Military Healthcare Data Repository.	1	N/A	
Jarin 2017	Retrospective pre-post single group study	4.5	Four large local clinics. Data extracted from pre-existing databases.	1	Low follow-up rates at each timepoint.	0	Data extracted from pre-existing databases.	1	N/A		Separate analyses were conducted for gender groups. No other covariates were adjusted for.	0.5	0	Outcomes were assessed beyond 6 months	1	Assessed as part of clinical practice.	1	N/A	
Kaltiala 2020	Retrospective pre-post single group study	4.5	Recruited from one of two gender services in Finland. Of 57 diagnosed, 5 were excluded.	1	All followed up.	1	Information in paper provides confidence that clinic data used.	1	N/A		Logistic regression examined whether age and sex were predictive of outcomes, but these variables were not taken into account when examining change pre-post.	0	0	Time between start of treatment and follow-up given as approximately one year	1	Collected by the clinical team via structured and free format assessments, through evaluation of existing files.	0.5	N/A	
Khatchadourian 2014	Retrospective pre-post single group study	3	Single-clinic study, included all patients.	0.5	No information given on missing data.	0	Data obtained from clinical records.	1	N/A		Descriptive summaries were presented separately for males and females.	0.5	0	No information given on time between start of treatment and assessment of outcomes	0	Clinical outcomes assessed as part of routine medical care.	1	N/A	
Klaver 2018	Retrospective pre-post study	3.5	Single-clinic study, participants who had not undergone wholebody DXA were excluded (n=5). 66 participants excluded on different treatment protocol - reason unclear.	0	No information given on follow-up rates.	0	Data collected from medical records.	1	N/A		Analyses were carried out separately for sex. No other covariates were adjusted for.	0.5	0	Final follow-up at 22 years old, and average age at start of CSH was under 17, with an SD of approximately 1	1	Collected from medical records.	1	N/A	
Klaver 2020	Retrospective pre-post study	3.5	Single-clinic study. Study excluded those without whole-body dual-energy radiograph absorptiometry and with no consultation in early adulthood. No numbers reported.	0	No information given on follow-up timepoint.	0	Data collected from medical records.	1	N/A		Separate analyses were carried out for males and females. No other covariates were adjusted for.	0.5	0	At 22 years olds - sufficient follow-up indicated by age at starting hormones	1	Collected from medical records.	1	N/A	
Klink 2015	Retrospective pre-post study	4.5	Single-clinic study. Study only included participants for whom data available at each timepoint. Number of patients excluded not reported.	0	High follow-up rates at final timepoint.	1	Detailed information on timing of treatment given.	1	N/A		Separate analyses were carried out for males and females. No other covariates were adjusted for.	0.5	0	Mean age at start was <17 SD 1.4-2.3, with final follow-up at 22 years old	1	Collected from medical records.	1	N/A	

Kuper 2020	Prospective pre-post single group study	3	Single-clinic study that excluded 22/209 patients due to missing follow-up.	0.5	Despite those with follow-up data being excluded, less than 90% of participants included in analysis of each outcome.	0	Clinician data were entered into a research database.	1	N/A		Hypothesis testing carried out (not separately by age or sex). Regression controlling for confounders planned, but no correlations between change scores and demographic/treatment variables.	0	0	Mean treatment duration 10.9 months, range 1-18 - not all participants sufficient follow-up	0.5	Validated scales used.	1	N/A		
Laurenzano 2021	Retrospective pre-post single group study	4	Single-center study. Included all eligible.	0.5	No information given on follow-up rates.	0	De-identified clinical data entered institutional review board approved endocrine database.	1	N/A		Only birth-registered females were included in the study. Unadjusted analyses were used.	0.5	0	Minimum follow-up was 6 months, with the median being 1.9 years.	1	Collected as part of clinical practice.	1	N/A		
Madsen 2021	Retrospective pre-post single group study	4.5	Large database from single-clinic. 431 were excluded due to missing data, 894 were excluded due to lack of available laboratory results.	0	All included in analysis.	1	Clinic data on treatment reported.	1	N/A		The study only included birth-registered females. Prevalences were summarised descriptively.	0.5	0	Every 3 to 6 months in first year, then yearly / 2-yearly after - follow-up varied although sufficient.	1	Outcomes collected via routine clinical measurements.	1	Data not presented on participants with erythrocytosis at baseline.	0	
Millington 2019	Retrospective pre-post single group study	3	Single clinic study - excluded 5/90 patients for indications other than gender transition (n=2) and no outcome measurements (n=3).	0.5	Thirty-six subjects (42%) had at least one potassium measurement, 48 subjects (56%) had a measurement within the first 6 months.	0	Data collected from medical records.	1	N/A		Unadjusted analyses were used.	0	0	42% within first 3 months of therapy, 56% within first 6 months. Up to 7 years follow-up for some.	0.5	Routine clinical testing.	1	Hyperkalemia was present in one baseline measurement.	0	
Millington 2022	Prospective pre-post study	4.5	Small number of clinics in USA. No information given on consent rates.	0.5	Low follow-up rates at each timepoint.	0	Data collected from medical records.	1	N/A		Age and sex matched z scores were calculated and summarised descriptively.	1	0	Follow-ups to 24 months post-treatment	1	Laboratory, medication, and anthropometric data abstracted from the medical record. Creatinine measurements performed at clinical laboratories of study sites and at outside facilities.	1	N/A		
Mullins 2021	Retrospective pre-post single group study	4	Single clinic that included those initiating treatment and age 13 to 24 years at initiation of GAHT.	0.5	All included in analysis.	1	Data collected from medical records.	1	N/A		Unadjusted analyses were used, most descriptive summaries combined the data from gender groups.	0	0	Median duration of treatment 574 days (IQR: 283-962) - minimum duration unclear	0.5	Data collected as part of routine clinical practice.	1	No indication patients were tested for thrombosis before inclusion.	0	
Olson 2014	Prospective pre-post single group study	4.5	Single-clinic study. No information provided on consent rates.	0	One participant was missing information on testosterone levels and excluded from the analysis.	1	Information on average dose provided - confident that clinic data used.	1	N/A		Only birth-registered females were included in the study. No other covariates were adjusted for.	0.5	0	6 months after starting treatment	1	Hormone levels, lab values, anthropometric measurements and menstrual history were obtained via chart review.	1	N/A		
Olson-Kennedy 2018	Prospective pre-post single group study	4.5	Single-clinic study. No information provided on consent rate. Authors state that 101 participants were evaluated at baseline, but only 59 presented in study.	0	High follow-up.	1	Detailed information on treatment provided.	1	N/A		Gender groups analysed separately. Unadjusted analyses were used.	0.5	0	Follow-up carried out 21-31 months after initiation of hormones	1	Baseline and follow-up physiologic data were abstracted from the medical charts of the participants.	1	N/A		
Perl 2020	Retrospective pre-post single group study	5	Participants recruited from a national clinic, only 3 participants were excluded due to missing data.	1	Those with missing data were excluded from the study.	1	Medical records data used to identify those on treatment.	1	N/A		Only birth-registered females were included in study. No information is given on adjustment for baseline variables.	0.5	0	Follow-up average 4 months (SD 2) - some but not all participants sufficient follow-up	0.5	Data extracted from medical records. BP measured during a clinic visit within 1–4 weeks of GnRHa and testosterone injections using a Welch Allyn Vital Signs Monitor VSM 300 (Welch Allyn, Inc., Beaverton, OR).	1	N/A		
Perl 2021	Retrospective pre-post single group study	5	Participants were recruited from a national clinic, only 1 participant was excluded due to missing data.	1	Those with missing data were excluded from the study.	1	Data extracted from medical records.	1	N/A		Only birth-registered males were included in the study. Unadjusted analyses were used.	0.5	0	Follow-up average 18.5 months, range 3-63 months - some not all participants sufficient follow-up	0.5	Data extracted from medical records. BP measured using a Welch Allyn Vital Signs Monitor VSM 300 (Welch Allyn, Inc., Beaverton, OR).	1	N/A		
Schagen 2018	Prospective pre-post single group study	4	National clinic. No information on consent rates but selected from all eligible.	0.5	No information given on follow-up rates.	0	Details on duration of treatment provided.	1	N/A		Separate analyses carried out for males and females. No other covariates were adjusted for.	0.5	0	Analyses used data up to 2 years post-treatment	1	Detailed information given on laboratory investigations.	1	N/A		
Schagen 2020	Prospective pre-post single group study	5	National clinic. Small number of all treated excluded due to DXA scans not being available at the start of GnRHa.	1	No information given on missing data rates at follow-up.	0	Detailed treatment protocol provided.	1	N/A		Analyses adjusted for pubertal stage and sex. No other covariates were adjusted for.	1	0	Analyses presented up to 36 months of treatment	1	Dual-energy x-ray absorptiometry (DXA) performed using Hologic QDR 4500. Markers of bone formation and resorption determined in fasting blood samples, drawn on day of scans.	1	N/A		
Segev-Becker 2020	Retrospective pre-post single group study	3	National clinic. Consecutive participants recruited.	1	No information given on follow-up rates.	0	Information on treatment delivery presented.	1	N/A		Some but not all descriptive summaries stratified by gender/sex. Participants were split into pre-pubertal and pubertal groups.	0	0	No information given on follow-up period	0	Data collected retrospectively from clinical records.	1	N/A		
Sequeira 2019	Retrospective pre-post single group study	5	Single-clinic study. No information given on number excluded.	0	All included in model.	1	Information in paper provides confidence that clinic data used.	1	N/A		Only birth-registered females were included. The analysis controlled for age, hormone dose rate and baseline BMI z-score.	1	0	Follow-up carried out to 12 months post-initiation of treatment	1	Height and weight documented in each clinical encounter were used to calculate BMI in kg/m2.	1	N/A		
Stoffers 2019	Retrospective pre-post single group study	4	Single-clinic study. Only 2/64 participants declined to participate.	0.5	High rates of follow-up at 6 months post-treatment, but low rates at 12 and 24 months post-treatment.	0.5	Information in paper provides confidence that clinic data used.	1	N/A		Only birth-registered females were included. Unadjusted analyses were used.	0.5	0	The median duration of follow-up was 12 months (range 5-33 months)	0.5	Data collected via chart review.	1	N/A		
Tack 2016	Retrospective pre-post single group study	4	Single-centre study in country with three clinics. Small number (5 out of 43) excluded due to missing data.	0.5	No information given on follow-up rates at each timepoint.	0	Information in paper provides confidence that clinic data used.	1	N/A		Only birth-registered female adolescents were included. Unadjusted analyses were used.	0.5	0	Baseline, 6 and 12 month follow-up	1	Data collected as part of clinical follow-up.	1	N/A		
Tack 2017	Retrospective pre-post single group study	4.5	Single-centre study in country with three clinics. All those who received CA for at least 6 months included.	1	No information given on follow-up rates at each timepoint.	0	Information in paper provides confidence that clinic data used.	1	N/A		Only birth-registered males were included in the study. Unadjusted analyses were used.	0.5	0	Baseline, 6 and 12 month follow-up	1	Data collected as part of clinical follow-up.	1	N/A		
van der Loos 2021	Retrospective pre-post study	4.5	Single-clinic study. 123 excluded due to DXA not being available.	0	Only participants who had a DXA were included.	1	Information in paper provides confidence that clinic data used.	1	N/A		Separate analyses were carried out for males and females.	0.5	0	Follow up >2 years after treatment initiation	1	Detailed information on DXA testing given.	1	N/A		
Vlot 2017	Retrospective pre-post single group study	4	Single-clinic study. A large number of eligible participants were excluded due to incomplete data.	0	Data indicates that more than 10% were missing data for outcomes.	0	Data collection took place at point of treatment.	1	N/A		Analysis stratified on sex and bone age. Unadjusted analyses were used.	1	0	Follow-up 24 months after start of hormone treatment	1	Detailed information on DXA testing provided.	1	N/A		
Cross-sectional																					
Arcelus 2016	Cross-sectional study with controls	3.5	299 eligible patients - 31 did not answer questions regarding NSSI and were excluded. National clinic.	1	More than 10% excluded from analysis - no information provided on those or explanation.	0	Self-reported data on treatments received prior to assessment at adult clinic.	0	Those not treated with hormones from same clinic sample.	1	Controlled for gender, self-esteem, transphobia, interpersonal problems, social support.	0.5	0	N/A		Validated assessment tools used.	1	N/A		
Burke 2020	Cross-sectional study with controls	5	Single clinic population - no information provided about recruitment and response, or number eligible.	0	All participants included in analysis.	1	Clinic data used to select / categorise treatment groups.	1	Treatment naïve from same source plus controls with no gender incongruence which was appropriate for outcome.	1	Controlled for puberty stage / age, sex assigned at birth but no other treatments. Cross-sectional so no baseline control.	1	0	N/A		Standard assessment - equipment and procedure explained in full - same applied to all participants (treatments and controls).	1	N/A		
Fontanari 2020	Cross-sectional study with controls	3	Self-selecting survey.	0	All participants who completed the survey were included in the analysis.	1	Self-report.	0	Non-exposed group from same survey sample.	1	No adjustment made for age, sex, co-interventions or socio-demographic confounders.	0	0	N/A		Validated scales used.	1	N/A		
Grannis 2021	Cross-sectional study with controls	4	Single-clinic population. Participants excluded on ability to participate in MRI based research, but no numbers are given on this.	0	Information on those included in analysis not provided.	0	Data collected from medical records.	1	Drawn from same source.	1	Age was adjusted for. Only birth-registered females were included.	1	0	N/A		Validated scales and detailed brain imaging protocol.	1	N/A		
Green 2022	Cross-sectional study with controls	4	Self-selecting survey	0	2895 participants missing data on treatment and excluded from analyses. Missingness could be related to the underlying value.	0	Self-report.	0	Drawn from same source as exposed group.	1	Analysis controlled for age, sex, socio-demographic characteristics, also controlled for parental support, victimisation, receipt of puberty blockers, receipt of gender identity conversion therapy.	1	1	N/A		Validated scale used to measure depression, items on suicidal thoughts and behaviours taken from Youth Risk Behaviour Survey.	1	N/A		
Millington 2021b	Cross-sectional study with controls	2.5	Single-clinic study with no information given on numbers excluded.	0	No information given on data collection rates.	0	Detailed information on treatment provided.	1	No information given on selection of non-exposed group.	0	Only birth-registered females were included. Mostly unadjusted analyses were carried out.	0.5	0	N/A		Results collected as part of clinical practice.	1	N/A		
Nokoff 2020	Cross-sectional study with controls	4	Single-clinic study. No information provided on consent rate.	0	All participants included in analysis according to table data.	1	Information in paper provides confidence that clinic data used.	1	Controls from Colorado RESistance to InSulin in Type 1 ANd Type 2 diabetes, and Health Influences in Puberty studies. Different ages in both and skewed clinical characteristics in one.	0	Separate analyses were carried out for sex, and analyses either matched on Tanner stage or adjusted for age. Analyses also matched on BMI.	1	0	N/A		Body composition measured using DXA and detailed information on laboratory assays provided.	1	N/A		
Strang 2022	Cross-sectional study with controls	4	Shared study protocol in two locations. No information given on consent rates.	0	Only those with complete report forms were included.	1	Collected through parent and self-report, and only verified through medical records when dates not recalled.	0	Drawn from same population as exposed group.	1	Analyses adjusted for assigned sex and age.	1	0	N/A		Validated scales and evaluations used.	1	N/A		

Turban 2022	Cross-sectional study with controls	3	National survey covering 50 states in collaboration with 400+ lesbian, gay, bisexual and transgender organisations. Population covers 18-36 year olds.	1	No information given on number of participants excluded from analyses due to missing data.	0	Self-reported by participants.	0	Drawn from same population as exposed group.	1	Separate analyses were carried out for participants receiving hormones in early adolescence, late adolescence and adulthood. Some but not all analyses adjusted for sex assigned at birth.	0.5	0	N/A		One validated scale used, the rest appear to be bespoke for the study.	0.5	N/A	

Supplementary Table S5 - Gender-related, body image, psychological, psychosocial and cognitive outcomes

Study ID	Country	Study design	Study quality	Treated sample	Average age CSH treatment started	Comparator	Intervention	Outcome (measure)	Follow-up specific to outcome	Study results
Gender dysphoria										
Lopez de Lara 2020	Spain	Cohort	Moderate	23 (16 brf, 7 brm)	Mean age 16 y (range 14-18 y)	30 (no GD)	Hormones (with GnRHa)	Gender dysphoria (UGDS)	12m	Decrease (imrpovement) in gender dysphoria score. Using clinical cut-off, no gender dysphoria at follow-up compared to all at baseline.
Body image										
Grannis 2021	US	Cross-sectional	Moderate	19 brf	Mean age at data collection 17 y (SD 1.2 y) Mean treatment duration 13.1 m (SD 10.3m)	23	Testosterone	Body image dissatisfaction (BIS)	N/A	Lower levels of dissatisfaction with body image in those treated compared to those not treated.
Psychological / mental health										
Depression										
Lopez de Lara 2020	Spain	Cohort	Moderate	23 (16 brf, 7 brm)	Mean age 16 y (range 14-18 y)	30 (no GD)	Hormones (with GnRHa)	Depressive symptoms (BDI II)	12m	Decrease in depression (~70% in normal range at follow-up) - symptoms higher compared to controls.
Kaltiala 2020	Finland	Pre-post	Moderate	52 (11 brm, 41 brf)	Mean age at diagnosis 18.1 y (SD 1.1y)	N/A	Hormones	Need for treatment due to depression	12m	Need for treatment decreased at follow-up.
Grannis 2021	US	Cross-sectional	Moderate	19 brf	Mean age at data collection 17 y (SD 1.2 y) Mean treatment duration 13.1 m (SD 10.3m)	23	Testosterone	Depressive symptoms (CDI)	N/A	Depressive symptoms were lower in the treated group compared to those not treated.
Green 2022	US	Cross-sectional	Moderate	274 (205 brf, 27 brm, 42 not reported)	Not reported	2961	Hormones	Frequency of depressed mood and anhedonia (PHQ-2)	N/A	Prevalence of recent depression lower in those treated (~61%) compared to those not treated (75%).
Anxiety										
Lopez de Lara 2020	Spain	Cohort	Moderate	23 (16 brf, 7 brm)	Mean age 16 y (range 14-18 y)	30 (no GD)	Hormones (with GnRHa)	Anxiety (STAI (state and trait subscales))	12m	Anxiety decreased over time for both subscales, but continued to be higher compared to controls at follow-up.
Kaltiala 2020	Finland	Pre-post	Moderate	52 (11 brm, 41 brf)	Mean age at diagnosis 18.1 y (SD 1.1y)	N/A	Hormones	Need for treatment due to anxiety	12m	Need for treatment decreased.
Grannis 2021	US	Cross-sectional	Moderate	19 brf	Mean age at data collection 17 y (SD 1.2 y) Mean treatment duration 13.1 m (SD 10.3m)	23	Testosterone	Anxiety disorders (CARED); social anxiety (LSAS)	N/A	Decreased levels of anxiety compared to those not treated.
Self-harm and suicidality										
Allen 2019	US	Pre-post	Moderate	47 (33 brf, 14 brm)	Mean age 16.5 y	N/A	Hormones (plus/minus GnRHa)	Suicidality (Ask Suicide-Screening Questions)	Single (mean 349d, range 113-1016d)	Suicidality scores decreased.
Kaltiala 2020	Finland	Pre-post	Moderate	52 (11 brm, 41 brf)	Mean age at diagnosis 18.1 y (SD 1.1y)	N/A	Hormones	Need for treatment due to suicidality/self-harm	12m	Need for treatment decreased.
Grannis 2021	US	Cross-sectional	Moderate	19 brf	Mean age at data collection 17 y (SD 1.2 y) Mean treatment duration 13.1 m (SD 10.3m)	23	Testosterone	Suicidality (SBQ-R), Lifetime suicidality)	N/A	No evidence for difference between groups in suicidality.
Green 2022	US	Cross-sectional	Moderate	274 (205 brf, 27 brm, 42 not reported)	Not reported	2961	Hormones	Suicidality/non-suicidal self-injury (SBQ-R)	N/A	Treated participants less likely to have seriously considered suicide or attempted suicide compared to untreated.
Need for treatment										

Kaltiala 2020	Finland	Pre-post	Moderate	52 (11 brm, 41 brf)	Mean age at diagnosis 18.1 y (SD 1.1y)	N/A	Hormones	Need for treatment (conduct problems, psychosis, substance abuse, autism, ADHD, eating disorders)	12m	No change in need for treatment for all outcomes, although baseline need for treatment was low.
Internalising problems										
Lopez de Lara 2020	Spain	Cohort	Moderate	23 (16 brf, 7 brm)	Mean age 16 y (range 14-18 y)	30 (no GD)	Hormones (with GnRHa)	Emotional symptoms (subscale of SDQ)	12m	Emotional symptoms decreased at follow-up and were similar at follow up to adolescents not experiencing GD.
Externalising problems										
Lopez de Lara 2020	Spain	Cohort	Moderate	23 (16 brf, 7 brm)	Mean age 16 y (range 14-18 y)	30 (no GD)	Hormones (with GnRHa)	Conduct problems and hyperactivity (SDQ subscales)	12m	Conduct problems and hyperactivity decreased and were lower at follow-up compared to adolescents not experiencing GD.
Strengths and Difficulties										
Lopez de Lara 2020	Spain	Cohort	Moderate	23 (16 brf, 7 brm)	Mean age 16 y (range 14-18 y)	30 (no GD)	Hormones (with GnRHa)	Mental health (SDQ)	12m	Difficulties decreased with fewer in borderline/abnormal range at follow-up, and were similar at follow up to adolescents not experiencing GD.
Psychosocial										
Family functioning and peer relationships										
Lopez de Lara 2020	Spain	Cohort	Moderate	23 (16 brf, 7 brm)	Mean age 16 y (range 14-18 y)	30 (no GD)	Hormones (with GnRHa)	Family functioning (FAT), peer problems (SDQ), prosocial (SDQ)	12m	No change in family functioning or peer problems but a small improvement in prosocial skills. At follow-up, family functioning similar to adolescents not experiencing GD, but fewer peer problems and more prosocial skills (small significant difference).
Kaltiala 2020	Finland	Pre-post	Moderate	52 (11 brm, 41brf)	Mean age at diagnosis 18.1 y (SD 1.1y)	N/A	Hormones	Peer relationships (normative vs restricted)	12m	Small decrease in proportion with normative peer relationships.
Wellbeing										
Allen 2019	US	Pre-post	Moderate	47 (33 brf, 14 brm)	Mean age 16.5 y	N/A	Hormones (plus/minus GnRHa)	Wellbeing (PQLI General Wellbeing Scale)	Single (mean 349d, range 113-1016d)	Increase in wellbeing.
Other										
Kaltiala 2020	Finland	Pre-post	Moderate	52 (11 brm, 41brf)	Mean age at diagnosis 18.1 y (SD 1.1y)	N/A	Hormones	Living arrangements, school / work participation, romantic involvement, competence in managing everyday matters	12m	Decrease in participants living with parents/guardians. No change in other outcomes.
Cognitive										
Beking 2020	Netherlands	Cohort	Moderate	21 brf	Mean age 16.1 y (SD 0.7)	41 (no GD)	Testosterone (with GnRHa)	Lateralisation index of the amygdala (during emotional face matching task with angry and fearful faces)	Single (mean 9.8m, range 5.6-14.8)	Mean lateralisation index decreased (more rightward), and at follow up was similar to controls.
Burke 2016	Netherlands	Cohort	Moderate	21 brf	Mean age at data collection 16.1 y (SD 0.8) Mean treatment duration 10 m (range 6-15)	41 (no GD)	Testosterone (with GnRHa)	Visuospatial working memory (brain activation pattern, performance on a mental rotation task)	Single (mean 10m, range 6-15)	No difference between groups in performance. The treated group and male controls showed stronger activations at follow-up.
Grannis 2021	US	Cross-sectional	Moderate	19 brf	Mean age at data collection 17 y (SD 1.2 y) Mean treatment duration 13.1 m (SD 10.3m)	23	Testosterone	Amygdala activation (face processing task)	N/A	Higher activation in left amygdala and cluster of stronger connectivity in right amygdala in treated compared to the controls.
Strang 2022	US	Cross-sectional	Moderate	52 (brs not reported)	Received GAH <1y: mean age 16.7 (SD 1.7) Received GAH >1y: mean age 16.1 (SD 1.4)	72	Hormones (plus/minus GnRHa)	Executive functioning (BRIEF Global Executive Composite)	N/A	Treated groups (<1y and >1y treated) had better executive functioning, cognitive flexibility and working memory compared to untreated.

Abbreviations: ADHD - Attention Deficit Hyperactivity Disorder; BDI - Beck's Depression Inventory; BIS - Body Image Scale; brf - birth-registered females; brm - birth-registered males; BRIEF - Behaviour Rating Inventory of Executive Function; CARED - Child Anxiety Related Emotional Disorders; CDI - Children's Depression Inventory; FAT - Family Apgar Test; GD - gender dysphoria; GnRHa - gonadotrophin releasing-hormone analogues; LSAS - Liebowitz Social Anxiety Scale; m = months; PHQ - Patient Health Questionnaire; PQLI - Paediatric Quality of Life Inventory; SBQ-R - Suicidal Behaviours Questionnaire - Revised; SD - standard deviation; SDQ - Strengths and Difficulties Questionnaire; STAI - State-Trait Anxiety Inventory; UGDS - Utrecht Gender Dysphoria Scale; y = years

Supplementary Table S6 - Physical health outcomes, fertility and side effects

Study ID	Country	Study design	Study quality	Treated sample	Average age CSH treatment started	Comparator	Intervention	Outcome (measure)	Follow-up specific to outcome	Study results
Physical health outcomes										
Bone health										
Klink 2015	Netherlands	Pre-post	Moderate	34 (15 brm, 19 brf)	Mean age for brm: 16.6 y (SD 1.4 y) Mean age for brf: 16.4 y (SD 2.3 y)	N/A	Hormones	aBMD, BMAD (absolute, z-scores using natal sex)	Single (22 years of age)	No evidence for change in measures (small sample size).
Schagen 2020	Netherlands	Pre-post	Moderate	78 (36 brm, 42 brf)	Mean age for brm: 16.2 y (SD 1.2 y) Mean age for brf: 16.9 y (1.1 y)	N/A	Hormones (with GnRHa)	aBMD, BMAD (absolute, z-scores using natal sex), serum bone markers.	36m	Increase in bone density (both absolute and in comparison to natal sex references) in males and females.
Stoffers 2019	Netherlands	Pre-post	Moderate	62 brf	Median age 17.2 y (range 14.9-18.4 y)	N/A	Testosterone	BMD, BMAD (absolute, z-scores using natal sex)	6m, 12m, 24m	Increase in bone density (both absolute and in comparison to natal sex reference).
Vlot 2017	Netherlands	Pre-post	Moderate	70 (28 brm, 42 brf)	Median age for brm: 16.0 y (range 14.0-18.9 y) Median age for brf: 16.3 y (15.9-19.5)	N/A	Hormones (with GnRHa)	BMAD (absolute, z-scores using natal sex), bone-turnover markers (P1NP, OC and ICTP)	24m	No evidence for change in measures (small sample size).
Body mass index (BMI)/body weight										
van de Grift 2020	Netherlands	Cohort	Moderate	43 (17 brf, 26 brm)	Mean age Tanner 2/3 group: 15 y (SD 0.5 y) Mean age Tanner 4/5 group: 17 y (SD 1.0 y)	157	Hormones	BMI	At initiation of surgery	Adolescents who started hormones earlier had a lower BMI (although not clinically significant) before initiation of surgery than those who started later.
Hannema 2017	Netherlands	Pre-post	Moderate	28 brm	Median age 16.0 y (range 13.9-18.9)	N/A	Oestrogen (with GnRHa)	BMI and BMI SD score (reference to natal sex and affirmed gender)	12m, 24m, 36m	BMI remained constant and BMI SD score decreased over time (for both male and female references).
Jarin 2017	US	Pre-post	Moderate	116 (72 brf, 44 brm)	Mean age brm: 18 y (range 14-25 y) Mean age brf: 16 y (range 13-22 y)	N/A	Hormones (brm plus/minus anti-androgens)	BMI	1-3m, 4-6m, 6m+	No change in BMI.
Klink 2015	Netherlands	Pre-post	Moderate	34 (15 brm , 19 brf	Mean age brm: 16.6 y (SD 1.4 y) Mean age brf: 16.4 y (SD 2.3 y)	N/A	Hormones	BMI and BMI SD score (reference to natal sex)	Single (22 years of age)	No clinically significant increase in BMI but an increase in BMI SD score.
Laurenzano 2021	US	Pre-post	Moderate	119 brf	Mean age 16.5 (range 13.0-19.9)	N/A	Testosterone	BMI and BMI SD score (reference unspecified)	Single (median 1.9y, range 6m to 5.5y)	No change in BMI and BMI z-score.
Millington 2022	US	Pre-post	Moderate	286 (92 brm, 194 brf)	Median age for brm: 17.3 y (IQR 16.2-18.6 y) Median age for brf: 16.2 y (IQR 15.1-17.5 y)	N/A	Hormones (brm plus/minus anti-androgens)	BMI	6m, 12m	No change in BMI.
Olson 2014	US	Pre-post	Moderate	36 brf	Mean age 18.7 y (SD 2.6 y)	N/A	Testosterone	BMI	6m	No change in BMI.
Olson-Kennedy 2018	US	Pre-post	Moderate	59 (34 brf, 25 brm)	Mean age 18 y (range 12-23 y)	N/A	Hormones (brm plus/minus progestins)	BMI	24m (range 21-31 months)	No change in BMI.
Perl 2020	Israel	Pre-post	Moderate	9 brf	Mean age 15.1 y (SD 0.9 y)	N/A	Testosterone	BMI and BMI SD score (reference unspecified)	Single (mean 4m, SD 2m)	No change in BMI and BMI SD score.
Perl 2021	Israel	Pre-post	Moderate	15 brm	Mean age 16.1 y (SD 1.5 y)	N/A	Oestrogen (with GnRHa)	BMI and BMI SD score (reference unspecified)	Single (median 18.5m, range 3-63m)	No change in BMI and BMI SD score.
Sequeira 2019	US	Pre-post	Moderate	46 brf	Not reported	N/A	Testosterone	BMI and BMI SD score (reference to natal sex)	6m, 12m	No change in BMI and BMI z-score.
Stoffers 2019	Netherlands	Pre-post	Moderate	62 brf	Median age 17.2 y (range 14.9-18.4 y)	N/A	Testosterone	BMI and BMI SD score (reference unspecified)	6m, 12m, 24m	No change in BMI and BMI SD score
Tack 2016	Belgium	Pre-post	Moderate	38 brf	Mean age 17 y 5 m	N/A	Testosterone (with Lynestrenol)	BMI and BMI SD score (reference to natal sex)	6m, 12m	Increase in BMI and BMI SD score.
Tack 2017	Belgium	Pre-post	Moderate	27 brm	Mean age 17 y 7 m	N/A	Oestrogen (with Cyproterone acetate)	BMI and BMI SD score (reference to natal sex)	6m, 12m	No change in BMI and BMI SD score.
van der Loos 2021	Netherlands	Pre-post	Moderate	322 (106 brm, 216 brf)	Early-puberty group median age 15.7 y (IQR 15.3-16.0 y) Mid-puberty 16.0 y (IQR 15.8-16.6 y) Late-puberty 16.4 y (IQR 16.0-17.4)	N/A	Hormones (with GnRHa)	BMI	Single (> 2y, median 3-4y across groups)	Increase in BMI in early puberty group.
Nokoff 2020	US	Cross-sectional	Moderate	35 (21 brf, 14 brm)	Mean age at data collection for brm 16.3 y (SD 1.4 y, mean treatment duration 12.3 m (9.9m) Mean age at data collection for brf 17.0 y (SD 1.4 y, mean treatment duration T 11.2 m (5.9m)	108 (no GD)	Hormones (plus/minus GnRHa)	BMI percentile	N/A	No evidence of differences in BMI percentile.
Blood pressure										

Hannema 2017	Netherlands	Pre-post	Moderate	28 brm	Median age 16.0 y (range 13.9-18.9)	N/A	Oestrogen (with GnRHa)	Systolic and diastolic blood pressure	12m, 24m, 36m	No change.
Jarin 2017	US	Pre-post	Moderate	116 (72 brf, 44 brm)	Mean age brm: 18 y (range 14-25 y) Mean age brf: 16 y (range 13-22 y)	N/A	Hormones (brm plus/minus anti-androgens)	Systolic and diastolic blood pressure	1-3m, 4-6m, 6m+	No change.
Laurenzano 2021	US	Pre-post	Moderate	119 brf	Mean age 16.5 (range 13.0-19.9)	N/A	Testosterone	Hypertension	Single (median 1.9y, range 6m to 5.5y)	No participants developed hypertension.
Olson 2014	US	Pre-post	Moderate	36 brf	Mean age 18.7 y (SD 2.6 y)	N/A	Testosterone	Systolic and diastolic blood pressure	6m	No change.
Olson-Kennedy 2018	US	Pre-post	Moderate	59 (34 brf, 25 brm)	Mean age 18 y (range 12-23 y)	N/A	Hormones (brm plus/minus progestins)	Systolic and diastolic blood pressure	24m (range 21-31 months)	No change.
Perl 2020	Israel	Pre-post	Moderate	9 brf	Mean age 15.1 y (SD 0.9 y)	N/A	Testosterone	Systolic and diastolic blood pressure	Single (mean 4m, SD 2m)	No change.
Perl 2021	Israel	Pre-post	Moderate	15 brm	Mean age 16.1 y (SD 1.5 y)	N/A	Oestrogen (with GnRHa)	Systolic and diastolic blood pressure	Single (median 18.5m, range 3-63m)	No change.
Stoffers 2019	Netherlands	Pre-post	Moderate	62 brf	Median age 17.2 y (range 14.9-18.4 y)	N/A	Testosterone	Systolic and diastolic blood pressure	6m, 12m, 24m	No clinically significant change.
Nokoff 2020	US	Cross-sectional	Moderate	35 (21 brf, 14 brm)	Mean age at data collection for brm 16.3 y (SD 1.4 y, mean treatment duration 12.3 m (9.9m) Mean age at data collection for brf 17.0 y (SD 1.4 y, mean treatment duration T 11.2 m (5.9m)	108 (no GD)	Hormones (plus/minus GnRHa)	Systolic and diastolic blood pressure	N/A	Similar blood pressure (no clinically significant differences) in adolescents receiving hormones compared to untreated adolescents not experiencing gender incongruence.
Metabolic measures										
Hannema 2017	Netherlands	Pre-post	Moderate	28 brm	Median age 16.0 y (range 13.9-18.9)	N/A	Oestrogen (with GnRHa)	HbA1c	12m, 24m, 36m	No change
Jarin 2017	US	Pre-post	Moderate	116 (72brf, 44 brm)	Mean age brm: 18 y (range 14-25 y) Mean age brf: 16 y (range 13-22 y)	N/A	Hormones (brm plus/minus anti-androgens)	Total cholesterol, LDL, HDL, triglycerides, triglyceride:HDL ratio, HbA1c	1-3m, 4-6m, 6m+	No evidence for change, except for a decrease in HDL in birth-registered females.
Laurenzano 2021	US	Pre-post	Moderate	119 brf	Mean age 16.5 (range 13.0-19.9)	N/A	Testosterone	Total cholesterol, LDL, HDL, triglycerides.	Single (median 1.9y, range 6m to 5.5y)	No evidence for change, except for a decrease in HDL.
Olson 2014	US	Pre-post	Moderate	36 brf	Mean age 18.7 y (SD 2.6 y)	N/A	Testosterone	Non-fasting total cholesterol.	6m	No evidence for change.
Olson-Kennedy 2018	US	Pre-post	Moderate	59 (34 brf, 25 brm)	Mean age 18 y (range 12-23 y)	N/A	Hormones (brm plus/minus progestins)	Total cholesterol, HDL, triglycerides, glucose	24m (range 21-31 months)	No evidence for change, except for an increase in HDL.
Stoffers 2019	Netherlands	Pre-post	Moderate	62 brf	Median age 17.2 y (range 14.9-18.4 y)	N/A	Testosterone	Total cholesterol, HDL, LDL, triglycerides, HbA1c	6m, 12m, 24m	Evidence for decrease in HDL. Some evidence for a small, early decrease in total cholesterol, no change for other outcomes.
Tack 2016	Belgium	Pre-post	Moderate	38 brf	Mean age 17 y 5 m	N/A	Testosterone (with Lynestrenol)	Total cholesterol, triglycerides, HDL, LDL, fasting insulin, HbA1c, glucose, HOMA-IR	6m, 12m	No evidence for change.
Tack 2017	Belgium	Pre-post	Moderate	27 brm	Mean age 17 y 7 m	N/A	Oestrogen (with Cyproterone acetate)	Triglycerides, total cholesterol, HDL, LDL, HbA1c, glucose, insulin	6m, 12m	No evidence for change.
Nokoff 2020	US	Cross-sectional	Moderate	35 (21 brf, 14 brm)	Mean age at data collection for brm 16.3 y (SD 1.4 y, mean treatment duration 12.3 m (9.9m) Mean age at data collection for brf 17.0 y (SD 1.4 y, mean treatment duration T 11.2 m (5.9m)	108 (no GD)	Hormones (plus/minus GnRHa)	Fasting insulin, HOMA-IR, fasting glucose, total cholesterol, triglycerides, HDL, LDL, HbA1c	N/A	Brf receiving hormones had lower HDL than controls, whereas brm had higher HDL than controls. Brm had a lower inverse of fasting insulin and higher HOMA-IR than controls.
Other physical parameters										
Hannema 2017	Netherlands	Pre-post	Moderate	28 brm	Median age 16.0 y (range 13.9-18.9)	N/A	Oestrogen (with GnRHa)	Prolactin, ALT, AST, ALP, γ-glutamyl transferase, creatinine, haematocrit, haemoglobin	12m, 24m, 36m	Alkaline phosphatase decreased, no other changes were observed.
Jarin 2017	US	Pre-post	Moderate	116 (72brf, 44 brm)	Mean age brm: 18 y (range 14-25 y) Mean age brf: 16 y (range 13-22 y)	N/A	Hormones (brm plus/minus anti-androgens)	AST, ALT, haemoglobin, haematocrit, prolactin, serum urea nitrogen, creatinine	1-3m, 4-6m, 6m+	No evidence for change.
Laurenzano 2021	US	Pre-post	Moderate	119 brf	Mean age 16.5 (range 13.0-19.9)	N/A	Testosterone	Haematocrit, AST, ALT	Single (median 1.9y, range 6m to 5.5y)	Evidence for an increase in haematocrit.
Madsen 2021	Netherlands	Pre-post	Moderate	1073 brf	Median age 22.5 (IQR 18.4-31.8)	N/A	Testosterone	Erythrocytosis (haematocrit levels)	Annually up to 20 years (>12m)	Haematocrit levels of >0.50L/L occurred in 24% of brf. Levels of >0.52L/L and >0.54L/L occurred 7.6% and 2.2% respectively.
Millington 2022	US	Pre-post	Moderate	286 (92 brm, 194 brf)	Median age for brm: 17.3 y (IQR 16.2-18.6 y) Median age for brf: 16.2 y (IQR 15.1-17.5 y)	N/A	Hormones (brm plus/minus anti-androgens)	Kidney function (serum creatinine, estimated glomerular filtration rate (eGFR)	6m, 12m, 18m, 24m	Serum creatinine increased in brf and decreased in brm. eGFR increased initially in brm and decreased in brf, and then returned to baseline levels.

Mullins 2021	US	Pre-post	Moderate	611 (428 brf, 183 brm)	Not reported	N/A	Hormones	Occurrence of thrombosis	Single (median 554/7d brm/f, range 283-1037)	No thrombosis occurred whilst receiving hormones.
Olson 2014	US	Pre-post	Moderate	36 brf	Mean age 18.7 y (SD 2.6 y)	N/A	Testosterone	Haemoglobin, ALT, AST	6m	There was an increase in haemoglobin levels.
Olson-Kennedy 2018	US	Pre-post	Moderate	59 (34 brf, 25 brm)	Mean age 18 y (range 12-23 y)	N/A	Hormones (brm plus/minus progestins)	AST, ALT, potassium, prolactin, haemoglobin	24m (range 21-31m)	No change except for a decrease in AST.
Schagen 2018	Netherlands	Pre-post	Moderate	127 (73 brf, 54 brm)	Mean age for brm: 16.3 y (SD 1.2y) Mea age for brf: 16.8 (SD 1.1)	N/A	Hormones (with GnRHa)	DHEAS and A4	12m, 24m	DHEAS remained constant. A4 remained constant in brm and increased in brf.
Stoffers 2019	Netherlands	Pre-post	Moderate	62 brf	Median age 17.2 y (range 14.9-18.4 y)	N/A	Testosterone	SHBG, TSH, prolactin, free thyroxine, DHEAS, A4, haemoglobin, haematocrit, creatinine, ALP, vitamin D, ureum	6m, 12m, 24m	Decrease in SHBG and increase in both haemoglobin and haematocrit. No change in others.
Tack 2016	Belgium	Pre-post	Moderate	38 brf	Mean age 17 y 5 m	N/A	Testosterone (with Lynestrenol)	Haemoglobin, haematocrit, creatinine, AST, ALT, TSH, free thyroxine, anti-Müllerian hormone, SHBG	6m, 12m	Increases in haemoglobin, haematocrit and creatinine. Decrease in free thyroxin.
Tack 2017	Belgium	Pre-post	Moderate	27 brm	Mean age 17 y 7 m	N/A	Oestrogen (with Cyproterone acetate)	DHEAS, haemoglobin, haematocrit, creatinine, AST, ALT, prolactin, TSH, free thyroxin, SHBG	6m, 12m	Evidence for an increase in SHBG and prolactin. No change in others.
Nokoff 2020	US	Cross-sectional	Moderate	35 (21 brf, 14 brm)	Mean age at data collection for brm 16.3 y (SD 1.4 y, mean treatment duration 12.3 m (9.9m) Mean age at data collection for brf 17.0 y (SD 1.4 y, mean treatment duration T 11.2 m (5.9m)	108 (no GD)	Hormones (plus/minus GnRHa)	AST, ALT, SHBG, free androgen index	N/A	No evidence of differences, except for higher AST, lower SHBG and higher free androgen index compared to controls (brf only).
Fertility										
de Nie 2022	Netherlands	Cohort	Moderate	78 brm	Not reported	136	Hormones	Germ cell type, Johnsen's score, hyalinisation and lumen status	Single (at time of surgery when mean age 29.6 y (SD 12.4))	Mature spermatozoa only observed in those starting treatment at Tanner stage 4 or higher. Immature germ cells present in all treated in early puberty.
Side effects										
Jensen 2019	US	Cohort	High	17 (11 brf, 6 brm)	Median age of GnRHa group: 14.9 y (range 14.1-15.7 y) Median age of no GnRHa group: 16.7 y (14.4-18.2 y)	66*	Hormones (with or without GnRHa)	Side-effects recorded by clinicians and in electronic medical record notes	Single (range 6.4-53.0m)	In brm, breast tenderness common; increased liver enzymes, oestradiol levels above limit less common. In brf, acne, mood changes, elevated red blood markers, increased appetite common. Headaches, hot flashes, fatigue, hair loss less common. Similar in GnRHa / no GnRHa.
Laurenzano 2021	US	Pre-post	Moderate	119 brf	Mean age 16.5 (range 13.0-19.9)	N/A	Testosterone	Acne	Single (median 1.9y, range 6m to 5.5y)	Acne severity progressed in ~65% of participants, advanced acne management documented in ~20%.
Tack 2016	Belgium	Pre-post	Moderate	38 brf	Mean age 17 y 5 m	N/A	Testosterone (with Lynestrenol)	Patient-reported side-effects	6m, 12m	Acne increased during testosterone treatment, and metrorrhagia increased slightly.
Tack 2017	Belgium	Pre-post	Moderate	27 brm	Mean age 17 y 7 m	N/A	Oestrogen (with Cyproterone acetate)	Patient-reported side-effects	6m, 12m	Breast tenderness, mood swings and hunger were frequently reported during oestradiol (no figures given).

Abbreviations: A4 – androstenedione; ALP – alkaline phosphatase; ALT - alanine aminotransferase; AST – aspartate aminotransferase; aBMD – areal bone mineral density; BMAD – bone mineral apparent density; BMD – bone mineral density; BMI – body mass index; brf – birth-registered females; brm – birth-registered males; CSH – cross-sex hormones; d – days; DHEAS – dehydroepiandrosterone sulfate; GnRHa – Gonadotropin-Releasing Hormone analogues; m – months; HBA1c – glycated haemoglobin; HDL – high-density lipoprotein; HOMA-IR – Homeostatic Model Assessment for Insulin Resistance; ICTP – Type I collagen degradation product; IQR – inter-quartile range; LDL – low-density lipoprotein; OC – osteocalcin; P1NP – procollagen type I N-terminal propeptide; QTc – heart-rate corrected QT interval; SD – standard deviation; SHBG - sex hormone binding globulin; TSH – thyroid stimulating hormone, y – years.

* This study compared the effect of hormones taken concurrently with or without GnRHa. Comparator group received no GnRHa.

Supplementary Table S7 - Pubertal development

Study ID	Country	Study design	Study quality	Treated sample	Average age CSH treatment started	Comparator	Intervention	Outcome (measure)	Follow-up specific to outcome	Study results
Hormone levels										
Beking 2020	Netherlands	Cohort	Moderate	21 brf	Mean age 16.1 y (SD 0.7) Mean treatment duration 9.8 m (SD 2.9 m)	41 (no GD)	Testosterone (with GnRHa)	Testosterone	Single (range 5.6-14.8m)	Increase in testosterone in brf at follow-up - lower than in male controls and higher than female controls.
Burke 2016	Netherlands	Cohort	Moderate	21 brf	Mean age 16.1 y (SD 0.8) Mean treatment duration 10 m (range 6-15)	41 (no GD)	Testosterone (with GnRHa)	Testosterone	Single (range 6-15m)	At follow-up, testosterone levels much higher than female controls and slightly lower than male controls.
Hannema 2017	Netherlands	Pre-post	Moderate	28 brm	Median age 16.0 y (range 13.9-18.9)	N/A	Oestrogen	Oestradiol, LH, FSH	12m, 24m, 36m	LH and FSH remained the same over time, oestradiol increased over time.
Jarin 2017	US	Pre-post	Moderate	116 (72 brf, 44 brm)	Mean age brm: 18 y (range 14-25 y) Mean age brf: 16 y (range 13-22 y)	N/A	Hormones (brm plus/minus anti-androgens)	Testosterone, oestradiol	1-3m, 4-6m, 6m+	In brf, testosterone levels increased and oestradiol levels remained the same. In brm, testosterone levels decreased and oestradiol levels increased.
Laurenzano 2021	US	Pre-post	Moderate	119 brf	Mean age 16.5 (range 13.0-19.9)	N/A	Testosterone	Testosterone (total and free), oestradiol	Single (median 1.9y, range 6m to 5.5y)	Total and free testosterone levels increased. Oestradiol levels decreased.
Mullins 2021	US	Pre-post	Moderate	611 (428 brf, 183 brm)	Not reported	N/A	Hormones	Testosterone, oestradiol	Single (median 554/7d brm/f, range 283-1037)	In oestradiol users, level at follow-up was 47.2 pg/mL (IQR: 27.2–99.5), and testosterone was 189.5 ng/dL (IQR: 15.2–367). In testosterone users, level at follow-up was 413.0 ng/dL, and oestradiol was 33.2 pg/mL (IQR: 24.0–47.9).
Olson 2014	US	Pre-post	Moderate	36 brf	Mean age 18.7 y (SD 2.6 y)	N/A	Testosterone	Testosterone (total and free), oestradiol	6m	Total testosterone and free testosterone increased. Oestradiol levels decreased.
Olson-Kennedy 2018	US	Pre-post	Moderate	59 (34 brf, 25 brm)	Mean age 18 y (range 12-23 y)	N/A	Hormones (brm plus/minus progestins)	Testosterone (total and free), oestradiol	24m (range 21-31m)	Total and free testosterone levels decreased in brm and increased in brf. Oestradiol increased in brm and decreased in brf.
Perl 2020	Israel	Pre-post	Moderate	9 brf	Mean age 15.1 y (SD 0.9 y)	N/A	Testosterone	Testosterone, oestradiol, LH, FSH	Single (mean 4m, SD 2m)	Testosterone and oestradiol levels increased. LH and FSH levels remained constant.
Perl 2021	Israel	Pre-post	Moderate	15 brm	Mean age 16.1 y (SD 1.5 y)	N/A	Oestrogen (with GnRHa)	Testosterone, oestradiol, LH, FSH	Single (median 18.5m, range 3-63m)	Oestradiol levels increased, testosterone remained constant. LH remained constant, FSH levels decreased slightly.
Stoffers 2019	Netherlands	Pre-post	Moderate	62 brf	Median age 17.2 y (range 14.9-18.4 y)	N/A	Testosterone	Testosterone, oestradiol, LH, FSH	6m, 12m, 24m	Testosterone and oestradiol levels increased. LH and FSH levels remained constant.
Tack 2016	Belgium	Pre-post	Moderate	38 brf	Mean age 17 y 5 m	N/A	Testosterone (with Lynestrenol)	Testosterone (total and free), oestradiol, LH, FSH	6m, 12m	Total and free testosterone levels increased. Oestradiol remained same. LH and FSH remained constant.
Tack 2017	Belgium	Pre-post	Moderate	27 brm	Mean age 17 y 7 m	N/A	Oestrogen (with Cyproterone acetate)	Testosterone (total and free), oestradiol, LH, FSH	6m, 12m	Oestradiol levels increased. Total and free testosterone levels decreased. LH and FSH decreased.
van der Loos 2021	Netherlands	Pre-post	Moderate	322 (106 brm, 216 brf)	Early-puberty group median age 15.7 y (IQR 15.3-16.0 y) Mid-puberty 16.0 y (IQR 15.8-16.6 y) Late-puberty 16.4 y (IQR 16.0-17.4)	N/A	Hormones (with GnRHa)	Testosterone, oestradiol	Single (> 2y, median 3-4y across groups)	Testosterone levels increased in brf and oestradiol levels increased in brm. Oestradiol levels increased in brf and testosterone levels decreased slightly in brm.
Nokoff 2020	US	Cross-sectional	Moderate	35 (21 brf, 14 brm)	Mean age at data collection for brm 16.3 y (SD 1.4 y, mean treatment duration 12.3 m (9.9m) Mean age at data collection for brf 17.0 y (SD 1.4 y, mean treatment duration T 11.2 m (5.9m)	108 (no GD)	Hormones (plus/minus GnRHa)	Testosterone, oestradiol, LH, FSH	N/A	Brf higher testosterone than female controls, slightly lower than males. Oestradiol lower than females, higher than males. Brm higher testosterone than female controls, lower than males. Oestradiol levels similar to females, higher than males.
Induced pubertal progression										
Hannema 2017	Netherlands	Pre-post	Moderate	28 brm	Median age 16.0 y (range 13.9-18.9)	N/A	Oestrogen (with GnRHa)	Tanner breast stage	12m, 24m, 36m	Tanner breast stage increased over time.
Stoffers 2019	Netherlands	Pre-post	Moderate	62 brf	Median age 17.2 y (range 14.9-18.4 y)	N/A	Testosterone	Hair growth (facial, abdominal, chest and extremities) and deepening of voice	3m, 6m, 12m	Presence of hair (facial, abdominal, chest and extremities) increased over time. Voice deepened in all followed up.
Tack 2017	Belgium	Pre-post	Moderate	27 brm	Mean age 17 y 7 m	N/A	Oestrogen (with Cyproterone acetate)	Tanner breast stage	6m, 12m	Majority reached Tanner breast stage 3, with a small percentage reaching stage 4, but objectively small breast volume in most cases.
Vlot 2017	Netherlands	Pre-post	Moderate	70 (28 brm, 42 brf)	Median age for brm: 16.0 y (range 14.0-18.9 y) Median age for brf: 16.3 y (15.9-19.5)	N/A	Hormones (with GnRHa)	Tanner breast stage (brf only), genital stage (brm only) and pubic hair stages (brf and brm).	24m	Tanner breast stage remained same in brf. Tanner genital stage remained same in brm. Tanner pubic hair stage remained same for both.
Height/growth										
van de Grift 2020	Netherlands	Cohort	Moderate	43 (17 brf, 26 brm)	Mean age Tanner 2/3 group: 15 y (SD 0.5 y) Mean age Tanner 4/5 group: 17 y (SD 1.0 y)	157	Hormones	Height	At initiation of surgery	Brf who had hormones for longer (started puberty suppression earlier) were taller at follow-up than those who started later. For brm no difference.
Hannema 2017	Netherlands	Pre-post	Moderate	28 brm	Median age 16.0 y (range 13.9-18.9)	N/A	Oestrogen (with GnRHa)	Height and height SD score (reference to natal sex and affirmed gender)	12m, 24m, 36m	Height increased over time. Height SD score with reference to natal sex and female sex remained the same over time.

Klink 2015	Netherlands	Pre-post	Moderate	34 (15 brm , 19 brf)	Mean age for brm: 16.6 y (SD 1.4 y) Mean age for brf: 16.4 y (SD 2.3 y)	N/A	Hormones	Height and height SD score (reference to natal sex)	Single (22 years of age)	Absolute height increased for both groups. Height SD score increased for brm and remained the same for brf.
Stoffers 2019	Netherlands	Pre-post	Moderate	62 brf	Median age 17.2 y (range 14.9-18.4 y)	N/A	Testosterone	Height and height SD score (reference to natal sex and affirmed gender)	6m, 12m, 24m	Height increased over time. Height SD score with reference to natal sex and female sex remained the same.
Tack 2017	Belgium	Pre-post	Moderate	27 brm	Mean age 17 y 7 m	N/A	Oestrogen (with Cyproterone acetate)	Height SD score (reference to natal sex)	6m, 12m	Height SD score increased over time.
van der Loos 2021	Netherlands	Pre-post	Moderate	322 (106 brm, 216 brf)	Early-puberty group median age 15.7 y (IQR 15.3-16.0 y) Mid-puberty 16.0 y (IQR 15.8-16.6 y) Late-puberty 16.4 y (IQR 16.0-17.4)	N/A	Hormones (with GnRHa)	Height	Single (> 2y, median 3-4y across groups)	For both males and females, average height at follow-up was higher for those who started hormones at an earlier age compared to those who started later.
Vlot 2017	Netherlands	Pre-post	Moderate	70 (28 brm, 42 brf)	Median age for brm: 16.0 y (range 14.0-18.9 y) Median age for brf: 16.3 y (15.9-19.5)	N/A	Hormones (with GnRHa)	Height	24m	Height increased in both males and females.
Waist and hip measurements										
Hannema 2017	Netherlands	Pre-post	Moderate	28 brm	Median age 16.0 y (range 13.9-18.9)	N/A	Oestrogen (with GnRHa)	Waist and hip circumference and SD scores, waist-hip ratio and SD score (references for males and females)	12m, 24m, 36m	Waist circumference remained the same and waist-hip ratio decreased. SD score with reference to males and females decreased. Hip circumference increased, no increase in SD score.
Body composition										
Hannema 2017	Netherlands	Pre-post	Moderate	28 brm	Median age 16.0 y (range 13.9-18.9)	N/A	Oestrogen (with GnRHa)	Fat percentage and lean body mass percentage	12m, 24m, 36m	Fat percentage and lean body mass percentage remained the same over time.
Nokoff 2020	US	Cross-sectional	Moderate	35 (21 brf, 14 brm)	Mean age at data collection for brm 16.3 y (SD 1.4 y, mean treatment duration 12.3 m (9.9m) Mean age at data collection for brf 17.0 y (SD 1.4 y, mean treatment duration T 11.2 m (5.9m)	108 (no GD)	Hormones (plus/minus GnRHa)	Total body fat percentage, fat mass percentage, lean tissue percentage and lean mass percentage	N/A	Brf had lower body fat and higher lean tissue than female controls but the converse to males. Brm higher body fat and lower lean tissue than male controls, but the converse than females.
Menstrual suppression										
Grimstad 2021a	US	Pre-post	Moderate	232 brf	Mean age 16.3 y	N/A	Testosterone	Breakthrough bleeding - defined as bleeding after more than 1 year of treatment	Single (>12 months)	Approximately 20% experienced breakthrough bleeding during the duration of the study.
Laurenzano 2021	US	Pre-post	Moderate	119 brf	Mean age 16.5 (range 13.0-19.9)	N/A	Testosterone	Cessation of menses and time to cessation	Single (median 1.9y, range 6m to 5.5y)	Cessation in nearly all participants on 200mg dose, just over half on 140mg dose. Average time between start of hormones and cessation was 4.7 months (SD 3.0).
Olson 2014	US	Pre-post	Moderate	36 brf	Mean age 18.7 y (SD 2.6 y)	N/A	Testosterone	Cessation of menses and time to cessation	Single (6m)	Cessation of menses obtained in 85% of participants by 6 months. Average number of months to cessation was 2.9 months (SD 1.5 months).
Bone age and geometry										
Hannema 2017	Netherlands	Pre-post	Moderate	28 brm	Median age 16.0 y (range 13.9-18.9)	N/A	Oestrogen (with GnRHa)	Bone age	12m, 24m, 36m	Bone age increased over time.
van der Loos 2021	Netherlands	Pre-post	Moderate	322 (106 brm and 216 brf)	Early-puberty group median age 15.7 y (IQR 15.3-16.0 y) Mid-puberty 16.0 y (IQR 15.8-16.6 y) Late-puberty 16.4 y (IQR 16.0-17.4)	N/A	Hormones (with GnRHa)	Subperiosteal width and endocortical diameter of the hip bone	Single (> 2y, median 3-4y across groups)	In brm, subperiosteal width and endocortical diameter increased in those who started GnRHa in mid or late puberty, but not early. In brf there was no change.
Vlot 2017	Netherlands	Pre-post	Moderate	70 (28 brm, 42 brf)	Median age for brm: 16.0 y (range 14.0-18.9 y) Median age for brf: 16.3 y (15.9-19.5)	N/A	Hormones (with GnRHa)	Bone age	24m	Bone age increased.
Abbreviations: Abbreviations: brf – birth-registered females; brm – birth-registered males; CSH – cross-sex hormones; d – days; FSH – follicle-stimulating hormone; GD - gender dysphoria; GnRHa - Gonadotropin-Releasing Hormone analogues; IQR – inter-quartile range; LH – luteinising hormone; m – months; SD – standard deviation; y – years.										

EXHIBIT 90

Psychosocial support interventions for children and adolescents experiencing gender dysphoria or incongruence: a systematic review

Claire Heathcote, Jo Taylor, Ruth Hall, Stuart William Jarvis, Trilby Langton, Catherine Elizabeth Hewitt, Lorna Fraser

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/archdischild-2023-326347).

Department of Health Sciences, University of York, York, UK

Correspondence to
Dr Jo Taylor, Department of Health Sciences, University of York, York, UK; dohs-gender-research@york.ac.uk

Received 22 September 2023
Accepted 11 December 2023

► http://dx.doi.org/10.1136/archdischild-2023-326348
► http://dx.doi.org/10.1136/archdischild-2023-326112
► http://dx.doi.org/10.1136/archdischild-2023-326499
► http://dx.doi.org/10.1136/archdischild-2023-326669
► http://dx.doi.org/10.1136/archdischild-2023-326670
► http://dx.doi.org/10.1136/archdischild-2023-326500
► http://dx.doi.org/10.1136/archdischild-2023-326760
► http://dx.doi.org/10.1136/archdischild-2023-326681

To cite: Heathcote C, Taylor J, Hall R, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2023-326347

ABSTRACT

Background National and international guidelines recommend that psychosocial support should be a key component of the care offered to children and adolescents experiencing gender dysphoria/incongruence. However, specific approaches or interventions are not recommended.

Aim To identify and summarise evidence on the outcomes of psychosocial support interventions for children and adolescents (age 0-18) experiencing gender dysphoria/incongruence.

Methods Systematic review and narrative synthesis. Database searches (MEDLINE; EMBASE; CINAHL; PsycINFO; Web of Science) were performed in April 2022, with results assessed independently by two reviewers. Peer-reviewed articles reporting the results of studies measuring outcomes of psychosocial support interventions were included. Quality was assessed using the Mixed Methods Appraisal Tool.

Results Ten studies were included. Half were conducted in the US, with others from Australia, Canada, New Zealand and the UK. Six were pre–post analyses or cohort studies, three were mixed methods, and one was a secondary analysis of intervention data from four trials. Most studies were of low quality. Most analyses of mental health and psychosocial outcomes showed either benefit or no change, with none indicating negative or adverse effects.

Conclusions The small number of low-quality studies limits conclusions about the effectiveness of psychosocial interventions for children/adolescents experiencing gender dysphoria/incongruence. Clarity on the intervention approach as well as the core outcomes would support the future aggregation of evidence. More robust methodology and reporting is required.

PROSPERO registration number CRD42021289659.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The number of children and adolescents identifying as a gender different from the sex they were registered at birth has increased markedly over the last 10-15 years.
⇒ Children and adolescents experiencing gender dypshoria/incongruence have higher rates of mental health needs compared with their peers.
⇒ National and international guidelines recommend that psychosocial interventions should be a key component of the care offered to children and adolescents experiencing gender dysphoria/incongruence.

WHAT THIS STUDY ADDS

⇒ There is limited evidence on the outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence.
⇒ The evidence base for outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence is of low quality.
⇒ Most analyses of mental health, psychological and/or psychosocial outcomes showed either benefit or no change, with none indicating negative or adverse effects.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Identification of the core approach and outcomes for psychosocial interventions would ensure they are addressing key clinical goals, attending to the needs of children/adolescents and families as well as supporting future aggregation of evidence. More robust methodology and reporting is required.

INTRODUCTION

The number of children and adolescents who are experiencing gender dysphoria/incongruence has risen markedly over the last 10-15 years.[1] A considerably higher proportion of children and adolescents who present to specialised gender services experience mental health difficulties compared with their peers in the general population, with evidence showing higher recorded rates of psychiatric diagnoses,[2–4] including depression,[3–6] anxiety[3 4 7] and eating disorders,[4 8] and higher recorded rates of suicidality[9 10] and self-harm.[10 11]

The causes of mental health concerns and the ways in which well-being issues might contribute to the emergence of distress in this population are not fully understood. Some authors argue that children and adolescents experiencing gender dysphoria/incongruence present with complex and diverse needs so a developmental approach is necessary to understand the multiple factors that might be contributing to social and emotional distress.[12–14] There is also evidence that the experience of being in a minority group can have a negative impact on development and well-being.[15 16] Meyer's minority

stress model proposes that protective or coping factors can help to interrupt or moderate the impact of minority stress.[17 18] Identifying, strengthening or developing coping and psychosocial support factors is reported to help build well-being and improve mental health.[19 20]

National and international guidelines recommend that psychosocial interventions should be a key component of the care offered to children and adolescents experiencing gender dysphoria/incongruence. It is recommended that support should be offered to enhance psychological functioning, improve mood and well-being, and support coping factors, in addition to managing any co-occurring or contributory mental health difficulties.[21–24]

This systematic review aims to identify and summarise the current evidence on the effectiveness of psychosocial support interventions for children and adolescents experiencing gender dysphoria/incongruence.

METHODS

The review forms part of a linked series of systematic reviews examining the epidemiology, care pathways, outcomes and experiences of children and adolescents experiencing gender dysphoria/incongruence and is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[25] The systematic review protocol was registered on PROSPERO (CRD42021289659).[26]

Search strategy

A single search strategy was used to identify studies comprising two combined concepts: 'children', which included all terms for children and adolescents; and 'gender dysphoria', which included associated terms such as gender-related distress and gender incongruence, and gender identity terms including transgender, gender diverse and non-binary. MEDLINE (see online supplemental table 1), Embase and PsycINFO through OVID, CINAHL Complete through EBSCO and Web of Science (Social Science Citation Index) were searched (13–23 May 2021; updated 27 April 2022). The reference lists of eligible studies and any relevant identified systematic reviews were also checked.[27 28]

Inclusion criteria

Studies were included in relation to the following criteria:

Population: children and adolescents up to 18 years with gender incongruence, gender dysphoria/gender-related distress or referral to a paediatric or adolescent gender service. Studies with a mixed population of adolescents/young adults (up to 25) were included, as were studies of other mixed populations if separate analyses of the groups were undertaken or if most participants (80% or more) were from the population of interest.

Intervention: any psychological or psychosocial intervention provided to children and/or adolescents. Unstructured peer support groups and interventions designed to modify gender behaviours or identity were excluded. Interventions only provided to parents were excluded.

Comparator: any.

Outcomes: any child/adolescent outcome related to the intervention.

Study design: studies published in English in a peer-reviewed journal of any design apart from case series or case reports.

Study selection

The results of the database and other searches were uploaded to Covidence and screened independently by two reviewers.[29] Full texts for potentially relevant articles were retrieved and reviewed against the inclusion criteria by two reviewers independently. Disagreements were resolved through discussion and the inclusion of a third reviewer.

Data extraction

Data was extracted by one reviewer and checked by another using a piloted extraction sheet.

Quality assessment

Quality was assessed using the Mixed Methods Appraisal Tool (MMAT),[30] a tool designed to appraise methodological quality in systematic reviews that include a combination of quantitative, qualitative and/or mixed methods research. Critical appraisal was undertaken by two reviewers independently, with consensus reached through discussion and involvement of a third reviewer where necessary. A score of 0–2 was deemed low quality, 3 medium, and 4–5 high (max score 5).

Synthesis methods

Due to extensive heterogeneity, a narrative approach to synthesising outcome data was adopted. This included any qualitative data pertaining to perceived or experienced effects as well as quantitatively measured outcomes. The Template for Intervention Description and Replication (TIDieR) Checklist[31] was used to describe intervention reporting. For TIDieR items 1–10 (which cover intervention aims, theory, content and delivery), studies were rated as providing 'full', 'partial' or no ('none') information.

RESULTS

Overall, searches yielded 28 147 records, of which 3181 were identified as potentially relevant for the linked series of systematic reviews (see figure 1). From these, nine studies met the inclusion criteria for this review of psychosocial intervention studies. One additional study meeting the inclusion criteria was identified from citation searches.[32] Therefore, 10 studies were included in this review.[32–41]

Study characteristics

There were four cohort studies,[36 39–41] two pre–post studies[32 34] (one of which included analysis of open-ended survey responses in addition to outcome data[34]), three mixed methods,[33 35 37] and one was a secondary analysis of intervention group data from four randomised controlled trials (RCTs)[38] (the individual RCTs were excluded because they presented combined results for those experiencing and not experiencing gender dysphoria/incongruence). Five studies included a comparator group of children and/or adolescents not experiencing gender dysphoria/incongruence[36 38–41] and one included a historical cohort of adolescents with gender dysphoria/incongruence.[33] Half of the studies were conducted in the US (n=5),[32 35 38 40 41] two in the UK[36 37] and single studies from Australia,[33] Canada[34] and New Zealand.[39] Table 1 provides a summary of study characteristics.

Studies were published between 2015 and 2021 with data from 2012 to 2021. In total, studies included analyses of 10 583 individuals (854 who were transgender and gender diverse or experiencing gender dysphoria/incongruence, 2 sexual minority youth from a mixed population study[32] and 9727 who did not identify as transgender or experience gender dysphoria/incongruence). Study sample sizes ranged from 8 to 9079. The age of participants ranged from 7 to 25 years with average age ranging from 10 to 19 years. Three studies included a mixed sample

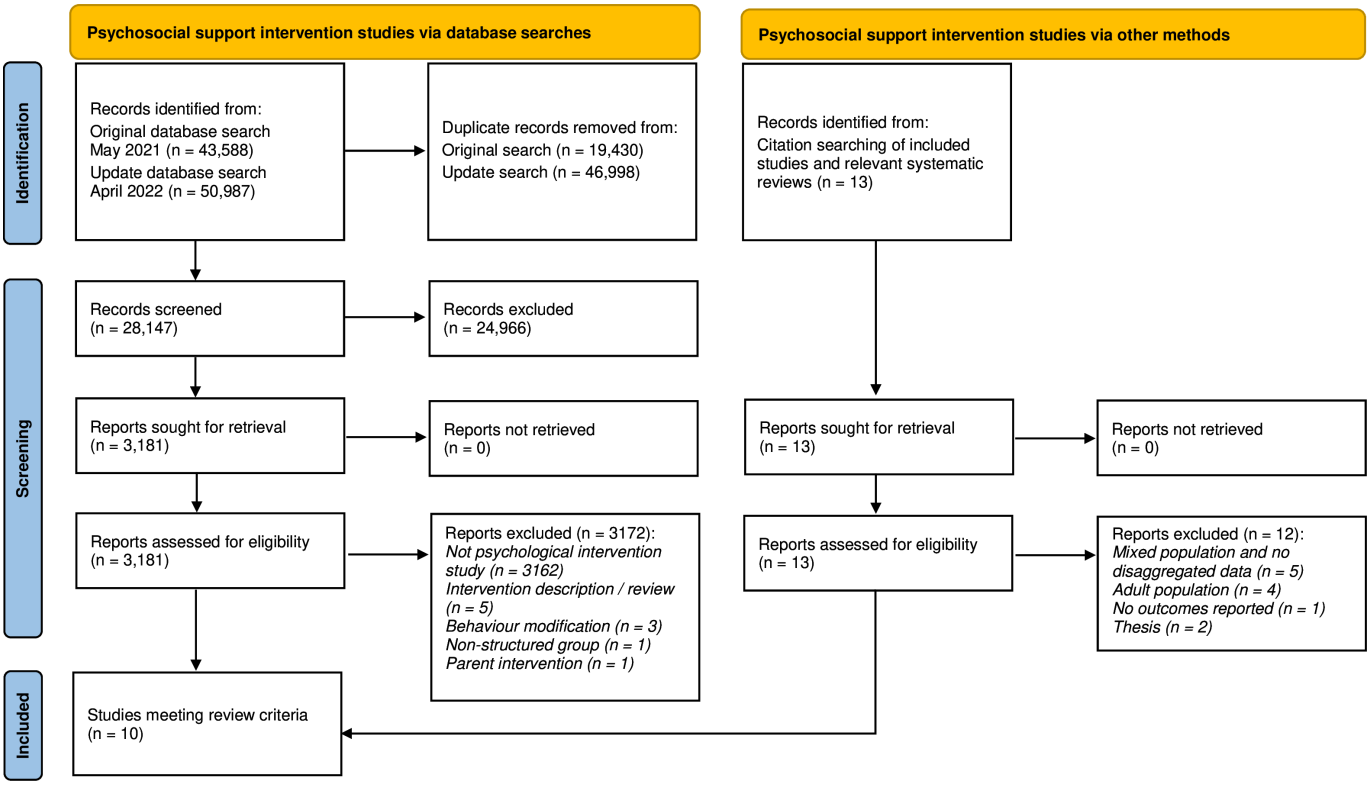


Figure 1 Study flow diagram.

of adolescents and young adults[32 39 41] and only two studies included children under the age of 12 years.[33 38]

The gender identity of participants experiencing gender dysphoria/incongruence and how this was reported varied across the studies. Birth-registered sex was reported in four studies,[33 36–38] with more birth-registered females in three of the four studies.[33 36 37] Four studies reliably reported the ethnicity of participants experiencing gender dysphoria/incongruence, with the percentage from a minority ethnic group ranging from 19.5% to 50%.[32 35 38 39]

Outcomes

Studies employed a range of measures across different mental health and well-being outcomes with little congruence between studies (see table 1). All studies used validated instruments to measure outcomes. One study also devised a measure to determine the level of social support, degree of social transition, medication use and healthcare usage.[33] Most relied on self-report measures and the timing of outcomes varied, with four studies measuring outcomes post-intervention only[32 37 39 41] and others including a later follow-up ranging from 1 to 18 months.

Interventions

Various interventions were used: cognitive behavioural therapy (CBT) (n=2),[34 39] mindfulness and self-compassion (n=1),[35] attachment-based family therapy (n=1),[32] 'a community system of care approach' (n=1),[41] a gender service triage model including psychosocial support (n=1)[33] and interventions using multiple different therapeutic approaches/techniques (n=4).[36–38 40] All studies stated the goal of the intervention, and nine described the modality or theoretical approach.[32 34–41] Table 2 provides a summary of intervention characteristics.

Three interventions were developed for children and/or adolescents with mental health difficulties or diagnoses,[38–40] one for sexual and gender minority adolescents,[34] and two for sexual or gender minority adolescents and young adults with specific needs (clinical levels of suicidal ideation or moderate depression[32]; housing, mental health or substance misuse problems[41]). Three interventions were developed for children and/or adolescents referred to a specialist gender service,[33 36 37] and one was a self-compassion intervention partially modified for adolescents experiencing gender dysphoria/incongruence.[35]

The majority of studies gave an indication of intervention content, activities and/or processes used in the intervention,[33–35 37–39] although this varied from a brief explanation[33 38–40] to more detailed content.[34 35] Eight studies provided information about who delivered the intervention, which included staff (professionals/roles not reported),[36] psychologists[37] and a specialist nurse[33] working in gender services, trained facilitators/instructors[34 35] or therapists,[32 38] and case managers.[41]

Most interventions were delivered face-to-face (n=8)[32–34 36–38 40 41] with two online.[35 39] Interventions were delivered individually (n=3),[33 38 39] in groups (n=3),[34 35 37] in families (n=1)[32] or in combination (n=3).[36 40 41] The setting for face-to-face interventions varied including specialist gender services (n=3),[33 36 37] community settings for sexual and gender minorities (n=2),[32 41] community mental health clinics (n=1),[38] a weekend retreat format[34] and an acute residential treatment programme (n=1)[40] (the specific setting for these last two was not reported).

Intervention duration ranged from a single session[33] to having no fixed duration or number of sessions,[36 38] with some participants receiving psychosocial care for around 18 months from these. The number and/or frequency of sessions varied from a single 90 minute session[33] to three times weekly for 3–6 months.[41] Three interventions had 8–9 sessions[34 35 37] and one had 16,[32] with frequency ranging from daily to weekly. Three studies reported session duration, all were 90 minutes.[33 35 37] The

Table 1 Study characteristics

First author	Study design	Data collection	Intervention population*	Participants with gender dysphoria/ incongruence*	Comparator/control group*	Intervention and setting	Outcome and measurement	Time to follow-up(s)
Allen *et al*,[33] Australia	Pre–post with historical controls Qualitative interviews Mixed methods design	Pre–post: January 2017 to January 2019 Historical controls: mid-2016	Transgender and gender diverse children and young people (aged 8–17) awaiting treatment from The Royal Children's Hospital Gender Service (RCHGS)	*Quantitative study (n=142)* Median age 15 years (IQR 13.7–16.2) Birth-assigned sex, n (%): female 105 (73.9), male 37 (26.1) Gender identity, n (%): Transgender male 80 (56.3) Transgender female 29 (20.4) Non-binary 16 (11.3) Unsure 16 (11.3) Prefer not to answer 1 (0.7) *Qualitative study (n=14, sub-sample of above)* Age range 13–17 years Birth-assigned sex: female (13), male (1) Gender identity: transgender male (12), transgender female (1), unsure (1)	Within group: pre-intervention measures Historical controls (n=120) Children and adolescents who attended RCHGS prior to the start of triage clinic. Median age 14.9 years (IQR 12.4–16.7) Birth-assigned sex, n (%): female 61 (50.8), male 59 (49.2)	First Assessment Single Session Triage (FAAST) clinic led by clinical nurse consultant. Includes information, education and support. Setting: specialist gender clinic for children and adolescents	*Depression and anxiety* Parent-rated Child Behaviour Checklist (CBCL) and self-reported Youth Self-Report (YSR) *Suicidality* Columbia Suicidality Severity Rating Scale (C-SSRS) self-report age≥12 *Quality of Life* Child Health Utility 9D (CHU9D) self-report *Family Functioning* Family Assessment Device (FAD) General Functioning Subscale self-report *Support, social transition, medication and health professional use* Developed by RCHGS; medication and health professional use parent report; support and social transition self-report	Median time pre–post was 259 days (IQR 154–308)
Austin *et al*,[34] Canada	Longitudinal pre–post Open-ended survey questions Pilot study	2014	Young people aged 14–18 years who identify as non-heterosexual and/or non-cisgender Transgender young people attending intervention were recruited to this study	n=8 Age range 16–18 years Gender identity: non-binary (6), queer (5), female (2), transgender (2), male (1), two-spirit (1), gender independent (1), 'figuring things out' (1) (most selected at least two categories)	Comparator: pre-intervention measures	AFFIRM— affirmative CBT skills group intervention Setting: weekend retreat at a community centre for sexual and gender minority communities	*Depression:* The Beck Depression Inventory (BDI) self-report *Coping*: Adolescent Proactive Coping Inventory (PCI-A) self-report	Post-test and 3 months
Bluth *et al*,[35] USA	Longitudinal pre–post End-of-programme qualitative interviews and open-ended survey questions Mixed methods design	Date not reported	Young people aged 13–17 years who identify as transgender or gender expansive	*Quantitative study (n=41)* Median age 14.5 years SD 1.49 Gender identity: transfemale (9), transmale (18), non-binary (12), gender fluid (3), questioning (2), agender (1) *Qualitative study (n=11, sub-sample of above)* Median age 14.5 years SD (1.04) Gender identity: transmale (8), non-binary (2), gender fluid (1)	Comparator: pre-intervention measures	Mindful Self-Compassion for Teens (MSC-T) group intervention Setting: online	All self-report *Self compassion:* Self-compassion Scale Youth (SCS-Y) *Global evaluation of well-being:* Student Life Satisfaction Scale (SLSS) *Anxiety:* Spielberger State-Trait Anxiety Inventory (STAI) - short form *Depression:* Patient Health Questionnaire-9 (PHQ-9) *Suicidality:* Interpersonal Needs Questionnaire (INQ) *Resilience:* Brief Resilience Scale (BRS)	Post-test and 3 months

Continued

Table 1 Continued

First author	Study design	Data collection	Intervention population*	Participants with gender dysphoria/ incongruence*	Comparator/control group*	Intervention and setting	Outcome and measurement	Time to follow-up(s)
Costa *et al*,[36] UK	Longitudinal cohort study	Date not reported	Adolescents referred to the Gender Identity Development Service (GIDS) (age <18) who completed diagnostic procedure (all diagnosed with gender dysphoria)	n=201 Mean age 15.5 years SD 1.4, range 12–17 years Birth-assigned sex, n (%): female 125 (62.2), male 76 (37.8) The sample was divided into groups of immediately eligible for puberty suppression (101) and delayed eligible (100)	Adolescents without observed psychological/ psychiatric symptoms who took part in a cohort study of children and adolescents who attended child and adolescent mental health services (n=169)	Range of psychotherapeutic interventions (individual, family and group) Setting: National gender service for children and young people	*General psychosocial functioning:* Children's Global Assessment Scale (CGAS) clinician rated	Every 6 months for 18 months. Time 1—after 6 months of psychological support Time 2—after 12 months of psychological support for delayed eligible adolescents, and after 12 months of psychological support+6 months of puberty suppression for immediately eligible adolescents Time 3—after 18 months of psychological support for delayed eligible adolescents, and after 18 months of psychological support+12 months of puberty suppression for immediately eligible adolescents
Davidson *et al*,[37] UK	Single pre–post Open-ended survey questions Mixed methods design	2011	Gender diverse young people aged 12–18 who were attending GIDS	n=11 Mean age 16.27±1.1 years, range 15–18 years Birth-assigned sex: female (10), male (1)	None	Facilitated group drawing on variety of therapeutic techniques including CBT Setting: Specialist gender clinic for young people	*Subjective health and well-being:* Kidscreen-52 self report	Post group (after last session)
Hollinsaid *et al*,[38] USA	Secondary analysis of intervention group from 4 randomised controlled trials	2013, 2018, 2018, 2019	Clinically referred children and adolescents (age 7–15) determined to have a primary problem of anxiety, depression, conduct or trauma	Children and adolescents who endorsed a wish to be the opposite sex (n=64) Mean age 10.7 SD 2.3 Birth-assigned sex, n (%): female 31 (48.4), male 33 (51.6)	Children and adolescents who did not endorse a wish to be the opposite sex (n=368) Mean age 10.6 SD 2.2 Female (162), male (206)	Standard and Modular psychotherapy treatments (ESTs) Setting: Community mental health sites for young people	*Internalising and externalising symptoms:* Parent-rated Child Behaviour Checklist (CBCL) and self-reported Youth Self-Report (YSR)	A total of four evaluations over 18 months (at baseline, 6, 12, 18 months)
Lucassen *et al*,[39] New Zealand	Longitudinal cohort	April 2014 onwards for 5 years	Young people aged 12–19 with symptoms of depression (with a New Zealand IP address)	Self-identified transgender adolescents who completed registration (n=207) Age range 12–15 (131), 16–19 (76) Specific gender identity not reported—male, female or transgender-only options for participants	Self-identified male or female adolescents who completed registration (n=8872) Age range 12–15 (5522), 16–19 (3350) Female (5968), male (2904)	SPARX self-help CBT-based e-therapy Setting: online	*Depression:* Patient Health Questionnaire-9 modified for Adolescents (PHQ-A) self-report	Assessed at baseline (post module 1), at mid-point (post module 4) and post-intervention (post module 7)

Continued

Table 1 Continued

First author	Study design	Data collection	Intervention population*	Participants with gender dysphoria/ incongruence*	Comparator/control group*	Intervention and setting	Outcome and measurement	Time to follow-up(s)
Russon *et al*,[32] USA	Longitudinal pre–post analyses Pilot study	Date not reported	Adolescents or young adults who identify as a sexual and/or gender minority and have clinical levels of suicidal ideation and moderate depression	n=10 Mean age 18.2, range 15–25 years (half of sample <18) Majority of sample identified as transgender and gender diverse (8)	None	Attachment-based family therapy (ABFT) Settings: a gender service for children and young people and a community youth centre	*Suicidality:* Suicidal Ideation Questionnaire (SIQ-JR) self-report *Depression:* Beck Depression Inventory-II (BDI-II) self-report	Assessments collected at baseline and at weeks 1, 4, 8 and 16
Silveri *et al*,[40] USA	Longitudinal cohort study	Data analysed October 2019 to March 2021	Adolescents aged 13–17 seeking treatment for a psychiatric disorder	Self-identified transgender and gender diverse adolescents (n=35) Mean age 15.5 SD 1.5 Gender identity: transgender boys (9), transgender girls (2), gender non-conforming or gender queer (22), another gender identity (9) (seven participants endorsed more than one identity)	Self-identified cisgender adolescents receiving the intervention (n=165) Mean age 16.4 SD 1.5 Girls (76), boys (89)	Acute 2-week residential treatment (ART) programme Setting: Psychiatric hospital for young people	*Depression:* Centre for Epidemiologic Studies Depression Scale (CES-D) self-report *Anxiety:* Multidimensional Anxiety Scale for Children (MASC) self-report *Emotional dysregulation:* The Difficulties in Emotion Regulation Scale (DERS) self-report All completed under supervision of hospital staff	Assessment at 48 hours after admission and 48 hours before discharge Voluntary 1-month remote follow-up, added after the study began, so only a portion of participants had opportunity to complete follow-up assessment
Stevens *et al*,[41] USA	Longitudinal cohort	March 2010 to January 2015	Young people aged 15–24 years who self-identify as LGBTQ+ and who are experiencing housing instability, mental health and/or substance abuse treatment needs (non-LGBTQ+ young people with these problems who are allies of the LGBTQ+ population also eligible)	Transgender or gender non-conforming young people (n=17) Mean age 19.6 years (all participants) Gender identity: transgender (12), gender queer (3), poly-gendered (1), intersex (1)	Young people not identifying as transgender (n=153) Mean age 19.6 years (all participants) Female (76), male (77)	iTEAM—Affirming system of care management programme Setting: Community based	*Mental Health status (depression/ anxiety):* The Substance Abuse and Mental Health Services Administration's Client Outcome Measures for Discretionary Programmes Government Performance and Results Act (GPRA) (unclear whether self-report or professional report) *Self-acceptance:* Self- Acceptance Scale self-report	Assessment at 6 months post-intake and at discharge from intervention (up to 12 months later)

*The terminology from included studies to describe the included participants is used for accuracy of reporting.
CBT, cognitive behavioural therapy; LGBTQ+, lesbian, gay, bisexual, transgender, queer or questioning.

Table 2 Intervention characteristics

Study ID, country	Intervention and goals	Intervention content and structure	Mode of delivery	Modifications/adaptations
Allen *et al*,[33] Australia	First Assessment Single-Session Triage (FAAST) individual triage clinic for specialist gender service Aims to decrease wait time into service by providing initial assessment and triage, and to deliver information, education and support to gender questioning young people and their families.	Thirty-minute biopsychosocial assessment with young person using (Home, Education, Activities, Drugs, Sexuality and Suicide (HEADSS) framework. Followed by a joint consultation with the young person and primary caregiver(s) to provide information, education and support. Topics for discussion tailored to individual need. May involve onward referrals to relevant local community support services including mental health services, school support and peer support groups.	Individual format delivered face-to-face in single 90 min consultation session. Delivered by specialist nurse at specialist gender service.	Developed specifically for children and adolescents referred to specialist gender service.
Austin *et al*,[34] Canada	AFFIRM—Affirmative cognitive behavioural coping skills group intervention Aims to improve coping and reduce emotional distress using cognitive behavioural therapy (CBT) techniques that target underlying, problematic cognitions, and by promoting positive change and healthy coping via the creation of a safe, affirming and collaborative therapeutic experience.	Manualised intervention comprising eight modules that covered; 1. Introduction to CBT and understanding minority stress 2. Understanding the effect of anti-transgender attitudes and behaviours on stress 3. Understanding how thoughts affect feelings 4. Using thoughts to change feelings 5. Exploring how activities affect feelings 6. Planning to overcome counterproductive thoughts and negative feelings by building hope 7. Understanding the impact of minority stress and homo/transphobia on social relationships 8. Developing safe, supportive and identity-affirming social networks.	Group format (10 young people and two co-facilitators) delivered face-to-face over eight sessions (duration/frequency not reported). Facilitators had minimum 1 year of experience working with sexual and gender minority youth, with some history of using CBT-based interventions. Facilitators received 5 hours of training. Designed for delivery in a variety of community settings. Pilot delivered as weekend group retreat format.	CBT was adapted for youth with sexual and/or gender-minority identities. Intervention developed in partnership with a transgender-identified intern with expertise in developing identity-affirming and inclusive materials. Feedback from stakeholders also informed adaptations. Examples included using real-world examples relevant to the unique experiences of transgender youth to illustrate CBT strategies, addressing impact of transphobia and cisgenderism, creating affirming environment by using community centre with gender-neutral restrooms, gender-diverse staff, displaying events for gender-diverse people, etc.
Bluth *et al*,[35] USA	Mindful Self-Compassion for Teens (MSC-T) group intervention Aims to improve mental health and psychosocial outcomes using self-compassion training and mindfulness techniques.	Each session began with a brief mindfulness art activity to allow participants to settle in and orient themselves. The intervention included hands-on exercises, videos, games, mindful movement and music meditation. Home practice was encouraged to reinforce techniques. Eight sessions covered; 1. Introduction to concepts of mindfulness and self-compassion. 2. Paying attention on purpose—concept of mindfulness and wandering mind; mindful eating. 3. Loving kindness practice is introduced; adolescent brain development. 4. Self-compassion exercise to encourage young people to challenge the inner critic with a compassionate voice. 5. Self-compassion vs self-esteem—exploring differences between these and perils of social comparison. 6. Living deeply—core values exercise; giving and receiving meditation. 7. Managing difficult emotions—soften, soothe, allow practice introduced; tools to contend with anger and unmet needs are practiced; two developing systems of the adolescent brain explained. 8. Embracing your life with gratitude—gratitude and self-appreciation practices; wrap-up of course via writing an online letter to oneself to be delivered a month later.	Group format delivered online via Zoom over 8 sessions of 90 min in duration. First cohort delivered over 8 days (one session per day) in the summer holiday, second cohort twice weekly in the evenings for 4 weeks. Delivered by two trained MSC-T instructors.	Modifications to MSC-T, which was developed for all teenagers, were made to accommodate needs of transgender adolescents. An example reported was omitting the body scan in case bringing attention to body parts was triggering. No other information was provided.

Continued

Table 2 Continued

Study ID, country	Intervention and goals	Intervention content and structure	Mode of delivery	Modifications/adaptations
Costa *et al*,[36] UK	Psychosocial support is provided within specialist gender services for children and adolescents Aims to improve psychosocial functioning.	Starts with standardised psychological assessment of gender dysphoria and identity, and psychosocial difficulties. Individual needs are met using various psychotherapeutic interventions ranging from individual to family and group therapy. Social and educational interventions are also provided if necessary.	Individual, family or group format delivered face-to-face depending on need. Carried out regularly (at least once a month). Provided for duration of study (up to 18 months). No other details provided. Delivered by staff working in specialist gender service (no other details provided).	Developed specifically for children and adolescents referred to specialist gender service.
Davidson *et al*,[37] UK	Structured therapeutic peer-support group for young people attending specialist gender service Aims to explore young people's difficulties in the context of their social systems and to provide concrete strategies to help them in their interpersonal relationships, prepare them for gender transitions, sustain hope and manage challenging emotions.	Multiple therapeutic techniques were used—CBT and systemic therapy were predominant approaches. Nine didactic and interactive sessions covered; 1. Establishing safety and a connection. 2. Managing worry and anxiety. 3. Managing low mood (including managing self-harm and suicidal feelings). 4. Dealing with frustration and anger. 5. Considering peer relationships (including responding to bullying). 6. Considering family relationships. 7. Considering intimate relationships and sexual health. 8. Considering different identities: perspectives from a transman, a transwoman and someone identified as non-binary/gender fluid. 9. Consolidating the learning. Each theme was problem oriented, with members encouraged to provide real-life examples from their own experiences in pairs, before feeding back to the larger group, where connections between experiences were made. Later in the session emphasis shifted to participants sharing solution focused strategies they found useful in addressing the issues.	Group format delivered face-to-face over 9 weekly sessions of 90 min in duration. Co-facilitated by three staff from the gender service (consultant clinical psychologist, trainee clinical psychologist, research psychologist). Specialist gender service setting—details not reported.	Developed specifically for young people referred to specialist gender service.
Hollinsaid *et al*,[38] USA	Standard and modular empirically supported psychotherapy treatments (ESTs) Aims to treat depression, anxiety, trauma or conduct problems using a range of therapeutic approaches matched to a child's primary problems.	Modular ESTs utilised a multidiagnostic framework—The Modular Approach to Therapy for Children with Anxiety, Depression, Trauma, or Conduct Problems (MATCH) that included treatment procedures from various ESTs, including CBT and behavioural parent training to individualised treatment for a young person's main problems over time. MATCH therapists chose and sequenced intervention components from 33 modules grouped across protocols for anxiety, depression, trauma and conduct problems. Examples include psychoeducation for anxiety or behavioural activation for depression. Standard ESTs used the same content but intervention components were delivered sequentially based on the young person's primary problems.	Individual format delivered face-to-face. Intervention duration and session numbers varied depending on treatment modules offered. Duration ranged from 8 to 589 days. Number of sessions ranged from 1 to 87. Delivered by trained therapists in community-based mental health clinics.	No modifications for gender diverse/incongruent participants.
Lucassen *et al*,[39] New Zealand	SPARX—Video game-based e-therapy Aims to provide a computerised cognitive behavioural therapy programme for the treatment of depression in adolescents.	Self-help cognitive behavioural therapy online game which involved participants joining a virtual fantasy world with a personalised avatar and embarking on a mission to rid the world of gloom. Completed over seven modules, each comprising a challenge to complete and including a direct teaching component where a core CBT skill is applied to the user's real-life context. Users aim to gain six 'gem stones' for their shield against depression, which correspond to CBT techniques taught in the modules. Homework tasks allow practice and facilitate skill generalisation. A 'Guide' or 'virtual therapist' introduces each module and reviews the content covered when completed. CBT techniques included relaxation training, behavioural activation, social skills training, naming cognitive distortions, problem-solving and cognitive restructuring.	Each of the seven modules designed to take around 30 min to complete.	No modifications for gender diverse/incongruent participants.

Continued

Table 2 Continued

Study ID, country	Intervention and goals	Intervention content and structure	Mode of delivery	Modifications/adaptations
Russon *et al*,[32] USA	Attachment-Based Family Therapy (ABFT) Aims to repair damage in the adolescent-caregiver attachment relationship and establish or resuscitate a secure, family-based environment. Provides an interpersonal, process-oriented, trauma-focused approach to treat depression, suicidality and trauma in LGBTQ+ youth.	Manualised therapy consisted of five treatment tasks that encouraged young person to take developmentally appropriate responsibility and challenged parents to find the right balance of support and encouragement. 1. Relational reframe (one session) helps move family from a focus on young person's symptoms to improvement in parent(s)–child relationship. 2. Adolescent alliance-building task (two to four sessions), exploring adolescent's strengths and interests, ruptures in attachment security that impact mental health and inhibit the adolescent from turning to parents for support. 3. Build alliance with the parents (two to four sessions)—discussion of parents' own history of attachment ruptures and current stressors that may impact parenting. 4. Attachment task (one to four sessions)—the central mechanism of therapy is to generate a 'corrective attachment experience' in which the young person expresses grievances in a more regulated manner and receives empathy and understanding from parents. 5. Autonomy-promoting task (one to ten sessions)—helping family members practice new relational skills, consolidating newly formed secure base. Attention shifts to promoting the adolescent's autonomy and/or focus on other causes of depression/suicide.	Individual format delivered face-to-face over 16 weeks with weekly sessions (three participants continued to 20–24 weeks). Session duration not reported. Delivered by trained ABFT therapists who were supervised by the lead therapist. Delivered within LGBTQ+ focused community organisations.	Modified for LGBTQ+ adolescents and young adults based on interviews with key stakeholders. The following changes were reported: 1. More individual sessions with young person before family therapy to build alliance. 2. Increased number of meetings with caregivers who showed rejecting behaviours to reduce anxiety and anger before family sessions. 3. Advocacy role for therapists with external systems of care (eg, schools and clinicians) about the needs of LGBTQ+ young people. 4. Discussed minority stressors and discrimination with parents to increase empathy for child's struggles.
Silveri *et al*,[40] USA	Acute residential treatment (ART) insurance-based programme Aims to reduce clinical psychiatric symptoms in young people.	Milieu-based treatment, comprised of cognitive behavioural therapy, dialectical behavioural therapy, motivational interviewing and individual, group and family therapy. Assessment by a psychiatrist twice a week and medical interventions introduced if deemed necessary.	Individual, family or group format delivered face-to-face over approximately 2 weeks (no other details provided). Delivered in residential setting (no other details provided).	No modifications for gender diverse/incongruent participants.
Stevens *et al*,[41] USA	iTEAM—Affirming system of care community intervention Aims to promote affirming forms of self-acceptance, increase self-esteem, lower psychological distress and mediate negative effects of discrimination in LGBTQ+ youth.	Used a system-of-care framework involving a co-ordinated network of multiple relevant agencies. Following an intake assessment, young people were assigned a case manager who provided on-going support and introduced iTEAM affirming services and provided referrals to other community-based services. iTEAM services included: Strength-based case management. Motivational Enhancement Therapy and Cognitive Behavioural Therapy. Street Smart (sexual health education intervention). Crisis and mental health counselling/therapy. Education and employment services. Direct enrolment in local housing programmes. Group-based services and activities.	Case management delivered individually face-to-face at least three times weekly during first 3 months and then reduced based on clinical need for additional 3–4 months. Delivered by case managers at the iTEAM programme site. Other intervention components also delivered at iTEAM programme site. Mode of delivery, duration and frequency of other elements not reported.	System-of-care framework model was adapted for LGBTQ+ youth. Adaptations included a welcoming space, LGBTQ+ pro-social activities; staff who were representative of multiple identities; on-going training provided for staff and volunteers with regard to affirming care for this population. Services involved in providing care were also adapted to address specific needs of LGBTQ+ youth, for example, family rejection, work-place discrimination.

CBT, cognitive behavioural therapy; LGBTQ+, lesbian, gay, bisexual, transgender, queer or questioning.

computerised CBT programme had seven modules, each taking around 30 minutes to complete.[39]

Intervention adherence was reported for the three group-based and family therapy interventions (100% completion,[32 34] 79% full attendance,[37] 73% retention[35]) and for the computerised CBT programme (53.6% completed module 1 but only 2.4% completed all seven).[39]

When studies were assessed against the TIDieR framework, the most comprehensive information was provided on intervention name/label, rationale/aims and mode of delivery, with varying detail on intervention procedures, setting and tailoring. The least detail was provided on intervention materials, facilitator expertise and training and whether modifications were made during study delivery (see table 3 for summary of TIDieR assessment).

Study quality

Nine studies were rated as low quality and one as moderate quality[32] (see table 4 for critical appraisals). Limited reporting of recruitment methods meant it was difficult to determine how representative samples were of the target population. Three studies had no control or comparator group,[32 35 37] and for others, the comparator was not always appropriate. Across the studies, significant confounding factors were not accounted for within the analysis. Other methodological issues included a small sample used for analysis,[32 34 35 37 39–41] and reliance on self-report or a proxy indicator of gender dysphoria/incongruence or gender identity, rather than a validated and widely used assessment tool.[38–41] There was also a lack of information about what happened to participants who dropped out,[36 39] and several interventions were single site, limiting potential generalisability.[33 34 36 37 40]

Synthesis of results

Eight studies reported outcomes related to mental health,[32–35 38–41] five to psychological changes[33–35 37 41] and five to psychosocial or healthcare changes.[33 35–37 41]

Mental health outcomes

Measures of depression were reported in six studies.[32–35 39 40] All six studies focused on within-group changes either at a single[33 39] or multiple[32 34 35 40] post-intervention timepoints. Four studies found significant reductions in depression levels post-intervention[33–35 40] and/or at a later timepoint (3 months[34 35]; 1 month[40]). Two studies found non-significant differences in depression levels during mid-treatment[32] and/or post-intervention.[32 39] Two studies provided comparisons with control groups (historical controls who did not receive the intervention[33]; adolescents not experiencing gender dysphoria/incongruence who received the same intervention[40]). One had a single timepoint post-intervention[33] and the other had multiple post-intervention timepoints.[40] One study compared the proportion of participants reaching borderline or clinical depression scores following an intervention, comparing children/adolescents experiencing gender dysphoria/incongruence with historical controls. The study reported significant reductions for those receiving the intervention in self-report but not caregiver-report measures.[33] The study comparing adolescents experiencing gender dysphoria/incongruence with those not experiencing gender dysphoria/incongruence found no significant difference between groups over time in self-reported and caregiver-reported depression levels.[40]

Measures of anxiety were reported in three studies.[33 35 40] All three reported within-group changes either

Table 3 TIDieR (Template for Intervention Description and Replication) assessment

Study ID	(Brief name) Provides name or phrase that describes the intervention	(Why) Describes the rationale, theory or goal of the intervention	(What) Materials: Describes information materials provided to participants before or during delivery or used to train providers	(What) Procedures: Describes the procedures, activities and processes used in the intervention	(Who) Describes the expertise of and specific training given to intervention providers	(How) Describes the modes of delivery (eg, face-to-face, internet) and whether it was provided individually or in a group	(Where) Describes the location(s) where the intervention occurred, including any infrastructure or relevant features	(When and how much) Describes the number of times intervention was delivered, over what period and number, schedule and duration of sessions	(Tailoring) If tailored/personalised, describes how the intervention was adapted/developed for children with gender dysphoria/incongruence	(Modifications) If modified during study, describes changes made to the intervention (including the what, why, when and how)
Allen *et al*[33]	Full	Full	None	Partial	Partial	Full	Partial	Full	Partial	None
Austin *et al*[34]	Full	Full	None	Full	Partial	Partial	Partial	Partial	Full	None
Bluth *et al*[35]	Full	Full	None	Full	Partial	Full	Partial	Full	Full	None
Costa *et al*[36]	Full	Full	None	Partial	Partial	Partial	Partial	None	Partial	None
Davidson *et al*[37]	Full	Full	None	Full	Partial	Full	Partial	Full	Full	None
Hollinsaid *et al*[38]	Full	Full	None	Partial	Partial	Partial	Partial	None	*	None
Lucassen *et al*[39]	Full	Full	None	Partial	†	Full	Partial	Full	*	None
Russon *et al*[32]	Full	Full	None	Full	Partial	Partial	Partial	Partial	Full	None
Silveri *et al*[40]	Full	Full	None	Partial	Partial	Partial	Partial	Partial	*	None
Stevens *et al*[41]	Full	Full	None	Partial	None	Full	Partial	Partial	Partial	None

*Study assessed whether intervention offered to the general population was suitable for children and/or adolescents experiencing gender dysphoria/incongruence without modifications.
†No provider—virtual online platform.

Table 4 MMAT assessment

Study ID	Screening questions		Non-randomised studies					Overall quality; low (0–2 criteria met); medium (3 criteria met); high (4–5 criteria met)
	S1. Clear research questions?	S2. Does the data collected address the research questions?	1. Are participants representative of the target population?	2. Measurements appropriate re-outcome and intervention?	3. Complete outcome data (>80%)?	4. Confounders accounted for in design and analysis?	5. Intervention administered as intended?	
Austin *et al*[34]	Yes	No	Can't tell	Yes	No	No	Can't tell	Low
Costa *et al*[36]	Yes	Yes	Can't tell	Yes	No	No	Can't tell	Low
Hollinsaid *et al*[38]	Yes	Can't tell	Can't tell	Yes	Can't tell	No	Can't tell	Low
Lucassen *et al*[39]	Yes	Yes	Can't tell	Yes	No	No	Can't tell	Low
Russon *et al*[32]	Yes	Yes	Can't tell	Yes	Yes	No	Yes	Medium
Silveri *et al*[40]	Yes	Yes	Can't tell	Yes	No	No	Can't tell	Low
Stevens *et al*[41]	Yes	Yes	Can't tell	Yes	Can't tell	No	Yes	Low

Study ID	Mixed methods studies								Overall quality; low (0–2 criteria met); medium (3 criteria met); high (4–5 criteria met)
	S1. Clear research questions?	S2. Does the data collected address the research questions?	1. Adequate rationale for using mixed methods design?	2. Are qual/quant components effectively integrated?	3. Outputs of the integration of qual/quant components adequately interpreted?	4. Inconsistencies between qual/quant results adequately addressed?	5. Do qual/quant components both meet quality criteria of both methods?	QUAL component overall quality score	QUANT component overall quality score	
Allen *et al*[33]	Yes	Yes	Yes	No	Yes	No	No	Low	Low	Low
Bluth *et al*[35]	Yes	Yes	Yes	No	No	Yes	No	High	Low	Low
Davidson *et al*[37]	Yes	Yes	Yes	Can't tell	No	Yes	No	Low	Low	Low

MMAT, Mixed Methods Appraisal Tool.

at a single[33] or multiple[35 40] post-intervention timepoints. All three studies found significant reductions in anxiety levels post-intervention.[33 35 40] One study found significant reductions at a later timepoint (1 month[40]) and one did not (3 months[35]). The same two studies that provided comparisons with control groups for depression also did this for symptoms of anxiety (historical controls[33]; adolescents not experiencing gender dysphoria/incongruence[40]). The study including a historical control group found significantly greater reductions in self-reported but not carer-reported anxiety among those receiving the intervention.[33] The final study found no significant difference between groups (those experiencing and not experiencing gender dysphoria/incongruence) over time in anxiety levels.[40]

Two studies provided a combined mental health outcome.[38 41] One study looked at within-group changes in mental health issues (anxiety or depression in past 30 days) and found no significant, although marginal, difference from baseline to 6 months.[41] The second study measured internalising and externalising symptoms, comparing children and adolescents experiencing and not experiencing gender dysphoria/incongruence. The study found similar improvements between groups over time in self-report and caregiver report for internalising symptoms and in self-report for externalising symptoms. The caregiver report for externalising symptoms showed slower improvement among those experiencing gender dysphoria/incongruence compared with the control group. A significantly greater proportion of the participants experiencing gender dysphoria/incongruence had clinically elevated internalising problems post-intervention compared with those not experiencing gender dysphoria/incongruence.[38]

One study looked at emotional dysregulation. This found significant reductions post-intervention and at a later timepoint (1 month), but no significant differences between adolescents experiencing and not experiencing gender dysphoria/incongruence over time.[40]

Three studies evaluated the impact of the psychosocial intervention on suicidality and related outcomes.[32 33 35] Two studies found significant decreases in suicidality scores,[32] thwarted belongingness[35] or perceived burdensomeness[35] from baseline to mid-treatment[32] and/or post-intervention[32 35] and/or at a later timepoint (3 months[35]). One study found no difference in the proportion of patients at high suicide risk before and after the intervention (nurse triage; median time pre–post was 259 days).[33]

Psychological changes

Five studies focused on psychological changes[33–35 37 41]: three explored relationships quantitatively[34 35 41] and four reported qualitative findings.[33–35 37] For resilience,[35] self-compassion[35] and self-acceptance,[41] there were significant increases in scores between baseline and post-intervention,[35] and between baseline and 3 months for self-compassion[35] and 6 months for self-acceptance,[41] but the difference was no longer observed for resilience at 3-month follow-up (although it was of marginal significance).[35] No significant differences were found in coping scores between baseline and post-intervention or between post-intervention and a later timepoint (3 months[34]).

In the studies that reported qualitative data about perceived effects, participants reported more positive coping and problem-solving[34 35 37] and increased confidence.[33 37] Participants also talked about being more comfortable and accepting of their identity,[33 35 37] having a better sense of self and self-worth,[33 35] and reduced feelings of isolation and distrust towards others.[35 37] These changes were reported to contribute to the adolescents having more agency over their lives in one study,[33] increased life satisfaction in another[35] and a different outlook in three studies,[33 35 37] including more positivity and certainty about the future. In the group-based interventions, being able to talk openly with and learn from others about gender issues in a safe and supportive environment was reported to contribute to these positive outcomes[34 35 37]; whereas in the triage intervention, receiving information about what is available to them in terms of transition-related interventions was reported as a key mechanism leading to change.[33]

Psychosocial and other changes

Five studies focused on psychosocial changes[33 35–37 41]: all explored relationships quantitatively and three also reported qualitative findings.[33 35 37]

Three studies found significant improvements in quality of life/global functioning/well-being post-intervention[33 35 36] and/or at later timepoints[36]; however, for well-being the significant difference was no longer observed at 3 months.[35] One study found no significant differences in well-being scores (physical and psychological) before and after receiving the intervention.[37]

One study evaluated the impact of a single assessment and triage appointment in which information and signposting support was given to young people and families on a waiting list for a paediatric gender service. Clinical measures and qualitative interviews looked at rates of depression, anxiety, quality of life and access to health professional input and medication use, as well as knowledge relating to social transition, perceived support from social networks and family functioning.[33] In the group who had received the single session intervention, there were improvements in mental health and well-being measures, family functioning was found to be significantly improved, and there were higher rates of social transition and knowledge about social transition. There was no significant change to participants' reports of social support, no changes seen in access to broader healthcare input and overall safety had not increased. Significantly more birth-registered females had commenced medication to suppress menstruation having been signposted to information relating to this.[33]

Significant improvements were also recorded, 6 months post-intake, for measures of employment and housing stability, in participants of a community system of care intervention.[41]

In the studies that reported qualitative data pertaining to perceived effects, participants reported having better peer relationships and increased acceptance and/or support from peers (from meeting and forging relationships with others in the same situation).[35 37] Some participants reported increased parental support or acceptance, while others did not.[33]

DISCUSSION

There is limited research evaluating the outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence. Low study quality and inadequate reporting in the 10 studies included limit any firm conclusions about their effects. Selection criteria for participation were not clearly defined, a range of different interventions were used, studies included heterogeneous measurements of different treatment outcomes and lacked appropriate comparators. This review highlights that to date there has been a lack of robust research and inadequate methodologies have been used to assess the effects of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence.

Assessed interventions included those developed specifically for children and/or adolescents experiencing gender dysphoria/incongruence,[33 36 37] interventions developed or adapted for gender and sexual minority youth,[32 34 41] and broader psychological interventions for adolescents with mental health difficulties either partially modified for those experiencing gender dysphoria/incongruence[35] or with no tailoring.[38–40] Only three were designed for children and/or adolescents referred to a specialist gender service and these varied considerably: one being a structured CBT and systemic theory-informed peer support group delivered over 8 weeks,[37] one a specialist single session nurse-led triage clinic[33] and one comprising the range of psychosocial support provided by a paediatric gender service.[36]

Low study quality, inadequate reporting of intervention details and heterogeneity of interventions and their aims and outcome measurement prevented comparison of the different types of interventions identified or of different psychological approaches.

Similar results were reported across studies, which showed either benefit or no change with no indication of adverse or negative effects. This result suggests that existing evidence-based interventions tailored for children and/or adolescents with gender dysphoria/incongruence as well as those developed explicitly for this population have the potential to result in positive outcomes. However, there remain unanswered questions about which specific approach works best, for whom and in what circumstances, and the acceptability and feasibility of these different approaches. There is also limited understanding of how psychosocial interventions might support a reduction of gender-related distress and the sorts of interventions that might be most suitable for prepubertal children and for adolescents with more complex needs.

Strengths and limitations

Strengths include a published protocol with robust search strategies and comprehensive synthesis. As searches were conducted to April 2022 this review does not include more recently published studies; as this is a rapidly evolving area this is a limitation.

CONCLUSIONS

There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made. Most analyses of mental health, psychological and/or psychosocial outcomes showed either benefit or no change, with none indicating any negative/adverse effects of the interventions offered. Identification of the core approach and outcomes for these interventions would ensure they are addressing key clinical goals, attending to the needs of children and families as well as supporting future aggregation of evidence. More robust methodology and reporting is required.

Contributors LF, CEH and TL contributed to the conception of this study. LF, CH, CEH, JT, and TL designed the study. Data collection was led by CH, JT and RH. Analyses was undertaken by CEH, RH, SWJ, JT and LF. CH drafted the first version of the manuscript. All authors reviewed the manuscript prior to submission. CEH accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was funded by NHS England to inform the Cass Review (Independent review of gender identity services for children and young people). The funder and Cass Review team had a role in commissioning the research programme but no role in the study conduct, interpretation or conclusion.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement Data sharing is not applicable as no datasets were generated and/or analysed for this study.

ORCID iDs
Jo Taylor http://orcid.org/0000-0001-5898-0900
Stuart William Jarvis http://orcid.org/0000-0001-8447-0306
Catherine Elizabeth Hewitt http://orcid.org/0000-0002-0415-3536

REFERENCES

1 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender dysphoria literature: 1) epidemiology. *PLOS Glob Public Health* 2022;2:e0000245.
2 Spack NP, Edwards-Leeper L, Feldman HA, *et al*. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics* 2012;129:418–25.
3 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender dysphoria literature: 2) mental health. *PLOS Glob Public Health* 2022;2:e0000426.
4 Frew T, Watsford C, Walker I. Gender dysphoria and psychiatric comorbidities in childhood: a systematic review. *Aust J Psychol* 2021;73:255–71.
5 Pinna F, Paribello P, Somaini G, *et al*. Mental health in transgender individuals: a systematic review. *Int Rev Psychiatry* 2022;34:292–359.
6 Turban JL, Ehrensaft D. Research review: gender identity in youth: treatment paradigms and controversies. *J Child Psychol Psychiatry* 2018;59:1228–43.
7 Millet N, Longworth J, Arcelus J. Prevalence of anxiety symptoms and disorders in the transgender population: a systematic review of the literature. *Int J Transgend* 2017;18:27–38.
8 Coelho JS, Suen J, Clark BA, *et al*. Eating disorder diagnoses and symptom presentation in transgender youth: a scoping review. *Curr Psychiatry Rep* 2019;21:107.
9 Clements-Nolle K, Marx R, Katz M. Attempted suicide among transgender persons: the influence of gender-based discrimination and victimization. *J Homosex* 2006;51:53–69.
10 Surace T, Fusar-Poli L, Vozza L, *et al*. Lifetime prevalence of suicidal Ideation and suicidal behaviors in gender non-conforming youths: a meta-analysis. *Eur Child Adolesc Psychiatry* 2021;30:1147–61.
11 Aitken M, VanderLaan DP, Wasserman L, *et al*. Self-harm and suicidality in children referred for gender dysphoria. *J Am Acad Child Adolesc Psychiatry* 2016;55:513–20.
12 Spivey LA, Edwards-Leeper L. Future directions in affirmative psychological interventions with transgender children and adolescents. *J Clin Child Adolesc Psychol* 2019;48:343–56.
13 Coyne CA, Yuodsnukis BT, Chen D. Gender dysphoria: optimizing healthcare for transgender and gender diverse youth with a multidisciplinary approach. *Neuropsychiatr Dis Treat* 2023;19:479–93.
14 Churcher Clarke A, Spiliadis A. Taking the lid off the box': the value of extended clinical assessment for adolescents presenting with gender identity difficulties. *Clin Child Psychol Psychiatry* 2019;24:338–52.
15 Hendricks ML, Testa RJ. 2012 A conceptual framework for clinical work with transgender and gender nonconforming clients: an adaptation of the minority stress model. *Professional Psychology: Research and Practice*;43:460–7.
16 Testa RJ, Michaels MS, Bliss W, *et al*. Suicidal Ideation in transgender people: gender minority stress and Interpersonal theory factors. *J Abnorm Psychol* 2017;126:125–36.
17 Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. *Psychol Bull* 2003;129:674–97.
18 Frost DM, Meyer IH. Minority stress theory: application, critique, and continued relevance. *Curr Opin Psychol* 2023;51:101579.
19 Toomey RB, Ryan C, Diaz RM, *et al*. Coping with sexual orientation-related minority stress. *J Homosex* 2018;65:484–500.

20 Tankersley AP, Grafsky EL, Dike J, *et al*. Risk and resilience factors for mental health among transgender and gender nonconforming (TGNC) youth: a systematic review. *Clin Child Fam Psychol Rev* 2021;24:183–206.
21 Council for Choices in Healthcare in Finland. Medical treatment methods for Dysphoria associated with variations in gender identity in minors – recommendation. 2020. Available: https://palveluvalikoima.fi/en/recommendations#genderidentity
22 The Swedish National Board of Health and Welfare. Care of children and young people with gender dysphoria - national knowledge support with recommendations for the profession and decision makers; 2022.
23 Coleman E, Radix AE, Bouman WP, *et al*. Standards of care for the health of transgender and gender diverse people, version 8. *Int J Transgend Health* 2022;23:S1–259.
24 Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-dysphoric/gender-Incongruent persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017;102:3869–903.
25 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
26 Fraser L, Hall R, Taylor J, *et al*. The epidemiology, management and outcomes of children with gender-related distress / gender dysphoria: a systematic review. PROSPERO 2021 Crd42021289659; 2021.
27 Expósito-Campos P, Pérez-Fernández JI, Salaberria K. Empirically supported affirmative psychological interventions for Transgender and non-binary youth and adults: A systematic review. *Clin Psychol Rev* 2023;100:S0272-7358(22)00114-3:102229.:.
28 Van Der Pol-Harney E, McAloon J. Psychosocial interventions for mental illness among LGBTQIA youth: A PRISMA-based systematic review. *Adolescent Res Rev* 2019;4:149–68.
29 Veritas Health Innovation. *Covidence systematic review software*. Melbourne, Australia: Veritas Health Innovation, 2023.
30 Hong QN, Fàbregues S, Bartlett G, *et al*. The mixed methods appraisal tool (MMAT) version 2018 for information professionals and researchers. *Educ Inform* 2018;34:285–91.
31 Hoffmann TC, Glasziou PP, Boutron I, *et al*. Better reporting of interventions: template for intervention description and replication (Tidier) checklist and guide. *BMJ* 2014;348:bmj.g1687.
32 Russon J, Smithee L, Simpson S, *et al*. Demonstrating attachment-based family therapy for transgender and gender diverse youth with suicidal thoughts and behavior: a case study. *Fam Process* 2022;61:230–45.
33 Allen SD, Tollit MA, McDougall R, *et al*. A waitlist intervention for transgender young people and psychosocial outcomes. *Pediatrics* 2021;148:e2020042762.
34 Austin A, Craig SL, D'Souza SA. An affirmative cognitive behavioral intervention for transgender youth: preliminary effectiveness. *Prof Psychol-Res Pract* 2018;49:1–8.
35 Bluth K, Lathren C, Clepper-Faith M, *et al*. Improving mental health among transgender adolescents: implementing mindful self-compassion for teens. *J Adolescent Res* 2023;38:271–302.
36 Costa R, Dunsford M, Skagerberg E, *et al*. Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. *J Sex Med* 2015;12:2206–14.
37 Davidson S, Morrison A, Skagerberg E, *et al*. A therapeutic group for young people with diverse gender identifications. *Clin Child Psychol Psychiatry* 2019;24:241–57.
38 Hollinsaid NL, Weisz JR, Chorpita BF, *et al*. The effectiveness and acceptability of empirically supported treatments in gender minority youth across four randomized controlled trials. *J Consult Clin Psychol* 2020;88:1053–64.
39 Lucassen MF, Stasiak K, Fleming T, *et al*. Computerized cognitive behavioural therapy for gender minority adolescents: analysis of the real-world implementation of SPARX in New Zealand. *Aust N Z J Psychiatry* 2021;55:874–82.
40 Silveri MM, Schuttenberg EM, Schmandt K, *et al*. Clinical outcomes following acute residential psychiatric treatment in transgender and gender diverse adolescents. *JAMA Netw Open* 2021;4:e2113637.
41 Stevens S, Haverly K, Powell C. Improvements in self-acceptance for LGBTQ plus and straight allied youth and young adults enrolled in an affirming system of care program. *Child Youth Serv Rev* 2020;118:105382.

Supplementary Table S1: Final search strategy for Ovid MEDLINE

1 exp Child/ or Child Behavior/ or Child Health/ or Child Welfare/ or Psychology, Child/ or Child Psychiatry/ or Child Health Services/ or Child Development/ (1984459)
2 Minors/ (2638)
3 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or emerging adult$).ti,ab,kf,jn. (1862660)
4 (young$ adj (people$ or person$1 or adult$ or man$1 or men$1 or woman$ or women$ or male$1 or female$1)).ti,ab,kf,jn. (224878)
5 pediatrics/ (55388)
6 (pediatric$ or paediatric$ or peadiatric$).ti,ab,kf,jn. (543516)
7 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Psychology, Adolescent/ or Adolescent Psychiatry/ or Adolescent Health Services/ or Adolescent Medicine/ or Adolescent Development/ (2088552)
8 Puberty/ (13562)
9 (adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or underage$ or under-age$).ti,ab,kf,jn. (522801)
10 Schools/ or Schools, Nursery/ (42221)
11 exp Child Day Care Centers/ or Child Care/ (11287)
12 (school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1).ti,ab,kf,jn. (356157)
13 or/1-12 (4333601)
14 Gender Dysphoria/ (581)
15 "Sexual and Gender Disorders"/ (79)
16 Transsexualism/ (3895)
17 Transgender Persons/ (3835)
18 Health Services for Transgender Persons/ (152)
19 exp Sex Reassignment Procedures/ (969)
20 "Sexual and Gender Minorities"/ (4924)
21 ((gender$ and dysphori$) or (gender$ adj5 incongru$) or sexual dysphori$).ti,ab,kf. (1784)
22 (gender$ adj (disorder$ or identi$)).ti,ab,kf. or (gender identity/ and dysphori$.ti,ab,kf.) (4568)
23 (GID or GIDS or GIDC or GIDCS).ti,ab,kf. (456)
24 (gender$ adj5 (confusion or confused or questioning or distress$ or discomfort)).ti,ab,kf. (980)
25 (gender$ adj5 (minority or minorities)).ti,ab,kf. (1593)
26 (gender$ adj5 (variant$ or variance$ or nonconform$ or non-conform$ or diverse or diversity or atypical$)).ti,ab,kf. (3409)
27 (non-binary or nonbinary or enby or genderqueer or gender-queer or neutrois).ti,ab,kf. (796)
28 (agender$ or genderless$ or gender-less$ or genderfree or gender-free or ungender$ or un-gender$ or non-gender$ or nongender$ or bigender$ or bi-gender$ or dual gender$ or dualgender$ or demi-gender$ or demigender$ or genderfluid$ or gender-fluid$ or trigender$ or tri-gender$).ti,ab,kf. (315)

29 two spirit$.ti,ab,kf. (84)
30 (trans adj3 (female$ or feminin$ or woman$ or women$ or male$1 or man or mans or men or mens or masculin$ or person$1 or peopl$ or population$ or individual$)).ti,ab,kf. (1362)
31 (transgend$ or trans-gend$ or transex$ or transsex$ or trans-sex$ or transfemale$ or transfeminin$ or transwom$ or transmale$ or transman$ or transmasculin$ or transmen$ or transperson$ or transpeopl$ or transpopulation$ or transindividual$).ti,ab,kf. (10832)
32 (trans adj3 identi$).ti,ab,kf. or (gender identity/ and trans.ti,ab,kf.) or (trans and dysphori$).ti,ab,kf. (1447)
33 (crossgender$ or cross-gender$ or crossex$ or crosssex$ or cross-sex$).ti,ab,kf. (836)
34 ((sex or gender$) adj3 (reassign$ or re-assign$ or affirm$ or confirm$ or transition$)).ti,ab,kf. (3963)
35 ((gender$ or sex) adj (change or changes or changing or changed)).ti,ab,kf. (825)
36 (detransition$ or de-transition$ or desister$ or de-sister$).ti,ab,kf. (134)
37 ((desist$ or persist$) adj5 (transition$ or trans or dysphori$)).ti,ab,kf. (823)
38 or/14-37 (28731)
39 (trans and (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ti. (339)
40 (trans adj5 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ab,kf. (397)
41 (transchild$ or transminor$ or transboy$ or transgirl$ or transkid or transkids or transyoung$ or transyouth$ or transteen$ or transtween$ or transadoles$ or transjuvenil$).ti,ab,kf. (15)
42 13 and 38 (9819)
43 39 or 40 or 41 or 42 (10343)
44 exp animals/ not humans/ (4823832)
45 (editorial or news or comment or case reports).pt. or case report.ti. (3692318)
46 43 not (44 or 45) (9429)
47 limit 46 to english language (9029)

Key to Ovid symbols and commands:
$ Unlimited right-hand truncation symbol
$N Limited right-hand truncation - restricts the number of characters following the word to N

ti,ab,kf,	Searches are restricted to the Title (ti), Abstract (ab), Keyword Heading Word (kf) fields
.jn	Searches are restricted to the Journal name field
adj	Retrieves records that contain terms next to each other (in the shown order)
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-12	Combines sets 1 to 12 using OR

EXHIBIT 91

Impact of social transition in relation to gender for children and adolescents: a systematic review

Ruth Hall, Jo Taylor, Catherine Elizabeth Hewitt, Claire Heathcote, Stuart William Jarvis, Trilby Langton, Lorna Fraser

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/archdischild-2023-326112).

Department of Health Sciences, University of York, York, UK

Correspondence to
Professor Catherine Elizabeth Hewitt, Department of Health Sciences, University of York, York, UK;
dohs-gender-research@york.ac.uk

Received 25 July 2023
Accepted 28 October 2023

► http://dx.doi.org/10.1136/archdischild-2023-326347
► http://dx.doi.org/10.1136/archdischild-2023-326348
► http://dx.doi.org/10.1136/archdischild-2023-326499
► http://dx.doi.org/10.1136/archdischild-2023-326500
► http://dx.doi.org/10.1136/archdischild-2023-326669
► http://dx.doi.org/10.1136/archdischild-2023-326670
► http://dx.doi.org/10.1136/archdischild-2023-326760
► http://dx.doi.org/10.1136/archdischild-2023-326681

To cite: Hall R, Taylor J, Hewitt CE, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2023-326112

ABSTRACT

Background Increasing numbers of children and adolescents experiencing gender dysphoria or incongruence are being referred to specialist gender services. Historically, social transitioning prior to assessment was rare but it is becoming more common.

Aim To identify and synthesise studies assessing the outcomes of social transition for children and adolescents (under 18) experiencing gender dysphoria/incongruence.

Methods A systematic review and narrative sythesis. Database searches (Medline, Embase, CINAHL, PsycINFO, Web of Science) were perfomed in April 2022. Studies reporting any outcome of social transition (full or partial) for children and adolescents experiencing gender dysphoria/incongruence were included. An adapted version of the Newcastle-Ottawa Scale for cohort studies was used to appraise study quality.

Results Eleven studies were included (children (n=8) and adolescents (n=3)) and most were of low quality. The majority were from the US, featured community samples and cross-sectional analyses. Different comparator groups were used, and outcomes related to mental health and gender identity reported. Overall studies consistently reported no difference in mental health outcomes for children who socially transitioned across all comparators. Studies found mixed evidence for adolescents who socially transitioned.

Conclusions It is difficult to assess the impact of social transition on children/adolescents due to the small volume and low quality of research in this area. Importantly, there are no prospective longitudinal studies with appropriate comparator groups assessing the impact of social transition on mental health or gender-related outcomes for children/adolescents. Professionals working in the area of gender identity and those seeking support should be aware of the absence of robust evidence of the benefits or harms of social transition for children and adolescents.

PROSPERO registration number CRD42021289659.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Increasing numbers of children and adolescents experiencing gender dysphoria/incongruence are being referred for care at specialist paediatric gender services.
⇒ Historically, social transitioning prior to assessment in gender services was rare. Social role transition is increasingly common in children and adolescents.
⇒ The rates of mental health conditions in children/adolescents experiencing gender dysphoria/incongruence are higher than those of the general population.

WHAT THIS STUDY ADDS

⇒ The evidence base for all outcomes of social transitioning in childhood or adolescence is both limited and of low quality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Guidelines should reflect the limited evidence regarding the outcomes of social transition for children and adolescents experiencing gender dysphoria/incongruence. Robust high-quality research is needed.

INTRODUCTION

The number of children and adolescents identifying as a gender different from the sex they were registered as at birth has increased markedly across the world over the last 10-15 years.[1] While there is no single definition of the term social transition, it is broadly understood to refer to social changes such as name change, using different pronouns or altering hair or clothing in order to live socially as a different gender,[2 3] but the degree and context of a social transition can vary widely. For some, using a preferred name or clothing may be limited to home while others may change their name officially and seek to make changes across all social settings. Additionally, some may publicly acknowledge that they have made a social transition while others may wish to keep their birth-registered sex private and only known by a few significant others.

Social transition is becoming more common with children and adolescents changing key social characteristics to fit more closely with a different gender role. Children and adolescents presenting at gender services are increasingly likely to have undergone a full social transition. In the UK, 54.6% of children and adolescents referred to the Gender Identity Development Service in 2012–2013 had socially transitioned,[4] with increasing numbers internationally.[5–7]

Social transition among children is contentious with diverging views between clinicians as to its role and potential benefits or harms.[3 8] Social transition can be regarded as important for a child's mental health and well-being with a child leading the way in their gender expression, in line with a model of gender affirming care.[3 8] Social transition is also seen as a significant intervention which

may alter the course of gender development with medical and surgical interventions being sought by children whose gender dysphoria/incongruence might not have otherwise persisted beyond puberty.[9] Guidelines for children and adolescents experiencing gender dysphoria/incongruence published by the World Professional Association for Transgender Health (WPATH),[10] with version 8 published in 2022,[11] have shifted from recommending an approach to social transition of 'watchful waiting' for children, to a position of advocating for social transition as a way to improve a child's mental health. Social transitioning among adolescents has not received the same level of interest in academic debate, nor do WPATH version 7 or 8 contain any specific discussion about the risks or benefits for adolescents.

Understanding what the evidence shows about possible benefits or harms is important for children and adolescents experiencing gender dysphoria/incongruence, parents who may be contemplating their child socially transitioning and for healthcare professionals and others whose advice and support may be sought on this question. Therefore, this systematic review aimed to synthesise primary research on outcomes related to social transition for children and adolescents experiencing gender dysphoria/incongruence.

METHODS

The review forms part of a linked series of systematic reviews examining the epidemiology, care pathways, outcomes and experiences for children and adolescents experiencing gender dysphoria/incongruence and is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12] The protocol was registered on PROSPERO (CRD42021289659).[13]

Search strategy

A single search strategy was developed to identify studies examining gender dysphoria/incongruence in children/adolescents (see online supplemental file 1). The following bibliographic databases were searched with no date restrictions: MEDLINE (OVID), EMBASE (OVID), CINAHL (EBSCO), PsycINFO (OVID) and Web of Science (Social Science Citation Index). The first search was conducted between 13 and 23 May 2021 and updated on 27 April 2022. The reference lists of eligible studies and any relevant systematic reviews or clinical guidelines that were identified were also checked.

Inclusion criteria

Studies were included in relation to the following criteria:

Population: children and adolescents up to age 18, or adults who experienced as a child/adolescent, gender dysphoria/incongruence or gender-related distress, or referral to a paediatric/adolescent gender identity service.

Intervention/exposure: a broad definition of social transition was adopted including any element of what is commonly understood to comprise a social transition,[3] for example, name change, use of pronouns, change in appearance.

Outcomes: any outcome of social transition in childhood or adolescence (eg, mental health).

Study design: primary studies published in English in a peer-reviewed journal of any design apart from case series and case reports.

Study selection

All search results were entered into Covidence and deduplicated.[14] Two reviewers independently assessed all titles and abstracts and full texts of those identified as potentially eligible. Conflicts were resolved through discussion or consensus with a third reviewer.

Data extraction

Data were extracted by one reviewer and second-checked by another. Replication of participants across studies was noted.

Quality assessment

Quality was assessed using a modified version of the Newcastle-Ottawa Scale,[15] a validated scale of eight items assessed across three domains: selection, comparability and outcome. Modification included, not scoring question(s) related to cross-sectional or longitudinal studies where relevant. The maximum possible score was 8. A score of 0–3.5 was deemed low quality, 4–5.5 moderate and 6–8 high. Two reviewers rated the papers independently with discussion to reach consensus.

Synthesis methods

Due to extensive differences in definition of social transition and measurement and reporting of outcomes, a narrative approach to synthesis and, where feasible an analysis of p values, effect direction and vote counting were used. The synthesis of data was led by the main comparisons in the included studies: child/adolescent, outcome and comparison group. Strength and direction of effects of social transition on outcomes was analysed from reported p values using albatross plots.[16] Vote counting[17] was also conducted and combined with quality assessment scores using harvest plots[18] and bar charts showing the number of studies reporting effects by direction and quality scores.

RESULTS

Overall, the searches identified 28 147 records, of which 3181 were considered as potentially relevant for the linked series of systematic reviews. From these, 13 studies were identified as relevant to this review of social transition.[19–31] On closer inspection, four studies were excluded: social transition not treated as an exposure (n=3)[22 24 26] or replication of analyses already published (n=1).[25] Two studies were identified as meeting the inclusion criteria from reference lists of guidelines[32 33] (figure 1). Therefore, 11 studies were included in this review.

Study characteristics

Of the included studies, eight were cross-sectional,[19–21 23 27 28 30 33] one was a reanalysis of previously published cross-sectional data,[31] one a prospective longitudinal study,[32] and one a retrospective cohort study.[29] The majority (n=7) were conducted in the US and/or Canada[19 21 23 27 30–32]; two in the Netherlands[29 33]; one in Brazil[20] and one in Germany.[28] Community samples were recruited in eight studies[19–21 23 27 30–32] and gender service patients were recruited in three studies[28 29 33] (online supplemental table 1).

Five US studies[19 21 23 30 32] included participants from the TransYouth Project, which is a longitudinal study of gender development among socially transitioned prepubertal children experiencing gender dysphoria/incongruence (age 3–12 years at start of study in 2013).[24] Four studies reported results from cross-sectional analyses of the cohort,[19 21 23 30] and one study from longitudinal analyses.[32] Children and their families were recruited to this cohort using convenience sampling from support groups (online and face to face) and the sample includes more children from affluent families than expected. Most had parents supportive of early social transition. There is some crossover

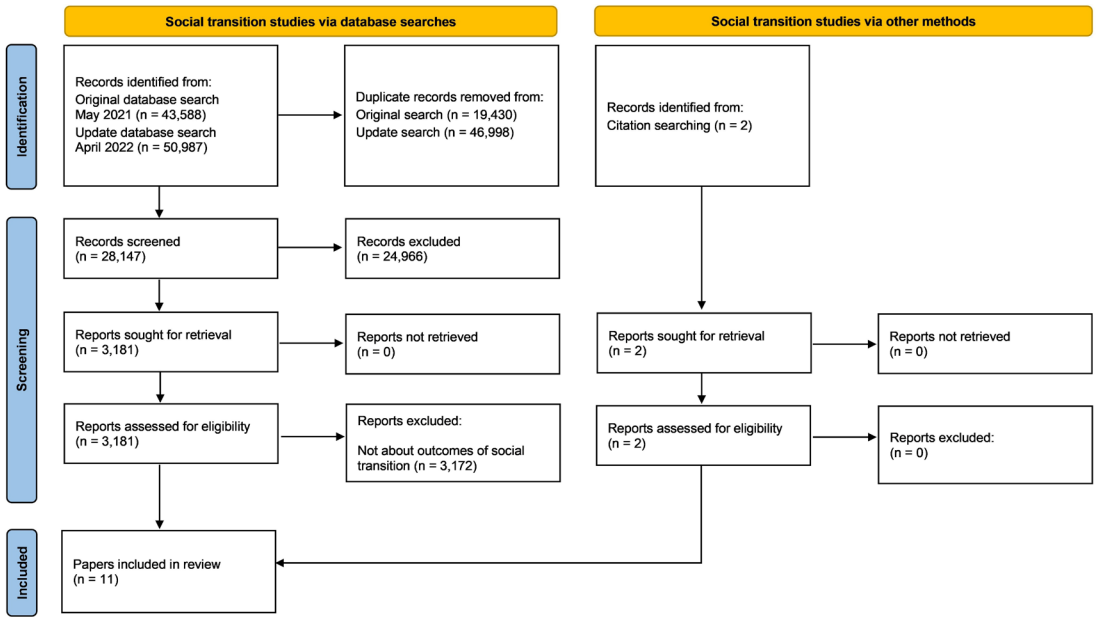


Figure 1 Study flow diagram.

of the samples between these studies but, as they are reporting different outcomes or child versus parent reports, all five studies were included. Two studies from the Amsterdam clinical population may also include overlapping samples, but this cannot be quantified so both were included.[29 33]

Children and/or adolescents were recruited in eight studies,[19 21 23 28 29 31–33] and two studies recruited a mixed group of adolescents and young adults.[20 27] The final study recruited adults with a history of childhood/adolescent gender dysphoria/incongruence and created subgroups based on age of social transition (3–9 years childhood, 10–17 years adolescence, 18+ years adulthood).[30] How gender identity and/or gender dysphoria/incongruence were determined and definitions of social transition and how this was established varied between studies (online supplemental table 1).

A range of mental health outcomes were reported across nine studies[19–21 23 27 28 30 31 33]; internalising symptoms, externalising symptoms, self-worth, self-esteem, self-perception, suicidality, severe psychological distress, and drug and alcohol misuse. One study also included measures of gender positivity and gender distress.[20] The remaining two studies focused on the constancy of gender identity across time as the outcome.[29 32]

Quality assessment

Overall, the quality of the papers was low to moderate with scores ranging from 1.5 to 5 (figure 2). Across all studies, the key methodological limitation was the approach to recruitment, relying on self-selecting groups or referral to gender services leading to samples which were unrepresentative of the broader population. A follow-up period between social transition and outcomes being measured was reported in three studies,[29 30 32] one of which relied on recall from adulthood.[30]

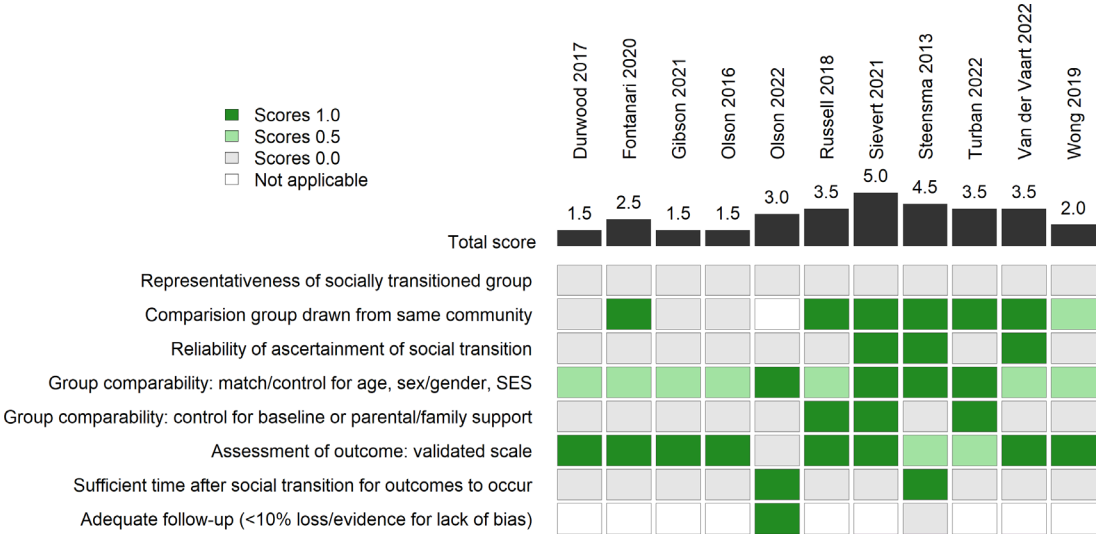


Figure 2 Quality scores for included studies assessed using a modified Newcastle-Ottawa Scale. The grid indicates individual scores for each study on each of the criteria. Bars at the top (and numbers at top of bars) indicate overall score. SES, socioeconomic status.

Three studies used a standardised method of ascertaining social transition.[28 29 33] The remaining studies used parent or self-report measures. All studies controlled or matched to some extent for age, birth-registered sex or gender identity, and socioeconomic status, however, three additionally controlled for baseline parental/family support.[27 28 30]

Seven studies used a comparison group drawn from the same population.[20 27–31 33] None of the studies using community samples of children included a suitable comparison group. Three studies compared children experiencing gender dysphoria/incongruence who had socially transitioned with a comparator group presumed not to experience gender dysphoria/incongruence, which included average population scores, and/or sibling and matched controls.[19 21 23] One study used previously published data for children with the same level of gender variance who had not socially transitioned,[31] however, they were reported by parents as having a gender identity that matched their birth-registered sex and so were not from the same population.

FINDINGS

The findings are presented in online supplemental table 2 and a visual summary of key outcomes is provided in figure 3.

Socially transitioned children

Six studies reported outcomes related to mental health[19 21 23 28 31 33] and two studies reported gender stability/persistence.[29 32]

Comparison group A: children not experiencing gender dysphoria/incongruence

Four studies reported mental health outcomes[19 21 23 31] (figure 3A). Three studies using the TransYouth Project data[19 21 23] found no significant difference in depressive symptoms compared with population averages,[19 23] siblings or matched controls across parent[19 21 23] and self-reported measures.[19 21]

Variation was seen in results for levels of anxiety across groups and between parent and self-report measures.[19 21 23] Parent-reported levels of anxiety were significantly higher than population averages[19 23] or matched controls,[19 21 23] but this was not seen for self-report comparisons to population averages,[19] and there were inconsistent results for the comparisons with matched controls.[19 23] No significant, although some marginal, differences were seen in anxiety levels when compared to siblings across parent and self-reported measures.[19 21 23] Self-worth was explored in a single study and not found to be significantly different from matched controls or siblings.[19]

One study used data from three published studies[22 23 34] to make comparisons between children who socially transitioned and children who were gender variant but who identified with their birth-registered sex.[31] They found no significant differences in parent-reported internalising scores, externalising symptoms or poor peer relations.

Comparison group B: children experiencing gender dysphoria/incongruence who have not socially transitioned

Three studies used this comparator[28 30 33] (figure 3B).

One clinic-based study found that the degree to which a child had socially transitioned was not associated with psychological functioning,[28] rather, socioeconomic status and poor peer relations were associated with internalising problems, and general family functioning and poor peer relations were associated with externalising problems. Another clinic-based study found no association between social transition status and any element of self-perception.[33] However, it found some differences when the sample was stratified by sex; birth-registered males who had socially transitioned reported poorer self-perception in scholastic competence and behavioural conduct compared with non-socially transitioned birth-registered males.[33] Conversely, birth-registered females who had socially transitioned scored higher on athletic competence than non-socially transitioned birth-registered females.

The third study's comparison group were transgender adults who experienced gender dysphoria/incongruence as a child but did not socially transition until adulthood.[30] They looked at past-month severe psychological distress, lifetime illicit drug use, lifetime marijuana use, past-month binge drinking, and various measures of suicidality. The only significant result in either direction was lower odds of lifetime use of marijuana for those socially transitioning in childhood. Harassment based on gender identity during kindergarten to year 12 was not considered within the initial analysis, but post hoc analyses found that those who socially transitioned in childhood were significantly more likely to have been subject to harassment due to being thought of as transgender than those socially transitioning in adulthood. The study made no adjustment for other confounding variables when considering likelihood of harassment between groups that socially transitioned at different ages.

Socially transitioned adolescents

Comparison group C: adolescents experiencing gender dysphoria/incongruence who have not socially transitioned

Three studies used this comparator group [20 27 30] (figure 3C).

Internalising symptoms were assessed by two studies.[20 27] Adolescents who preferred to be called by another name compared with no preferred name use reported fewer symptoms of depression but there was no signficant difference in anxiety.[20] In another study it was found that among those with a preferred name, chosen name use in more social contexts was associated with fewer depressive symptoms.[27]

One study assessed severe psychological distress and found no significant association between social transition in adolescence compared with adulthood.[30] Outcomes related to suicide and suicidal ideation were assessed in two studies.[27 30] It was found that chosen name use in more contexts was associated with lower suicidal ideation and behaviour,[27] and social transition during adolescence was associated with greater odds of past-year suicidal ideation and lifetime suicide attempts compared with transition during adulthood.[30] In the latter paper, six different measures of suicidality were explored and these were the only significant findings (online supplemental table 2).

A single study reported gender-related outcomes.[20] Adolescents who preferred to be called by another name compared with no preferred name use reported higher levels of gender distress but there was no signficant difference in gender positivity.

Comparison group: socially transitioned children

Only one study compared outcomes between children who socially transitioned and those transitioning in adolescence, and found no difference on any measure of mental health, suicidality or drug and alcohol use between the two groups.[30]

Gender identity outcomes

Two studies assessed gender identity outcomes.[29 32] One study found a higher odds of persistence of gender dysphoria/incongruence in adolescence for children who had socially transitioned compared with those who had not socially transitioned. Analysis by birth-registered sex showed significant findings for

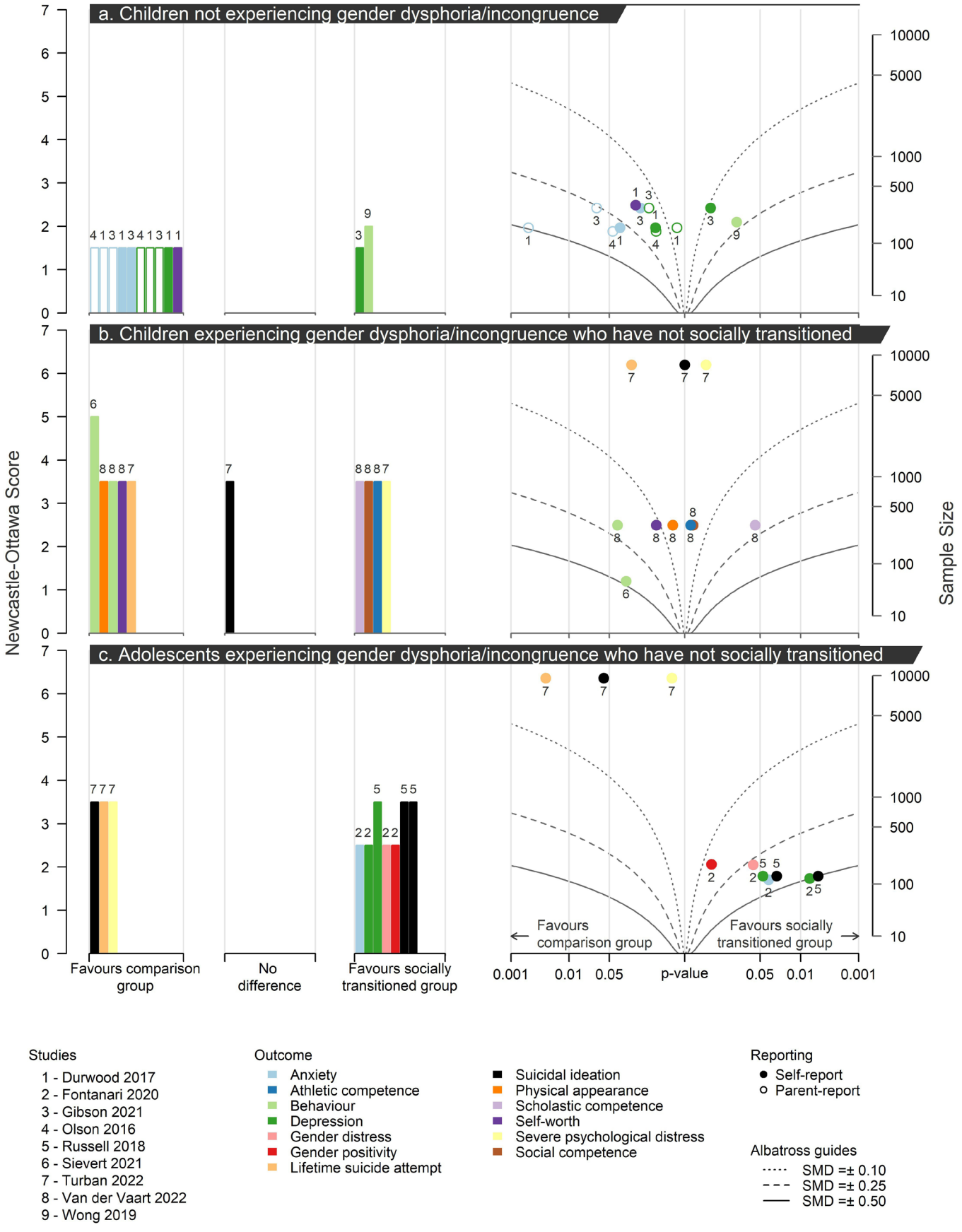


Figure 3 Harvest plots showing direction of effect and quality scores (left) and albatross plots showing direction of effect, statistical significance and sample size (right) for included studies. Panels a, b and c separate studies into those comparing social transition against either those not expriencing gender dysphoria/incongruence (a) or those experiencing gender dysphoria/incongruence who have not socially transitioned (b, c), and also separates studies for children (a, b) and adolescents (c). SMD, standardised mean difference.

birth-registered males but not for birth-registered females.[29] Another study found that 92.7% of those who socially transitioned between ages 3 and 12 continued to experience gender dysphoria/incongruence at the end of the study (on average, 5.4 years after socially transitioning).[32] The other 7.3% 're-transitioned' at least once; 2.5% identified with their birth-registered sex, 3.5% identified as non-binary and 1.3% had retransitioned twice. They found those socially transitioning before age 6 were more likely to retransition than those socially transitioning after age 6. There was no association between birth-registered sex and retransitioning.[32]

DISCUSSION

There is limited, low-quality evidence on the impact of social transition for children and adolescents experiencing gender dysphoria/incongruence. Most published studies are cross-sectional with non-representative samples and lack an appropriate comparator group, and most studies were undertaken in the US. Of note, there are no prospective longitudinal studies with appropriate comparator groups which have assessed the impact of social transition on the mental health or gender-related outcomes for children or adolescents.

Given the poor quality of studies and multiple comparisons across studies, all findings from this review should be interpreted with caution. There were also inconsistent results between studies. For example, two studies suggest there may be some benefit associated with use of chosen name in adolescence.[20–27] However, in another study lifetime suicide attempt and past-year suicidal ideation was higher among those socially transitioning as adolescents compared with those socially transitioning in adulthood.[30]

Social transition has become the subject of clinical and academic debate, mainly centred on whether social transition is an active intervention with potential for benefits as well as risks or longer term consequences. Questions focus on the ways in which a social transition might alter the trajectory and development of gender identity and dysphoria/incongruence over time. Those concerned about altering the course of gender development in children cite previous studies demonstrating that only small numbers of prepubertal children who experienced gender dysphoria/incongruence continued to experience this after puberty. Published estimates on those 'persisting' range from 2% to 39% with an average of 15%.[35] The concern then is that if children undergo an early social transition they may find it difficult to socially revert to their former gender.[2] By extension, some children may also then unnecessarily pursue medical and surgical interventions, so raising concerns about iatrogenic harm.[9]

In this review, two studies suggest that children who socially transition are more likely to continue to experience gender dysphoria/incongruence in adolescence, though one study found differences by birth-registered sex.[29 32] One of these studies also reported that the majority of those who socially transitioned progressed to medical interventions.[32]

There has been a shift over time in recommendations around social transitioning for children. In WPATH version 7[10] the evidence base was insufficient to understand long-term outcomes of an early social transition and therefore it advised, in line with a watchful waiting approach, that parents treat social transition as ongoing exploration rather than an 'irreversible situation'. Furthermore, it suggested that healthcare professionals could provide support in finding 'in-between' solutions rather than recommending full social transition. However, WPATH version 8[11] advocates more strongly in favour of childhood social transition, although continues to recommend psychosocial care to support gender exploration for prepubertal children. Three main arguments are put forward for supporting social transition; first, that there is now evidence of improved mental health outcomes; second, that fluidity of identity is an insufficient justification not to socially transition; and third, that not allowing a child to socially transition may in itself be harmful. These statements are not supported from the findings of this systematic review.

Social transitioning among adolescents has not been subject to the same level of debate as for children and there are no specific recommendations in either version of the WPATH guidelines. Version 7 states that adolescents are more likely to persist in their gender identity than children, citing a study in which adolescents were prescribed puberty suppression[36] and acknowledge the lack of prospective studies. Version 8 includes a separate chapter for adolescents containing recommendations that healthcare professionals should '*work with parents, schools and other organisations to promote acceptance and affirmation for instance through using preferred pronouns, preferred name, and supporting choices of clothing and hairstyle*'. There is not, however, discussion about potential benefits or harms of social transition and indeed no mention of this term.

This review has shown that we have little evidence of the benefits or harms of social transition for children and adolescents.

Strengths and limitations

Strengths include a published protocol with robust search strategies and comprehensive synthesis. The review only included studies published in English which is a limitation. The primary research included in this review was of low quality which limited the conclusions that could be drawn. As searches were conducted in April 2022 this review does not include more recently published studies; as this is a rapidly evolving area this is a limitation.

There is an urgent need to undertake high-quality and robust research to address the key unanswered questions:

1. Does social transition alter the trajectory of gender development?
2. Does social transition improve (or worsen) gender dysphoria?
3. Does social transition improve mental health outcomes?
4. What is the relationship between socially transitioning and outcomes not examined (eg, impact on peer relations/social difficulties, quality of life, body satisfaction)?
5. What are the long-term outcomes of social transition?

CONCLUSIONS

The studies included in this review are of low quality, therefore, it is difficult to assess the impact of social transition in this population. Importantly, there are no prospective longitudinal studies with appropriate comparator groups which have assessed the impact of social transition on the mental health or gender-related outcomes for children or adolescents experiencing gender dysphoria/incongruence. Healthcare professionals, clinical guidelines and advocacy organisations should acknowledge the lack of robust evidence of the benefits or harms of social transition when working with children, adolescents and their families.

Contributors LF, CEH and TL contributed to the conception and design of this review. Data collection was led by CH, JT and RH. Analyses were undertaken by RH, SWJ and LF. RH drafted the first version of the manuscript. All authors reviewed the manuscript prior to submission. CEH accepts full responsibility for the finished work

and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was funded by NHS England to inform the Cass Review (Independent review of gender identity services for children and young people). The funder and Cass Review team had a role in commissioning the research programme but no role in the study conduct, interpretation or conclusion.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement Data sharing is not applicable as no datasets were generated and/or analysed for this study.

ORCID iDs
Jo Taylor http://orcid.org/0000-0001-5898-0900
Catherine Elizabeth Hewitt http://orcid.org/0000-0002-0415-3536

REFERENCES

1 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender dysphoria literature: 1) epidemiology. *PLOS Glob Public Health* 2022;2:e0000245.
2 Steensma TD, Cohen-Kettenis PT. Gender transitioning before puberty. *Arch Sex Behav* 2011;40:649–50.
3 Ehrensaft D, Giammattei SV, Storck K, *et al*. Prepubertal social gender transitions: what we know; what we can learn—a view from a gender affirmative lens. *Int J Transgend* 2018;19:251–68.
4 Holt V, Skagerberg E, Dunsford M. Young people with features of gender dysphoria: demographics and associated difficulties. *Clin Child Psychol Psychiatry* 2016;21:108–18.
5 Chiniara LN, Bonifacio HJ, Palmert MR. Characteristics of adolescents referred to a gender clinic: are youth seen now different from those in initial reports. *Horm Res Paediatr* 2018;89:434–41.
6 Condat A, Mendes N, Cohen D. Variations in genital development, gender identities and consent to care. Rue Camille Desmoulins, Issy Les Moulineaux Elsevier Masson SAS; 2022. 418–23.
7 De Castro C, Solerdelcoll M, Plana MT, *et al*. High persistence in Spanish transgender minors: 18 years of experience of the gender identity unit of catalonia. *Revista de Psiquiatria y Salud Mental* 2022.
8 Hidalgo MA, Ehrensaft D, Tishelman AC, *et al*. The gender affirmative model: what we know and what we aim to learn. *Hum Dev* 2013;56:285–90.
9 Zucker KJ. Debate: different strokes for different folks. *Child Adolesc Ment Health* 2020;25:36–7.
10 Coleman E, Bockting W, Botzer M, *et al*. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgend* 2012;13:165–232.
11 Coleman E, Radix AE, Bouman WP, *et al*. Standards of care for the health of transgender and gender diverse people, version 8. *Int J Transgend Health* 2022;23(Suppl 1):S1–259.
12 Page MJ, McKenzie JE, Bossuyt PM, *et al*. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. *J Clin Epidemiol* 2021;134:103–12.
13 Fraser L, Hall R, Taylor J, *et al*. The epidemiology, management and outcomes of children with gender-related distress / gender dysphoria: a systematic review. *PROSPERO 2021:CRD42021289659*.
14 Veritas Health Innovation. *Covidence systematic review software*. Melbourne, Australia: Veritas Health Innovation, 2023.
15 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
16 Harrison S, Jones HE, Martin RM, *et al*. The albatross plot: a novel graphical tool for presenting results of diversely reported studies in a systematic review. *Res Synth Methods* 2017;8:281–9.
17 McKenzie JE, Brennan SE. Synthesizing and presenting findings using other methods. In: *Cochrane handbook for systematic reviews of interventions*. 2019: 321–47.
18 Ogilvie D, Fayter D, Petticrew M, *et al*. The harvest plot: a method for Synthesising evidence about the differential effects of interventions. *BMC Med Res Methodol* 2008;8:8.
19 Durwood L, McLaughlin KA, Olson KR. Mental health and self-worth in socially transitioned transgender youth. *J Am Acad Child Adolesc Psychiatry* 2017;56:116–23.
20 Fontanari AMV, Vilanova F, Schneider MA, *et al*. Gender affirmation is associated with transgender and gender nonbinary youth mental health improvement. *LGBT Health* 2020;7:237–47.
21 Gibson DJ, Glazier JJ, Olson KR. Evaluation of anxiety and depression in a community sample of transgender youth. *JAMA Netw Open* 2021;4:e214739.
22 Kuvalanka KA, Weiner JL, Munroe C, *et al*. Trans and gender-nonconforming children and their caregivers: gender presentations, peer relations, and well-being at baseline. *J Fam Psychol* 2017;31:889–99.
23 Olson KR, Durwood L, DeMeules M, *et al*. Mental health of transgender children who are supported in their identities. *Pediatrics* 2016;137:e20153223.
24 Olson KR, Gülgöz S. Early findings from the transyouth project: gender development in transgender children. *Child Dev Perspectives* 2018;12:93–7.
25 Pollitt AM, Ioverno S, Russell ST, *et al*. Predictors and mental health benefits of chosen name use among transgender youth. *Youth Soc* 2019;2019:320–41.
26 Rae JR, Gülgöz S, Durwood L, *et al*. Predicting early-childhood gender transitions. *Psychol Sci* 2019;30:669–81.
27 Russell ST, Pollitt AM, Li G, *et al*. Chosen name use is linked to reduced depressive symptoms, suicidal Ideation, and suicidal behavior among transgender youth. *J Adolesc Health* 2018;63:503–5.
28 Sievert ED, Schweizer K, Barkmann C, *et al*. Not social transition status, but peer relations and family functioning predict psychological functioning in a German clinical sample of children with gender dysphoria. *Clin Child Psychol Psychiatry* 2021;26:79–95.
29 Steensma TD, McGuire JK, Kreukels BPC, *et al*. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry* 2013;52:582–90.
30 Turban JL, King D, Li JJ, *et al*. Timing of social transition for transgender and gender diverse youth, K-12 harassment, and adult mental health outcomes. *J Adolesc Health* 2021;69:991–8.
31 Wong WI, van der Miesen AIR, Li TGF, *et al*. Childhood social gender transition and psychosocial well-being: a comparison to cisgender gender-variant children. *Clin Pract Pediatr Psychol* 2019;7:241–53.
32 Olson KR, Durwood L, Horton R, *et al*. Gender identity 5 years after social transition. *Pediatrics* 2022;150:e2021056082.
33 van der Vaart LR, Verveen A, Bos HM, *et al*. Differences in self-perception and social gender status in children with gender Incongruence. *Clin Child Psychol Psychiatry* 2022;27:1077–90.
34 van der Miesen AIR, Nabbijohn AN, Santarossa A, *et al*. Behavioral and emotional problems in gender-nonconforming children: a Canadian community-based study. *J Am Acad Child Adolesc Psychiatry* 2018;57:491–9.
35 Ristori J, Steensma TD. Gender dysphoria in childhood. *Int Rev Psychiatry* 2016;28:13–20.
36 de Vries ALC, Steensma TD, Doreleijers TAH, *et al*. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med* 2011;8:2276–83.

Supplemental Table 1 – Study Characteristics. Please note terminology is reported as per authors of original papers.

Author, year, country	Study design and setting	Population	Criteria for inclusion	Intervention	Comparison group/s	Follow up period	Outcomes	Method of outcome measurement
Durwood, 2017 (19), US and Canada	Cross-sectional with matched controls Community	For anxiety and depression measures: N = 164 (n = 63 socially transitioned transgender children, age 9-14y, mean age 10.8, SD 1.3, birth-registered males 48%; n = 63 cisgender controls, mean age 10.9, SD 1.4, birth-registered males 52%; n = 38 cisgender siblings, mean age 10.6, SD 1.2, birth-registered males 55%) For self-worth measures N = 310 (n = 116 socially transitioned transgender children, age 6-14y, mean age 9.3y, SD 2.0), birth-registered males 59%; n = 122, mean age 9.2, SD 2.0, birth-registered males 40%; n = 72 siblings, mean age 9.1, SD 1.8, birth-	Children included as transgender if they were reported by parents as identifying as the gender opposite to their birth-registered sex in everyday life	Full social transition: use of the pronouns associated with their asserted gender in all contexts	Two control groups of non-transgender children: 1.Age and gender identity matched controls 2.Siblings of transgender participants in the broader Trans Youth Project	None	Depression Anxiety Self-worth	Depression and anxiety symptoms - children completed paediatric short form PROMIS, and parents completed parental proxy short form For self-worth, children completed the Global self-worth Subscale from the Harter Self-perception profile for children

Author, year, country	Study design and setting	Population	Criteria for inclusion	Intervention	Comparison group/s	Follow up period	Outcomes	Method of outcome measurement
		registered males 56%)						
Fontanari, 2020 (20), Brazil	Cross-sectional Community	N = 350 transgender and nonbinary youth Of the total with a preferred name, n = 326 Of the total able to express their true gender n = 349 Age 16-24y (mean 18.61, SD not reported) birth-registered sex % not reported.149 self- identified as transgender boys, 85 as transgender girls and 116 as nonbinary.	Participants included if their answers to a two-part question about self-reported gender identity and sex at birth did not align. Participants then divided into categories 'transgender girls', 'transgender boys' or 'gender nonbinary' by researchers	Social affirmation: Use of preferred name by mother and/or father Able to express their gender identity in everyday life (no further detail provided)	For those with a preferred name a comparison was made between those whose mother or father used their name always, sometimes, or never For those able to express their true gender a comparison was made between those able to do so all of the time, half of the time, or never.	None	Anxiety Depression Gender Distress Gender positivity	The Overall Anxiety Severity and Impairment Scale (OASIS), the Modified Depression Scale (MDS), the Gender Distress Scale, and Gender positivity scale (GPS)

Author, year, country	Study design and setting	Population	Criteria for inclusion	Intervention	Comparison group/s	Follow up period	Outcomes	Method of outcome measurement
Gibson, 2021 (21) US and Canada	Cross-sectional with matched controls Community	N = 375 (n = 148 socially transitioned transgender children, age 8-14y, mean age 10.1, SD 1.0), birth-registered males: 64%; n = 139 cisgender controls, mean age 10.1, SD 1.0, birth-registered males 35%; n = 88 cisgender siblings, mean age 10.2, SD 1.2, birth-registered males 53%)	Children needed to use the pronouns opposite their birth-registered sex in all contexts to be included as 'transgender'	Full social transition: Use of the pronoun 'opposite' their sex in all contexts	Two control groups of non-transgender children: 1.Age and gender identity matched controls 2.Siblings of transgender participants in the broader Trans Youth Project	None	Depression and anxiety	Depression and anxiety symptoms - children completed paediatric short form PROMIS, and parents completed parental proxy short form
Olson, 2016 (23) US and Canada	Cross-sectional with matched controls Community	N = 195 (n = 73 socially transitioned transgender children, age 3-12y, mean age 7.7y, SD 2.2, birth-registered males 70%; n = 73 cisgender controls, mean age 7.8y, SD 2.2, birth-registered males 30%; n = 49 cisgender siblings, mean age 8.3y, SD 2.5, birth-registered males 61%)	Children included as 'transgender' if they were reported by parents as identifying as the gender opposite their birth-registered sex in everyday life	Full social transition: Presenting in all contexts (at school and in public) as the gender consistent with their identity and use of the pronouns associated with gender identity rather than sex	Two control groups of non-transgender children: 1.Age and gender identity matched controls 2.Siblings of transgender participants	None	Anxiety and depression	National Institute of Health Patient Reported Outcomes Measurement Information System (PROMIS) parental proxy short forms for anxiety and depression

Author, year, country	Study design and setting	Population	Criteria for inclusion	Intervention	Comparison group/s	Follow up period	Outcomes	Method of outcome measurement
Olson, 2022 (32), US and Canada	Longitudinal Community	N = 317 socially transitioned, initially transgender youth Age at recruitment 3-12 (mean age 8.1y, SD 2.36), birth-registered males: 66%	Children included as 'transgender' if they were reported by parents as identifying as the gender opposite their birth-registered sex in everyday life	Full social transition: Presenting in all contexts (at school and in public) as the gender consistent with their identity and use of the pronouns associated with gender identity rather than sex	Comparisons made between those socially transitioning before or after age 6 and between males and females.	Average of 5.37 years (SD = 1.74 years) after their initial social transition (average of 3.8 years in the study)	Gender identity based on use of pronouns and classified as binary transgender, non-binary, or cisgender	Notes review of last recorded interaction with research team to ascertain which pronouns used
Russell, 2018 (27), US	Cross-sectional Community	N = 129 youth aged 15-21 (mean age 18.70, SD 1.74) self-identified as transgender or gender queer (n = 74 with a chosen name, mean age 19.05, SD 1.66, birth-registered males: 45%; n = 55 without a chosen name, mean age 18.22, SD 1.75, birth-registered males: 45%)	No description of how gender identity was established. Participants were categorised into male birth sex to female gender identity (MTF), female birth sex to male gender identity (FTM), male birth sex to a different gender (MTDG), female birth sex to a different gender identity (FTDG)	Part of social transition: chosen name use in different contexts (home, school, work)	Comparison between those able to use their chosen name in different contexts and those not able to	None	Depressive symptoms Suicidal ideation and behaviour	Beck Depression Inventory for Youth scale Self-harm Behaviour Questionnaire

Author, year, country	Study design and setting	Population	Criteria for inclusion	Intervention	Comparison group/s	Follow up period	Outcomes	Method of outcome measurement
Sievert, 2021 (28), Germany	Cross-sectional Gender clinic	N = 54 children diagnosed with Gender Dysphoria Age 11 and under (mean age 9.05 years, SD 2.08). Birth-registered males: 54%	Participants included if they met the diagnostic criteria for Gender Dysphoria (DSM 5). This was established by clinicians during a comprehensive diagnostic and psychological evaluation	Social transition - classified as no social transition, partial, almost complete, and complete social transition, scale 1-4 based on whether the child was living in preferred gender role at home/with peers / at school	Comparison between children who had undergone different degrees of social transition	None	Internalising and Externalising problems.	Child Behaviour Checklist (CBCL).
Steensma, 2013 (29), The Netherlands	Retrospective cohort study Gender clinic	N = 127 adolescents who were referred and assessed in childhood (<12y) Age at follow up, range 15-19 years, age in childhood range 6-12 years. No overall mean age and SD reported. Birth-registered males: 62%	Participants were included if they were assessed for Gender Identity Disorder (DSM IV). Included both those meeting the full diagnostic criteria and those subthreshold for a diagnosis	Social transition: classified as no social transition, partial transition (clothing and hairstyle but not name and pronouns) or complete transition (clothing, hairstyle, name and pronouns). Established by 2 questions posed to parents around time of referral.	Those who had either partially or completely socially transitioned in childhood were compared to those who had not socially transitioned in childhood	Minimum follow up 3 years (from age 12 to 15 years). Mean follow up period not reported	'Persistence' or 'desistance' of Gender Dysphoria in adolescence.	Outcome established by reviewing clinical notes. Re-applying to the gender clinic in adolescence, being diagnosed with GID and being eligible for medical treatment counted as persistence. Those not returning to the gender clinic in adolescence were counted as desisters.

Author, year, country	Study design and setting	Population	Criteria for inclusion	Intervention	Comparison group/s	Follow up period	Outcomes	Method of outcome measurement
Turban, 2022 (30), US	Cross-sectional retrospective Community	N = 9711 socially transitioned trans and gender diverse adults aged 18+. Mean age 34.8 (SD 13.9). Birth-registered male 45.8% (Sub groups: childhood social transition n = 165, adolescent social transition n = 1196, adult social transition n = 8350)	The US Trans Survey 2015 included participants with a diverse range of gender identities, included in this study if they reported having a different gender identity to birth sex during childhood. Categorised as: woman, man, transwoman, transman, Nonbinary/Genderqueer	Social transition: self-reported by answering yes to the question 'do you currently live full time in a gender that is different to the one assigned to you at birth?'	Three groups compared based on age of social transition in 1. Childhood (age 3-9 years), 2. Adolescence (10-17 years) or 3. Adulthood (age 18 years and older)	None	Past month severe psychological distress; Lifetime illicit drug use; Lifetime marijuana use; Past-month binge drinking; Suicidality (6 sub-measures)	Kessler-6 psychological distress scale Other outcomes measured by survey questions (non-validated)
van der Vaart, 2022 (33), The Netherlands	Cross-sectional Gender clinic	N = 312 children aged 7-13y, mean age 9.4 years (SD 1.2). Birth-registered male 47.1% (Sub-groups; socially transitioned children n=194; and not socially transitioned n=118)	Children referred to the Gender clinic for assessment of Gender Dysphoria. Not reported if diagnostic criteria were met.	Social transition: defined as using preferred name and pronouns and, or, wearing clothing and hairstyle incongruent to birth assigned sex	Socially transitioned and non-socially transitioned children.	None	Aspects of self-perception: scholastic, social, athletic competence, physical appearance, behavioural conduct, global self-worth	Dutch version of the self-perception profile for children (SPPC)

Author, year, country	Study design and setting	Population	Criteria for inclusion	Intervention	Comparison group/s	Follow up period	Outcomes	Method of outcome measurement
Wong, 2019 (31), US and Canada	Re-analysis of data from 3 cross-sectional studies using statistical bootstrapping to match samples Community	N = 266 gender variant children aged 3-12 years (n = 162 cisgender gender-variant children, mean age 8.8 years, SD 2.01, birth-registered males 36%; n = 31, socially transitioned cross-gender identified children, mean age 8.7 years, SD 1.9, birth-registered males 55%; n = 73 socially transitioned transgender children, mean age 7.7 years, SD 2.2, birth-registered males 70%)	Cisgender gender variant (CGV) children included if they had levels of gender variance similar to clinic-referred children on Gender Identity Questionnaire for Children but gender identity and birth-registered sex were aligned. Children included as transgender or cross-gender identified, if they identified as the opposite gender to their birth-registered sex.	Social transition not defined by Wong. Original studies defined social transition as switching pronouns; presenting in all contexts and changing pronouns	Non-socially transitioned, cisgender gender-variant children compared to socially transitioned transgender and cross-gender identified children	None	Emotional (internalising) and behavioural (externalising) problems	Child Behaviour Checklist (CBCL) Patient reported outcome measurement information system (PROMIS)

Supplemental Table 2: Summary of findings. Please note terminology is reported as per authors of original papers.

Outcome	Paper	Comparison group(s)	Reported measure	Reported value	Total sample (socially transitioned sample)	Direction of reported effect (* =significant at p < 0.05)	Reported value for socially transitioned (SD or 95%CI)	Reported value for comparison(s) (SD or 95%CI)	P-value (method used)	Additional relevant reported comparisons
Socially transitioned children compared to non-transgender children										
Anxiety	Olson 2016	Non-transgender age and gender-identify matched controls; siblings	Parent - PROMIS (Patient-Reported Outcomes Measurement Information System).	Mean scores	146 (73)	Favours comparison	54.2	Matched controls: 50.9; Siblings 52.3	0.057 (ANOVA, three groups)	National average, favours comparison, p <0.001
	Durwood 2017				164 (63)	Favours comparison*	54.9 (9)	Matched: 49.6 (8.6); Siblings: 51.0 (8.2)	0.002 (ANOVA, three groups)	Matched controls, favours comparison, p = 0.002; National average, favours comparison, p<0.001
	Gibson 2021				287 (148)	Favours comparison*	52.62 (9.41)	Matched: 49.94 (8.84); Siblings: 50.23 (9.32)	0.03 (ANOVA, three way)	
	Durwood 2017		Self - PROMIS (Patient-Reported Outcomes Measurement Information System).		164 (63)	Favours comparison	52 (9.6)	Matched: 49.0 (7.7); Siblings: 52.8 (10.5)	0.076 (ANOVA, three groups)	Matched controls, favours comparison, p = 0.16; national average, favours comparison, p=0.29

Outcome	Paper	Comparison group(s)	Reported measure	Reported value	Total sample (socially transitioned sample)	Direction of reported effect (* =significant at p < 0.05)	Reported value for socially transitioned (SD or 95%CI)	Reported value for comparison(s) (SD or 95%CI)	P-value (method used)	Additional relevant reported comparisons
	Gibson 2021				287 (148)	Favours comparison	52.21 (8.92)	Matched: 50.53 (8.25); Siblings: 52.41 (8.82)	0.17 (ANOVA, three way)	
Depression	Olson 2016	Non-transgender age and gender-identify matched controls; siblings	Parent - PROMIS (Patient-Reported Outcomes Measurement Information System).	Mean scores	146 (73)	Favours comparison	50.1	Matched controls: 48.4; Siblings 49.3	0.32 (ANOVA, three groups)	National average, favours comparison, p = 0.883
	Durwood 2017				164 (63)	Favours comparison	50.2 (8.8)	Matched: 49.4 (7.8); 48.9 (7.1)	0.728 (ANOVA, three groups)	National average, favours comparison, p=0.14)
	Gibson 2021				287 (148)	Favours comparison	51.41 (8.06)	Matched: 49.86 (7.65); Siblings: 51.1 (8.52)	0.24 (ANOVA, three way)	
	Durwood 2017		Self - PROMIS (Patient-Reported Outcomes Measurement Information System).		164 (63)	Favours comparison	48.7 (9.4)	Matched: 46.4 (8.0); Siblings: 47.9 (7.9)	0.311 (ANOVA, three groups)	National average, favours social transition, p=0.96)
	Gibson 2021				287 (148)	Favours social transition	46.38 (9.13)	Matched: 46.46 (8.99); Siblings: 48.01 (9.05)	0.36 (ANOVA, three way)	
Self-worth	Durwood 2017	Cisgender age and gender-identify matched controls; siblings	Self - Global Self-Worth Subscale from Harter Self-Perception Profile for Children	Mean scores	309 (116)	Favours comparison	3.46 (0.54)	Matched: 3.61 (0.42); Siblings: 3.62 (0.44)	0.142 (ANOVA, three way)	

Outcome	Paper	Comparison group(s)	Reported measure	Reported value	Total sample (socially transitioned sample)	Direction of reported effect (* =significant at p < 0.05)	Reported value for socially transitioned (SD or 95%CI)	Reported value for comparison(s) (SD or 95%CI)	P-value (method used)	Additional relevant reported comparisons
Behavioural problems	Wong 2019	Non-transgender children (bootstrap matched sample)	Self - CBCL (Child Behaviour Check List) Total Problem score	Mean scores	193 (31)	Favours social transition	27.97 (19.59)	33.49 (4.36)	0.127 (T-test)	
			Self - CBCL (Child Behaviour Check List) Internalizing score	Mean scores	193 (31)	Favours social transition	53.23 (9.92)	54.57 (1.92)	0.458 (T-test)	
			Self -CBCL (Child Behaviour Check List) Externalizing score	Mean scores	193 (31)	Favours social transition	51.16 (10.29)	52.4 (1.97)	0.508 (T-test)	
			Self - CBCL (Child Behaviour Check List) Peer relations score	Mean scores	193 (31)	Favours social transition	0.74 (1.21)	0.84 (0.22)	0.649 (T-test)	
Socially transitioned children compared to non-socially transitioned transgender children										
Behavioural problems	Sievert 2021	Extent of social transition compared	Self - CBCL (Child Behaviour Check List) Total Problem score	Linear regression coefficient	54 (not disclosed, four level scoring))	Favours comparison	2.64 (linear regression coefficient with ST score)	0 (ref)	0.097 (linear regression)	
Scholastic competence	Van der Vaart 2022	Non-socially transitioned transgender children	Self - Dutch version of Self-Perception profile for Children (SPPC)	Mean	312 (194)	Favours social transition	50.9 (33.8)	47.7 (29.1)	0.061 (ANCOVA)	
Social competence	Van der Vaart 2022	Non-socially transitioned transgender children	Self - Dutch version of Self-Perception	Mean	312 (194)	Favours social transition	58.3 (31.2)	50.1 (31.8)	0.720 (ANCOVA)	

Outcome	Paper	Comparison group(s)	Reported measure	Reported value	Total sample (socially transitioned sample)	Direction of reported effect (* =significant at p < 0.05)	Reported value for socially transitioned (SD or 95%CI)	Reported value for comparison(s) (SD or 95%CI)	P-value (method used)	Additional relevant reported comparisons
			profile for Children (SPPC)							
Athletic competence	Van der Vaart 2022	Non-socially transitioned transgender children	Self - Dutch version of Self-Perception profile for Children (SPPC)	Mean	312 (194)	Favours social transition	61.3 (30.6)	47.8 (31.5)	0.791 (ANCOVA)	
Physical appearance	Van der Vaart 2022	Non-socially transitioned transgender children	Self - Dutch version of Self-Perception profile for Children (SPPC)	Mean	312 (194)	Favours comparison	29.7 (26.4)	32.2 (30.5)	0.621 (ANCOVA)	
Behavioural conduct	Van der Vaart 2022	Non-socially transitioned transgender children	Self - Dutch version of Self-Perception profile for Children (SPPC)	Mean	312 (194)	Favours comparison	42.9 (31.5)	53.4 (31.6)	0.069 (ANCOVA)	
Global self-worth	Van der Vaart 2022	Non-socially transitioned transgender children	Self - Dutch version of Self-Perception profile for Children (SPPC)	Mean	312 (194)	Favours comparison	27.9 (30.8)	33.4 (31.7)	0.322 (ANCOVA)	
Lifetime suicidal ideation	Turban 2022	People who socially transitioned as adults	Self - Survey question	Odds ratio	8515 (165)	Favours social transition	0.8 (0.4-2.0)	1 (ref)	0.80 (logistic regression	
Past-year suicidal ideation	Turban 2022	People who socially transitioned as adults	Self - Survey question	Odds ratio	8515 (165)	None	1.0 (0.6-1.8)	1 (ref)	0.89 (logistic regression)	

Outcome	Paper	Comparison group(s)	Reported measure	Reported value	Total sample (socially transitioned sample)	Direction of reported effect (* =significant at p < 0.05)	Reported value for socially transitioned (SD or 95%CI)	Reported value for comparison(s) (SD or 95%CI)	P-value (method used)	Additional relevant reported comparisons
Past-year suicidal ideation with plan	Turban 2022	People who socially transitioned as adults	Self - Survey question	Odds ratio	8515 (165)	Favours comparison	1.3 (0.7-2.6)	1 (ref)	0.45 (logistic regression)	
Lifetime suicide attempt	Turban 2022	People who socially transitioned as adults	Self - Survey question	Odds ratio	8515 (165)	Favours comparison	1.5 (0.9-2.6)	1 (ref)	0.12 (logistic regression)	
Past-year attempt	Turban 2022	People who socially transitioned as adults	Self - Survey question	Odds ratio	8515 (165)	Favours comparison	1.3 (0.5-3.1)	1 (ref)	0.63 (logistic regression)	
Past-year suicide attempt resulting in medical attention	Turban 2022	People who socially transitioned as adults	Self - Survey question	Odds ratio	8515 (165)	Favours comparison	1.8 (0.5-6.7)	1 (ref)	0.36 (logistic regression)	
Severe psychological distress	Turban 2022	People who socially transitioned as adults	Self - Kesler 6 (score >= 13)	Odds ratio	8515 (165)	Favours social transition	0.8 (0.4-1.4)	1 (ref)	0.43 (logistic regression)	
Persistence of gender dysphoria	Steensma 2013	Non-socially transitioned transgender children	Records - Return to clinic	Odds ratio	127 (37)	Social transition increases persistence*	5.06 (1.61-15.87)	1 (ref)	<0.01 (logistic regression	
Socially transitioned adolescents compared to non-socially transitioned transgender adolescents										
Anxiety	Fontanari 2020	Non-socially transitioned transgender adolescents	Self - OASIS (Overall Anxiety Severity and	Mean	115 (87)	Favours social transition*	Full ST: 9.23 (8.17-10.30); Partial ST:	12.00 (10.13-13.89)	0.036 (ANCOVA)	

Outcome	Paper	Comparison group(s)	Reported measure	Reported value	Total sample (socially transitioned sample)	Direction of reported effect (* =significant at p < 0.05)	Reported value for socially transitioned (SD or 95%CI)	Reported value for comparison(s) (SD or 95%CI)	P-value (method used)	Additional relevant reported comparisons
			Impairment Scale)				10.38 (9.12-11.63)			
Depression	Fontanari 2020	Non-socially transitioned transgender adolescents	Self - MDS (Modified Depression Scale)	Mean	120 (88)	Favours social transition*	Full ST: 16.74 (15.88-17.59)	19.38 (17.96-20.81)	0.007 (ANCOVA)	
	Russell 2018		Self - Beck Depression Inventory for Youth	Linear regression coefficient	129 (74)	Favours social transition*	'-5.37 (-8.20 - -2.55)	0	0.045 (calculated from linear regression 95% CI)	
Gender distress	Fontanari 2020	Non-socially transitioned transgender adolescents	Self - GDS (Gender Distress Scale)	Mean	182 (132)	Favours social transition	Full ST: 4.10 (3.99-4.21); Partial ST: 3.94 (3.81-4.06)	4.16 (3.98-4.34)	0.066 (ANCOVA)	
Gender positivity	Fontanari 2020	Non-socially transitioned transgender adolescents	Self - GPS (Gender Positivity Scale)	Mean	184 (135)	Favours social transition	Full ST: 3.36 (3.32-3.49); Partial ST: 3.38 (3.24-3.52)	3.19 (2.97-3.41)	0.346 (ANCOVA)	
Lifetime suicidal ideation	Turban 2022	People who socially transitioned as adults	Self - Survey question	Odds ratio	9546 (1196)	None	1 (0.7-1.3)	1 (ref)	0.90 (logistic regression)	
Past-year suicidal ideation	Turban 2022	People who socially transitioned as adults	Self - Survey question	Odds ratio	9546 (1196)	Favours comparison*	1.2 (1.0-1.5)	1 (ref)	0.04 (logistic regression)	
Past-year suicidal ideation with plan	Turban 2022	People who socially transitioned as adults	Self - Survey question	Odds ratio	9546 (1196)	Favours comparison	1.2 (0.9-1.5)	1 (ref)	0.22 (logistic regression)	

Outcome	Paper	Comparison group(s)	Reported measure	Reported value	Total sample (socially transitioned sample)	Direction of reported effect (* =significant at p < 0.05)	Reported value for socially transitioned (SD or 95%CI)	Reported value for comparison(s) (SD or 95%CI)	P-value (method used)	Additional relevant reported comparisons
Lifetime suicide attempt	Turban 2022	People who socially transitioned as adults	Self - Survey question	Odds ratio	9546 (1196)	Favours comparison*	1.3 (1.1-1.7)	1 (ref)	0.004 (logistic regression)	
Past-year suicide attempt	Turban 2022	People who socially transitioned as adults	Self - Survey question	Odds ratio	9546 (1196)	Favours comparison	1.2 (0.9-1.7)	1 (ref)	0.28 (logistic regression)	
Past-year suicide attempt resulting in medical attention	Turban 2022	People who socially transitioned as adults	Self - Survey question	Odds ratio	9546 (1196)	Favours comparison	1.1 (0.8-1.3)	1 (ref)	0.82 (logistic regression)	
Severe psychological distress	Turban 2022	People who socially transitioned as adults	Self - Kesler 6 (score >= 13)	Odds ratio	9546 (1196)	Favours comparison	1.1 (0.8-1.3)	1 (ref)	0.60 (logistic regression)	
Suicidal ideation	Russell 2018	Non-socially transitioned transgender adolescents	Self - Self-Harm Behaviour Questionnaire	Incidence rate ratio	129 (74)	Favours social transition*	0.71 (0.52-0.95)	1 (ref)	0.026 (calculated from Poisson regression 95% CI)	
Suicidal behaviour	Russell 2018	Non-socially transitioned transgender adolescents	Self - Self-Harm Behaviour Questionnaire	Incidence rate ratio	129 (74)	Favours social transition*	0.44 (0.25-0.78)	1 (ref)	0.005 (calculated from Poisson regression 95% CI)	
Observational follow-up of socially transitioned children										
Persistence of transgender	Olson 2022	N/A (longitudinal	Self - maintaining pronouns	%	317 (317)	N/A	Persistence: 94%;	N/A	N/A	Retransition more likely

Outcome	Paper	Comparison group(s)	Reported measure	Reported value	Total sample (socially transitioned sample)	Direction of reported effect (* =significant at p < 0.05)	Reported value for socially transitioned (SD or 95%CI)	Reported value for comparison(s) (SD or 95%CI)	P-value (method used)	Additional relevant reported comparisons
identity after social transition		follow-up of socially transitioned group)	associated with transgender identity				Retransition to cisgender: 2.5%; Retransition to non-binary: 3.5%			when social transition before age 6 (p=0.02)

Supplementary file 1: Final search strategy for Ovid MEDLINE

1 exp Child/ or Child Behavior/ or Child Health/ or Child Welfare/ or Psychology, Child/ or Child Psychiatry/ or Child Health Services/ or Child Development/ (1984459)
2 Minors/ (2638)
3 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or emerging adult$).ti,ab,kf,jn. (1862660)
4 (young$ adj (people$ or person$1 or adult$ or man$1 or men$1 or woman$ or women$ or male$1 or female$1)).ti,ab,kf,jn. (224878)
5 pediatrics/ (55388)
6 (pediatric$ or paediatric$ or peadiatric$).ti,ab,kf,jn. (543516)
7 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Psychology, Adolescent/ or Adolescent Psychiatry/ or Adolescent Health Services/ or Adolescent Medicine/ or Adolescent Development/ (2088552)
8 Puberty/ (13562)
9 (adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or underage$ or under-age$).ti,ab,kf,jn. (522801)
10 Schools/ or Schools, Nursery/ (42221)
11 exp Child Day Care Centers/ or Child Care/ (11287)
12 (school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1).ti,ab,kf,jn. (356157)
13 or/1-12 (4333601)
14 Gender Dysphoria/ (581)
15 "Sexual and Gender Disorders"/ (79)
16 Transsexualism/ (3895)
17 Transgender Persons/ (3835)
18 Health Services for Transgender Persons/ (152)
19 exp Sex Reassignment Procedures/ (969)
20 "Sexual and Gender Minorities"/ (4924)
21 ((gender$ and dysphori$) or (gender$ adj5 incongru$) or sexual dysphori$).ti,ab,kf. (1784)
22 (gender$ adj (disorder$ or identi$)).ti,ab,kf. or (gender identity/ and dysphori$.ti,ab,kf.) (4568)
23 (GID or GIDS or GIDC or GIDCS).ti,ab,kf. (456)
24 (gender$ adj5 (confusion or confused or questioning or distress$ or discomfort)).ti,ab,kf. (980)
25 (gender$ adj5 (minority or minorities)).ti,ab,kf. (1593)
26 (gender$ adj5 (variant$ or variance$ or nonconform$ or non-conform$ or diverse or diversity or atypical$)).ti,ab,kf. (3409)
27 (non-binary or nonbinary or enby or genderqueer or gender-queer or neutrois).ti,ab,kf. (796)
28 (agender$ or genderless$ or gender-less$ or genderfree or gender-free or ungender$ or un-gender$ or non-gender$ or nongender$ or bigender$ or bi-gender$ or dual gender$ or dualgender$ or demi-gender$ or demigender$ or genderfluid$ or gender-fluid$ or trigender$ or tri-gender$).ti,ab,kf. (315)
29 two spirit$.ti,ab,kf. (84)
30 (trans adj3 (female$ or feminin$ or woman$ or women$ or male$1 or man or mans or men or mens or masculin$ or person$1 or peopl$ or population$ or individual$)).ti,ab,kf. (1362)
31 (transgend$ or trans-gend$ or transex$ or transsex$ or trans-sex$ or transfemale$ or transfeminin$ or transwom$ or transmale$ or transman$ or transmasculin$ or transmen$ or transperson$ or transpeopl$ or transpopulation$ or transindividual$).ti,ab,kf. (10832)

32 (trans adj3 identi$).ti,ab,kf. or (gender identity/ and trans.ti,ab,kf.) or (trans and dysphori$).ti,ab,kf. (1447)
33 (crossgender$ or cross-gender$ or crossex$ or crosssex$ or cross-sex$).ti,ab,kf. (836)
34 ((sex or gender$) adj3 (reassign$ or re-assign$ or affirm$ or confirm$ or transition$)).ti,ab,kf. (3963)
35 ((gender$ or sex) adj (change or changes or changing or changed)).ti,ab,kf. (825)
36 (detransition$ or de-transition$ or desister$ or de-sister$).ti,ab,kf. (134)
37 ((desist$ or persist$) adj5 (transition$ or trans or dysphori$)).ti,ab,kf. (823)
38 or/14-37 (28731)
39 (trans and (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ti. (339)
40 (trans adj5 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ab,kf. (397)
41 (transchild$ or transminor$ or transboy$ or transgirl$ or transkid or transkids or transyoung$ or transyouth$ or transteen$ or transtween$ or transadoles$ or transjuvenil$).ti,ab,kf. (15)
42 13 and 38 (9819)
43 39 or 40 or 41 or 42 (10343)
44 exp animals/ not humans/ (4823832)
45 (editorial or news or comment or case reports).pt. or case report.ti. (3692318)
46 43 not (44 or 45) (9429)
47 limit 46 to english language (9029)

Key to Ovid symbols and commands:

$	Unlimited right-hand truncation symbol
$N	Limited right-hand truncation - restricts the number of characters following the word to N
ti,ab,kf,	Searches are restricted to the Title (ti), Abstract (ab), Keyword Heading Word (kf) fields
.jn	Searches are restricted to the Journal name field
adj	Retrieves records that contain terms next to each other (in the shown order)
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-12	Combines sets 1 to 12 using OR

EXHIBIT 92

OPEN ACCESS

Care pathways of children and adolescents referred to specialist gender services: a systematic review

Jo Taylor , Ruth Hall, Trilby Langton, Lorna Fraser, Catherine Elizabeth Hewitt

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/archdischild-2023-326760).

Department of Health Sciences, University of York, York, UK

Correspondence to
Professor Catherine Elizabeth Hewitt, Department of Health Sciences, University of York, York, UK;
dohs-gender-research@york.ac.uk

Received 16 December 2023
Accepted 17 January 2024

► http://dx.doi.org/10.1136/archdischild-2023-326112
► http://dx.doi.org/10.1136/archdischild-2023-326347
► http://dx.doi.org/10.1136/archdischild-2023-326348
► http://dx.doi.org/10.1136/archdischild-2023-326670
► http://dx.doi.org/10.1136/archdischild-2023-326500
► http://dx.doi.org/10.1136/archdischild-2023-326499
► http://dx.doi.org/10.1136/archdischild-2023-326669
► http://dx.doi.org/10.1136/archdischild-2023-326681

To cite: Taylor J, Hall R, Langton T, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2023-326760

ABSTRACT

Background Increasing numbers of children and adolescents experiencing gender dysphoria/incongruence are being referred to specialist gender services. However, little is currently known about the proportions accessing different types of care and treatment following referral.

Aim This systematic review examines the range of care pathways of children/adolescents (under 18) referred to specialist gender or endocrinology services.

Methods Database searches were performed (April 2022), with results assessed independently by two reviewers. Peer-reviewed articles providing data for numbers of children and/or adolescents at referral/assessment and their treatment pathways were included. A narrative approach to synthesis was used and where appropriate proportions were combined in a random-effects meta-analysis.

Results 23 studies across nine countries were included, representing 6133 children and/or adolescents with a median age at assessment of 14–16 and overall a higher percentage of birth-registered females. Of those assessed, 36% (95% CI 27% to 45%) received puberty suppression, 51% (95% CI 40% to 62%) received masculinising or feminising hormones, 68% (95% CI 57% to 77%) received puberty suppression and/or hormones and 16% (95% CI 10% to 24%) received surgery. No study systematically reported information about the full pathway or psychological care received by children/adolescents. Follow-up in many studies was insufficient or unclear. Reasons for discontinuation were rarely provided.

Conclusions Prospective studies with long-term follow-up reporting information about the full range of pathways are needed to understand what happens to children and adolescents referred to specialist gender services. Information about provision of psychological care is needed considering high rates of psychosocial difficulties in this population.

PROSPERO registration number CRD42021289659.

WHAT IS ALREADY KNOWN?

⇒ Increasing numbers of children and adolescents experiencing gender dysphoria/incongruence are being referred for care at specialist paediatric gender services.
⇒ Several countries have or are modifying referral and care pathways and provision in response to increasing numbers of referrals, changing demographics and ongoing uncertainty about the benefits, risks and long-term effects of medical interventions for these children and adolescents.
⇒ Little is currently known about the trajectories and outcomes of children and adolescents referred to specialist gender services.

WHAT THIS STUDY ADDS?

⇒ Approximately two-thirds of adolescents referred to specialist gender services receive puberty suppression or hormones, although the rates vary considerably across services.
⇒ There is very little information about children/adolescents who do not receive medical intervention, or about the psychological care received by those under the care of a specialist gender service.
⇒ Studies consistently report small proportions of adolescents who discontinue medical treatment; however, systematic reporting and reasons for discontinuation are rarely provided and follow-up periods are limited.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Prospective studies that follow up children into adulthood and report information about the range of pathways followed are needed to understand longer-term outcomes for those referred to specialist paediatric gender services.

INTRODUCTION

Over the last 10-15 years, increasing numbers of children and adolescents experiencing gender incongruence are being referred to specialist paediatric gender services.[1 2] Literature also highlights changes in the demographics of referrals, with a much higher proportion of birth-registered female adolescents now being referred.[1 3] Many of those referred will experience gender dysphoria, which can cause significant distress.[4] Mental health difficulties, neurodevelopmental conditions and psychosocial complexity are higher in referred children and adolescents compared with their peers who do not experience gender incongruence; the relationship between gender dysphoria and these co-occurring conditions is poorly understood.[4–9]

Specialist gender services are evolving to the changing demand for gender-related care by establishing new triage processes,[10] developing multiple care pathways for those presenting with different needs,[11] provision of psychological care by local mental health services[11 12] and expanding provision.[13 14] Uncertainties in the evidence base about the benefits, risks and long-term effects of care pathways and medical interventions for this population are also driving these changes.[15–23]

National and international guidelines have recently been developed or updated in response to these uncertainties and/or the changing demand for specialist care.[11 12 24 25] Historically, a staged pathway was outlined first involving a comprehensive gender-related and psychosocial assessment and psychoeducational support, along with provision of psychological interventions to address any co-occurring or contributory psychosocial difficulties identified.[26] For adolescents experiencing gender dysphoria/incongruence that intensified during early puberty and who met the criteria for a diagnosis of gender dysphoria, puberty suppression could be considered. In later adolescence, masculinising or feminising hormones were considered for those continuing to medically transition, with surgical interventions delayed until adulthood. While this approach still broadly underpins current guidelines,[11 12 24 25 27] there is a lack of consensus regarding access to medical interventions, with the latest World Professional Association for Transgender Health guideline containing no minimum age criteria or requirement for diagnosis of gender dysphoria,[24] while in contrast the latest Swedish guideline outlines much stricter eligibility criteria and recommends that medical interventions are provided under a research framework due to uncertainties in the evidence base.[12]

Although a common care pathway is described by guidelines, little is known about the trajectories and outcomes for children or adolescents referred to specialist gender services. It is not known how many of those referred complete an assessment and access interventions, or how many leave services or discontinue treatment or subsequently 'desist' (no longer continue to experience gender dysphoria or incongruence), or how many who have started to medically transition will 'de/re-transition' (revert to living as their birth-registered sex or develop a new gender identity). This review aims to synthesise research reporting the care pathways for children and/or adolescents referred to specialist paediatric gender or endocrinology services, reporting the following:

- Number referred, assessed, diagnosed with gender dysphoria/incongruence, considered eligible for medical intervention and subsequently receiving medical intervention.
- Number who later desist or detransition/retransition.
- Reasons why they leave the service pathway or cease the assessment and/or medical intervention.
- Provision of psychological care while under the care of a specialist gender service.

METHODS

The review forms part of a linked series of systematic reviews examining the epidemiology, care pathways, outcomes and experiences of children and adolescents experiencing gender dysphoria/incongruence and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[28] The protocol was registered on PROSPERO (CRD42021289659).[29]

Search strategy

A single search strategy was used comprising two combined concepts: 'children', which included all terms for children and adolescents; and 'gender dysphoria', which included associated terms such as gender incongruence and gender-related distress, and gender identity terms including transgender, gender diverse and non-binary. MEDLINE (online supplemental table S1), EMBASE and PsycINFO through OVID, CINAHL Complete through EBSCO, and Web of Science (Social Science Citation Index) were searched (13-23 May 2021, updated 27 April 2022).

Inclusion criteria

Peer-reviewed articles that reported, at a minimum, the number of children and/or adolescents at referral/assessment and the number progressing to treatment in paediatric or adolescent gender/endocrinology services were included (table 1).

Selection process

Search results were uploaded to Covidence[30] and screened independently by two reviewers. Full texts for potentially relevant articles were retrieved and reviewed against the inclusion criteria by two reviewers independently. Disagreements were resolved through discussion.

Data extraction

Data were extracted into a prepiloted template by one reviewer and checked by another. Data were extracted from graphs using the PlotDigitizer tool (https://plotdigitizer.com/). Study quality was not formally assessed.

Synthesis

A narrative approach to synthesis was used and where appropriate proportions were combined in a random-effects meta-analysis using metaprop (Stata V.18), with variances stabilised using the Freeman-Tukey double arcsine transformation.[31] The synthesis was performed by one reviewer and double-checked by another.

RESULTS

Our searches yielded 28 147 records, 3181 of which were identified as potentially relevant for the linked series of systematic

Table 1 Inclusion and exclusion criteria

Population	► Children and adolescents (ages 0–18) referred to paediatric or adolescent gender service or paediatric or adolescent endocrinology service that provides specialist gender-related healthcare. ► Articles reporting on child or adolescent populations or the combined population of children and adolescents were included. ► Mixed populations of adolescents and adults included if referred to child or adolescent gender service, eg, some services provide healthcare to age 24; or where data reported separately for all-age services. ► Studies of other selected subsamples were excluded, eg, those eligible for or receiving treatment, one gender group, or studies recruiting a specific or convenience sample.
Comparator	► Any or none.
Variables	► Article reports as a minimum the number of referred or assessed children and/or adolescents AND the progression of these children/adolescents to treatment.
Study design	► Studies of any design or articles reporting data from gender services. ► Systematic or other literature reviews were excluded.
Publication	► Published in the English language in a peer-reviewed journal. ► Conference abstracts and letters were excluded.

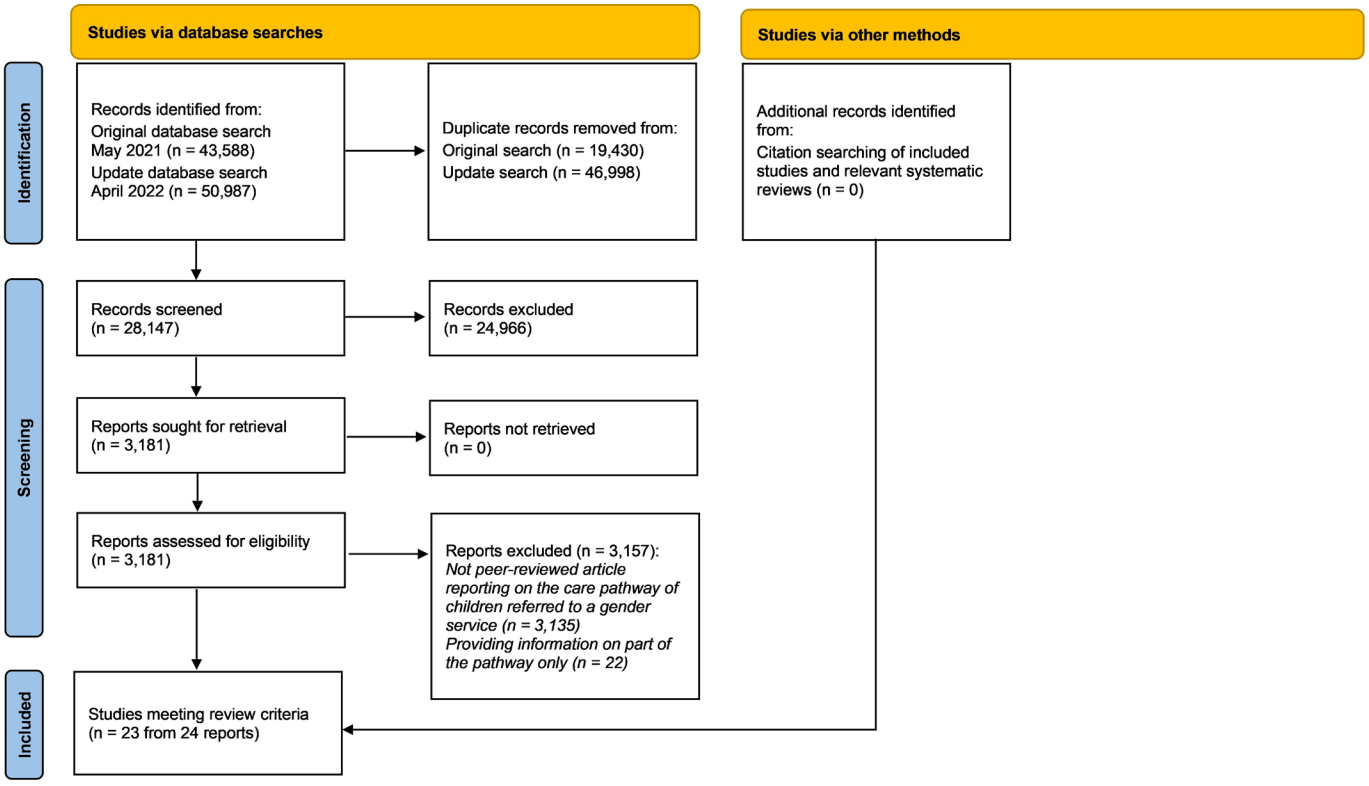


Figure 1 Study flow diagram.

reviews and for which full texts were reviewed. From these, there were 24 papers including 23 studies that met the inclusion criteria for this review (figure 1, online supplemental table S2).

Study characteristics

Studies included specialist gender services (n=14)[32–46] or endocrinology services (n=9)[47–55] in Australia (n=2),[32 33] Canada (n=3),[34 47 48] the Netherlands (n=4),[36–39 50] Spain (n=2)[40 41] and the US (n=8),[43–46 52–55] and single studies from Finland,[49] Israel,[35] Scotland[51] and the UK.[42] Eight studies commented on the length of follow-up, but not at standardised points and so this varied for each person.[34–39 41 42 51] The longest time from assessment to follow-up was 10 years, but this study also included some patients who had only recently been assessed and so they had limited follow-up within the same study.[34] Most studies reporting follow-up times had a median of 1–2 years of follow-up.[35 41 42 51] Studies included referrals/assessments from 1972 to 2019, although most were from 2000 onwards.

Overall, 6133 children/adolescents were included across studies, with samples ranging from 38 to 1360. Nine studies included referred adolescents only,[34 37 38 42 47–51 53] whereas others included all referrals. Two US[45 46] and three Dutch[37–39 50] studies likely included overlapping samples. The median age at referral was 14–15 and at assessment was 14–16. Most studies reported a higher percentage of birth-registered females compared with males (online supplemental table S2).

Referral, assessment, diagnostic and treatment pathways

Ten studies reported the numbers referred, whereas all reported the numbers assessed within services (table 2). The numbers being assessed ranged from 46% to 100% of those referred.

Seven studies reported both the numbers assessed and receiving a diagnosis of gender dysphoria/incongruence.[32 33 36 41 42 50 53] The numbers receiving a diagnosis ranged from 44% to 100% of those assessed. Less than half of the studies (n=11) reported the reasons why individuals either discontinued during the assessment process or did not receive a diagnosis, with studies that reported these often not distinguishing between these two outcomes. Reasons included the following: being referred for other reasons than gender dysphoria/incongruence, experiencing resolution of gender dysphoria or acceptance of gender incongruence with ongoing counselling, no longer seeking medical treatment, not attending clinic after the first visit, coexisting problems interfering with the diagnostic process and/or might interfere with successful treatment, confusion about their gender identity and sexual orientation, being referred to mental health professionals, and being prepubertal and continuing with psychological counselling.

Five studies reported the numbers considered eligible or referred for further treatment out of the children/adolescents receiving a diagnosis of gender dysphoria/incongruence.[32 33 36 42 50] This varied between studies, ranging from 60% to 100% of those diagnosed and considered eligible for further treatment. Eighteen studies reported the total number of adolescents who started either puberty suppression and/or masculinising or feminising hormone interventions (referred to hereon as hormones). Of the 4797 assessed in these 18 studies, 68% (95% CI 57% to 77%) received either puberty suppression and/or hormones; however, the proportions varied considerably between services (from 21%[32] to 100%[49]) and there were differences between gender (60%; 95% CI 50% to 69%) and endocrine (83%; 95% CI 68% to 94%) services. Receipt of psychological treatment was unclear in most studies, and where it was reported the details of what this included and who received it were absent (online supplemental table S2).

Table 2 Summary of care pathways of included studies

Authors	Country	Service	Data collection period	Referred	Assessed	Diagnosed	Eligible/referred for medical treatment	Received	PS	MFH	Surgery
Hewitt *et al*[32]	Australia	Gender clinic	2003–2011	39	39	17	17	8	6	6	
Tollit *et al*[33]	Australia	Gender clinic	2007–2016	359	359	291	234	118	54	48	
Chiniara *et al*[47]	Canada	Endocrinology	2014–2016	218	203				115	75	
Khatchadourian *et al*[48]	Canada	Endocrinology	1998–2011		84				52	63	13
Zucker *et al*[34]	Canada	Gender clinic	2000–2009	165	109		71	45	43		
Vehmas *et al*[49]	Finland	Endocrinology	2011–2018		124		124	124	56	124	
Segev-Becker *et al*[35]	Israel	Gender clinic	2013–2018	106	106		96	77	77	61	19
Arnoldussen *et al*[50]	The Netherlands	Endocrinology	2000–2016	1072	965	908	908	846			
Brik *et al*[36]	The Netherlands	Gender clinic	2010–2018		269	147	147	143	143	125	
de Vries *et al*[37 38]	The Netherlands	Gender clinic	2000–2008	196	196		140	140	111	99	62
Wiepjes *et al*[39]	The Netherlands	Gender clinic	1972–2015		1360			816	554	589	
McCallion *et al*[51]	Scotland	Endocrinology	2011–2019		91		79	79	79	41	
DeCastro *et al*2022[41]	Spain	Gender clinic	1999–2016		140	124			13	35	
Esteva de Antonio *et al*[40]	Spain	Gender clinic	2000–2012		141			89	7	82	36
Costa *et al*[42]	UK	Gender clinic	2010–2014	436	201	201	121	121	121		
Chen *et al*[43]	USA	Endocrinology	2002–2015		38			15	15	8	
Chen *et al*[52]	USA	Gender clinic	2013–2016		220			116	34	82	7
Handler *et al*[44]	USA	Gender clinic	2015–2018	417	417						89
Kuper *et al*[53]	USA	Endocrinology	2014–2017	158	158	158		146	49	139	
Leon *et al*[45]	USA	Gender clinic	2017–2019		185			159	49	119	17
Nahata *et al*[54]	USA	Endocrinology	2014–2016		79				9	40	
O'Bryan *et al*[46]	USA	Gender clinic	Unclear		139			123	41	106	20
Spack *et al*[55]	USA	Endocrinology	1998–2009		97			56	11	39	

MFH, masculinising or feminising hormone interventions; PS, puberty suppression.

Interventions to suppress puberty

Twenty-one studies reported the numbers receiving puberty suppression from 13 specialist paediatric and 8 endocrinology services.[32–43 45–49 51–55] Of the referred population, the pooled estimate was 36% (95% CI 23% to 51%, n=1677, 8 studies), with similar figures reported when focusing on those completing an assessment (36%; 95% CI 27% to 45%, n=4338, 21 studies) or diagnosed with gender dysphoria/incongruence (43%; 95% CI 15% to 74%, n=938, 6 studies). Higher percentages were reported from those considered eligible for medical intervention (75%; 95% CI 49% to 94%, n=1029, 9 studies).

The age at which children/adolescents received puberty suppression was between 9 and 18 years, with an average of 15. Three studies reported age by birth-registered sex, but inconsistent results were found.[33 36 51] Most studies did not report the reasons why individuals did not receive puberty suppression. Where the reasons were stated, they included needing more time, co-occurring psychiatric problems and/or psychological difficulties, lost to follow-up, and financial considerations, including not receiving coverage from insurance.

Seven studies reported the number of discontinuations and three reported the reasons why.[32 33 36 39 46 48 51] Discontinuation with puberty suppression ranged from no patients[32] to 8%.[51] Reasons for discontinuation included emotional distress, undecided on gender, reidentifying or happy being birth-registered gender, side effects, not complying with treatment protocol and difficulties attending clinic/pharmacy for injection/medication. One study reported that six (8%) young people discontinued gonadotropin-releasing hormone analogues (GnRH-a) for puberty suppression following a median duration of 6 months (range 6-18 months). Compared with those who continued with treatment, young people who discontinued had initiated treatment at an older age and included a higher proportion of those with mental health conditions and autism spectrum condition.[51]

Masculinising and feminising hormone interventions

Nineteen studies reported the numbers receiving hormones from 11 specialist paediatric and 8 endocrinology services.[32 33 35–41 43 45–49 51–55] Of the referred population, the pooled estimate was 43% (95% CI 19% to 69%, n=1076, 6 studies), with slightly higher figures reported when focusing on those completing an assessment (51%; 95% CI 40% to 62%, n=4028, 19 studies) or diagnosed with gender dysphoria/incongruence (52%; 95% CI 17% to 86%, n=737, 5 studies). Higher percentages were reported from those considered eligible for medical intervention (65%; 95% CI 36% to 89%, n=837, 7 studies). Few studies provided a breakdown of those who progressed to hormones following puberty suppression and those who started hormones as their first medical intervention.

The age at which adolescents received hormones was between 13 and 19 years, with an average age of 17. Three studies reported age by birth-registered sex, but inconsistent results were found.[33 36 51] Most studies did not report the reasons why eligible individuals did not receive hormones. Where reasons were stated, they included being close to 18 when court approval is not required within the specific country, family not supporting treatment, financial considerations including not receiving coverage from insurance, delaying interventions for fertility preservation or other reasons, not wishing to receive hormone treatment, and needle phobia.

Six studies reported whether hormones were continued or discontinued, all reporting either no discontinuations or one or two individuals discontinuing.[32 33 35 46 48 51] Four of these reported the reasons or context.[35 46 48 51] In one study, a single person stopped treatment after 4 months as their gender dysphoria had resolved.[51] In another, two discontinued, with one reverting to living as their birth-registered sex and the second continuing to take GnRH-a while exploring an emerging gender identity.[46] In the third study, two birth-registered males who had been taking GnRH-a and low-dose oestrogen for 3 months decided not to transition. In the final study, three birth-registered females stopped treatment temporarily (two due to psychiatric difficulties and one due to distress over androgenic alopecia) but reported later resuming.[48]

Surgical interventions

Nine studies reported the numbers receiving surgical interventions from the referred/assessed populations of eight specialist paediatric and one endocrinology service.[35 37 39 40 43–46 48] A Dutch study reported that of those treated with hormones for at least 1.5 years and were at least 18 years old, 78.2% received surgery (actual numbers were not reported).[39] For the remaining eight studies, the pooled estimates for those adolescents receiving surgical interventions varied from 16% to 34% across the different stages; referred 24% (95% CI 17% to 31%, n=719, 3 studies), assessed 16% (95% CI 10% to 24%, n=1488, 8 studies) and eligible for medical intervention 34% (95% CI 28% to 40%, n=236, 2 studies). Six studies reported the types of surgery received and included chest, facial feminisation and genital surgery.[35 39 40 43 44 48]

Three studies commented on the age at the time of surgery.[35 44 48] A US study reported that 57 (of 89) had surgery before they were age 18.[44] An Israeli study reported that the median age of 15 birth-registered females who had mastectomy was 17.6 (range 15–19).[35] In the same study, two birth-registered males had breast augmentation and two had vaginoplasty at age over 18. Finally, in a Canadian study, nine people had mastectomy at a median age of 18.1 (range 15–22), six had hysterectomy and salpingo-oophorectomy at a median age of 18.9 (range 17–22), and two had penectomy, orchidectomy and vaginoplasty at 18 and 21 years of age.[48]

DISCUSSION

This review of 23 studies from nine countries found that children and adolescents referred to or assessed in specialist paediatric gender and endocrinology services leave the care pathway at all stages following referral for multiple reasons. However, the numbers leaving at each possible stage of care were rarely reported, and follow-up in many studies was insufficient or unclear and in others varied considerably, with some participants followed up for several years while others had only just completed assessment, meaning their subsequent care trajectories were not reported. Few studies provided information about adolescents who completed assessment but did not subsequently receive medical intervention, estimated to be around a third of those entering assessment with differences between gender and endocrine services. No study provided clear information about psychological care received by children/adolescents under the care of gender services.

There is mixed and partial evidence about the numbers of children completing an assessment or receiving a diagnosis of gender dysphoria or incongruence. Most studies did not report the numbers referred, instead starting with the numbers assessed. Given increasing referral numbers and waiting times, a better understanding of the needs of all children/adolescents referred would provide needed insights into service provision.[56]

Studies published more recently have systematically examined data on assessment and treatment pathways for national services in the Netherlands[56 57] and the UK.[58 59] However, only one reported data on those not completing assessment, which was presented for different time periods and age at first visit (range 6%–38%).[56] Of 1401 adolescents who were eligible for puberty suppression, 882 (63%) received this, with higher rates in birth-registered females compared with males (73% vs 47%). Of 707 adolescents who received GnRH-a and were eligible for hormones during follow-up, 93% progressed. Only three adolescents received hormones without first receiving GnRH-a. A second Dutch study reported a similarly high progression from GnRH-a to hormones (98%).[57]

The recent UK studies report data for a subset of adolescents who had been under the care of a national paediatric gender service and were subsequently referred onto the endocrine pathway within the service.[58 59] Of 439 adolescents referred with a view to start medical intervention, 431 (98%) commenced GnRH-a and 8 (2%) commenced hormones only. At follow-up of 2–3 years, 183 (42%) had progressed to hormones after receiving GnRH-a.[59] In this review, an average of 36% and 51% of those assessed received puberty suppression and hormones, respectively, which differ from the more recent UK and Dutch studies. Having said that, the pooled estimate presented here for those receiving either treatment was 69%, which was similar to the proportion starting GnRH-a in the Netherlands, with study authors concluding that GnRH-a may be used as the start of transition rather than being seen as an extension of the diagnostic phase. Overall, there was considerable variation between services, which likely reflects country differences in intervention criteria, regulations, insurance coverage and clinical practice, as well as whether services focus on medical interventions or provide care to children and adolescents across the care pathway.

In both the UK and the Netherlands, a similar approach is followed, with most adolescents first receiving puberty suppression before progressing to masculinising/feminising hormones.[56 57 59] However, a recent study of 434 adolescents who had at least two encounters for gender-related care in the US Military Healthcare System found no association between GnRH-a use and subsequent hormone initiation, with 16.1% prescribed GnRH-a and 46.4% prescribed hormones within 1 year of the initial encounter and 88.3% within 4 years.[60] Few of the reviewed studies provided clarity about which adolescents who received hormones had first received puberty suppression, although many reported a higher proportion of adolescents receiving hormones than those receiving puberty suppression. In wider research, little is known about any difference in outcomes for adolescents who start hormones with or without first receiving puberty suppression.[15]

Discontinuation of medical treatments was similar across reviewed studies. In the seven studies reporting data for puberty suppression, discontinuation ranged from no patients to 8%. In the recent Dutch study, five (0.8%) birth-registered females and nine (3.4%) birth-registered males discontinued treatment during follow-up, and in the UK 30 (7%) adolescents consenting to GnRH-a did not start or discontinued treatment.[56] For masculinising/feminising hormones, six studies reported discontinuation, with very low rates (0–2 individuals) reported.[57] High rates of continuation were also reported in the recent Dutch study, with 98% still prescribed them at follow-up (average 3.2 years for birth-registered females, 6.1 years for birth-registered males), and the UK study which found no discontinuation at 2–3 years of follow-up.[59] A second UK study which reported discharge outcomes (length of follow-up unclear) found that of 1089 adolescents referred to the endocrine pathway, 90 (8.3%) stopped identifying as gender incongruent, 58 (5.3%) of whom had started puberty suppression or hormones and subsequently stopped these and reverted to their birth-registered sex.[58] The lack of reporting on reasons for discontinuation makes drawing conclusions problematic. Longer-term follow-up into adulthood is necessary to understand trajectories more comprehensively. Detransitioning has been reported to occur on average around 3.9 years later,[61] with expressions of regret reported as ranging between 3.8 and 22 years after transition.[39 62]

There was variation in the percentages of referred, assessed and eligible for medical intervention populations receiving surgical interventions (16%–34%). However, the numbers receiving surgery were only at the observation point, which was often unclear and/or relatively short, and therefore unlikely to include surgery received later in adulthood, which is often when it occurs. A Spanish study reported the numbers receiving and waiting for surgery (36 received surgery and 46 were awaiting surgery), which combined would lead to a much higher proportion of adolescents going on to receive surgery.[40] Numbers receiving surgery are also likely to differ by country due to different regulations, insurance coverage, service provision and the clinical guideline informing practice. A key difference is whether adolescents under the age of 18 are considered for surgery. However, only three of the nine studies reporting information on surgery provide this detail.[35 44 48] These studies suggest surgery is relatively common among adolescents under the age of 18. However, in the recently published Dutch study, surgery is only provided to young people aged 18 or over.[56] Longer-term follow-up is therefore required to gain a fuller picture about the proportion of children/adolescents who go on to request and receive surgery to modify their bodies.

Like the studies reviewed here, these more recent studies do not report systematic information about any psychological care provision. In some countries, there is now an expectation that psychological care is provided by local mental health services, in part due to increasing demand for specialist gender services.[11] At the same time, clinical guidelines recommend that psychological care for this population is provided by professionals with expertise in gender development and gender dysphoria/incongruence.[24 63] Currently, there is limited understanding about the provision of psychological care for children and adolescents experiencing gender dysphoria/incongruence by specialist gender or local mental health services, or about professional competence in this area of practice. There is also little evidence about the effectiveness of psychosocial interventions for this population.[23 40]

Strengths and limitations

Strengths include a published protocol with robust search strategies and comprehensive synthesis. As searches were conducted to April 2022 this review does not include more recently published studies; as this is a rapidly evolving area this is a limitation. Pooled estimates for each stage of the care pathway must be interpreted with caution due to inadequate and/or unclear reporting of follow-up and studies not reporting data on the full care pathway, in particular not reporting the numbers referred. This review did not extract information about fertility care for adolescents, which was reported by few of the identified studies and has been examined in separate studies.[64–67]

CONCLUSION

This review aids our understanding of the assessment and treatment trajectories of children and adolescents who are referred to specialist gender and endocrinology services, showing children/adolescents leave at different stages, suggesting there is not just one care pathway. However, prospective studies that follow up children into adulthood and report information about all possible trajectories and outcomes are needed. A better understanding is also needed about what care is provided to around a third of adolescents who undergo assessment within a gender service but do not go on to receive medical intervention. Information about provision of psychological care is needed, particularly considering the high prevalence of mental health and psychosocial difficulties in this population.

Contributors JT and CEH conducted the selection, extraction and synthesis, and drafted the manuscript. All authors contributed to the design of the review, assisted with interpretation of synthesis, and contributed to and reviewed the manuscript before submission. CEH accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was funded by NHS England to inform the Cass Review (Independent review of gender identity services for children and young people). The funder and Cass Review team had a role in commissioning the research programme but no role in the study conduct, interpretation or conclusion.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

ORCID iDs
Jo Taylor http://orcid.org/0000-0001-5898-0900
Catherine Elizabeth Hewitt http://orcid.org/0000-0002-0415-3536

REFERENCES

1 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender dysphoria literature: 1) epidemiology. *PLOS Glob Public Health* 2022;2:e0000245.
2 Kaltiala R, Bergman H, Carmichael P, *et al*. Time trends in referrals to child and adolescent gender identity services: a study in four nordic countries and in the UK. *Nord J Psychiatry* 2020;74:40–4.
3 Masala B, Love A, Carmichael P, *et al*. Demographics of referrals to a specialist gender identity service in the UK between 2017 and 2020. *Clin Child Psychol Psychiatry* 2023.
4 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender dysphoria literature: 2) mental health. *PLOS Glob Public Health* 2022;2:e0000426.
5 Kallitsounaki A, Williams DM. Autism spectrum disorder and gender dysphoria/Incongruence. A systematic literature review and meta-analysis. *J Autism Dev Disord* 2023;53:3103–17.
6 Thoma BC, Rezeppa TL, Choukas-Bradley S, *et al*. Disparities in childhood abuse between transgender and cisgender adolescents. *Pediatrics* 2021;148:e2020016907.
7 Feil K, Riedl D, Böttcher B, *et al*. Higher prevalence of adverse childhood experiences in transgender than in cisgender individuals: results from a single-center observational study. *J Clin Med* 2023;12:4501.
8 Surace T, Fusar-Poli L, Vozza L, *et al*. Lifetime prevalence of suicidal Ideation and suicidal behaviors in gender non-conforming youths: a meta-analysis. *Eur Child Adolesc Psychiatry* 2021;30:1147–61.
9 Frew T, Watsford C, Walker I. Gender dysphoria and psychiatric comorbidities in childhood: a systematic review. Aust J Psychol 2021;73:255–71.
10 Dahlgren Allen S, Tollit MA, McDougall R, *et al*. A waitlist intervention for transgender young people and psychosocial outcomes. *Pediatrics* 2021;148.
11 Council for Choices in Healthcare in Finland. Medical treatment methods for Dysphoria associated with variations in gender identity in minors – recommendation. Council for Choices in Healthcare in Finland; 2020. Available: https://palveluvalikoima.fi/en/recommendations#genderidentity
12 The Swedish National Board of Health and Welfare. Care of children and young people with gender Dysphoria - national knowledge support with recommendations for the profession and decision makers. The Swedish National Board of Health and Welfare; 2022. Available: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-12-8302.pdf
13 The Cass Review. Independent review of gender identity services for children and young people: interim report; 2022. Available: https://cass.independent-review.uk/publications/interim-report/
14 Kozlowska K, McClure G, Chudleigh C, *et al*. Australian children and adolescents with gender dysphoria: clinical presentations and challenges experienced by a multidisciplinary team and gender service. *Human Systems* 2021;1:70–95.
15 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS Glob Public Health* 2023;3:e0001478.
16 National Institute for Health and Care Excellence (NICE). Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender Dysphoria. NICE; 2020. Available: https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_GnRH-analogues_For-upload_Final.pdf
17 Pasternack I, Söderström I, Saijonkari M, *et al*. Medical approaches to treatment of dysphoria related to gender variations. A systematic review. 2019. Available: https://app.box.com/s/y9u791np8v9gsunwgpr2kqn8swd9vdtx
18 Ludvigsson JF, Adolfsson J, Höistad M, *et al*. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatr* 2023;112:2279–92.
19 Baker KE, Wilson LM, Sharma R, *et al*. Hormone therapy, mental health, and quality of life among transgender people: a systematic review. *J Endocr Soc* 2021;5.
20 Chew D, Anderson J, Williams K, *et al*. Hormonal treatment in young people with gender dysphoria: a systematic review. *Pediatrics* 2018;141:e20173742.
21 National Institute for Health and Care Excellence (NICE). Evidence review: gender-affirming hormones for children and adolescents with gender Dysphoria. NICE; 2020. Available: https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_Gender-affirming-hormones_For-upload_Final.pdf
22 Expósito-Campos P, Pérez-Fernández JI, Salaberria K. Empirically supported affirmative psychological interventions for transgender and non-binary youth and adults: a systematic review. *Clin Psychol Rev* 2023;100:102229.
23 Catelan RF, Costa AB, Lisboa C de M. Psychological interventions for transgender persons: a scoping review. Int J Sex Health 2017;29:325–37.
24 Coleman E, Radix AE, Bouman WP, *et al*. Standards of care for the health of transgender and gender diverse people, version 8. *Int J Transgend Health* 2022;23:S1–259.
25 Telfer MM, Tollit MA, Pace CC, *et al*. Australian standards of care and treatment guidelines for transgender and gender diverse children and adolescents. *Med J Aust* 2018;209:132–6.
26 de Vries ALC, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the Dutch approach. *J Homosex* 2012;59:301–20.
27 Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-dysphoric/gender-Incongruent persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017;102:3869–903.
28 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
29 Fraser L, Hall R, Taylor J, *et al*. The epidemiology, management and outcomes of children with gender-related distress / gender dysphoria: a systematic review. *PROSPERO* 2021.
30 Veritas Health Innovation. *Covidence systematic review software*. Melbourne, Australia: Veritas Health Innovation, 2023.
31 Nyaga VN, Arbyn M, Aerts M. Metaprop: a STATA command to perform meta-analysis of binomial data. *Arch Public Health* 2014;72:39.
32 Hewitt JK, Paul C, Kasiannan P, *et al*. Hormone treatment of gender identity disorder in a cohort of children and adolescents. *Med J Aust* 2012;196:578–81.
33 Tollit MA, May T, Maloof T, *et al*. The clinical profile of patients attending a large, Australian pediatric gender service: a 10-year review. *Int J Transgend Health* 2023;24:59–69.
34 Zucker KJ, Bradley SJ, Owen-Anderson A, *et al*. Puberty-blocking hormonal therapy for adolescents with gender identity disorder: a descriptive clinical study. J Gay Lesbian Ment Health 2010;15:58–82.
35 Segev-Becker A, Israeli G, Elkon-Tamir E, *et al*. Children and adolescents with gender dysphoria in Israel: increasing referral and fertility preservation rates. *Endocr Pract* 2020;26:423–8.

36 Brik T, Vrouenraets LJJJ, de Vries MC, *et al*. Trajectories of adolescents treated with gonadotropin-releasing hormone analogues for gender dysphoria. *Arch Sex Behav* 2020;49:2611–8.
37 de Vries ALC, McGuire JK, Steensma TD, *et al*. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics* 2014;134:696–704.
38 de Vries ALC, Steensma TD, Doreleijers TAH, *et al*. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med* 2011;8:2276–83.
39 Wiepjes CM, Nota NM, de Blok CJM, *et al*. The Amsterdam cohort of gender dysphoria study (1972-2015): trends in prevalence, treatment, and regrets. *J Sex Med* 2018;15:582–90.
40 Esteva de Antonio I, Gómez-Gil E, GIDSEEN Group. Coordination of healthcare for transsexual persons: a multidisciplinary approach. *Curr Opin Endocrinol Diabetes Obes* 2013;20:585–91.
41 De Castro C, Solerdelcoll M, Plana MT, *et al*. High persistence in Spanish Transgender minors: 18 years of experience of the gender identity unit of Catalonia. *Spanish Journal of Psychiatry and Mental Health* 2022. 10.1016/j.rpsm.2022.02.001 [Epub ahead of print]
42 Costa R, Dunsford M, Skagerberg E, *et al*. Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. *J Sex Med* 2015;12:2206–14.
43 Chen D, Hidalgo MA, Leibowitz S, *et al*. Multidisciplinary care for gender-diverse youth: a narrative review and unique model of gender-affirming care. *Transgend Health* 2016;1:117–23.
44 Handler T, Hojilla JC, Varghese R, *et al*. Trends in referrals to a pediatric transgender clinic. *Pediatrics* 2019;144:e20191368.
45 Leon K, O'Bryan J, Wolf-Gould C, *et al*. Prevalence and risk factors for nonsuicidal self-injury in transgender and gender-expansive youth at a rural gender wellness clinic. *Transgend Health* 2021;6:43–50.
46 O'Bryan J, Leon K, Wolf-Gould C, *et al*. Building a pediatric patient registry to study health outcomes among transgender and gender expansive youth at a rural gender clinic. *Transgend Health* 2018;3:179–89.
47 Chiniara LN, Bonifacio HJ, Palmert MR. Characteristics of adolescents referred to a gender clinic: are youth seen now different from those in initial reports? *Horm Res Paediatr* 2018;89:434–41.
48 Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in vancouver. *J Pediatr* 2014;164:906–11.
49 Vehmas N, Holopainen E, Suomalainen L, *et al*. Somatic health and psychosocial background among finnish adolescents with gender dysphoria seeking hormonal interventions. *Transgend Health* 2022;7:505–13.
50 Arnoldussen M, Steensma TD, Popma A, *et al*. Re-evaluation of the Dutch approach: are recently referred transgender youth different compared to earlier referrals *Eur Child Adolesc Psychiatry* 2020;29:803–11.
51 McCallion S, Smith S, Kyle H, *et al*. An appraisal of current service delivery and future models of care for young people with gender dysphoria. *Eur J Pediatr* 2021;180:2969–76.
52 Chen M, Fuqua J, Eugster EA. Characteristics of referrals for gender dysphoria over a 13-year period. *J Adolesc Health* 2016;58:369–71.
53 Kuper LE, Mathews S, Lau M. Baseline mental health and psychosocial functioning of transgender adolescents seeking gender-affirming hormone therapy. *J Dev Behav Pediatr* 2019;40:589–96.
54 Nahata L, Quinn GP, Caltabellotta NM, *et al*. Mental health concerns and insurance denials among transgender adolescents. *LGBT Health* 2017;4:188–93.
55 Spack NP, Edwards-Leeper L, Feldman HA, *et al*. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics* 2012;129:418–25.
56 van der Loos MATC, Klink DT, Hannema SE, *et al*. Children and adolescents in the Amsterdam cohort of gender dysphoria: trends in diagnostic- and treatment trajectories during the first 20 years of the Dutch protocol. *J Sex Med* 2023;20:398–409.
57 van der Loos M, Hannema SE, Klink DT, *et al*. Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: a cohort study in the Netherlands. *Lancet Child Adolesc Health* 2022;6:869–75.
58 Butler G, Adu-Gyamfi K, Clarkson K, *et al*. Discharge outcome analysis of 1089 transgender young people referred to paediatric endocrine clinics in England 2008-2021. *Arch Dis Child* 2022.
59 Masic U, Butler G, Carruthers P, *et al*. Trajectories of transgender adolescents referred for endocrine intervention in England. *Arch Dis Child* 2022;107:1012–7.
60 Nos AL, Klein DA, Adirim TA, *et al*. Association of gonadotropin-releasing hormone analogue use with subsequent use of gender-affirming hormones among transgender adolescents. *JAMA Netw Open* 2022;5:e2239758.
61 Littman L. Individuals treated for gender dysphoria with medical and/or surgical transition who subsequently detransitioned: a survey of 100 detransitioners. *Arch Sex Behav* 2021;50:3353–69.
62 Dhejne C, Lichtenstein P, Boman M, *et al*. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLOS One* 2011;6:e16885.
63 American Psychological Association. Guidelines for psychological practice with Transgender and gender Nonconforming people. The American psychologist; 2015. Available: doi:10.1037/a0039906
64 Cooper HC, Long J, Aye T. Fertility preservation in transgender and non-binary adolescents and young adults. *PLOS ONE* 2022;17:e0265043.
65 Ker A, Shaw RM, Byrne J, *et al*. Access to fertility preservation for trans and non-binary people in aotearoa New Zealand. *Cult Health Sex* 2022;24:1273–88.
66 Komorowski AS, Fisher AR, Jungheim ES, *et al*. Fertility preservation discussions, referral and follow-up in male-to-female and female-to-male adolescent transgender patients. *Hum Fertil (Camb)* 2023;26:903–7.
67 Mattelin E, Strandell A, Bryman I. Fertility preservation and fertility treatment in transgender adolescents and adults in a Swedish region, 2013–2018. *Hum Reprod Open* 2022.

Supplementary Table S1: Final search strategy for Ovid MEDLINE

1 exp Child/ or Child Behavior/ or Child Health/ or Child Welfare/ or Psychology, Child/ or Child Psychiatry/ or Child Health Services/ or Child Development/ (1984459)
2 Minors/ (2638)
3 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or emerging adult$).ti,ab,kf,jn. (1862660)
4 (young$ adj (people$ or person$1 or adult$ or man$1 or men$1 or woman$ or women$ or male$1 or female$1)).ti,ab,kf,jn. (224878)
5 pediatrics/ (55388)
6 (pediatric$ or paediatric$ or peadiatric$).ti,ab,kf,jn. (543516)
7 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Psychology, Adolescent/ or Adolescent Psychiatry/ or Adolescent Health Services/ or Adolescent Medicine/ or Adolescent Development/ (2088552)
8 Puberty/ (13562)
9 (adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or underage$ or under-age$).ti,ab,kf,jn. (522801)
10 Schools/ or Schools, Nursery/ (42221)
11 exp Child Day Care Centers/ or Child Care/ (11287)
12 (school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1).ti,ab,kf,jn. (356157)
13 or/1-12 (4333601)
14 Gender Dysphoria/ (581)
15 "Sexual and Gender Disorders"/ (79)
16 Transsexualism/ (3895)
17 Transgender Persons/ (3835)
18 Health Services for Transgender Persons/ (152)
19 exp Sex Reassignment Procedures/ (969)
20 "Sexual and Gender Minorities"/ (4924)
21 ((gender$ and dysphori$) or (gender$ adj5 incongru$) or sexual dysphori$).ti,ab,kf. (1784)
22 (gender$ adj (disorder$ or identi$)).ti,ab,kf. or (gender identity/ and dysphori$.ti,ab,kf.) (4568)
23 (GID or GIDS or GIDC or GIDCS).ti,ab,kf. (456)
24 (gender$ adj5 (confusion or confused or questioning or distress$ or discomfort)).ti,ab,kf. (980)
25 (gender$ adj5 (minority or minorities)).ti,ab,kf. (1593)
26 (gender$ adj5 (variant$ or variance$ or nonconform$ or non-conform$ or diverse or diversity or atypical$)).ti,ab,kf. (3409)
27 (non-binary or nonbinary or enby or genderqueer or gender-queer or neutrois).ti,ab,kf. (796)
28 (agender$ or genderless$ or gender-less$ or genderfree or gender-free or ungender$ or un-gender$ or non-gender$ or nongender$ or bigender$ or bi-gender$ or dual gender$ or dualgender$ or demi-gender$ or demigender$ or genderfluid$ or gender-fluid$ or trigender$ or tri-gender$).ti,ab,kf. (315)

29 two spirit$.ti,ab,kf. (84)
30 (trans adj3 (female$ or feminin$ or woman$ or women$ or male$1 or man or mans or men or mens or masculin$ or person$1 or peopl$ or population$ or individual$)).ti,ab,kf. (1362)
31 (transgend$ or trans-gend$ or transex$ or transsex$ or trans-sex$ or transfemale$ or transfeminin$ or transwom$ or transmale$ or transman$ or transmasculin$ or transmen$ or transperson$ or transpeopl$ or transpopulation$ or transindividual$).ti,ab,kf. (10832)
32 (trans adj3 identi$).ti,ab,kf. or (gender identity/ and trans.ti,ab,kf.) or (trans and dysphori$).ti,ab,kf. (1447)
33 (crossgender$ or cross-gender$ or crossex$ or crosssex$ or cross-sex$).ti,ab,kf. (836)
34 ((sex or gender$) adj3 (reassign$ or re-assign$ or affirm$ or confirm$ or transition$)).ti,ab,kf. (3963)
35 ((gender$ or sex) adj (change or changes or changing or changed)).ti,ab,kf. (825)
36 (detransition$ or de-transition$ or desister$ or de-sister$).ti,ab,kf. (134)
37 ((desist$ or persist$) adj5 (transition$ or trans or dysphori$)).ti,ab,kf. (823)
38 or/14-37 (28731)
39 (trans and (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ti. (339)
40 (trans adj5 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ab,kf. (397)
41 (transchild$ or transminor$ or transboy$ or transgirl$ or transkid or transkids or transyoung$ or transyouth$ or transteen$ or transtween$ or transadoles$ or transjuvenil$).ti,ab,kf. (15)
42 13 and 38 (9819)
43 39 or 40 or 41 or 42 (10343)
44 exp animals/ not humans/ (4823832)
45 (editorial or news or comment or case reports).pt. or case report.ti. (3692318)
46 43 not (44 or 45) (9429)
47 limit 46 to english language (9029)

Key to Ovid symbols and commands:
$ Unlimited right-hand truncation symbol
$N Limited right-hand truncation - restricts the number of characters following the word to N

ti,ab,kf,	Searches are restricted to the Title (ti), Abstract (ab), Keyword Heading Word (kf) fields
.jn	Searches are restricted to the Journal name field
adj	Retrieves records that contain terms next to each other (in the shown order)
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-12	Combines sets 1 to 12 using OR

Supplementary Table 2 - Included study characteristics and data

Author	Setting	Population	Data collection period	Follow-up period	Referred	Assessed	Age at referral / assessment	BR+ve at referral / assessment	Diagnosis / outcome of assessment	Reasons for discontinuing assessment	Receipt of psychological treatment	Eligible / referred for hormone treatment	Reasons for not seeking or receiving treatment	Started hormone treatment	Receipt of puberty / menstrual suppression	Receipt of masculinising/feminising hormones	Continuation / discontinuation of hormone treatment	Reasons for discontinuing treatment	Receipt of surgery
Australia																			
Hewitt 2012	Gender identity clinic in tertiary paediatric referral centre at the Royal Children's Hospital, Melbourne, Victoria	Children and adolescents age 0–17 referred to clinic for gender dysphoria.	Referred between 2003 and 2011	Follow-up ranged from 0 to 8.2 years	89	89	NR	NR	18 were pre-adolescent and continued with psychological counselling. 21 (13 born, 8 bf, age 10.0 (4.1-12) were approaching puberty or pubertal, and were referred for diagnosis of GD. Of these, 4 experienced resolution of GD or acceptance of gender variance with ongoing counselling and 17 experienced persistent GD with increased distress at puberty.	N/A	18 of the 39 were pre-adolescents who continued to have developmental psychological counselling	17 11 made or planned to make application to Family Court for treatment	Reasons for not seeking court-approved hormone treatment included: n=2 age close to 18 (court approval not required); n=1 court financial cost; n=1 family not supporting treatment; n=1 purchased oestrogen independently.	8 in total: 7 received court approved treatment (4 born, 4 bf) 1 brn purchased oestrogen independently 1 initiated before completion of puberty.	6 (4 received GnRH-a and CSH, 2 received GnRH-a only). Initiated age 10–16. 1 received oestrogen and progesterone then medroxyprogesterone acetate for menstrual suppression before phase 1 treatment with GnRH-a.	4 (4 received both GnRH-a and CSH; 2 received CSH only). Initiated age 15.6–16.	All patients who had GnRH-a went on to have CSH. Follow-up (ranging from 0–8.2 years) showed that no patient has ceased hormone treatment.	N/A	NR
Tollit 2021	Gender identity clinic in tertiary paediatric referral centre at the Royal Children's Hospital, Melbourne, Victoria	Children and adolescents age 0–17 referred to clinic with self-reported gender incongruence or seeking clinical guidance regarding their gender, and attended their first appointment within the study period.	First seen between January 2007 and December 2016	NR	359	359	Referral: All: *14.3 (3.6 to: 18.1) bf: *14.8 (3.6 to: 18.1) brn: *12.4 (3.8 to: 17.9)	Referral: 166 (46.4%) males and 193 (53.8%) females 41/356 (11.5%) changed gender identity over time; brn 21/165 (12.7%) and bf 20/191 (10.5%). Of those who were transgender at presentation 3.3% and 2.6% later identified as cisgender and non-binary respectively. Of the 26 patients who identified as non-binary at presentation, 81% later identified as transgender and 11.5% as cisgender.	296 (81.1%) diagnosed with gender dysphoria (DSM-5).	NR	NR	236 (112 bf, 122 brn)		23 patients (9.8%) received both GnRH-a and CSH 21 (13.2%) received GnRH-a alone 25 (10.7%) received CSH alone 79 patients (33.8%) received either GnRH-a and/or CSH 57 bf (50.9%) received menses suppression, and 7 brn (n= 7, 5.7%) were treated with anti-androgens Overall, 73/112 (65.2%) bf had at least one form of medical treatment and 45/122 of brn (36.9%). 39 received menses suppression or anti-androgens only. No children received any medical treatment GnRH-a treatment: brn in the young adolescent group (10–16) (65.1%) and adolescent group (16+) (63.6%), bf 10–16 (17.2%) and 16+ (14.7%) 11.2% bf in 10–16 and 40.3% in 16+ received medication to suppress their menses CSH treatment: 34.4% brn treated with oestrogen and 41.2% bf treated with testosterone; 1 assigned female <16 years accessed CSH	54/204 (26%) GnRH-a; brn 39/122 (32%) and bnf 15/112 (13.4%) and 39/234 menses suppression or anti-androgens only. Average age at initiation of GnRH-a was *14.7 (3.1, 10.3-17.8). For brn *15.0 (1.1, 10.3-17.2) and for bf *14.1 (4, 10.8-17.8). Average age at initiation of menses suppression in bnf was *16.8 (1, 11.2-19.0).	48/234 (20.5%) CSH; bnf 29/112 (25.9%) more likely to receive hormones than brn 18/122 (15.6%). Average age at initiation was *17.4 (1.1, 14.9-18.8). For brn *18.0 (1, 14.9-18.3) and for bf *17.0 (1.6, 15.1-18.8)	Single patient stopped GnRH-a without progressing to hormones Single patient stopped CSH unexpectedly	NR	NR
Canada																			
Chiniara 2018	Large paediatric gender clinic at Hospital for Sick Children, Toronto. Medical clinic developed towards meeting medical needs of transgender adolescents.	Adolescents (age 12–18) presenting to clinic. Eligibility: presence of gender dysphoria and desire for medical treatment.	Initial appointments from January 2014 to June 2016	Treatment initiation during study period	218	203	Assessment: bnf 16.3 (1.6-0), brn 14.1 (1.7).	156 (76.8%) bnf, 47 (23.2%) brn	12 adolescents did not follow up at the clinic after the first visit. 3 adolescents who were assessed were not included in the analysis because their initial visit had occurred at another clinic.	NR	NR	NR	NR	NR	115 treated with GnRH-a during study period.	75 received hormones during the study period.	NR	NR	NR
Khatchadourian 2014	British Columbia Children's Hospital Transgender Programme - multidisciplinary team approach providing medical care and psychosocial support where adolescents referred from broader gender clinic.	Adolescents referred to programme for medical therapy. Eligibility criteria: at least Tanner stage 2 and confirmed diagnosis of gender dysphoria.	Seen from January 1998 to December 2011	NR	NR	84	Assessment: 16.6 (1.2)	45 (53.6%) bnf, 39 (46.4%) brn	NR	NR	Most were receiving psychotherapy	NR	NR	NR	27 (32%) started GnRH-a (15 (33.3%) bf and 11 (29.7%) brn). Mean age at initiation 14.7 (1.9). 10 (37%) at Tanner stage 2-3 and 16 (59%) 4-5 (1 not reported). 12 received GnRH-a as first visit. Median time from first visit to treatment 0.2 month (range 0-2.1). 25 (67.6%) brn took spironolactone as alternative to GnRH-a (mean age 17.6 (1.9), all at Tanner stage 4-5).	43 (75%) adolescents treated during study period. 39 (87%) bf and 24 (65%) brn. Mean age 17.4 (1.9). 7 (11%) at Tanner stage 2-3 and 50 (89%) at 4-5 (3 not reported). 19 transitioned from GnRH-a (14 bf, 5 brn). Median time from GnRH-a initiation to CSH start 11.3 months (range 2.2-42). 11 received treatment at first visit. Median time from first visit to treatment 4.6 months (range 0-42).	GnRH-a: Of the 14 bf who progressed to CSH, 7 continued GnRH-a and 7 stopped after median 3 years (0.2-9.2). Of the 5 brn, 1 discontinued GnRH-a. Of other 6 brn, 3 discontinued GnRH-a. Data for remaining bnf not reported. Cross-sex hormones: no patient discontinued permanently. 3 bnf stopped temporarily (2 due to psychiatric difficulties, 1 due to distress over androgenic alopecia) but later resumed.	GnRH-a: Of those who progressed to CSH, GnRH-a was stopped at time of surgery (n=6), at start of CSH (n=2), due to side effects of GnRH-a after 2 months of treatment (n=1). Of 3 who discontinued GnRH-a monotherapy, 1 stopped after a few months due to emotional lability, 1 stopped but still wanted CSH (reason for stopping GnRH-a not reported), 1 was undecided on gender at initiation of treatment and discontinued after 13 months and chose not to pursue transition.	9 (21.4%) bf had mastectomy (median age 18.1, range 14.9-22.1) during observation period. Of these 9, 6 proceeded to hysterectomy and salpingo-oophorectomy (median age 18.9, range 16.1-22.1), 1 other had hysterectomy and salpingo-oophorectomy (no mastectomy). 1 brn underwent elective breast augmentation surgery and tracheal shaving. Two had penectomy, orchidectomy, and vaginoplasty (at 18 and 21 years of age) during observation period.
Zucker 2010	The Gender Identity Service, which is housed within the Child, Youth, and Family Program at the Centre for Addiction and Mental Health, Toronto	Adolescents referred consecutively to and then assessed by the service.	Referred and assessed from 2000 to 2009	Longest time from assessment to follow-up was 10 years. Some patients had only recently been assessed.	165	109	Assessment: 16.8 (1.7)	53 (50.5%) bnf, 54 (49.5%) brn	109 were assessed for gender dysphoria - outcome not reported. 56 of 165 adolescents were referred and assessed for other reasons: transvestic fetishism without co-occuring gender dysphoria (n=35), cross-gender behaviour with no explicit desire to be opposite sex and no differentiated sexual orientation (n=6), sexual minority adolescents referred due to parental concern and/or psychosocial or sexual problems (n=15).	N/A	NR	49/109 (60.6%) were recommended for puberty suppression (45 (74.5%) bnf, 26 (46.3%) brn). Mean age 17.05 (1.76). Of the 45 not recommended (14 bnf, 29 brn, mean age 16.58 (1.74)), 5 brn were later recommended for puberty suppression.	8 adolescents (6 bnf and 2 brn) decided against treatment. 2 adolescents (brn) did not receive recommendation for treatment as did not attend feedback session. Unknown for 11 (4 bnf, 3 brn) due to no follow-up.	Of the remaining 45, 5 patients were already receiving treatment at baseline (2 bnf receiving cpb, 2 brn receiving either puberty suppressing treatment or started csh). The other 40 started treatment following recommendation (23 bnf, 16 brn). 1 brn who was not recommended for treatment received puberty suppressing treatment via a therapist.	40 of those recommended, started puberty suppressing treatment (23 bnf, 16 brn) and 2 bnf received this at baseline. Status of 5 later recommended unknown. 1 additional brn not recommended for treatment received puberty suppressing treatment via a therapist.	NR	NR	NR	NR
Finland																			
Vohnsa 2021	Adolescent gynecology clinic at Helsinki University Hospital	Referred to gender identity service due to symptoms of gender dysphoria before the age of 18 years subsequently diagnosed with gender dysphoria (ICD-10) and further referred to the adolescent gynecology clinic at Helsinki University Hospital for CSH.	Referred between January 2011 and December 2018	NR	NR	124	Assessment: *17.7 (14 to 19.8)	104 (83.9%) bnf and 20 (16.1%) brn	NR	NR	NR	124	N/A	124	64 bnf prescribed lynestrenol (a progestin regimen) to suppress menstruation. At assessment, 12 bnf had already used a progestin / contraceptive to suppress or prevent menstruation.	124 started hormone treatment (no data provided) At assessment, 3 brn reported use of under-the-counter hormonal treatment (included estradiol, cyproterone acetate and spironolactone)	NR	NR	NR	NR
Israel																			
Segev-Becker 2020	Israeli Paediatric Gender Dysphoria Clinic at Dana-Dwek Children's Hospital in Tel Aviv Medical Centre	Consecutive children and adolescents with gender dysphoria (DSM-5) less than 18.	Referred between March 2013 and December 2018	Median follow up duration was 1.2 years (range 0 to 5.1 years)	106	106	Referral: *15.5 (4.6 to 16.1) Prepubertal group (n=30): *7.9 (4.3 to 10) Pubertal group (n=66): bnf 15.9 (1.7) and brn 15.2 (1.7)	47 (44.3%) brn and 59 (55.7%) bnf Prepubertal group: 18 brn and 18 bnf Pubertal group: 29 brn and 48 bnf	The majority of patients had been evaluated prior to referral and diagnosed with gender dysphoria according to the DSM-5 criteria prior to their first visit to the gender clinic. Those without a diagnosis were referred to mental health professionals experienced in child and adolescent gender development. Pre-pubertal children (n=30; brn=9 and bnf=21) were also offered psychological support.	NR	NR	96	NR	77	77 (80%) GnRH-a at 15.4 (1.4, range 11 to 18.5)	61 either concurrently or later (age 16.5 (1.3), range 13 to 18.8).	2 brn receiving GnRH-a and low dose oestrogen for 3 months discontinued. 19 patients chose not to pursue masculinising/feminising hormones at the time of analysis.	Discontinuation reasons: both chose not to continue to transition (1 autism spectrum condition, 1 homosexual male who was lost to follow up). Reasons for not starting masculinising / feminising hormones: Lack of complete GD diagnosis (n=12), lack of parental consent (n=1), delaying for fertility preservation (n=1) and others (n=3).	15 bnf underwent breast reduction at *17.4 (15.3 to 19.3), 2 brn underwent breast augmentation and 2 bnf underwent a vaginoplasty at >18.
Netherlands																			
Arnoldussen 2020	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	All consecutively referred adolescents registered at clinic who could be potentially eligible for medical interventions.	Referred and registered between 2000 and 2016	NR	1072	965 completed assessment	Assessment: 14.6 (2.2), range 10.5–18.5 years	668 (62.3%) bnf, 404 (37.7%) brn	908 (84.7%) were diagnosed with a form of gender dysphoria (using DSM-IV-TR between 2000 and 2014, and DSM-5 from 2015). 57 (5.3%) were not diagnosed. % of referred with diagnosis per year ranged from 75% to 97.6%. For 107 (10%) the diagnostic process ended early so diagnosis remained unknown.	For the majority, adolescents ended process due to discontinued wish for medical treatment. For a minority, psychologist ended process because psychological/social problems interfered with diagnostic assessment.	NR	908 (diagnosed)	NR	Mean % of adolescents diagnosed with gender dysphoria who started either treatment was 77.7% (range per year 53.8-94.9%). 846 extracted from graph.	NR	NR	NR	NR	NR
Brik 2020	Curium-Leiden University Medical Centre gender clinic in Leiden.	Children and adolescents registered at the clinic.	Started GnRH-a between Nov 2010 and 1 Jan 2018.	Follow-up to July 2018.	NR	269 (registered)	NR	NR	216 of those registered were pubertal and within appropriate age range for treatment. Of these, 39 were not diagnosed with gender dysphoria, 9 had co-existing problems that interfered with diagnostic process and/or might interfere with successful treatment, 10 diagnostic evaluation ongoing, 9 had stopped attending assessment appointments.	NR	11 adolescents who received prolonged GnRH-a treatment because of mental health and/or psychosocial problems had regular (approximately monthly) appointments with a psychologist at the gender clinic (n = 5) and/or received support from a local MHP (n = 9) during this period.	147	6 did not wish to receive hormone treatment	163	163 received GnRH-a (18 brn median age 15.0 (range 11.1-18.6), 105 bnf age 16.1 (10.1-17.9)). Median duration was 0.8 years (range 0.3–3.8). Prolonged use in 20 adolescents (8 brn, 17 bnf) - reasons reported in paper.	125 progressed to hormones at the service: 36 brn (median age 16.2 (range 14.1-16.6)) after 1.0 (0.1-3.8) year of GnRH-a, and 89 bnf (median age 17.1 (14.9-18.8)) after 0.8 (0.3-3.7) years. 6 not yet eligible, 6 referred to another gender clinic (1 needed more time to decide, 5 not yet eligible), 1 later started as adult, 5 did not want treatment.	9 (1 brn, 8 bnf) discontinued GnRH-a after a median duration of 0.6 years (0.1–3.0). Discontinuation of masculinising/feminising hormones not reported.	5 (4 bnf, 1 brn) no longer wanted medical treatment. 1 bf decided she did not want to live as a boy but dreaded breast development and menstruation; 1 bf still felt like a man but was happy to be "just me instead of a he or a she"; 1 bf felt in between genders; 1 bf expressed an inner feeling that she was a woman during treatment; 1 brn indicated he was happy living as a man. 2 later started masculinising/feminising hormones (1 as adolescent, 1 as adult), 1 re-started GnRH-a after 5 months and progressed to hormones, and 1 still wanted hormones but was not yet eligible. Of these 2 experienced side-effects from GnRH-a, 1 stopped treatment due to severe nausea and rapid weight loss 2.2 years into treatment - no cause determined, and 1 stopped due to difficulties attending clinic/pharmacy for injection/medication.	NR
de Vries 2011 and de Vries 2014	Center of Expertise on Gender Dysphoria, VU University Medical Center, Amsterdam	Consecutively referred adolescents.	Considered eligible for medical pubertal suppression between 2000 and 2008	To 2009 for masculinising or feminising hormones (de Vries 2011). To 2012 for surgery (de Vries 2014).	196	196	NR	NR	NR	NR	Treated adolescents were all regularly seen by one of the clinic's psychologists or psychiatrists. No other details provided.	140	NR	140 (111 prescribed GnRH-a and followed-up in the study plus 29 who were age 16 and over so started masculinising/feminising hormones)	Of 111 who started GnRH-a, 70 subsequently started hormones up to 2009 (43 brn, 17 bnf, mean age at initiation 14.6 (1.9)). Another 29 who were age 16 and over at diagnosis were prescribed hormones without first receiving puberty suppression.	NR	NR	Of 70 who started hormones, 42 had undergone surgery (1 brn died from jacksurgical problems), 3 were not eligible for surgery, 1 surgical status not known. Of 56 who had surgery and took part in study, mean age at surgery was 19.2 (0.9). There were 22 brn and 33 bnf.

Wiepjes 2018	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	All people who attended a gender identity clinic. Information on first visit presented. Registered but not visited were excluded.	Seen from 1972 to Dec 2015	% starting hormone treatment 5 years after initial visit, gonadectomy 5 years after starting hormone treatment.	NR	1360 (832 adolescents age 12-18, 528 children age <12)	Assessment: adolescent **14 [15, 17]; child **9 [7, 10]	737 (54.2%) brf, 633 (45.4%) brm	NR	NR	NR	NR	NR	816 (595 adolescents and 221 children)	333 (41.0%) adolescents (28.7% brm, 50.8% brf) 221 (40.3%) children (33.4% brm, 49.1% brf)	327 (98.1%) of 333 adolescents (95.9% of brm, 99.3% of brf) who started puberty suppression continued to hormone treatment. A further 262 (52.2%) adolescents (63.9% brm, 30.8% brf) started hormones without puberty suppression because they were too old to start puberty suppression at diagnosis.	4 (1.9%) adolescents (4 (4.1%) brm, 2 (0.7%) brf) who started puberty suppression stopped and did not start hormone treatment. Discontinuation of masculinising/feminising hormones not reported.	NR	Of adolescents who were treated with hormones for at least 1 ½ years and were at least 18 years old, 78.2% underwent gonadectomy (76.3% of brm - orchiectomy, 77.2% of brf - oophorectomy). Numbers not reported.
Scotland																					
McCallion 2021	Paediatric Endocrinology, Royal Hospital for Children, Glasgow	Young people diagnosed with gender dysphoria referred for puberty suppression with GnRH-a following assessment by mental health core professionals.	Referred between 2011 and 2019	Median follow up 1.9 years (range 0.1 to 5.9 years)	NR	91	Assessment: **14.6 [8.8 to 17.4]; brf **16.1 [8.7 to 17.6]; and brm **15.1 [9.8 to 17.5]	59 (65%) brf and 32 (35%) brm	NR	6 did not wish to proceed 2 pre-pubertal 3 medical comorbidities 1 unable to have appropriate assessments prior to starting treatment	NR	79	NR	79	79 at age **14.8 [9.7 to 18] (51 brf at age **14.2 [9.7 to 17.6] and 28 brm at age **15.3 [11 to 18]). In 15 of the young people who received puberty suppression (11 brf and 4 brm), treatment started at an early pubertal stage (Tanner stage 2 or 3).	81 at **16.6 [16 to 18.8] (59 brf at age **16.4 [16 to 17.5] and 13 brm at age **16.5 [16 to 18.8])	5w (6%) young people discontinued GnRH-a following a duration of **6 months [4 to 18]. Age at start of treatment was **15.3 [15.0 to 15.4]. 73 young people who continued treatment were age **14.6 [9.7 to 18.0]. One person discontinued masculinising/feminising hormones after 6 months.	Of the 4 who discontinued GnRH-a, for 3 gender dysphoria had desisted and for 1 treatment was stopped because they were not compliant with the treatment protocol. Of the 4, 3 (42%) had a mental health disorder and 3 (50%) had autism spectrum condition; the corresponding figures in those who continued treatment were 29 (40%) and 12 (18%); brm 4/28 (14%) and brf 2/51 (-4%). For the single person who stopped hormones, their gender dysphoria had desisted.	NR
Spain																					
DeCastro 2022	Catalonian Gender Identity Unit; Referrals made by pediatricians, general practitioners, mental health specialists or endocrinologists from Catalonia	All children and adolescents under 18 who attended the clinic	Attended between January 1999 and December 2016	Follow-up was an average of **2.6 years (4.7).	NR	140	Of 124 who were confirmed transgender minors, 116 were adolescents (age 12 to 17.9) and 21 were children (<12).	Of 140 assessed, brm:brf ratio was 2:1 in children and 1:1.2 in adolescents. Of 124 who were confirmed transgender minors, brm:brf ratio was 1:1.2 with no difference in age categories.	126 were confirmed transgender minors, 7 were under evaluation at the end of the study (6 of whom were children), 7 were not transgender, and 2 abandoned the follow-up before the assessment was completed. At the end of the study, 97.6% persisted in their identity, follow-up of **2.6 years (4.7). 56.4% followed-up for at least 2 years and 29.8% for at least 5 years. In the children all of them persisted in their affirmed gender, with follow-up of at least 2 years in 88.1% (+ = 81 and at least 5 years in 33.8% (n = 5). Three of the transgender children became adolescents and one reached adulthood during the follow-up period.	NR	NR	NR	1 of 3 adolescents (brm) who was identified as desisters at follow-up expressed doubts about being transgender during the third year of follow-up without having initiated hormonal treatment. Confusion regarding gender identity and sexual orientation was observed.	NR	13 (10 brm and 3 brf) were prescribed GnRH-a, average age 13.3 (6.5 to 17.4)	35 (13 brm and 21 brf) were prescribed hormones, average age 17.3 (15.1 to 26.2)	2 of 3 desisters (brms) identified at follow-up experienced doubts about being transgender after initiating hormones. For one, this occurred in adolescence in the second year of follow-up (confusion regarding both their gender identity and sexual orientation was observed). It is unclear whether they discontinued treatment. The other experienced doubts during adulthood, after >6 years of follow-up and a completed transition (socially, hormonally and surgically). At the end of follow-up, the subject was ambivalent about their gender identity, which resulted in low adherence to hormone treatment.	NR	NR
Esteva de Antonio 2013	Andalusian Gender Team which was formed in 1998 at Carlos Haya University Hospital, in Malaga, Spain	Children and adolescents with gender dysphoria.	Seen between 2000 to 2012	NR	NR	141	15 age <12 years (12 brm and 3 brf) and 126 age 12-17 (96 brm and 32 brf)	107 (75.9%) brm and 34 (24.1%) brf	Of the 15 children, gender dysphoria desisted in 2 brm and 11 were still under psychological evaluation. Of the 126 adolescents, 7 dropped out (all brm) and in 1 brm gender dysphoria desisted. Three were excluded (meaning unclear) and 28 were still under psychological evaluation.	NR	NR	NR	NR	n= 89 (3 children and 5 adolescents (all brm) received luteinising hormone-releasing hormone analogues and 82 adolescents received masculinising or feminising hormones)	7 brm (2 children and 5 adolescents)	82	NR	NR	14 brf had re-assignment surgery and 22 brm gonadectomy surgeries; 46 were awaiting surgery
UK																					
Costa 2015	Gender Identity Development Service (GIDS) in London	Consecutive series of adolescents referred to service.	Referred between 2010 and 2014	Time 0: baseline assessment Time 1: 6 months from baseline and eligibility for puberty supression Time 2: 12 months from baseline Time 3: 18 months from baseline	436	201	Referral: 15.74 (1.38) Assessment: 15.52 (1.41)	Referral: brm/brf ratio 1:1.7 Assessment: 1:1.4	All 201 adolescents who completed the diagnostic procedure fulfilled DSM-IV-TR criteria for Gender Identity Disorder. 235 adolescents did not complete the diagnostic procedure.	NR	201 received psychological support.	121	60 were classified as immediately eligible. 61 were classified as delayed eligible as clinicians needed more time to make the decision of starting GnRH-a because of comorbid psychiatric problems and/or psychological difficulties.	121	60 immediately eligible started GnRH-a 0.75 ± 0.59 years from baseline (after assessment) 61 delayed eligible started 1.1 ± 0.61 years from baseline	NR	NR	NR	NR
US																					
Chen 2016a	Paediatric Endocrinology clinic, Indianapolis	All patients seen in clinic for gender dysphoria, gender identity disorder or gender identity.	Seen in the clinic between January 2002 and April 2015	NR	NR	88	Assessment: 14.4 [1.2]	34 (62.1%) brm and 22 (37.9%) brf	At presentation, 29% had received a GD-specific psychological evaluation and recommendation for treatment. 57.9% had pursued an RLE (real life experience - living full-time as identified gender) which is a criteria for masculinising / feminising hormone treatment.	NR	NR	NR	NR	15 (5 brm and 10 brf)	15 received puberty suppression at average age of 15.1 (1.1) 9 GnRH-a (2 brm and 7 brf) 3 brf progestins 3 brm androgen-receptor blocker	8 of the 15 who received puberty suppression progressed to hormones (4 brm and 4 brf) at average age of 16.2 (1.4)	NR	NR	NR
Chen 2016b	Gender and Sex Development Program at the Ann & Robert H. Lurie Children's Hospital of Chicago (formerly known as Children's Memorial Hospital), Illinois.	Eligible patients are youth under 25 years of age, and parental participation is required for youth under the age of 18.	July 2013 to February 2016	NR	NR	220	Assessment: 14 were age <=15 (37 brm), 156 were 12-18 (59 brm) and 12 were >=19 (4 brm)	100 (45.5%) brm and 120 (54.5%) brf	NR	NR	103 patients had initial clinical appointments with a behavioral health clinician (masses / provision unclear)	NR	116	34 started on GnRH-a	20 started on oestrogen and 62 started on testosterone	NR	NR	To date, 24 patients have been seen for consultation and 7 have completed gender-affirming chest surgery.
Handler 2019	Specialty clinic in Oakland, California which was established for Kaiser Permanente Northern California members and serves as a referral hub for transition-related services for transgender and gender-non-conforming members.	Transgender and gender-non-conforming under 18 year olds throughout Northern California. Patients could be referred by any health care provider or by self-referral.	Referred between February 2015 and June 2018	NR	417	417	Referred: **15 [3 to 17]	116 (27%) brm and 303 (73%) brf	NR	NR	NR	NR	NR	NR	NR	NR	NR	Total N=106 surgeries involving 89 unique patients with 57 having at least one surgery before the age of 18 80 Mastectomy, 9 Hysterectomy, 7 Vaginoplasty, 6 Facial feminization surgery and/or chondrolaryngoplasty, 3 Phalloplasty and/or metoidioplasty, 2 Mammoplasty
Kuper 2019	Gender Education and Care Interdisciplinary Support program in Dallas, TX	Adolescents (12-18) presenting for an initial assessment before initiation of gender-affirming medical care	Initial assessments occurred between 2014 and 2017	NR	158	158 (data reported for 149)	Assessment: n=149, 15.3 (1.52, 12–18)	53 (35.6%) brm and 96 (64.4%) brf	All but 1 participant met full criteria for gender dysphoria at the time of assessment. This participant had not consistently identified with his gender identity for greater than the required 6 months but subsequently met criteria at a follow-up visit.	NR	NR	NR	2 lost to follow-up	106 (96 received CSH, 7 puberty supression only, 42 puberty suppression and CSH, 1 spironolactone only)	7 received puberty suppression only at a mean of 4.3 months (4.1, range 0–11) occuring between the initial assessment and start of treatment. 42 received puberty suppression and hormones with a mean of 2.4 months (2.1, range 0–11) for puberty suppression and 7.9 months (5.9, range 0–22) for hormones.	96 received hormones with a mean 1.8 months (1.4, range 0–36) occuring between the initial assessment and start of treatment. 42 received puberty suppression and hormones with a mean of 2.4 months (2.1, range 0–11) for puberty suppression and 7.9 months (5.9, range 0–22) for hormones.	NR	NR	NR
Leon 2021	Gender Wellness Center (GWC), a rural clinic providing primary and gender-affirming medical care to transgender and gender-expansive youth and adults in Upstate New York	Pediatric and young adult patients (ages 7–26) receiving care at the clinic agreeing to be included in the registry (66% of those referred)	Registered between April 2017 and December 2019	NR	NR	185	Assessment: **16.1 [4.1, 4.9 to 21.6]	151 (82.1%) brf and 53 (28.8%) brm	NR	NR	NR	NR	159 (86%) medically transitioning: 49 (30.8%) had lifetime or current use of GnRH-a, 119 (74.6%) had lifetime or current use of masculinising/feminising hormones, and 9 (10.8%) had a gender-affirming surgical procedure.	49 (30.8%) had lifetime or current use of GnRH-a.	119 (74.6%) had lifetime or current use of hormones.	NR	NR	17 (10.9%) had a gender-affirming surgical procedure.
Nahata 2017	Large multidisciplinary gender program for hormone therapy at a Midwestern pediatric academic center, established in 2014	All patients with ICD 9/10 codes for gender dysphoria, referred to endocrinology for hormone therapy (puberty suppression and/or hormones)	2014 to 2016	NR	NR	79	Assessment: **15 [9 to 18]	51 (64.6%) brf and 28 (35.4%) brm	NR	NR	NR	NR	18 of those prescribed GnRH-a did not start this (2 had no documented information about coverage and 16 were denied coverage [**15.3 years, range: 10.8–18.8, Tanner stages: 2–5] and could not start treatment)	9 began GnRH-a (mdi average age **15.3 [12.8–17.3], Tanner stage 2–5)	40 initiated hormones	NR	NR	NR
O'Bryan 2018	Gender Wellness Center (GWC), a rural clinic providing primary and gender-affirming medical care to transgender and gender-expansive youth and adults in Upstate New York	Pediatric patients (age <22) receiving care at the clinic agreeing to be included in the registry (98% of those referred)	Unclear	NR	NR	139	Enrollment: 17.3 (3.1, range 8 to 21) Assessment: 16.7 (3.0)	42 (30%) brm and 97 (70%) brf	NR	NR	NR	NR	123 (88.1%) were medically transitioning, defined in terms of use of GnRH-a, hormones and/or surgery.	41 (29.5%) had received puberty suppression (past or present use)	106 (76. 3%) had received hormones (past or present use)	2 discontinued treatment (1 after taking GnRH-a, 1 while taking GnRH-a and hormones). 1 stopped GnRH-a for a number of years but subsequently resumed treatment. 1 stopped hormone therapy but continued on GnRH-a.	One patient desisted after GnRH-a and one reverted to a gender identity concordant with their registered sex at birth after GnRH-a and hormones. The patient who stopped hormone therapy but continued on GnRH-a was still exploring an emerging gender identity.	20 (14.4%) had undergone gender-affirming surgery
Spack 2012	The Gender Management Service (GeMS), a multi-disciplinary gender identity clinic established in Jan 1998 and providing medical treatment, formerly the Endocrine Division at Children's Hospital, Boston.	Consecutive initial visits of patients with gender identity disorder seen at clinic. Prior to 2007, only adolescents referred by mental health professionals were accepted by the service. Following this, pre-pubertal children were also accepted.	Presented for an initial visit between Jan 1998 and Feb 2010	NR	NR	97	Assessment: 14.8 [1.4] **16 [+to 20]	54 (55.7%) brf and 43 (44.3%) brm	NR	NR	NR	NR	54 (57.7%) 50 started treatment within 1 week of initial visit. Others started later (average 9 (6.7) months after initial visit) although type of treatment for these not reported. reasons reported either not yet Tanner stage 3 or too pubertally advanced for suppression but too young for hormones. Medical intervention initiated at average age of 15.6 (2.8).	Of 50 who started treatment within 1 week of initial visit, 11 treated with GnRH-a at Tanner stage 2/3	Of 50 who started treatment within 1 week of initial visit, 39 started on hormones at Tanner stage 4/5	NR	NR	NR

BW-sex = Birth-registered sex; brm = birth-registered male; brf = birth-registered female; GnRH-a = Gonadotropin releasing hormone analogues; Csex = Cross sex hormones; NR = Not reported; N/A = Not applicable, ** [] = Median [range], * [] = Median [interquartile range], Values are mean (standard deviation) unless otherwise stated.

EXHIBIT 93

OPEN ACCESS

Characteristics of children and adolescents referred to specialist gender services: a systematic review

Jo Taylor , Ruth Hall, Trilby Langton, Lorna Fraser, Catherine Elizabeth Hewitt

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/archdischild-2023-326681).

Department of Health Sciences, University of York, York, UK

Correspondence to
Professor Catherine Elizabeth Hewitt, Department of Health Sciences, University of York, York, UK;
dohs-gender-research@york.ac.uk

Received 9 December 2023
Accepted 4 February 2024

► http://dx.doi.org/10.1136/archdischild-2023-326112
► http://dx.doi.org/10.1136/archdischild-2023-326347
► http://dx.doi.org/10.1136/archdischild-2023-326348
► http://dx.doi.org/10.1136/archdischild-2023-326500
► http://dx.doi.org/10.1136/archdischild-2023-326499
► http://dx.doi.org/10.1136/archdischild-2023-326760
► http://dx.doi.org/10.1136/archdischild-2023-326670
► http://dx.doi.org/10.1136/archdischild-2023-326669

To cite: Taylor J, Hall R, Langton T, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2023-326681

ABSTRACT

Background Increasing numbers of children/adolescents experiencing gender dysphoria/incongruence are being referred to specialist gender services. Services and practice guidelines are responding to these changes.

Aim This systematic review examines the numbers and characteristics of children/adolescents (under 18) referred to specialist gender or endocrinology services.

Methods Database searches were performed (April 2022), with results assessed independently by two reviewers. Peer-reviewed articles providing at least birth-registered sex or age at referral were included. Demographic, gender-related, mental health, neurodevelopmental conditions and adverse childhood experience data were extracted. A narrative approach to synthesis was used and where appropriate proportions were combined in a meta-analysis.

Results 143 studies from 131 articles across 17 countries were included. There was a twofold to threefold increase in the number of referrals and a steady increase in birth-registered females being referred. There is inconsistent collection and reporting of key data across many of the studies. Approximately 60% of children/adolescents referred to services had made steps to present themselves in their preferred gender. Just under 50% of studies reported data on depression and/or anxiety and under 20% reported data on other mental health issues and neurodevelopmental conditions. Changes in the characteristics of referrals over time were generally not reported.

Conclusions Services need to capture, assess and respond to the potentially co-occurring complexities of children/adolescents being referred to specialist gender and endocrine services. Agreement on the core characteristics for collection at referral/assessment would help to ensure services are capturing data as well as developing pathways to meet the needs of these children.

PROSPERO registration number CRD42021289659.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Increasing numbers of children and adolescents experiencing gender dysphoria/incongruence are being referred for care at specialist paediatric gender services.
⇒ Several countries have or are modifying referral and care pathways and provision, in response to both the reported increase in referral numbers and complexity of those referred.

WHAT THIS STUDY ADDS

⇒ There has been a twofold to threefold increase in the number of referrals and an increase in the ratio of birth-registered females to males referred to specialist paediatric gender services over time across countries.
⇒ Very few studies report data on gender status (self-reported gender identity, gender dysphoria/incongruence, age at onset and social transition) but from the limited data reported, approximately 60% of those referred were described as making steps to present themselves in their preferred gender.
⇒ Data published to date suggest that the presence of depression, anxiety, suicidality, self-harm, autism spectrum condition, attention deficit hyperactivity disorder and eating disorders may be higher in those referred to gender services than population estimates.

HOW THIS STUDY MIGHT AFFECT RESEARCH, POLICY OR PRACTICE

⇒ Specialist paediatric gender services need to respond to the potentially co-occuring complexities of children/adolescents being referred and agreement is needed on core characteristics for collection during assessment.

INTRODUCTION

Several countries have reported increasing numbers of children and adolescents experiencing gender dysphoria/incongruence being referred for care at specialist paediatric gender services over the last 10-15 years.[1 2] The research literature has also highlighted changes in the demographics of children being referred including reported mental health needs, neurodevelopmental conditions and psychosocial complexity.[3 4]

Specialist paediatric and adolescent gender services in several countries have modified or are currently modifying pathways and provision, partly in response to these reported trends.[5 6] This includes modifying referral criteria, processes and pathways as well as establishing new services.[7 8] In several countries, national guidelines and service specifications have been or are being reviewed and updated in response to concerns regarding the lack of high-quality evidence underpinning care for these children,[5 6 9 10] and the benefits, risks and long-term effects of medical intervention pathways.[11–16]

A better understanding of the numbers, characteristics and holistic needs of children and adolescents being referred to specialist gender services and how these may have changed over time would help to inform development in service provision

and referral and care pathways. This systematic review aims to answer the following questions:

1. What is the number of referrals to specialist gender identity/endocrinology services that provide healthcare for children/adolescents (age 0–18) experiencing gender dysphoria/incongruence and have these changed over time?
2. What are the characteristics of children/adolescents (age 0–18) referred to specialist gender/endocrinology services and have these changed over time?

METHODS

The review forms part of a linked series of systematic reviews examining the epidemiology, care pathways, outcomes and experiences of children and adolescents experiencing gender dysphoria/incongruence and is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17] The systematic review protocol was registered on PROSPERO (CRD42021289659).[18]

Search strategy

A single search strategy was used to identify studies comprising two combined concepts: 'children', which included all terms for children and adolescents; and 'gender dysphoria', which included associated terms such as gender incongruence and gender-related distress, and gender identity terms including transgender, gender diverse and non-binary. MEDLINE, EMBASE and PsycINFO through OVID, CINAHL Complete through EBSCO and Web of Science (Social Science Citation Index) were searched (13-23 May 2021 and updated 27 April 2022).

Inclusion criteria

The review included peer-reviewed articles that reported at least birth-registered sex or age of children and/or adolescents at referral/assessment to paediatric or adolescent gender/endocrinology services (table 1).

Selection process

The results of the database and other searches were uploaded to Covidence[19] and screened independently by two reviewers. Full texts for potentially relevant articles were retrieved and reviewed against the inclusion criteria by two reviewers independently. Disagreements were resolved through discussion and the inclusion of a third reviewer.

Table 1 Inclusion and exclusion criteria

Population	Children and adolescents (age 0–18) referred to paediatric or adolescent gender service or paediatric or adolescent endocrinology service that provides specialist gender-related healthcare. Articles reporting on child or adolescent populations or the combined population of children and adolescents were included. Mixed populations of adolescents and adults were included if referred to child or adolescent gender service, for example, some services provide healthcare to age 24; or where data are reported separately for all-age services. Studies of other selected subsamples were excluded, for example, those eligible for or receiving treatment, one gender group, studies recruiting a specific or convenience sample.
Comparator	Any or none.
Variables	Article reports as a minimum the birth-registered sex and/or age of the referred population. Studies reporting data from the time of referral or initial assessment were included.
Study design	Studies of any design or articles reporting data from gender services. Systematic or other literature reviews were excluded.
Publication	Published in the English language in a peer-reviewed journal. Conference abstracts and letters were excluded.

Data extraction

Data on study and population characteristics were extracted into a prepiloted template by one reviewer and checked by another. Data were extracted from graphs using the plot digitizer tool (https://plotdigitizer.com/). With reference to the literature and input from expert advisors, key demographics, gender, mental health, neurodevelopmental conditions and psychosocial characteristics were extracted. Study quality was not formally assessed.

Synthesis

A narrative approach to synthesis was used and where feasible proportions were combined in a random effects meta-analysis using metaprop (Stata V.18) with variances stabilised using the Freeman-Tukey double arcsine transformation.[20] A line graph was used to plot referrals and a scatter plot for birth-registered sex ratios over time by country. Where multiple studies reported data over time, a single study was selected with the largest study period and/or which represented the largest or most representative service within that country. For countries where there were no studies reporting changes over time in birth-registered sex ratios, the mid-point from studies reporting figures across years was used. The synthesis was performed by one reviewer and second-checked by another.

RESULTS

Our searches yielded 28 147 records, 3181 of which were identified as potentially relevant for the linked series of systematic reviews, and for which full texts were reviewed. From these, there were 143 studies from 131 papers that met the inclusion criteria for this review (figure 1; online supplemental table S2).

Studies reported data from Canada (n=35), US (n=34), Netherlands (n=26), UK (n=16), Australia (n=8), Germany (n=6), Finland (n=4), Italy (n=3), Belgium (n=2), Spain (n=2) and single studies from Brazil, Denmark, Israel, Norway, Sweden, Scotland and Switzerland (online supplemental table S3). There were 4 linked articles and 10 multiple country studies which are included in the individual country summaries. Data were reported from 1972 to 2021 with many samples overlapping from the same service within each country, although more data were reported from 2000 onwards (online supplemental table S4).

Demographics

The number of referrals over time was reported for 11 countries (figure 2).[2 21–26] Around 5–6 years into the data presented by year in the individual studies there is a sharp increase (twofold to threefold) in referral numbers across all countries except the Netherlands which started to increase in 2011[25] and Denmark which only had 2 years of data.[2]

There was a mixture of child and/or adolescent data presented across countries with the average age of children being 7/8 and adolescents 14–17 (online supplemental table S3). The combined child and adolescent data showed mixed findings, with a group of studies conducted relatively early having ages around 10/11,[27–30] and later studies of around 13–16, which is more closely aligned to studies with adolescent samples. This indicates a potential increase in the number of adolescents within the combined samples.

Over time, there is generally an increase in the ratio of birth-registered females to males being referred to child and adolescent gender services across countries

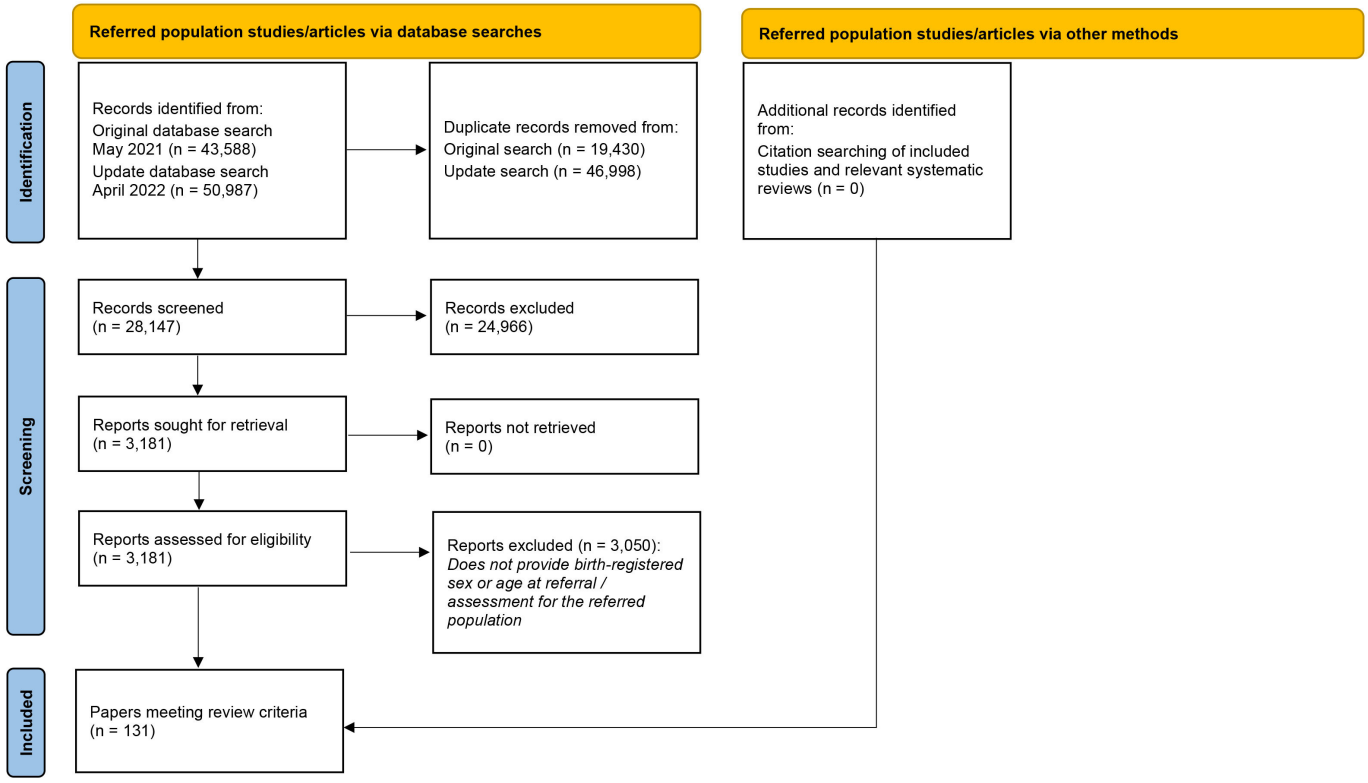


Figure 1 Study flow diagram.

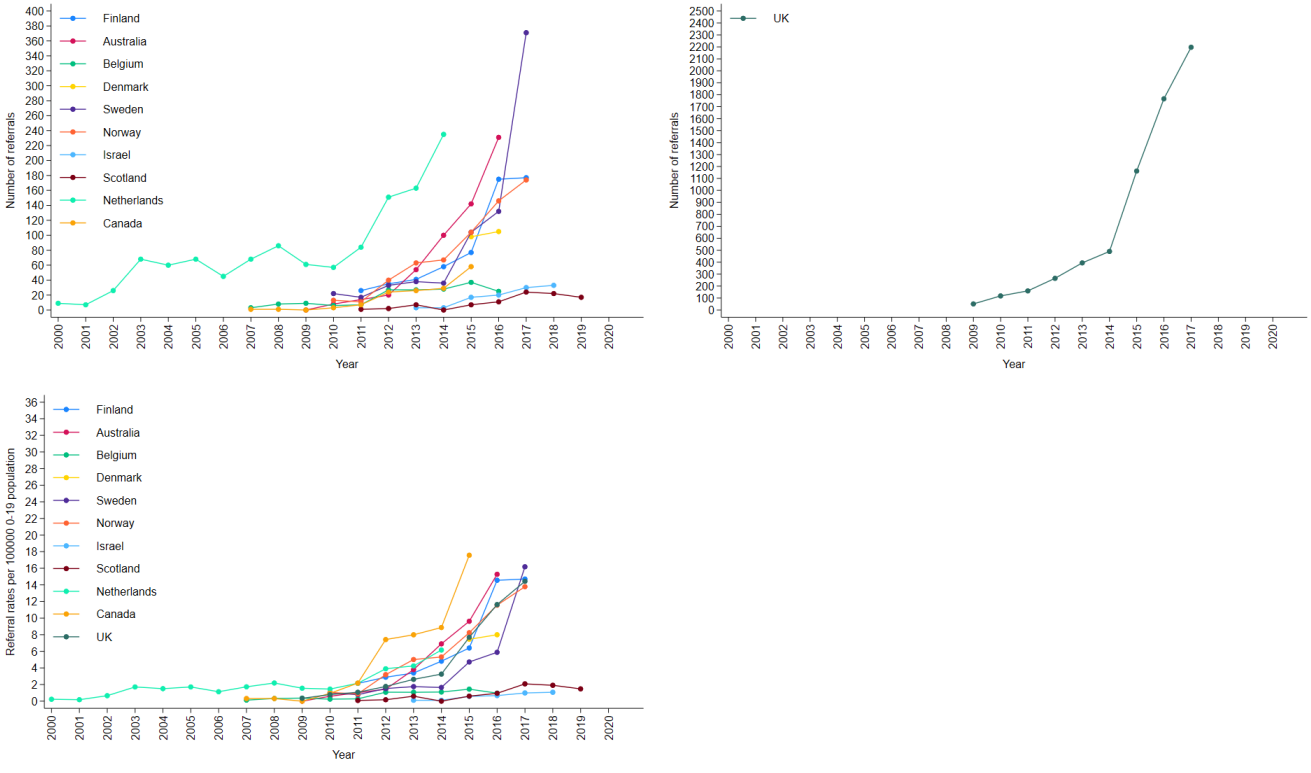


Figure 2 The number of referrals over time by country.

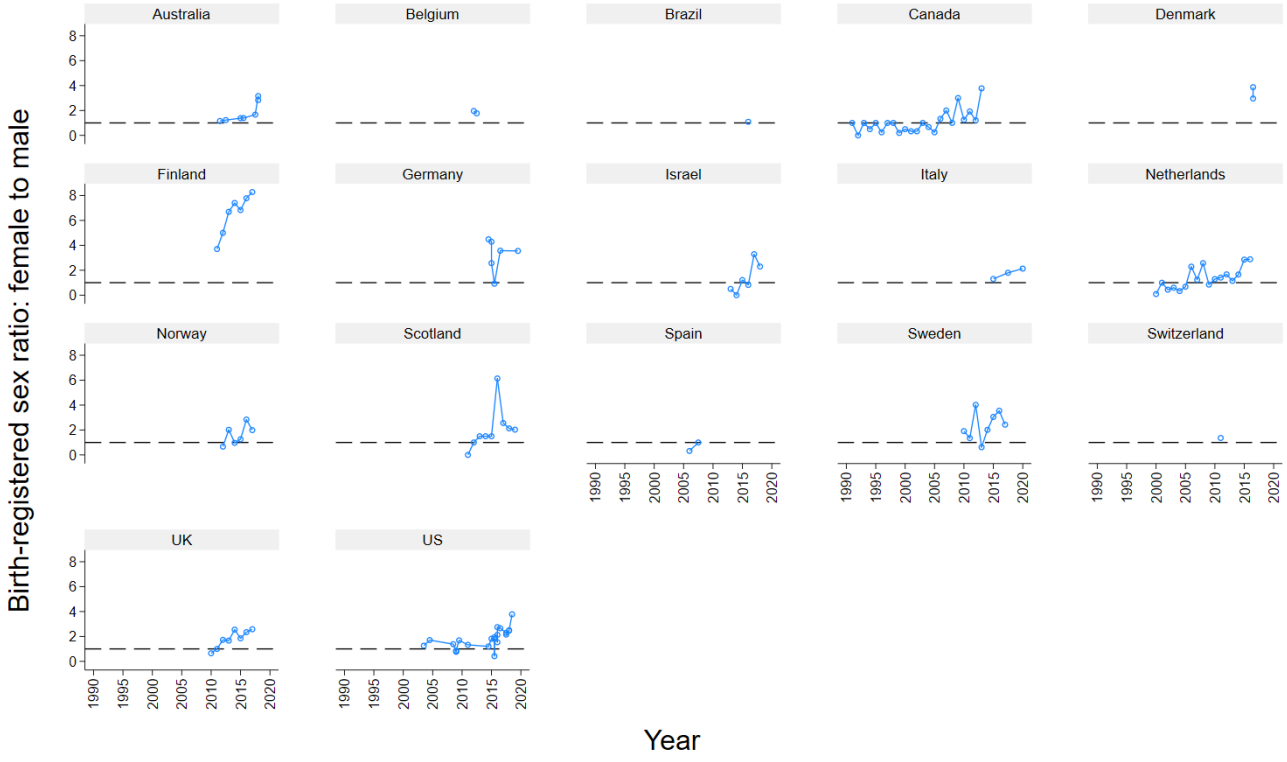


Figure 3 The ratio of birth-registered females to males being referred to child and adolescent gender services by country.

(figure 3).[2 3 7 8 21 22 24 26 31–70] There is no clear sudden increase but more of a steady increase over time; however, Finland reported a higher ratio throughout. Given the number of referrals is relatively low in some services/countries, there are fluctuations in the data with the ratios increasing one year and decreasing the next. Three studies in the Netherlands reported data by child/adolescent groupings and found that the ratio of birth-registered females to males was below 1 in children (indicating more birth-registered males compared with females) and at or above 1 in adolescents (indicating more birth-registered females compared with males) and approximately twice as high as the child ratios (online supplemental table S3).[25 28 71] Similar results were found in the only Canadian study that disaggregated data in 4-yearly blocks.[72]

Gender characteristics

There were country differences in reporting how the children/adolescents had defined their gender identity (online supplemental table S3). Across most studies, self-reported gender identity was either not reported or inconsistently reported. Of those studies reporting the proportion of children/adolescents identifying as non-binary, estimates ranged from 0% to 19%.[33 34 40 46 53 54 56 58–61 64 67 73–80]

Data on diagnosis of gender dysphoria (DSM-5) or gender identity disorder (DSM-4) were reported in 65 studies with reported proportions ranging from 29% to 100%, with 52 studies including over 70% (and 64 including over 50%) experiencing gender dysphoria/incongruence (online supplemental table S3). Gender dysphoria/incongruence was assessed usually by diagnostic interview but occasionally using a gender identity/dysphoria scale. Some studies had an explicit inclusion criterion of meeting diagnostic criteria for gender dysphoria or gender identity disorder (or subthreshold) whereas others included the full referred population.

Eleven studies reported the onset of the experience of gender incongruence (n=6)[32 38 67 70 81 82] or gender dysphoria (n=5).[34 45 82–84] For gender dysphoria, two studies reported mean/median ages which were approximately 7/8 (ranges 1–17)[34 83] and three studies reported the percentages in each age group, but they found different results.[45 82 84] For gender incongruence, three studies reported mean/median ages which were approximately 8–10 (ranges 5–15)[38 67 81] and three studies reported the percentages in each age group with two finding larger percentages in the under 8 group[32 70] but one finding a higher percentage in the 12+ category.[82]

Nineteen studies reported social transition data from seven countries.[3 7 38 42 44 48 55 56 67 74 76 81 84–90] The US reported higher proportions of social transition (combined 77%, 95% CI 70% to 90%) compared with most other countries (combined 59%, 95% CI 52% to 66%). There is no consensus on the definition of social transition and the studies included a wide range of changes. Estimates of changing name (n=6) ranged from 48% to 96%, pronouns (n=1) at 61% and changing appearance (n=2) between 75% and 99%. A single study reported details of where transitions took place and reported 61% home, 59% school and 7% online.[7] There were five studies reporting the data split by birth-registered sex.[84 85 88 89] All but one study found higher estimates of full social transition and all studies for name change in birth-registered females compared with males. The average age of social transition was approximately 14 (range 4–28, n=4) and two studies reported age bands (28% in the 6–11 and 81% in the >15 categories).

Mental health

Eating disorders

There were 16 (11%) studies from eight countries reporting eating disorder data for the referred population, with data reported from 1998 to 2019.[3 8 24 26 34 38 58 75 84 87 88 91–95] The combined estimate was 5% (95% CI 2% to 8%) with the lowest estimate of 0% (children) and highest of 23.4% (objective binge eating from a self-report scale). One study reported the data split by age groups and found all cases of eating disorders were identified in the age group of 12–18 years (16%) and 0 in the age group of 5–11 years.[84] Seven studies split data by birth-registered sex with inconsistent findings.[24 34 58 84 87 92 95] There was no consistency in the way in which eating disorders were recorded with some reporting any eating disorder and others a single type of eating disorder, a mixture of eating disorder symptoms, clinical diagnoses, those receiving psychiatric help for eating disorders, or it was unclear. Those reporting eating disorders using clinical diagnoses generally found lower estimates compared with those including symptomology alone or in addition (5.2% diagnosed and 15.5% when also including symptoms) (online supplemental figure S1).[87]

Suicide and/or self-harm

There were 39 (27%) studies from 11 countries reporting data on suicide attempts and/or self-harm of the referred population, with data recorded from 1976 to 2021. The combined estimate for suicide attempts was 14% (95% CI 11% to 17%, range 9%–30%, n=16), self-harm was 29% (95% CI 23% to 35%, range 8%–56%, n=14) and suicide/self-harm together reported by parents/carers was 23% (95% CI 8% to 41%, range 7%–45%, n=5) and children/adolescents was 34% (95% CI 24% to 44%, range 21%–45%, n=5); highlighting differences between parent/carer and child/adolescent reported measures. Sixteen studies explored differences in attempts of suicide (n=11), self-harm (n=6) or combined (n=3) by birth registered sex.[24 34 38 45 51 58 75 84 85 89 92 96 97] Of those studies, the majority found higher estimates of suicide attempts and/or self-harm in birth-registered females compared with males. Six studies explored differences in suicide attempts and/or self-harm by age groups, with estimates generally higher in older age categories.[41 75 81 84 97 98] Two studies explored differences in suicide attempts and/or self-harm over time in the referred populations.[35 89] One found no trend over time[35] and the other found a reduction in suicide attempts in 2015 (8.6%) compared with 2012 (13.3%).[89]

There were 30 (21%) studies from 10 countries reporting data on suicide and/or self-harm ideation, with data recorded from 2002 to 2021. The combined estimate for suicide ideation was 39% (95% CI 30% to 48%, range 10%–87%, n=17) and suicide/self-harm ideation together for parents/carers was 26% (95% CI 19% to 33%, range 19%–36%, n=5) and children/adolescents was 41% (95% CI 32% to 51%, range 10%–78%, n=11); again, highlighting differences between parent/carer and child/adolescent reports. Two studies reported self-harm ideation and estimates were 4.1% and 14.4%.[84 97] There were differences in the recording of suicide ideation as some studies reported any history and others reported current ideation only; one study reported both figures and found a marked difference (history 47.3% and current ideation 12%).[81] Of the seven studies reporting suicide ideation separately, four found higher estimates in birth-registered females compared with males,[24 34 45 85] two found the opposite[58 84] and one found similar figures.[51] Both studies reporting self-harm ideation found higher estimates in birth-registered males compared with females.[84 97] There were mixed findings in the four studies combining suicide and self-harm ideation and differences between parent/carer and child/adolescent reports.[50 96] Five studies explored differences in suicide and/or self-harm ideation by age groups and generally estimates were higher in older age categories.[41 81 84 97 98]

Depression and/or anxiety

There were 63 (44%) studies from 13 countries reporting data for depression and/or anxiety in the referred population, with data recorded from 1980 to 2021. There were eight studies only reporting data in continuous form (mean and SD) and there were different measures used, so it was not possible to synthesise.[30 42 43 47 99–102] The combined estimate for depression was 38% (95% CI 31% to 45%, range 3%–78%, n=32), for anxiety was 38% (95% CI 31% to 46%, range 8%–100%, n=28) and depression/anxiety together reported by parents/carers was 48% (95% CI 39% to 56%, range 26%–75%, n=15) and children/adolescents was 44% (95% CI 36% to 52%, range 28%–66%, n=13).

Twenty-eight studies explored differences in depression (n=16),[24 34 38 50 51 58 82 84 85 89 90 92 94 95 103 104] anxiety (n=11)[51 58 82 84 85 89 92 94 95 103] or combined (n=12)[23 28 36 40 105–108] by birth-registered sex, the majority reporting higher estimates of depression and anxiety in birth-registered females compared with males. There were six studies exploring differences by age groups.[28 81 84 97 105] Four focused on both depression and anxiety and three found higher estimates in older ages[28 105] with the other finding no significant difference.[97] There were two studies each looking at depression and anxiety separately and much higher estimates for depression were seen in adolescents (over 12) compared with children, whereas the estimates for anxiety were similar across age groups or slightly higher in adolescents.[81 84]

Neurodevelopmental conditions

The combined estimate of autism spectrum condition (ASC) was 9% (95% CI 6% to 11%, range 0%–26%, n=26, nine countries, data range 1998–2019). One study reported data separately for 2012 and 2015 and demonstrated an increase from 1.8% to 15.1%[89]; no other study reported data broken down over time. It was generally unclear how ASC was defined in each study, where it was reported it included signs or traits, clinical diagnosis or current intervention due to ASC. Two studies reported the data split by age groups,[81 109] one found similar estimates of ASC in under 15s and 15+ (6%)[81] and the other a higher percentage of adolescents with ASC compared with children (9% vs 6%).[109] Seventeen studies split data by birth-registered sex, but the results were inconsistent. One of these studies reported data separately for 2 years and found changes over time (birth-registered females vs males: 2012: 10.4% vs 20.0% and 2015: 15.4% vs 14.6%) (online supplemental figure S1).[89]

The combined estimate of attention deficit hyperactivity discorder (ADHD) was 10% (95% CI 7% to 13%, range 2.5%–27%, n=20, nine countries, data range 1998–2021). Fourteen studies split the data by birth-registered sex, 12 of them found a higher percentage of birth-registered males with ADHD compared with females[3 8 26 31 34 40 51 55 66 68 75 82 84 85 88 91 92] and 2 finding the opposite relationship.[24 103] Across studies, the estimate of ADHD was 14% (95% CI 8% to 20%) for birth-registered males and 6% (95% CI 3% to 9%) for birth-registered females.

Adverse childhood experiences

There were relatively few studies reporting data on the different categories referred to as adverse childhood experiences (ACES) (n=15, 10%).[3 8 32 45 46 48 56 62 82–84 86 89 91 95] Eight studies reported data on physical (n=3),[8 32 91] emotional (n=1)[8] or sexual (n=4) abuse,[8 32 82 91] and neglect or abuse or neglect alone (n=6). Combined neglect or abuse figures were reported in four studies (range 11.1%–67.4%)[45 56 84 89] and neglect alone in two studies (10.5% and 11.4%).[8 32] Physical abuse estimates ranged from 15.2% to 20%, sexual abuse from 5.2% to 19% and emotional abuse was assessed in a single study (13.9%). Parental mental illness or substance misuse was reported in two studies and maternal estimates were higher (52.6% and 49.4%) than paternal (38% in both studies).[8 32] Two studies reported data on exposure to domestic violence (22.8% and 24.6%).[8 32] Loss of a parent through abandonment was reported in 10 studies with 5 reporting adoption (range 0.9%–8.2%),[3 45 48 62 83] 6 foster care (range 1.1%–12.3%)[8 32 46 48 83 84] and 2 children's homes (5.3% and 0.5%).[84 86] Two studies reported data for those experiencing death or permanent hospitalisation of a parent (8.4% and 19%).[8 95]

DISCUSSION

This systematic review found that there has been a twofold to threefold increase in the number of referrals to specialist paediatric gender/endocrinology services over time across countries. An increase in the ratio of birth-registered females to males was also observed. Although coexisting complexity was reported in fewer studies, the presence of ASC, ADHD, anxiety, depression, suicidality, self-harm, eating disorders and ACES appears higher than seen in the general population of children and adolescents.[110–113]

There was limited data reported to allow patterns to be explored in birth-registered sex ratios by child/adolescent groupings; however, data from the Netherlands (1972–2016) suggest the increase in the ratio of females to males was only in adolescents. More recent UK data (2017–2020) reported more females than males for children and adolescents but considerably higher ratios in adolescents.[114] Very few studies reported data on gender characteristics but from the limited social transition data reported, approximately 60% of those referred to gender services had made steps to present themselves in their preferred gender.

For mental health, the largest number of studies reported data on depression and/or anxiety (<50% of the studies), with most other mental health outcomes reported in <20%. Frequency of mental health issues has been found to be similar to other systematic/scoping reviews of this population.[4 115–119] Co-occurrence of depression and anxiety, and of suicidality and/or self-harm appear to be considerably higher in children and adolescents experiencing gender dysphoria/incongruence compared with population estimates,[110–112] and children/adolescents were consistently reporting higher frequencies of self-harm/suicide than their parents. Eating disorders may be slightly higher than population estimates, although no clear conclusion can be drawn due to heterogeneity in measurement.[113] Less research focus has been given to those with eating issues among children and adolescents experiencing gender dysphoria or incongruence, which is reported to affect around 22% of children/adolescents in the wider population.[120]

Frequency of ASC was found to be similar to other systematic reviews and may also be higher than population estimates, supporting current guidance to screen for ASC in specialist gender services.[5 10] However, robust research is needed to confirm this and to assess levels of ADHD in this population which has not been adequately explored to date. This review indicates that rates of ADHD may be equal to those of ASC; however, issues with diagnosis must be considered.

This review indicates that the majority of studies have not routinely measured or recorded the presence of ACES in the histories and experiences of children and adolescents being referred to paediatric gender services so there is limited data despite the wider research indicating that gender-diverse youth and adults have experienced high rates of childhood adversity.[121–125] It is not possible for this review to speculate as to the relationship between ACES and the experience of gender-related distress in children and adolescents, but the results indicate that this is another important area in which systematic collection of data, at referral and across pathways of care can support care.

Strengths and limitations

Strengths include a published protocol with robust search strategies and comprehensive synthesis. As searches were conducted to April 2022 this review does not include more recently published studies; as this is a rapidly involving area this is a limitation.

Caution should be taken when interpreting any of the pooled estimates as they represent data for a wide period of time, reported data averaged over a large number of years, included often overlapping samples from the same service, and often discrepancies in the individual studies between the referred numbers and those included in the summaries of characteristics. Additionally, different measures were used to assess mental health outcomes, for example, any diagnosis of an eating disorder versus a single symptom such as binge eating, and inclusion of historical difficulties, for example, self-harm ever versus current self-harm.

As there were multiple studies in some countries reporting referrals by year, a single study was selected with the largest study period and/or which represented the largest or most representative service. This could have influenced the findings of referral patterns. It was not possible to make inferences about changes over time for most characteristics explored due to overlapping samples and data being reported over large time periods in individual studies. There were some studies that did not report changes over time in the ratio of birth-registered females to males hence the mid-point from studies reporting figures across years was used. This may have artificially created trends in the data as there were often overlapping samples from the same service that are likely to include the same individuals multiple times. Despite these caveats, the results do show similar trends in the ratios to those studies reporting data split by year.

Conclusions

There has been a twofold to threefold increase in referrals to specialist gender services for children/adolescents across many countries. These children/adolescents show higher than expected levels of ASC, ADHD, anxiety, depression, eating disorders, suicidality, self-harm and adverse childhood experiences. Agreement of core characteristics for collection at referral/assessment would help to ensure services measure key outcomes and enable them to develop to meet the needs of these children and adolescents. Services need to assess and respond to any co-occurring needs and complexities.

Contributors LF, CEH, TL and JT contributed to the conception of this review. LF, RH, CEH and JT contributed to screening and selection. CEH and JT completed data extraction and synthesis and drafted the manuscript. LF, RH, CEH, TL and JT contributed to data and synthesis interpretation. All authors reviewed and approved

the manuscript prior to submission. CEH accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was funded by NHS England to inform the Cass Review (Independent review of gender identity services for children and young people). The funder and Cass Review team had a role in commissioning the research programme but no role in the study conduct, interpretation or conclusion.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement Data sharing is not applicable as no datasets were generated and/or analysed for this study.

ORCID iDs
Jo Taylor http://orcid.org/0000-0001-5898-0900
Catherine Elizabeth Hewitt http://orcid.org/0000-0002-0415-3536

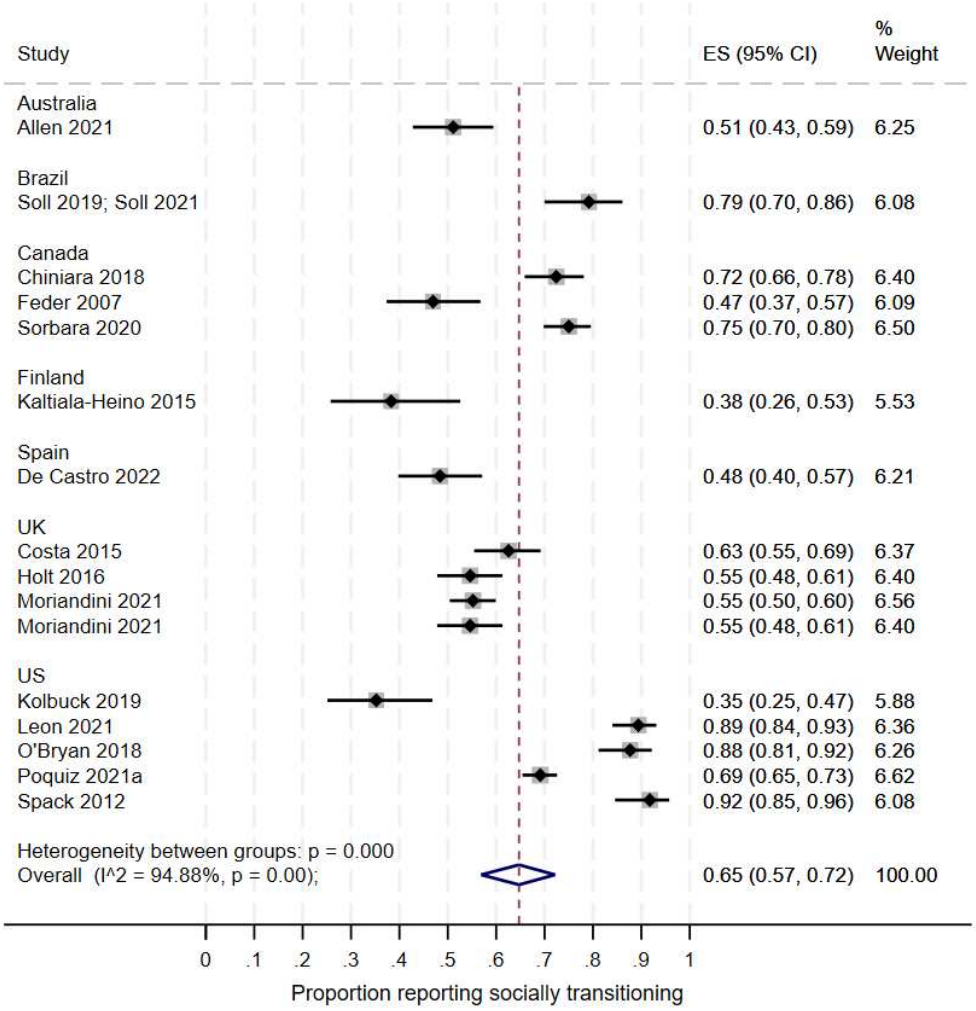
REFERENCES

1 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender Dysphoria literature: 1) epidemiology. *PLOS Glob Public Health* 2022;2:e0000245.
2 Kaltiala R, Bergman H, Carmichael P, *et al*. Time trends in referrals to child and adolescent gender identity services: a study in four Nordic countries and in the UK. *Nord J Psychiatry* 2020;74:40–4.
3 Spack NP, Edwards-Leeper L, Feldman HA, *et al*. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics* 2012;129:418–25.
4 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender Dysphoria literature: 2) mental health. *PLOS Glob Public Health* 2022;2:e0000426.
5 The Swedish National Board of Health and Welfare. Care of children and young people with gender Dysphoria - national knowledge support with recommendations for the profession and decision makers. 2022. Available: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-12-8302.pdf
6 Council for Choices in Healthcare in Finland. Medical treatment methods for Dysphoria associated with variations in gender identity in minors – recommendation. 2020. Available: https://palveluvalikoima.fi/en/recommendations#genderidentity
7 Dahlgren Allen S, Tollit MA, McDougall R, *et al*. A Waitlist intervention for Transgender young people and Psychosocial outcomes. *Pediatrics* 2021;148.
8 Kozlowska K, McClure G, Chudleigh C, *et al*. Australian children and adolescents with gender Dysphoria: clinical presentations and challenges experienced by a Multidisciplinary team and gender service. *Human Systems* 2021;1:70–95.
9 The Cass Review. Independent review of gender identity services for children and young people: interim report; 2022. Available: https://cass.independent-review.uk/publications/interim-report/
10 Coleman E, Radix AE, Bouman WP, *et al*. Standards of care for the health of Transgender and gender diverse people, version 8. *Int J Transgend Health* 2022;23:S1–259.
11 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender Dysphoria literature: 3) treatment. *PLOS Glob Public Health* 2023;3:e0001478.
12 National Institute for Health and Care Excellence (NICE). Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria, . 2020Available: https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_GnRH-analogues_For-upload_Final.pdf
13 Pasternack I, Söderström I, Saijonkari M, *et al*. Medical approaches to treatment of dysphoria related to gender variations. A systematic review, Available: https://app.box.com/s/y9u791np8v9gsunwgpr2kqn8swd9vdtx
14 Ludvigsson JF, Adolfsson J, Höistad M, *et al*. A systematic review of hormone treatment for children with gender Dysphoria and recommendations for research. *Acta Paediatrica* 2023;112:2279–92. 10.1111/apa.16791 Available: https://onlinelibrary.wiley.com/toc/16512227/112/11
15 Baker KE, Wilson LM, Sharma R, *et al*. Hormone therapy, mental health, and quality of life among Transgender people: A systematic review. *J Endocr Soc* 2021;5:bvab011.
16 Chew D, Anderson J, Williams K, *et al*. Hormonal treatment in young people with gender Dysphoria: A systematic review. *Pediatrics* 2018;141:e20173742.
17 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
18 Fraser L, Hall R, Taylor J, *et al*. The epidemiology, management and outcomes of children with gender-related distress / gender Dysphoria: a systematic review. *PROSPERO* 2021:CRD42021289659.
19 Veritas Health Innovation. *Covidence systematic review software*. Melbourne, Australia: Veritas Health Innovation, 2023.
20 Nyaga VN, Arbyn M, Aerts M. Metaprop: a STATA command to perform meta-analysis of binomial data. *Arch Public Health* 2014;72:39.
21 Pang KC, de Graaf NM, Chew D, *et al*. Association of media coverage of Transgender and gender diverse issues with rates of referral of Transgender children and adolescents to specialist gender clinics in the UK and Australia. *JAMA Netw Open* 2020;3:e2011161.
22 Van Cauwenberg G, Dhondt K, Motmans J. Ten years of experience in counseling gender diverse youth in Flanders, Belgium. A clinical overview. *Int J Impot Res* 2021;33:671–8.
23 Heard J, Morris A, Kirouac N, *et al*. Gender Dysphoria assessment and action for youth: review of health care services and experiences of Trans youth in Manitoba. *Paediatr Child Health* 2018;23:179–84.
24 Segev-Becker A, Israeli G, Elkon-Tamir E, *et al*. Children and adolescents with gender Dysphoria in Israel: increasing referral and fertility preservation rates. *Endocrine Practice* 2020;26:423–8.
25 Wiepjes CM, Nota NM, de Blok CJM, *et al*. The Amsterdam cohort of gender Dysphoria study (1972-2015): trends in prevalence, treatment, and regrets. *J Sex Med* 2018;15:582–90.
26 McCallion S, Smith S, Kyle H, *et al*. An appraisal of current service delivery and future models of care for young people with gender Dysphoria. *Eur J Pediatr* 2021;180:2969–76.
27 Hughes SK, VanderLaan DP, Blanchard R, *et al*. The prevalence of only-child status among children and adolescents referred to a gender identity service versus a clinical comparison group. *Journal of Sex & Marital Therapy* 2017;43:586–93.
28 Steensma TD, Zucker KJ, Kreukels BPC, *et al*. Behavioral and emotional problems on the teacher's report form: a cross-national, cross-clinic comparative analysis of gender Dysphoric children and adolescents. *J Abnorm Child Psychol* 2014;42:635–47.
29 van der Miesen AIR, de Vries ALC, Steensma TD, *et al*. Autistic symptoms in children and adolescents with gender Dysphoria. *J Autism Dev Disord* 2018;48:1537–48.
30 Zucker KJ, Owen A, Bradley SJ, *et al*. Gender-Dysphoric children and adolescents: A comparative analysis of demographic characteristics and behavioral problems. *Clin Child Psychol Psychiatry* 2002;7:398–411.
31 Hilton MN, Boulton KA, Kozlowska K, *et al*. The Co-occurrence of neurodevelopmental disorders in gender Dysphoria: characteristics within a Paediatric treatment-seeking cohort and factors that predict distress pertaining to gender. *J Psychiatr Res* 2022;149:281–6.
32 Kozlowska K, Chudleigh C, McClure G, *et al*. Attachment patterns in children and adolescents with gender Dysphoria. *Front Psychol* 2020;11:582688.
33 Mahfouda S, Panos C, Whitehouse AJO, *et al*. Mental health correlates of autism spectrum disorder in gender diverse young people: evidence from a specialised child and adolescent gender clinic in Australia. *J Clin Med* 2019;8:1503.
34 Tollit MA, May T, Maloof T, *et al*. The clinical profile of patients attending a large, Australian pediatric gender service: A 10-year review. *Int J Transgend Health* 2023;24:59–69.
35 Arnoldussen M, Steensma TD, Popma A, *et al*. Re-evaluation of the Dutch approach: are recently referred Transgender youth different compared to earlier referrals *Eur Child Adolesc Psychiatry* 2020;29:803–11.
36 de Graaf NM, Cohen-Kettenis PT, Carmichael P, *et al*. Psychological functioning in adolescents referred to specialist gender identity clinics across Europe: a clinical comparison study between four clinics. *Eur Child Adolesc Psychiatry* 2018;27:909–19.
37 Aitken M, Steensma TD, Blanchard R, *et al*. Evidence for an altered sex ratio in clinic-referred adolescents with gender Dysphoria. *J Sex Med* 2015;12:756–63.
38 Soll BMB, Brandelli Costa A, Vaitses Fontanari AM, *et al*. Use of the house-tree-person projective drawings and parental styles inventory in the global psychological evaluation of Transgender youth who seek Healthcare at the gender identity program. *Front Psychol* 2019;10:2488.

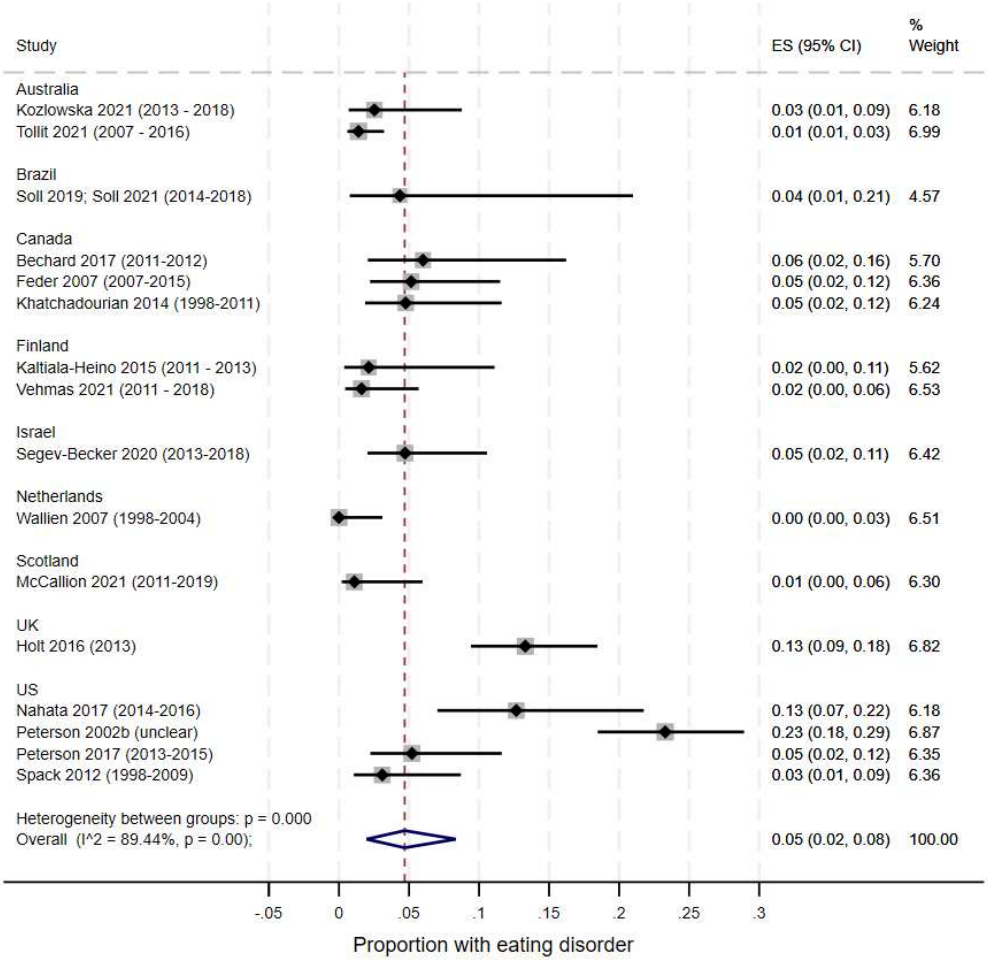
39 Becker-Hebly I, Fahrenkrug S, Campion F, *et al*. Psychosocial health in adolescents and young adults with gender Dysphoria before and after gender-affirming medical interventions: a descriptive study from the Hamburg gender identity service. *Eur Child Adolesc Psychiatry* 2021;30:1755–67.
40 Brecht A, Bos S, Ries L, *et al*. Assessment of psychological distress and peer relations among Trans adolescents-an examination of the use of gender norms and parent-child congruence of the YSR-R/CBCL-R among a treatment-seeking sample. *Children (Basel)* 2021;8:864.
41 Hartig A, Voss C, Herrmann L, *et al*. Suicidal and Nonsuicidal self-harming thoughts and behaviors in clinically referred children and adolescents with gender Dysphoria. *Clin Child Psychol Psychiatry* 2022;27:716–29.
42 Levitan N, Barkmann C, Richter-Appelt H, *et al*. Risk factors for psychological functioning in German adolescents with gender Dysphoria: poor peer relations and general family functioning. *Eur Child Adolesc Psychiatry* 2019;28:1487–98.
43 Röder M, Barkmann C, Richter-Appelt H, *et al*. Health-related quality of life in Transgender adolescents: associations with body image and emotional and behavioral problems. *Int J Transgend* 2018;19:78–91.
44 Sievert ED, Schweizer K, Barkmann C, *et al*. Not social transition status, but peer relations and family functioning predict psychological functioning in a German clinical sample of children with gender Dysphoria. *Clin Child Psychol Psychiatry* 2021;26:79–95.
45 Fisher AD, Ristori J, Castellini G, *et al*. Psychological characteristics of Italian gender Dysphoric adolescents: a case-control study. *J Endocrinol Invest* 2017;40:953–65.
46 Mirabella M, Piras I, Fortunato A, *et al*. Gender identity and non-binary presentations in adolescents attending two specialized services in Italy. *J Sex Med* 2022;19:1035–48.
47 Ristori J, Rossi E, Cocchetti C, *et al*. Sexual habits among Italian Transgender adolescents: a cross-sectional study. *Int J Impot Res* 2020;33:687–93.
48 De Castro C, Solerdelcoll M, Plana MT. High persistence in Spanish Transgender minors: 18 years of experience of the gender identity unit of Catalonia. *Spanish J Psychiatry Mental Health* 2022.
49 Esteva de Antonio I, Gómez-Gil E, GIDSEEN Group. Coordination of Healthcare for Transsexual persons: a Multidisciplinary approach. *Curr Opin Endocrinol Diabetes Obes* 2013;20:585–91.
50 Achille C, Taggart T, Eaton NR, *et al*. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of Transgender youths: preliminary results. *Int J Pediatr Endocrinol* 2020;2020:8.
51 Brocksmith VM, Alradadi RS, Chen M, *et al*. Baseline characteristics of gender Dysphoric youth. *J Pediatr Endocrinol Metab* 2018;31:1367–9.
52 Edwards-Leeper L, Feldman HA, Lash BR, *et al*. Psychological profile of the first sample of Transgender youth presenting for medical intervention in a U.S. pediatric gender center. *Psychology of Sexual Orientation and Gender Diversity* 2017;4:374–82.
53 Fornander MJ, Roberts T, Egan AM, *et al*. Weight status, medication use, and recreational activities of treatment-naive Transgender youth. *Child Obes* 2022;18:228–36.
54 Handler T, Hojilla JC, Varghese R, *et al*. Trends in referrals to a pediatric Transgender clinic. *Pediatrics* 2019;144:e20191368.
55 Kolbuck VD, Muldoon AL, Rychlik K, *et al*. Parenting stress, and parental support among clinic-referred Prepubertal gender expansive children. *Clin Pract Pediatr Psychol* 2019;7:254–66.
56 Leon K, O'Bryan J, Wolf-Gould C, *et al*. Prevalence and risk factors for Nonsuicidal self-injury in Transgender and gender-expansive youth at a rural gender wellness clinic. *Transgend Health* 2021;6:43–50.
57 McGuire FH, Carl A, Woodcock L, *et al*. Differences in patient and parent informant reports of depression and anxiety symptoms in a clinical sample of Transgender and gender diverse youth. *LGBT Health* 2021;8:404–11.
58 Nahata L, Quinn GP, Caltabellotta NM, *et al*. Mental health concerns and insurance denials among Transgender adolescents. *LGBT Health* 2017;4:188–93.
59 O'Bryan J, Scribani M, Leon K, *et al*. Health-related quality of life among Transgender and gender expansive youth at a rural gender wellness clinic. *Qual Life Res* 2020;29:1597–607.
60 Pariseau EM, Chevalier L, Long KA, *et al*. The relationship between family acceptance-rejection and Transgender youth Psychosocial functioning. *Clinical Practice in Pediatric Psychology* 2019;7:267–77.
61 Reguitti V, Poquiz JL, Jackson K, *et al*. Preliminary factor structure of the parental attitudes of gender expansiveness scale for parents (PAGES-P). *Clin Pract Pediatr Psychol* 2022;10:1–8.
62 Shumer DE, Abrha A, Feldman HA, *et al*. Overrepresentation of adopted adolescents at a hospital-based gender Dysphoria clinic. *Transgend Health* 2017;2:76–9.
63 Shumer DE, Reisner SL, Edwards-Leeper L, *et al*. Evaluation of Asperger syndrome in youth presenting to a gender Dysphoria clinic. *LGBT Health* 2016;3:387–90.
64 Tordoff DM, Wanta JW, Collin A, *et al*. Mental health outcomes in Transgender and Nonbinary youths receiving gender-affirming care. *JAMA Netw Open* 2022;5:e220978.
65 Chen D, Hidalgo MA, Leibowitz S, *et al*. Multidisciplinary care for gender-diverse youth: A narrative review and unique model of gender-affirming care. *Transgender Health* 2016;1:117–23.
66 Chen M, Fuqua J, Eugster EA. Characteristics of referrals for gender Dysphoria over a 13-year period. *J Adolesc Health* 2016;58:369–71.
67 Kuper LE, Lindley L, Lopez X. Exploring the gender development histories of children and adolescents presenting for gender affirming medical care. *Clin Pract Pediatric Psychol* 2019;7:217–28.
68 Kuper LE, Mathews S, Lau M. Baseline mental health and Psychosocial functioning of Transgender adolescents seeking gender-affirming hormone therapy. *J Dev Behav Pediatr* 2019;40:589–96.
69 Poquiz J, Moser CN, Grimstad F, *et al*. Gender-affirming care in the Midwest: reaching rural populations. *J Rural Mental Health* 2021;45:121–8.
70 Lynch MM, Khandheria MM, Meyer WJ. Retrospective study of the management of childhood and adolescent gender identity disorder using Medroxyprogesterone acetate. *Int J Transgen* 2015;16:201–8.
71 Alberse A-ME, de Vries AL, Elzinga WS, *et al*. Self-perception of Transgender clinic referred gender diverse children and adolescents. *Clin Child Psychol Psychiatry* 2019;24:388–401.
72 Wood H, Sasaki S, Bradley SJ, *et al*. Patterns of referral to a gender identity service for children and adolescents (1976-2011): age, sex ratio, and sexual orientation. *J Sex Marital Ther* 2013;39:1–6.
73 Moyer DN, Connelly KJ, Holley AL. Using the PHQ-9 and GAD-7 to screen for acute distress in Transgender youth: findings from a pediatric Endocrinology clinic. *J Pediatr Endocrinol Metab* 2019;32:71–4.
74 O'Bryan J, Leon K, Wolf-Gould C, *et al*. Building a pediatric patient Registry to study health outcomes among Transgender and gender expansive youth at a rural gender clinic. *Transgend Health* 2018;3:179–89.
75 Peterson CM, Matthews A, Copps-Smith E, *et al*. Self-harm, and body dissatisfaction in Transgender adolescents and emerging adults with gender Dysphoria. *Suicide & Life Threat Behav* 2017;47:475–82. 10.1111/sltb.12289 Available: https://onlinelibrary.wiley.com/toc/1943278x/47/4
76 Poquiz JL, Coyne CA, Garofalo R, *et al*. Comparison of gender minority stress and resilience among Transmasculine, Transfeminine, and Nonbinary adolescents and young adults. *J Adolesc Health* 2021;68:615–8.
77 Hedrick HR, Glover NT, Guerriero JT, *et al*. A new virtual reality: benefits and barriers to providing pediatric gender-affirming health care through Telehealth. *Transgend Health* 2022;7:144–9.
78 Cantu AL, Moyer DN, Connelly KJ, *et al*. Changes in anxiety and depression from intake to first follow-up among Transgender youth in a pediatric Endocrinology clinic. *Transgend Health* 2020;5:196–200.
79 Chodzen G, Hidalgo MA, Chen D, *et al*. Minority stress factors associated with depression and anxiety among Transgender and gender-Nonconforming youth. *J Adolesc Health* 2019;64:467–71.
80 Twist J, de Graaf NM. Gender diversity and non-binary presentations in young people attending the United Kingdom's National gender identity development service. *Clin Child Psychol Psychiatry* 2019;24:277–90.
81 Sorbara JC, Chiniara LN, Thompson S, *et al*. Mental health and timing of gender-affirming care. *Pediatrics* 2020;146:e20193600.
82 Kaltiala-Heino R, Työläjärvi M, Lindberg N. Sexual experiences of clinically referred adolescents with features of gender Dysphoria. *Clin Child Psychol Psychiatry* 2019;24:365–78.
83 Matthews T, Holt V, Sahin S, *et al*. Gender Dysphoria in looked-after and adopted young people in a gender identity development service. *Clin Child Psychol Psychiatry* 2019;24:112–28.
84 Holt V, Skagerberg E, Dunsford M. Young people with features of gender Dysphoria: demographics and associated difficulties. *Clin Child Psychol Psychiatry* 2016;21:108–18.
85 Chiniara LN, Bonifacio HJ, Palmert MR. Characteristics of adolescents referred to a gender clinic: are youth seen now different from those in initial reports? *Horm Res Paediatr* 2018;89:434–41.
86 Costa R, Dunsford M, Skagerberg E, *et al*. Psychological support, puberty suppression, and Psychosocial functioning in adolescents with gender Dysphoria. *J Sex Med* 2015;12:2206–14.
87 Feder S, Isserlin L, Seale E, *et al*. Exploring the association between eating disorders and gender Dysphoria in youth. *Eating Disorders* 2017;25:310–7.
88 Kaltiala-Heino R, Sumia M, Työläjärvi M, *et al*. Two years of gender identity service for minors: Overrepresentation of natal girls with severe problems in adolescent development. *Child Adolesc Psychiatry Ment Health* 2015;9:9.
89 Morandini JS, Kelly A, de Graaf NM, *et al*. Shifts in demographics and mental health Co-morbidities among gender Dysphoric youth referred to a specialist gender Dysphoria service. *Clin Child Psychol Psychiatry* 2022;27:480–91.
90 Soll BMB, Fontanari AM, Brandelli Costa A, *et al*. Descriptive study of Transgender youth receiving health care in the gender identity program in Southern Brazil. *Front Psychiatry* 2021;12:627661.
91 Bechard M, VanderLaan DP, Wood H, *et al*. "Psychosocial and psychological vulnerability in adolescents with gender Dysphoria: A "proof of principle" study". *J Sex Marital Ther* 2017;43:678–88.
92 Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender Dysphoria in Vancouver. *J Pediatr* 2014;164:906–11.

93 Peterson CM, Toland MD, Matthews A, *et al*. Exploring the eating disorder examination questionnaire in treatment seeking Transgender youth. *Psychol Sexual Orientation Gender Diversity* 2020;7:304–15.
94 Wallien MSC, Swaab H, Cohen-Kettenis PT. Psychiatric Comorbidity among children with gender identity disorder. *J Am Acad Child Adolesc Psychiatry* 2007;46:1307–14.
95 Vehmas N, Holopainen E, Suomalainen L, *et al*. Somatic health and Psychosocial background among Finnish adolescents with gender Dysphoria seeking hormonal interventions [Transgender health. 2021;7:505-13 Online]. *Transgend Health* 2022;7:505–13.
96 de Graaf NM, Steensma TD, Carmichael P, *et al*. Suicidality in clinic-referred Transgender adolescents. *Eur Child Adolesc Psychiatry* 2022;31:67–83.
97 Skagerberg E, Parkinson R, Carmichael P. Self-harming thoughts and behaviors in a group of children and adolescents with gender Dysphoria. *Int J Transgen* 2013;14:86–92.
98 Aitken M, VanderLaan DP, Wasserman L, *et al*. Self-harm and Suicidality in children referred for gender Dysphoria. *J Am Acad Child Adolesc Psychiatry* 2016;55:513–20.
99 Zucker KJ, Bradley SJ, Owen-Anderson A, *et al*. Demographics, behavior problems, and Psychosexual characteristics of adolescents with gender identity disorder or Transvestic Fetishism. *J Sex Marital Ther* 2012;38:151–89.
100 Zucker KJ, Bradley SJ, Sanikhani M. Sex differences in referral rates of children with gender identity disorder: some hypotheses. *J Abnorm Child Psychol* 1997;25:217–27.
101 Zucker KJ, Finegan JA, Doering RW, *et al*. Human figure drawings of gender-problem children: a comparison to Sibling, psychiatric, and normal controls. *J Abnorm Child Psychol* 1983;11:287–98.
102 Zucker KJ, Nabbijohn AN, Santarossa A, *et al*. Intense/Obsessional interests in children with gender Dysphoria: a cross-validation study using the teacher's report form. *Child Adolesc Psychiatry Ment Health* 2017;11:51.
103 de Vries ALC, Doreleijers TAH, Steensma TD, *et al*. Psychiatric Comorbidity in gender Dysphoric adolescents. *J Child Psychol Psychiatry* 2011;52:1195–202. 10.1111/j.1469-7610.2011.02426.x Available: http://doi.wiley.com/10.1111/jcpp.2011.52.issue-11
104 de Vries ALC, Kreukels BPC, Steensma TD, *et al*. Comparing adult and adolescent Transsexuals: an MMPI-2 and MMPI-A study. *Psychiatry Res* 2011;186:414–8.
105 de Graaf NM, Giovanardi G, Zitz C, *et al*. Sex ratio in children and adolescents referred to the gender identity development service in the UK (2009-2016). *Arch Sex Behav* 2018;47:1301–4.
106 de Vries ALC, Steensma TD, Cohen-Kettenis PT, *et al*. Poor peer relations predict Parent- and self-reported behavioral and emotional problems of adolescents with gender Dysphoria: a cross-national, cross-clinic comparative analysis. *Eur Child Adolesc Psychiatry* 2016;25:579–88.
107 Skagerberg E, Davidson S, Carmichael P. Internalizing and Externalizing behaviors in a group of young people with gender Dysphoria. *Int J Transgen* 2013;14:105–12.
108 van der Miesen AIR, Steensma TD, de Vries ALC, *et al*. Psychological functioning in Transgender adolescents before and after gender-affirmative care compared with Cisgender general population peers. *J Adolesc Health* 2020;66:699–704.
109 de Vries ALC, Noens ILJ, Cohen-Kettenis PT, *et al*. Autism spectrum disorders in gender Dysphoric children and adolescents. *J Autism Dev Disord* 2010;40:930–6.
110 Lim K-S, Wong CH, McIntyre RS, *et al*. Global lifetime and 12-month prevalence of suicidal behavior, deliberate self-harm and non-suicidal self-injury in children and adolescents between 1989 and 2018: A meta-analysis. *Int J Environ Res Public Health* 2019;16:4581.
111 Racine N, McArthur BA, Cooke JE, *et al*. Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19: A meta-analysis. *JAMA Pediatr* 2021;175:1142–50.
112 Salari N, Ghasemi H, Abdoli N, *et al*. The global prevalence of ADHD in children and adolescents: a systematic review and meta-analysis. *Ital J Pediatr* 2023;49:48.
113 Coelho JS, Suen J, Clark BA, *et al*. Eating disorder diagnoses and symptom presentation in Transgender youth: a Scoping review. *Curr Psychiatry Rep* 2019;21:107.
114 Masala B, Love A, Carmichael P, *et al*. Demographics of referrals to a specialist gender identity service in the UK between 2017 and 2020. *Clin Child Psychol Psychiatry* 2023;2023:13591045231202372.
115 Surace T, Fusar-Poli L, Vozza L, *et al*. Lifetime prevalence of suicidal Ideation and suicidal behaviors in gender non-conforming youths: a meta-analysis. *Eur Child Adolesc Psychiatry* 2021;30:1147–61.
116 Herrmann L, Bindt C, Schweizer K, *et al*. Autism spectrum disorders and gender Dysphoria among children and adolescents: systematic review on the Co-occurrence. *Psychiatr Prax* 2020;47:300–7.
117 Kallitsounaki A, Williams DM. Autism spectrum disorder and gender Dysphoria/Incongruence: A systematic literature review and meta-analysis. *J Autism Dev Disord* 2023;53:3103–17.
118 Frew T, Watsford C, Walker I. Gender Dysphoria and psychiatric Comorbidities in childhood: a systematic review. *Austr J Psychol* 2021;73:255–71.
119 Thrower E, Bretherton I, Pang KC, *et al*. Prevalence of autism spectrum disorder and attention-deficit hyperactivity disorder amongst individuals with gender Dysphoria: A systematic review. *J Autism Dev Disord* 2020;50:695–706.
120 López-Gil JF, García-Hermoso A, Smith L, *et al*. Global proportion of disordered eating in children and adolescents: A systematic review and meta-analysis. *JAMA Pediatr* 2023;177:363–72.
121 Thoma BC, Rezeppa TL, Choukas-Bradley S, *et al*. Disparities in childhood abuse between Transgender and Cisgender adolescents. *Pediatrics* 2021;148:e2020016907.
122 Barth J, Bermetz L, Heim E, *et al*. The current prevalence of child sexual abuse worldwide: a systematic review and meta-analysis. *Int J Public Health* 2013;58:469–83.
123 Broekhof R, Nordahl HM, Bjørnelv S, *et al*. Prevalence of adverse childhood experiences and their Co-occurrence in a large population of adolescents: a young HUNT 3 study. *Soc Psychiatry Psychiatr Epidemiol* 2022;57:2359–66.
124 Carlson JS, Yohannan J, Darr CL, *et al*. Prevalence of adverse childhood experiences in school-aged youth: a systematic review (1990–2015). *Int J School Educat Psychol* 2020;8:2–23.
125 Feil K, Riedl D, Böttcher B, *et al*. Higher prevalence of adverse childhood experiences in Transgender than in Cisgender individuals: results from a single-center observational study. *J Clin Med* 2023;12:4501.

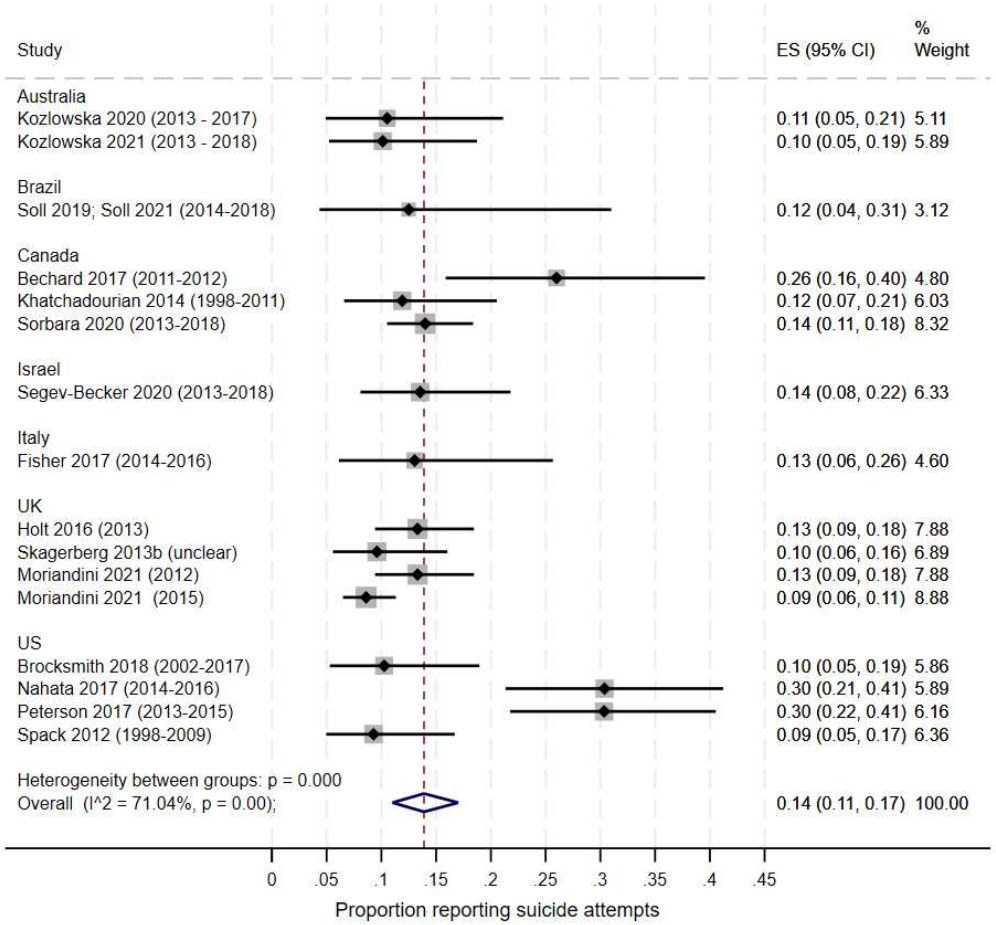
Proportion of children/adolescents at referral to gender service who report socially transitioning



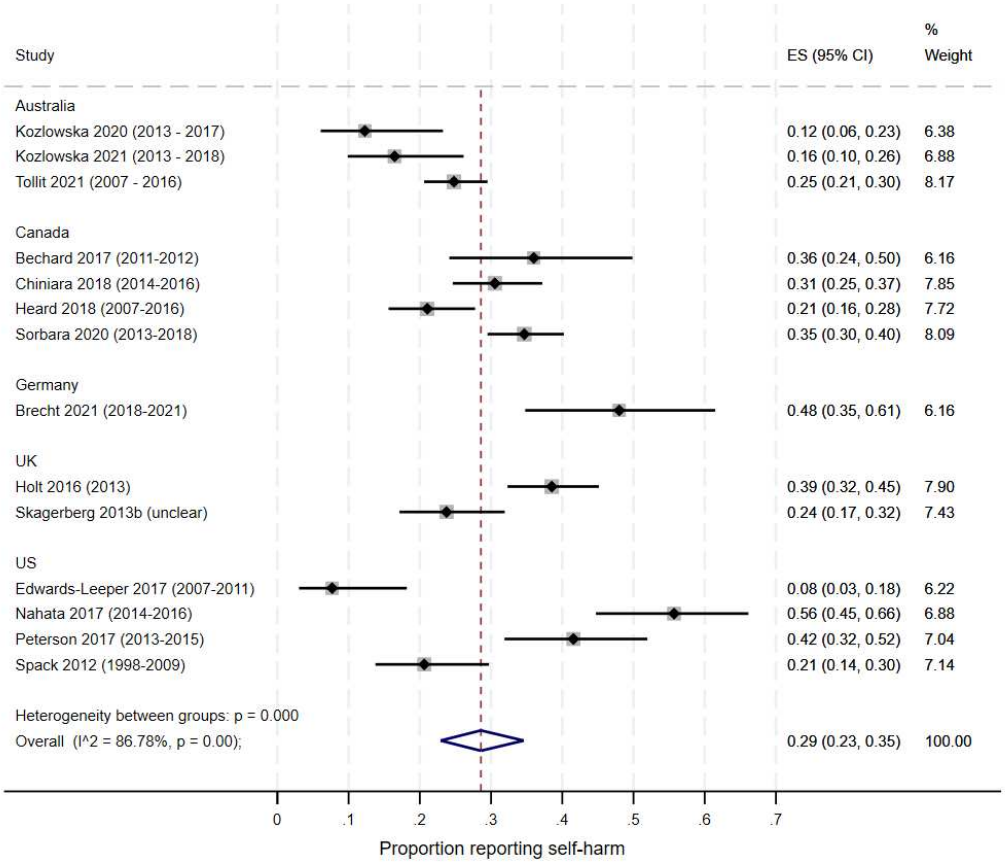
Proportion of children/adolescents with eating disorder at referral to gender service



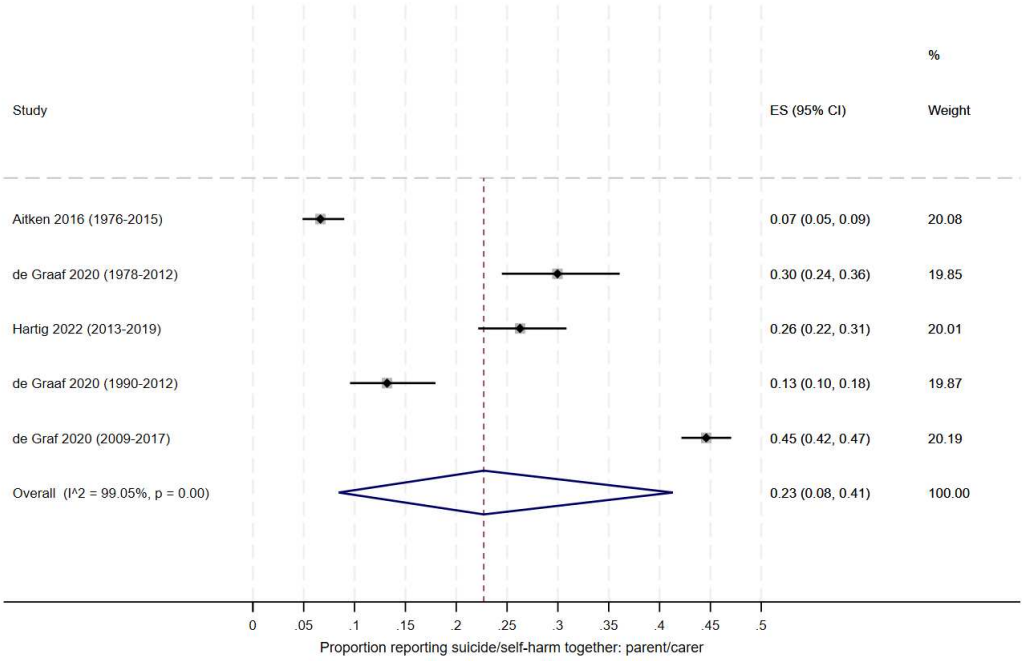
Proportion of children/adolescents at referral to gender service reporting suicidal attempt(s)



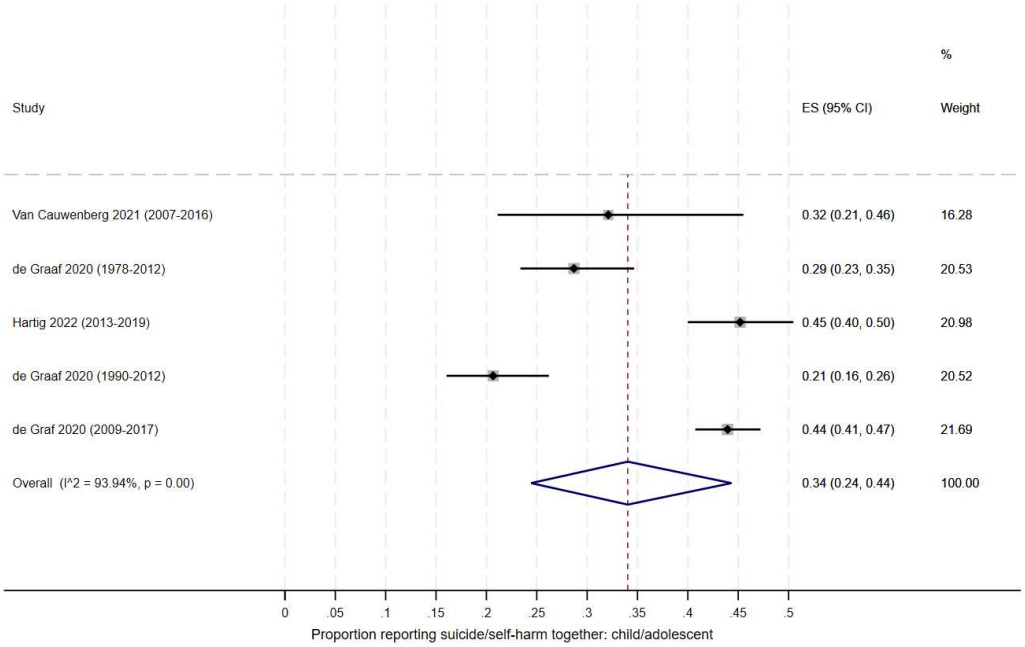
Proportion of children/adolescents at referral to gender service reporting self-harm



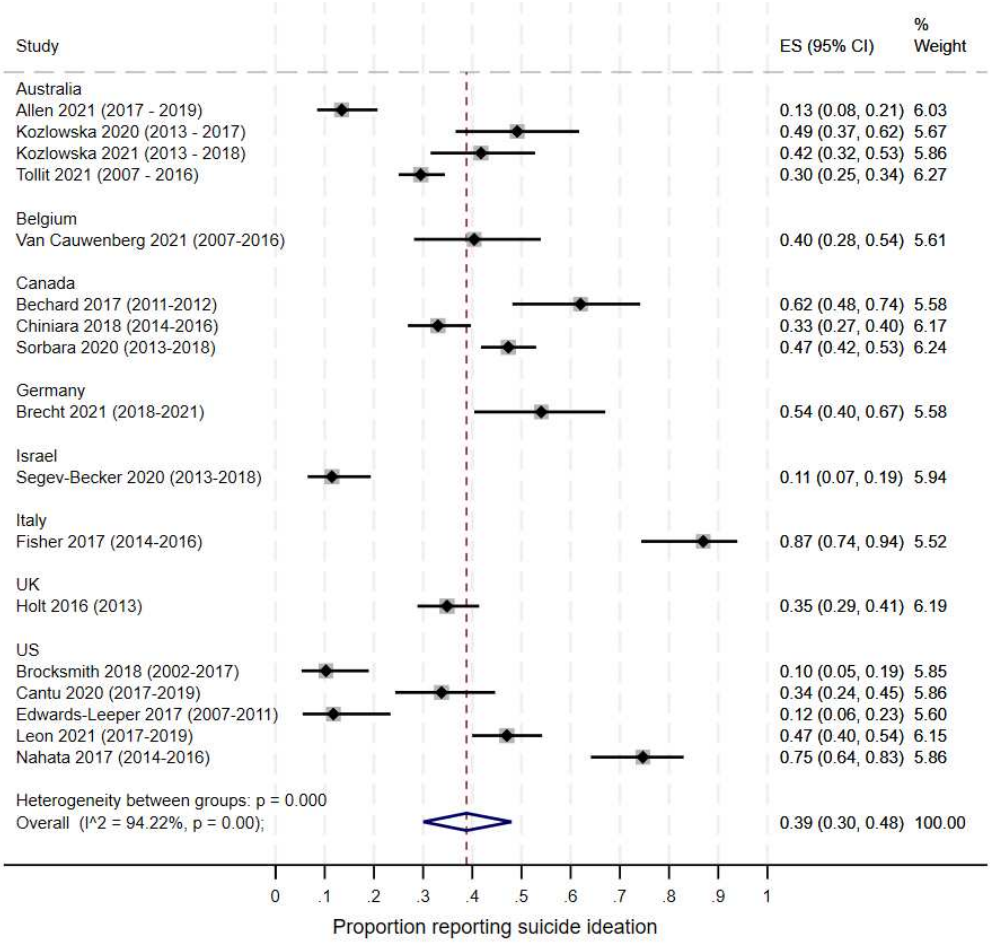
Proportion of children/adolescents at referral to gender service reporting suicide attempt and/or self-harm, as reported by parent/carer



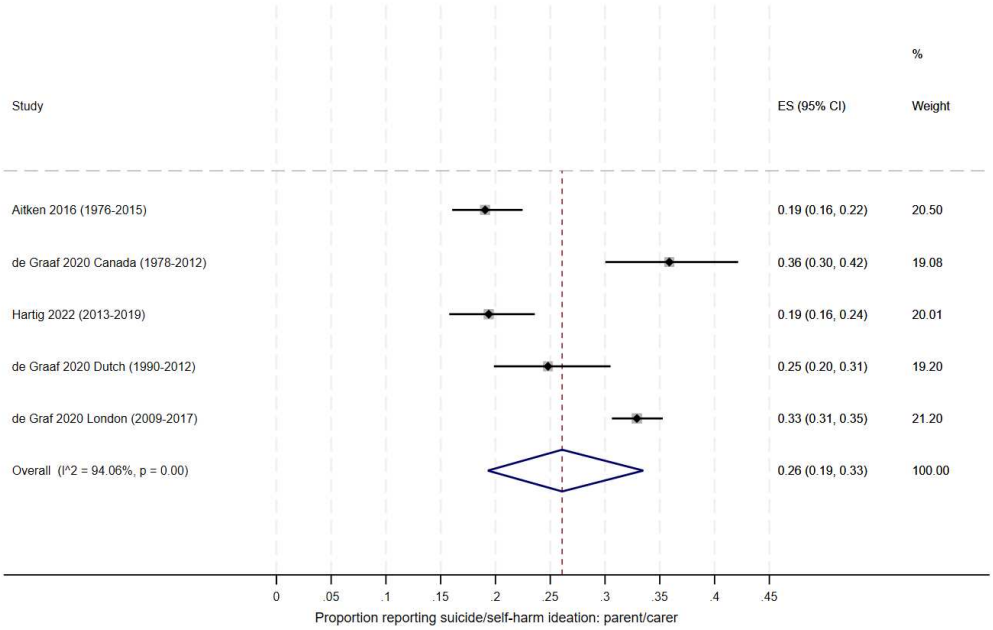
Proportion of children/adolescents at referral to gender service reporting suicide attempt and/or self-harm, as reported by child/adolescent



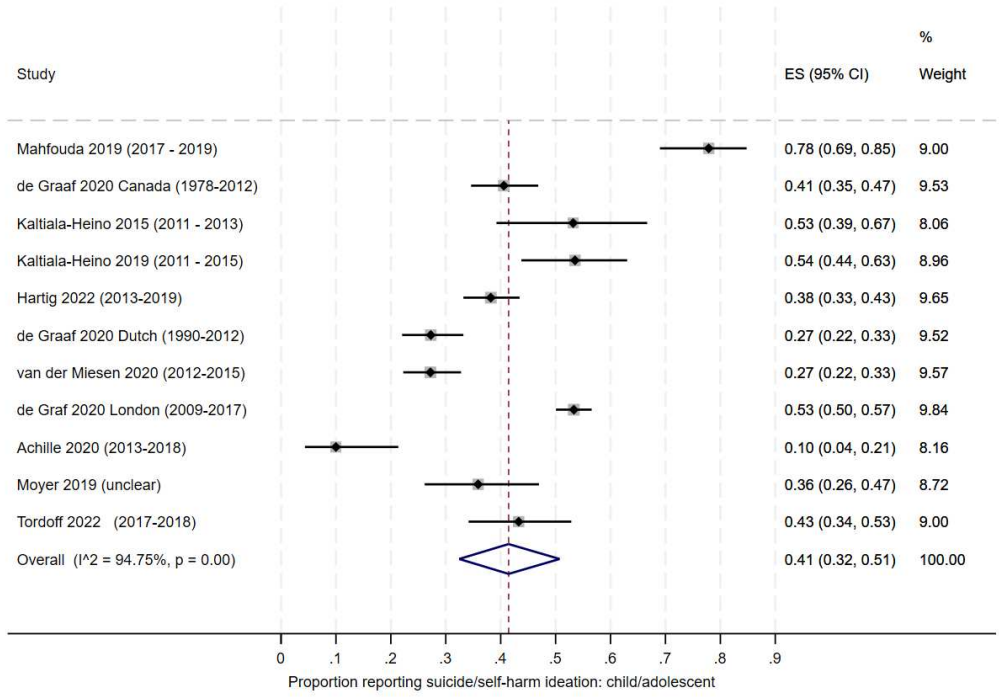
Proportion of children/adolescents at referral to gender service reporting suicide ideation



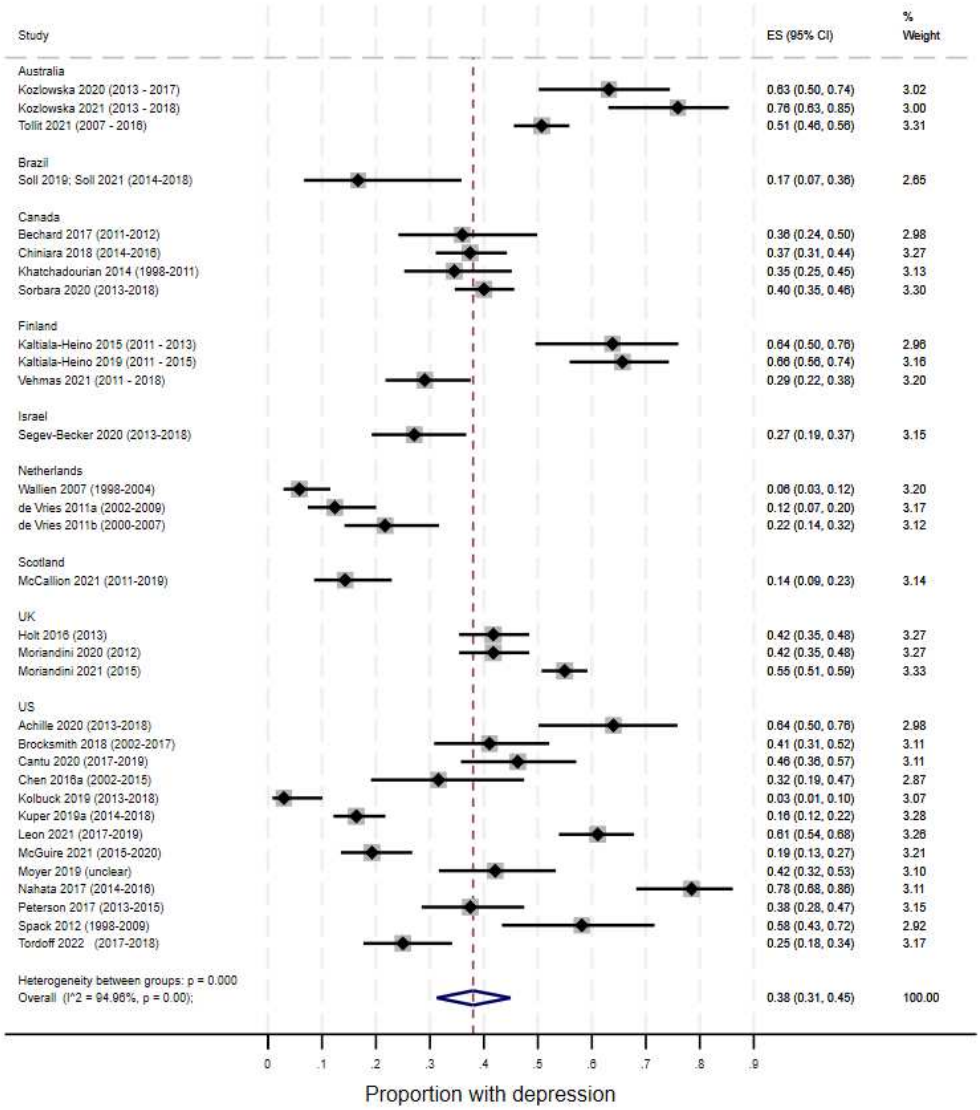
Proportion of children/adolescents at referral to gender service reporting suicide and/or self-harm ideation, as reported by parent/carer



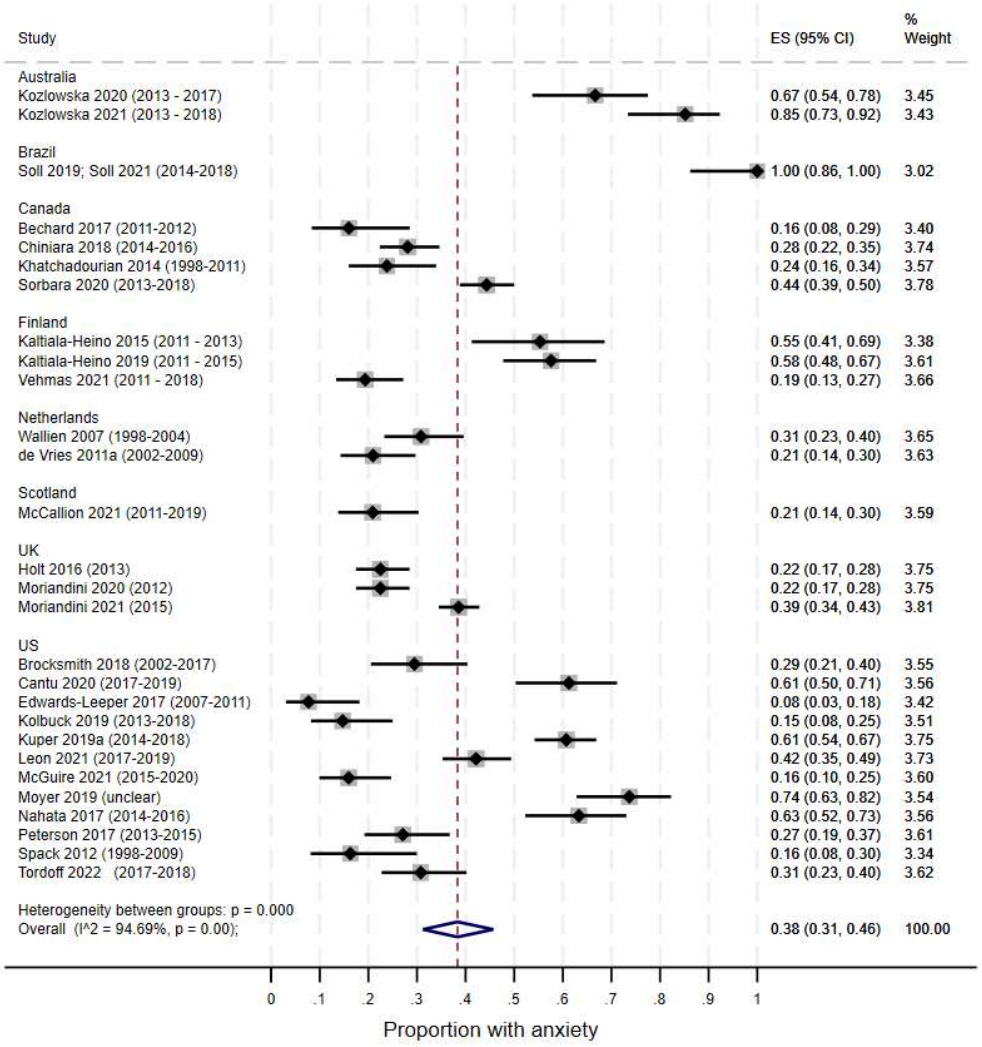
Proportion of children/adolescents at referral to gender service reporting suicide and/or self-harm ideation, as reported by child/adolescent



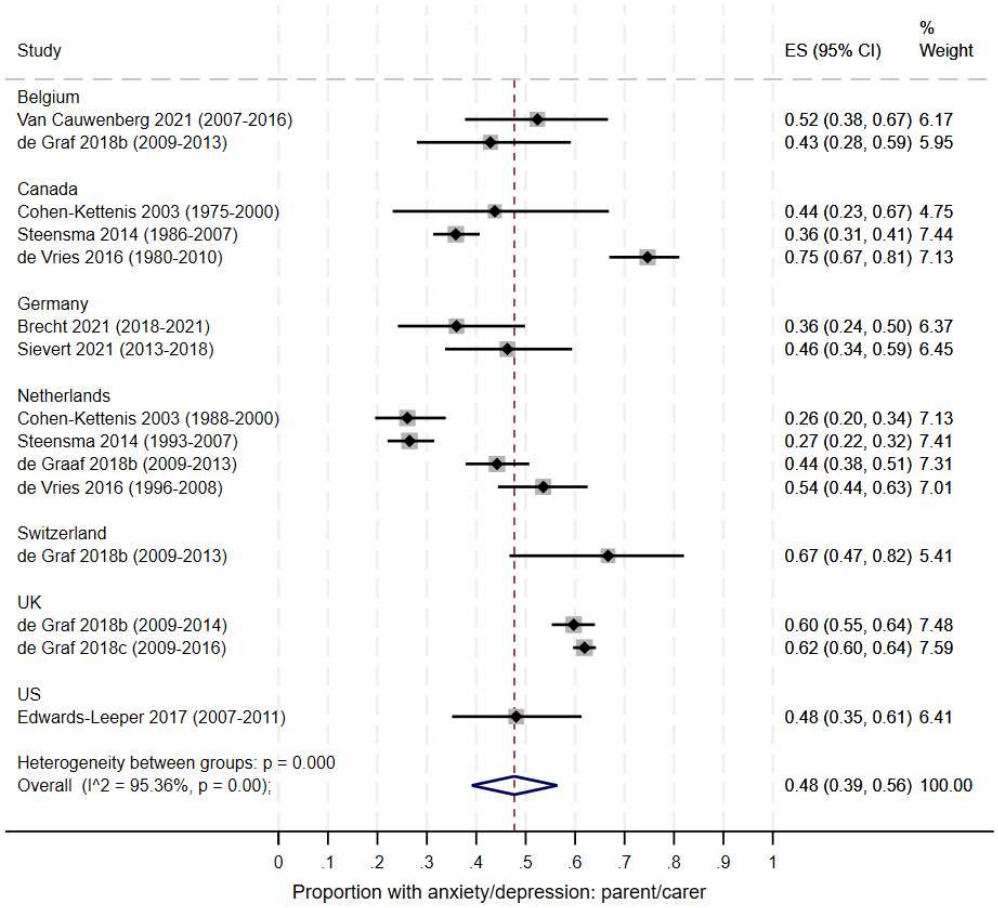
Proportion of children/adolescents with depression at referral to gender service



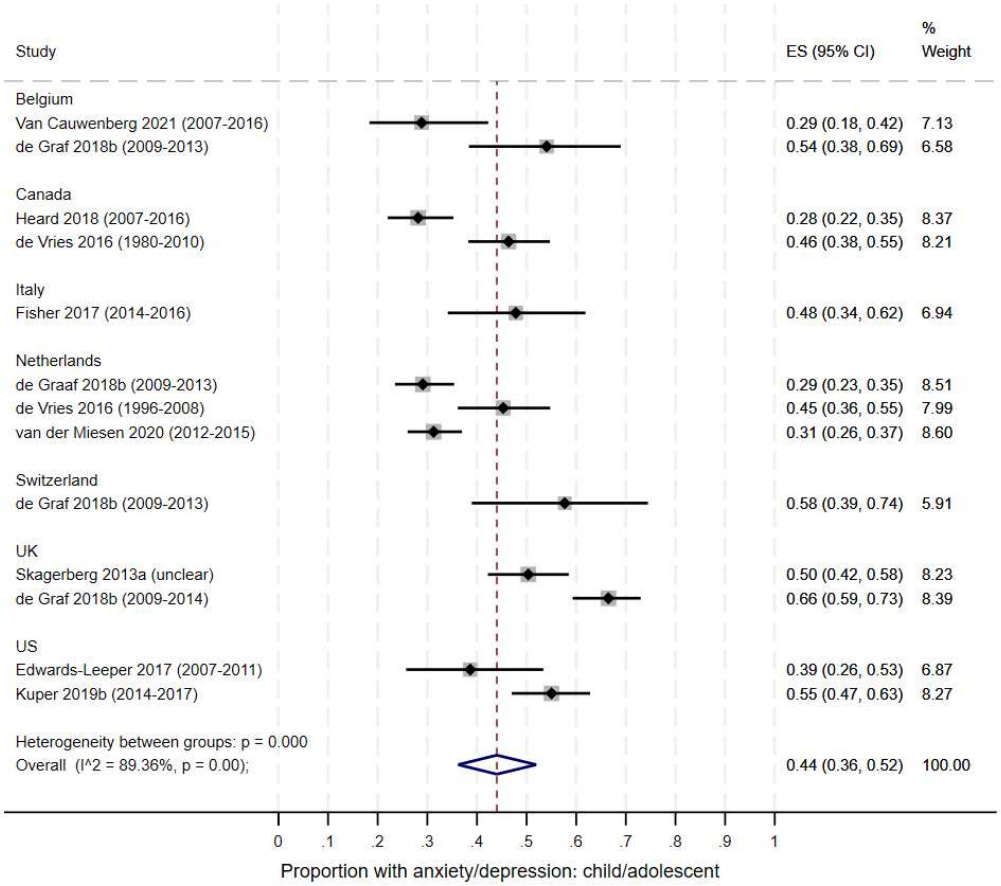
Proportion of children/adolescents with anxiety at referral to gender service



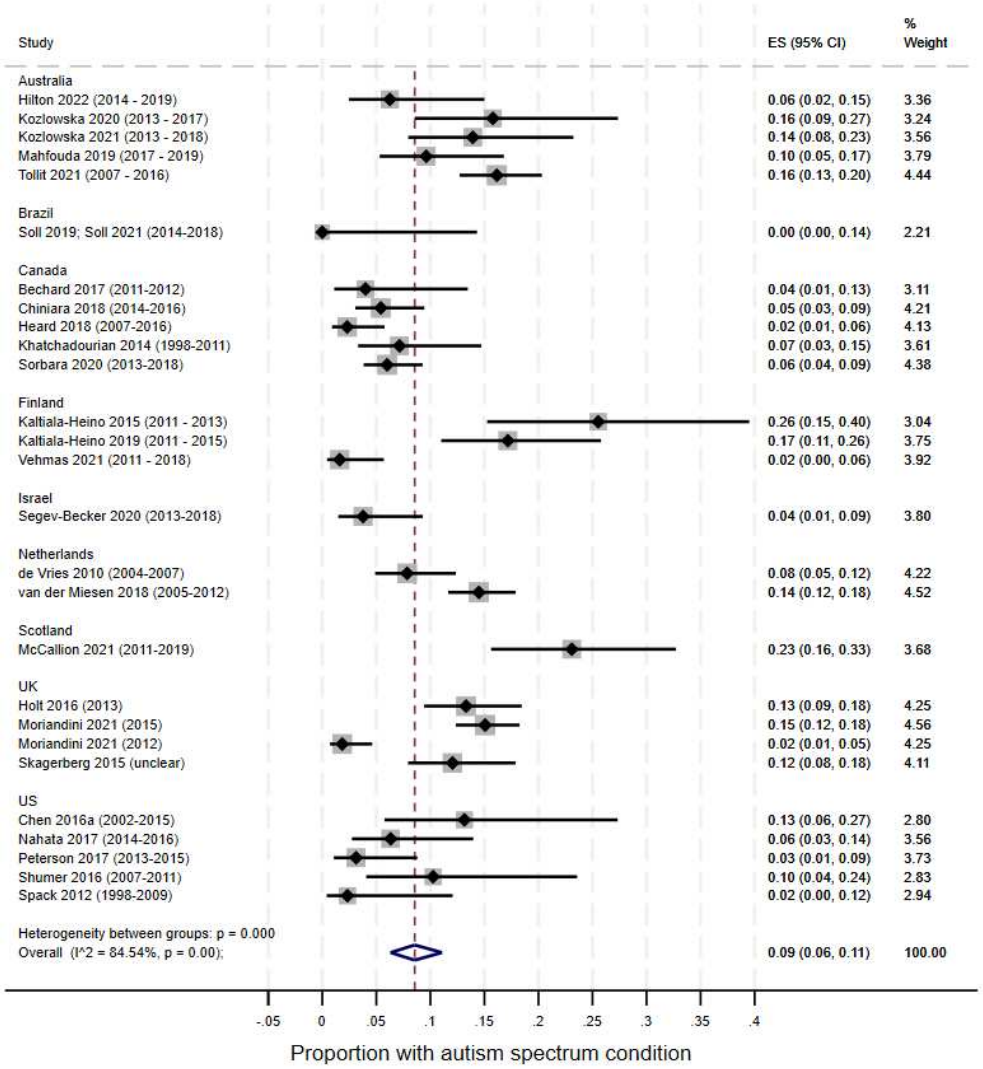
Proportion of children/adolescents with anxiety and/or depression at referral to gender service, as reported by parent/carer



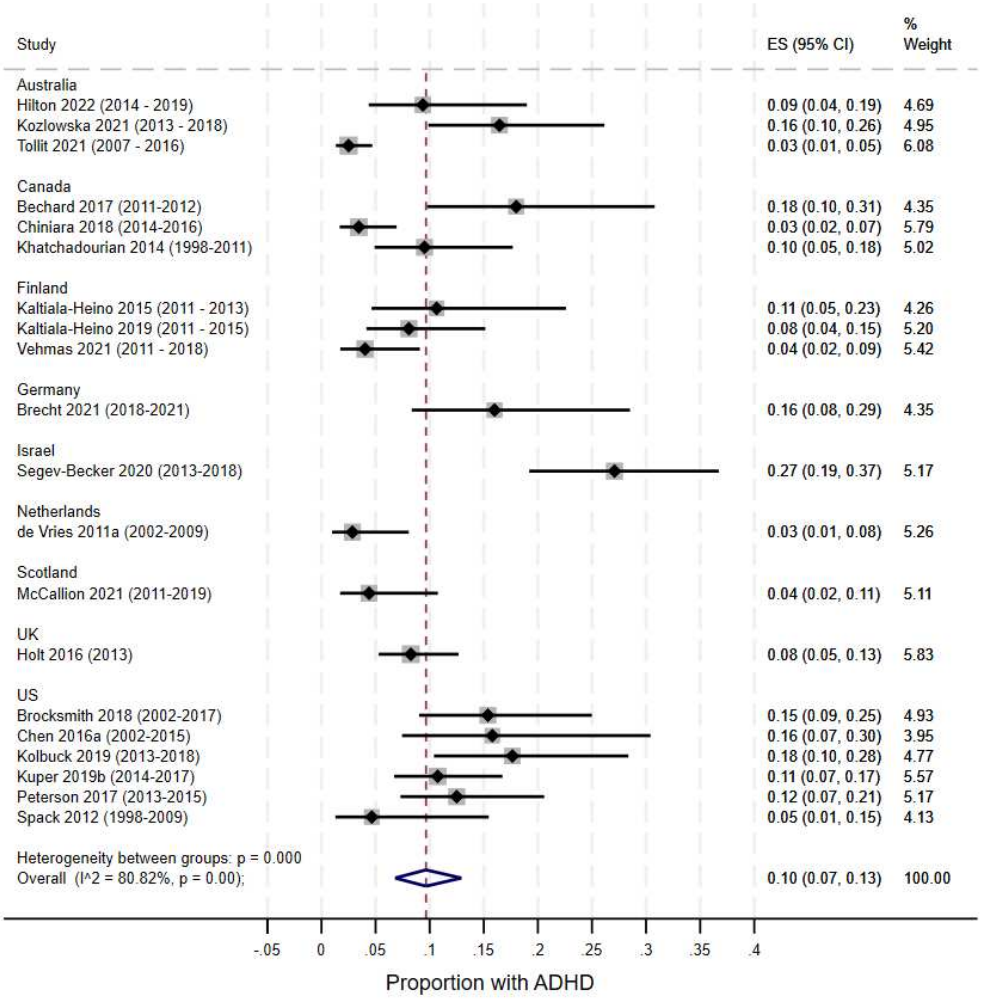
Proportion of children/adolescents with anxiety and/or depression at referral to gender service, as reported by child/adolescent



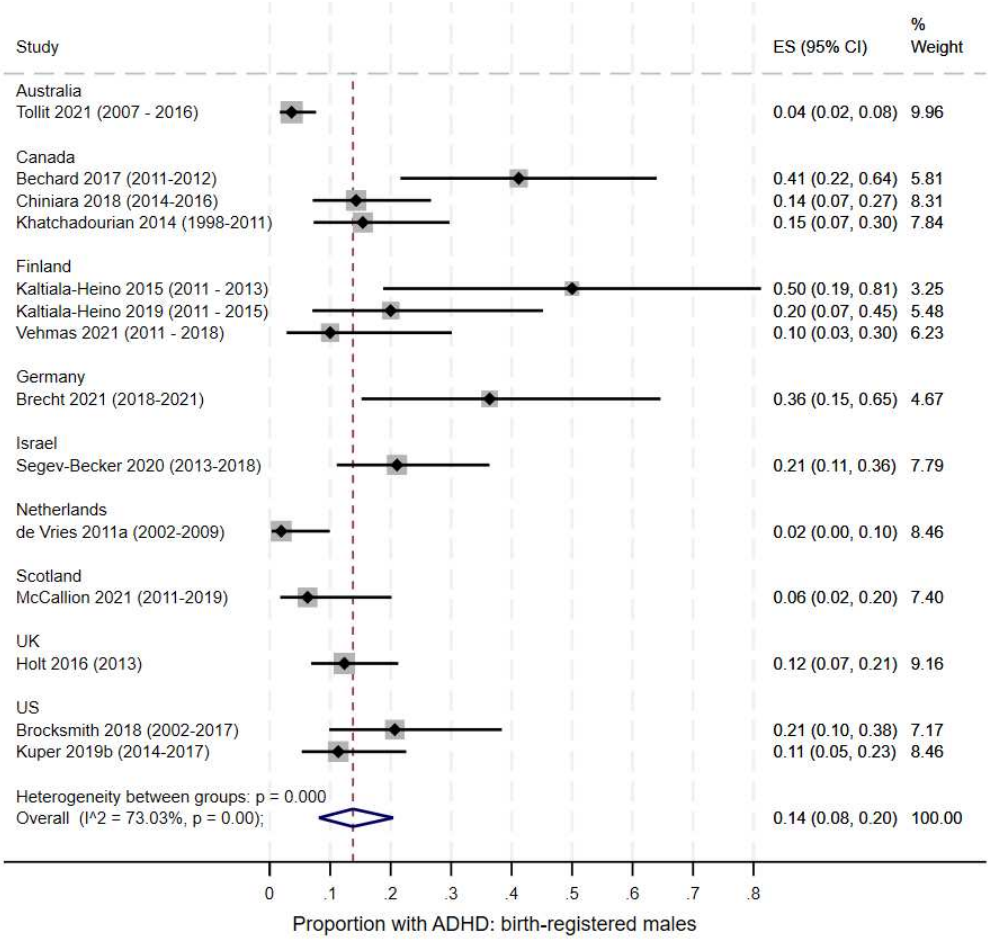
Proportion of children/adolescents with autism spectrum condition at referral to gender service



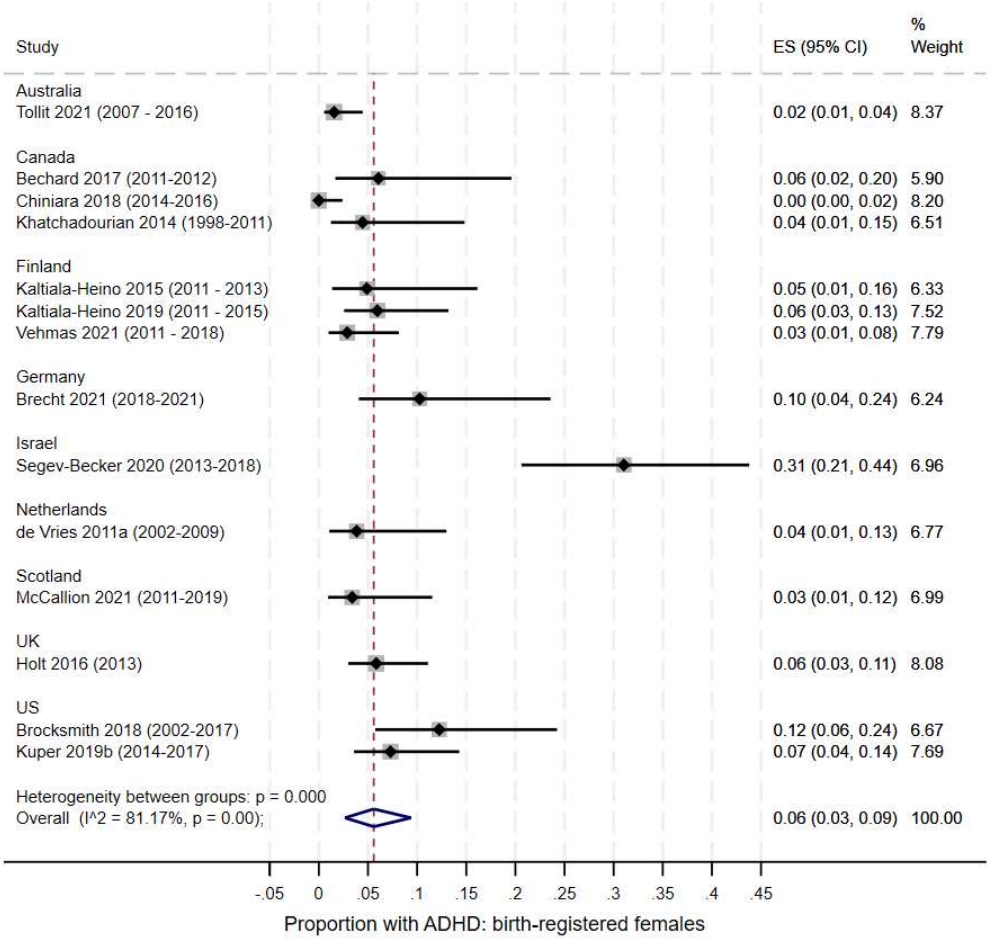
Proportion of children/adolescents with attention deficit hyperactivity disorder (ADHD) at referral to gender service



Proportion of birth-registered male children/adolescents with ADHD at referral to gender service



Proportion of birth-registered female children/adolescents with ADHD at referral to gender service



Supplementary Table S1: Final search strategy for Ovid MEDLINE

1 exp Child/ or Child Behavior/ or Child Health/ or Child Welfare/ or Psychology, Child/ or Child Psychiatry/ or Child Health Services/ or Child Development/ (1984459)
2 Minors/ (2638)
3 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or emerging adult$).ti,ab,kf,jn. (1862660)
4 (young$ adj (people$ or person$1 or adult$ or man$1 or men$1 or woman$ or women$ or male$1 or female$1)).ti,ab,kf,jn. (224878)
5 pediatrics/ (55388)
6 (pediatric$ or paediatric$ or peadiatric$).ti,ab,kf,jn. (543516)
7 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Psychology, Adolescent/ or Adolescent Psychiatry/ or Adolescent Health Services/ or Adolescent Medicine/ or Adolescent Development/ (2088552)
8 Puberty/ (13562)
9 (adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or underage$ or under-age$).ti,ab,kf,jn. (522801)
10 Schools/ or Schools, Nursery/ (42221)
11 exp Child Day Care Centers/ or Child Care/ (11287)
12 (school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1).ti,ab,kf,jn. (356157)
13 or/1-12 (4333601)
14 Gender Dysphoria/ (581)
15 "Sexual and Gender Disorders"/ (79)
16 Transsexualism/ (3895)
17 Transgender Persons/ (3835)
18 Health Services for Transgender Persons/ (152)
19 exp Sex Reassignment Procedures/ (969)
20 "Sexual and Gender Minorities"/ (4924)
21 ((gender$ and dysphori$) or (gender$ adj5 incongru$) or sexual dysphori$).ti,ab,kf. (1784)
22 (gender$ adj (disorder$ or identi$)).ti,ab,kf. or (gender identity/ and dysphori$.ti,ab,kf.) (4568)
23 (GID or GIDS or GIDC or GIDCS).ti,ab,kf. (456)
24 (gender$ adj5 (confusion or confused or questioning or distress$ or discomfort)).ti,ab,kf. (980)
25 (gender$ adj5 (minority or minorities)).ti,ab,kf. (1593)
26 (gender$ adj5 (variant$ or variance$ or nonconform$ or non-conform$ or diverse or diversity or atypical$)).ti,ab,kf. (3409)
27 (non-binary or nonbinary or enby or genderqueer or gender-queer or neutrois).ti,ab,kf. (796)
28 (agender$ or genderless$ or gender-less$ or genderfree or gender-free or ungender$ or un-gender$ or non-gender$ or nongender$ or bigender$ or bi-gender$ or dual gender$ or dualgender$ or demi-gender$ or demigender$ or genderfluid$ or gender-fluid$ or trigender$ or tri-gender$).ti,ab,kf. (315)
29 two spirit$.ti,ab,kf. (84)
30 (trans adj3 (female$ or feminin$ or woman$ or women$ or male$1 or man or mans or men or mens or masculin$ or person$1 or peopl$ or population$ or individual$)).ti,ab,kf. (1362)
31 (transgend$ or trans-gend$ or transex$ or transsex$ or trans-sex$ or transfemale$ or transfeminin$ or transwom$ or transmale$ or transman$ or transmasculin$ or transmen$ or transperson$ or transpeopl$ or transpopulation$ or transindividual$).ti,ab,kf. (10832)

32 (trans adj3 identi$).ti,ab,kf. or (gender identity/ and trans.ti,ab,kf.) or (trans and dysphori$).ti,ab,kf. (1447)
33 (crossgender$ or cross-gender$ or crossex$ or crosssex$ or cross-sex$).ti,ab,kf. (836)
34 ((sex or gender$) adj3 (reassign$ or re-assign$ or affirm$ or confirm$ or transition$)).ti,ab,kf. (3963)
35 ((gender$ or sex) adj (change or changes or changing or changed)).ti,ab,kf. (825)
36 (detransition$ or de-transition$ or desister$ or de-sister$).ti,ab,kf. (134)
37 ((desist$ or persist$) adj5 (transition$ or trans or dysphori$)).ti,ab,kf. (823)
38 or/14-37 (28731)
39 (trans and (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ti. (339)
40 (trans adj5 (child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or young$ people$ or young$ person$ or young$ adult$ or young$ man$1 or young$ men$1 or young$ woman$ or young$ women$ or young$ male$1 or young$ female$ or adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or emerging adult$ or underage$ or under-age$ or school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1 or pediatric$ or paediatric$ or peadiatric$)).ab,kf. (397)
41 (transchild$ or transminor$ or transboy$ or transgirl$ or transkid or transkids or transyoung$ or transyouth$ or transteen$ or transtween$ or transadoles$ or transjuvenil$).ti,ab,kf. (15)
42 13 and 38 (9819)
43 39 or 40 or 41 or 42 (10343)
44 exp animals/ not humans/ (4823832)
45 (editorial or news or comment or case reports).pt. or case report.ti. (3692318)
46 43 not (44 or 45) (9429)
47 limit 46 to english language (9029)

Key to Ovid symbols and commands:

$	Unlimited right-hand truncation symbol
$N	Limited right-hand truncation - restricts the number of characters following the word to N
ti,ab,kf,	Searches are restricted to the Title (ti), Abstract (ab), Keyword Heading Word (kf) fields
.jn	Searches are restricted to the Journal name field
adj	Retrieves records that contain terms next to each other (in the shown order)
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-12	Combines sets 1 to 12 using OR

Supplementary Table S2 - Summary of included studies

Study ID	Country	Multiple country studies	Study title	Doi / weblink
Allen 2021	Australia		A Waitlist Intervention for Transgender Young People and Psychosocial Outcomes	https://doi.org/10.1542/peds.2020-042762
Hilton 2022	Australia		The co-occurrence of neurodevelopmental disorders in gender dysphoria: Characteristics within a paediatric treatment-seeking cohort and factors that predict distress pertaining to gender	https://doi.org/10.1016/j.jpsychires.2022.02.018
Kozlowska 2020	Australia		Attachment Patterns in Children and Adolescents With Gender Dysphoria	https://doi.org/10.3389/fpsyg.2020.582688
Kozlowska 2021	Australia		Australian children and adolescents with gender dysphoria: Clinical presentations and challenges experienced by a multidisciplinary team and gender service	https://doi.org/10.1177/26344041211010777
Mahfouda 2019	Australia		Mental Health Correlates of Autism Spectrum Disorder in Gender Diverse Young People: Evidence from a Specialised Child and Adolescent Gender Clinic in Australia	https://doi.org/10.3390/jcm8101503
Tollit 2019	Australia		What are the health outcomes of trans and gender diverse young people in Australia? Study protocol for the Trans20 longitudinal cohort study	http://dx.doi.org/10.1136/bmjopen-2019-032151
Tollit 2021	Australia		The clinical profile of patients attending a large Australian pediatric gender service: a 10-year review	https://doi.org/10.1080/26895269.2021.1939221
Van Cauwenberg 2021	Belgium		Ten years of experience in counseling gender diverse youth in Flanders, Belgium. A clinical overview	https://doi.org/10.1038/s41443-021-00441-8
Soll 2019	Brazil		Use of the House-Tree-Person Projective Drawings and Parental Styles Inventory in the Global Psychological Evaluation of Transgender Youth Who Seek Healthcare at the Gender Identity Program	https://doi.org/10.3389/fpsyg.2019.02488
Soll 2021	Brazil		Descriptive Study of Transgender Youth Receiving Health Care in the Gender Identity Program in Southern Brazil	https://doi.org/10.3389/fpsyt.2021.627661
Aitken 2016	Canada		Self-Harm and Suicidality in Children Referred for Gender Dysphoria	https://doi.org/10.1016/j.jaac.2016.04.001
Bechard 2017	Canada		Psychosocial and Psychological Vulnerability in Adolescents with Gender Dysphoria: A "Proof of Principle" Study	https://doi.org/10.1080/0092623X.2016.1232325
Bradley 1978	Canada		Gender Identity Problems of Children and Adolescents the Establishment of a Special Clinic	https://doi.org/10.1177/070674377802300309
Chiniara 2018	Canada		Characteristics of Adolescents Referred to a Gender Clinic: Are Youth Seen Now Different from Those in Initial Reports?	https://doi.org/10.1159/000489608
Chiu 2006	Canada		Sex-Dimorphic Color Preference in Children with Gender Identity Disorder: A Comparison to Clinical and Community Controls	https://doi.org/10.1007/s11199-006-9089-9
Feder 2017	Canada		Exploring the association between eating disorders and gender dysphoria in youth	https://doi.org/10.1080/10640266.2017.1297112
Fridell 2006	Canada		The Playmate and Play Style Preferences Structured Interview: A Comparison of Children with Gender Identity Disorder and Controls	https://doi.org/10.1007/s10508-006-9085-8
Heard 2018	Canada		Gender dysphoria assessment and action for youth: Review of health care services and experiences of trans youth in Manitoba	https://doi.org/10.1093/pch/pxx156
Hughes 2017	Canada		The Prevalence of Only-Child Status Among Children and Adolescents Referred to a Gender Identity Service Versus a Clinical Comparison Group	https://doi.org/10.1080/0092623X.2016.1208702
Johnson 2004	Canada		A Parent-Report Gender Identity Questionnaire for Children	https://doi.org/10.1023/B:ASEB.0000014325.68094.f3
Khatchadourian 2014	Canada		Clinical Management of Youth with Gender Dysphoria in Vancouver	https://doi.org/10.1016/j.jpeds.2013.10.068
Singh 2010	Canada		The Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults: Further Validity Evidence	https://doi.org/10.1080/00224490902898728
Sorbara 2020	Canada		Mental Health and Timing of Gender-Affirming Care	https://doi.org/10.1542/peds.2019-3600
Wood 2013	Canada		Patterns of Referral to a Gender Identity Service for Children and Adolescents (1976–2011): Age, Sex Ratio, and Sexual Orientation	https://doi.org/10.1080/0092623X.2012.675022
Zucker 1982	Canada		Sex-Typed Play in Gender-Disturbed Children: A Comparison to Sibling and Psychiatric Controls	https://doi.org/10.1007/BF01541592
Zucker 1983	Canada		Human Figure Drawings of Gender-Problem Children: A Comparison to Sibling, Psychiatric, and Normal Controls	https://doi.org/10.1007/BF00912092
Zucker 1984	Canada		Two Subgroups of Gender-Problem Children	https://doi.org/10.1007/BF01542975
Zucker 1985	Canada		Sex-typed Behavior in Cross-Gender-Identified Children: Stability and Change at a One-Year Follow-up	https://doi.org/10.1016/S0002-7138(10)60114-8
Zucker 1992	Canada		Sex-Typed Responses in the Rorschach Protocols of Children With Gender Identity Disorder	https://doi.org/10.1207/s15327752jpa5802_9
Zucker 1993	Canada		A Gender Identity Interview for Children	https://doi.org/10.1207/s15327752jpa6103_2
Zucker 1997	Canada		Sex Differences in Referral Rates of Children with Gender Identity Disorder: Some Hypotheses	https://doi.org/10.1023/A:1025748032640
Zucker 1999	Canada		Gender Constancy Judgments in Children with Gender Identity Disorder: Evidence for a Developmental Lag	https://doi.org/10.1023/A:1018713115866
Zucker 2002	Canada		Gender-Dysphoric Children and Adolescents: A Comparative Analysis of Demographic Characteristics and Behavioral Problems	https://doi.org/10.1177/135910450200700307
Zucker 2010	Canada		Puberty-Blocking Hormonal Therapy for Adolescents with Gender Identity Disorder: A Descriptive Clinical Study	https://doi.org/10.1080/19359705.2011.530574
Zucker 2012a	Canada		Demographics, Behavior Problems, and Psychosexual Characteristics of Adolescents with Gender Identity Disorder or Transvestic Fetishism	https://doi.org/10.1080/0092623X.2011.611219
Zucker 2012b	Canada		A Developmental, Biopsychosocial Model for the Treatment of Children with Gender Identity Disorder	https://doi.org/10.1080/00918369.2012.653309
Zucker 2017	Canada		Intense/obsessional interests in children with gender dysphoria: a cross-validation study using the Teacher's Report Form	https://doi.org/10.1186/s13034-017-0189-9
VanderLaan 2015a	Canada		Birth Weight and Two Possible Types of Maternal Effects on Male Sexual Orientation: A Clinical Study of Children and Adolescents Referred to a Gender Identity Service	https://doi.org/10.1002/dev.21254
VanderLaan 2015c	Canada		Do children with gender dysphoria have intense/obsessional interests?	https://doi.org/10.1080/00224499.2013.860073
Kaltiala-Heino 2015	Finland		Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development	https://doi.org/10.1186/s13034-015-0042-y
Kaltiala-Heino 2019	Finland		Sexual experiences of clinically referred adolescents with features of gender dysphoria	https://doi.org/10.1177/1359104519827069
Sumia 2017	Finland		Current and recalled childhood gender identity in community youth in comparison to referred adolescents seeking sex reassignment	https://doi.org/10.1016/j.adolescence.2017.01.006
Vehmas 2021	Finland		Somatic Health and Psychosocial Background Among Finnish Adolescents with Gender Dysphoria Seeking Hormonal Interventions	https://doi.org/10.1089/trgh.2021.0084
Becker-Hebly 2020	Germany		Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: a descriptive study from the Hamburg Gender Identity Service	https://doi.org/10.1007/s00787-020-01640-2
Brecht 2021	Germany		Assessment of Psychological Distress and Peer Relations among Trans Adolescents—An Examination of the Use of Gender Norms and Parent–Child Congruence of the YSR-R/CBCL-R among a Treatment-Seeking Sample	https://doi.org/10.3390/children8100864
Hartig 2022	Germany		Suicidal and nonsuicidal self-harming thoughts and behaviors in clinically referred children and adolescents with gender dysphoria	https://doi.org/10.1177/13591045211073941
Levitan 2019	Germany		Risk factors for psychological functioning in German adolescents with gender dysphoria: poor peer relations and general family functioning	https://doi.org/10.1007/s00787-019-01308-6
Nieder 2021	Germany		Individual Treatment Progress Predicts Satisfaction With Transition-Related Care for Youth With Gender Dysphoria: A Prospective Clinical Cohort Study	https://doi.org/10.1016/j.jsxm.2020.12.010
Roder 2018	Germany		Health-related quality of life in transgender adolescents: Associations with body image and emotional and behavioral problems	https://doi.org/10.1080/15532739.2018.1425649
Sievert 2021	Germany		Not social transition status, but peer relations and family functioning predict psychological functioning in a German clinical sample of children with Gender Dysphoria	https://doi.org/10.1177/1359104520964530
Segev-Becker 2020	Israel		Children and Adolescents with Gender Dysphoria in Israel: Increasing Referral and Fertility Preservation Rates	https://doi.org/10.4158/EP-2019-0418
Fisher 2017	Italy		Psychological characteristics of Italian gender dysphoric adolescents: a case–control study	https://doi.org/10.1007/s40618-017-0647-5
Mirabella 2022	Italy		Gender Identity and Non-Binary Presentations in Adolescents Attending Two Specialized Services in Italy	https://doi.org/10.1016/j.jsxm.2022.03.215
Ristori 2021	Italy		Sexual habits among Italian transgender adolescents: a cross-sectional study	https://doi.org/10.1038/s41443-021-00427-6
Aitken 2015	Multiple	Canada, Netherlands	Evidence for an Altered Sex Ratio in Clinic-Referred Adolescents with Gender Dysphoria	https://doi.org/10.1111/jsm.12817

Cohen-Kettenis 2003	Multiple	Canada, Netherlands	Demographic Characteristics, Social Competence, and Behavior Problems in Children With Gender Identity Disorder: A Cross-National, Cross-Clinic Comparative Analysis	https://doi.org/10.1023/A:1021769215342
Cohen-Kettenis 2006	Multiple	Canada, Netherlands	A Parent-report Gender Identity Questionnaire for Children: A Cross-national, Cross-clinic Comparative Analysis	https://doi.org/10.1177/1359104506059135
deGraaf 2018b	Multiple	Belgium, Netherlands, Switzerland, UK	Psychological functioning in adolescents referred to specialist gender identity clinics across Europe: a clinical comparison study between four clinics	https://doi.org/10.1007/s00787-017-1098-4
deGraaf 2020	Multiple	Canada, Netherlands, UK	Suicidality in clinic-referred transgender adolescents	https://link.springer.com/article/10.1007/s00787-020-01663-9
deVries 2016	Multiple	Canada, Netherlands	Poor peer relations predict parent- and self-reported behavioral and emotional problems of adolescents with gender dysphoria: a cross-national, cross-clinic comparative analysis	https://doi.org/10.1007/s00787-015-0764-7
Kaltiala 2020	Multiple	Denmark, Finland, Norway, Sweden, UK	Time trends in referrals to child and adolescent gender identity services: a study in four Nordic countries and in the UK	https://doi.org/10.1080/08039488.2019.1667429
Pang 2020	Multiple	Australia, UK	Association of Media Coverage of Transgender and Gender Diverse Issues With Rates of Referral of Transgender Children and Adolescents to Specialist Gender Clinics in the UK and Australia	https://doi.org/10.1001/jamanetworkopen.2020.11161
Steensma 2014	Multiple	Canada, Netherlands	Behavioral and Emotional Problems on the Teacher's Report Form: A Cross-National, Cross-Clinic Comparative Analysis of Gender Dysphoric Children and Adolescents	https://doi.org/10.1007/s10802-013-9804-2
Wallien 2009	Multiple	Canada, Netherlands	Cross-National Replication of the Gender Identity Interview for Children	https://doi.org/10.1080/00223890903228463
Alberse 2019	Netherlands		Self-perception of transgender clinic referred gender diverse children and adolescents	https://doi.org/10.1177/1359104518825279
Arnoldussen 2020	Netherlands		Re-evaluation of the Dutch approach: are recently referred transgender youth different compared to earlier referrals?	https://doi.org/10.1007/s00787-019-01394-6
Bungener 2017	Netherlands		Sexual and Romantic Experiences of Transgender Youth Before Gender-Affirmative Treatment	https://doi.org/10.1542/peds.2016-2283
Cohen 1997	Netherlands		Psychological Functioning of Adolescent Transsexuals: Personality and Psychopathology	https://doi.org/10.1002/(SICI)1097-4679(199702)53:2%3C187::AID-JCLP12%3E3.0.CO;2-G
deVries 2010	Netherlands		Autism Spectrum Disorders in Gender Dysphoric Children and Adolescents	https://doi.org/10.1007/s10803-010-0935-9
deVries 2011a	Netherlands		Psychiatric comorbidity in gender dysphoric adolescents	https://doi.org/10.1111/j.1469-7610.2011.02426.x
deVries 2011b	Netherlands		Comparing adult and adolescent transsexuals: An MMPI-2 and MMPI-A study	https://doi.org/10.1016/j.psychres.2010.07.033
deVries 2012	Netherlands		Clinical Management of Gender Dysphoria in Children and Adolescents: The Dutch Approach	https://doi.org/10.1080/00918369.2012.653300
Rijn 2013	Netherlands		Self-perception in a clinical sample of gender variant children	https://doi.org/10.1177/1359104512460621
Schagen 2012	Netherlands		Sibling Sex Ratio and Birth Order in Early-Onset Gender Dysphoric Adolescents	https://doi.org/10.1007/s10508-011-9777-6
Steensma 2013	Netherlands		Factors Associated With Desistence and Persistence of Childhood Gender Dysphoria: A Quantitative Follow-Up Study	https://doi.org/10.1016/j.jaac.2013.03.016
van der Miesen 2018	Netherlands		Autistic Symptoms in Children and Adolescents with Gender Dysphoria	https://doi.org/10.1007/s10803-017-3417-5
van der Miesen 2020	Netherlands		Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers	https://doi.org/10.1016/j.jadohealth.2019.12.018
Verveen 2021	Netherlands		Body image in children with gender incongruence	https://doi.org/10.1177/13591045211000797
Wallien 2007	Netherlands		Psychiatric Comorbidity Among Children With Gender Identity Disorder	https://doi.org/10.1097/chi.0b013e3181373848
Wallien 2008	Netherlands		Psychosexual Outcome of Gender<Dysphoric Children	https://doi.org/10.1097/CHI.0b013e31818956b9
Wallien 2010	Netherlands		Peer Group Status of Gender Dysphoric Children: A Sociometric Study	https://doi.org/10.1007/s10508-009-9517-3
Wiepjes 2018	Netherlands		The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets	https://doi.org/10.1016/j.jsxm.2018.01.016
McCallion 2021	Scotland		An appraisal of current service delivery and future models of care for young people with gender dysphoria	https://doi.org/10.1007/s00431-021-04075-2
DeCastro 2022	Spain		High persistence in Spanish transgender minors: 18 years of experience of the Gender Identity Unit of Catalonia	https://doi.org/10.1016/j.rpsm.2022.02.001
EstevadeAntonio 2013	Spain		Coordination of healthcare for transsexual persons: a multidisciplinary approach	https://doi.org/10.1097/01.med.0000436182.42966.31
Butler 2018	UK		Assessment and support of children and adolescents with gender dysphoria	http://dx.doi.org/10.1136/archdischild-2018-314992
Costa 2015	UK		Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria	https://doi.org/10.1111/jsm.13034
deGraaf 2018a	UK		Evidence for a Change in the Sex Ratio of Children Referred for Gender Dysphoria: Data From the Gender Identity Development Service in London (2000-2017)	https://doi.org/10.1016/j.jsxm.2018.08.002
deGraaf 2018c	UK		Sex Ratio in Children and Adolescents Referred to the Gender Identity Development Service in the UK (2009–2016)	https://doi.org/10.1007/s10508-018-1204-9
deGraaf 2019	UK		Thinking about ethnicity and gender diversity in children and young people	https://doi.org/10.1177/1359104518805801
Holt 2016	UK		Young people with features of gender dysphoria: Demographics and associated difficulties	https://doi.org/10.1177/1359104514558431
Matthews 2019	UK		Gender Dysphoria in lookedafter and adopted young people in a gender identity development service	https://doi.org/10.1177/1359104518791657
Morandini 2021	UK		Shifts in demographics and mental health co-morbidities among gender dysphoric youth referred to a specialist gender dysphoria service	https://doi.org/10.1177/13591045211046813
Skagerberg 2013a	UK		Internalizing and Externalizing Behaviors in a Group of Young People with Gender Dysphoria	https://doi.org/10.1080/15532739.2013.822340
Skagerberg 2013b	UK		Self-Harming Thoughts and Behaviors in a Group of Children and Adolescents with Gender Dysphoria	https://doi.org/10.1080/15532739.2013.817321
Skagerberg 2015	UK		Brief Report: Autistic Features in Children and Adolescents with Gender Dysphoria	https://doi.org/10.1007/s10803-015-2413-x
Twist 2019	UK		Gender diversity and non-binary presentations in young people attending the United Kingdom's National Gender Identity Development Service	https://doi.org/10.1177/1359104518804311
Achille 2020	US		Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results	https://doi.org/10.1186/s13633-020-00078-2
Brocksmith 2018	US		Baseline characteristics of gender dysphoric youth	https://doi.org/10.1515/jpem-2018-0250
Cantu 2020	US		Changes in Anxiety and Depression from Intake to First Follow-Up Among Transgender Youth in a Pediatric Endocrinology Clinic	https://doi.org/10.1089/trgh.2019.0077
Chen 2016a	US		Characteristics of Referrals for Gender Dysphoria Over a 13-Year Period	https://doi.org/10.1016%2Fj.jadohealth.2015.11.010
Chen 2016b	US		Multidisciplinary Care for Gender-Diverse Youth: A Narrative Review and Unique Model of Gender-Affirming Care	https://doi.org/10.1089/trgh.2016.0009
Chodzen 2019	US		Minority Stress Factors Associated With Depression and Anxiety Among Transgender and Gender-Nonconforming Youth	https://doi.org/10.1016/j.jadohealth.2018.07.006
Cousino 2014	US		An Emerging Opportunity for Pediatric Psychologists: Our Role in a Multidisciplinary Clinic for Youth With Gender Dysphoria	https://psycnet.apa.org/doi/10.1037/cpp0000077
Edwards-Leeper 2017	US		Psychological Profile of the First Sample of Transgender Youth Presenting for Medical Intervention in a U.S. Pediatric Gender Center	https://psycnet.apa.org/doi/10.1037/sgd0000239
Fornander 2021	US		Weight Status, Medication Use, and Recreational Activities of Treatment-Naïve Transgender Youth	https://doi.org/10.1089/chi.2021.0155
Handler 2019	US		Trends in Referrals to a Pediatric Transgender Clinic	https://doi.org/10.1542/peds.2019-1368
Hedrick 2022	US		A New Virtual Reality: Benefits and Barriers to Providing Pediatric Gender-Affirming Health Care Through Telehealth	https://doi.org/10.1089/trgh.2020.0159
Hidalgo 2017	US		Perceived Parental Attitudes of Gender Expansiveness: Development and Preliminary Factor Structure of a Self-Report Youth Questionnaire	https://doi.org/10.1089/trgh.2017.0036
Hidalgo 2019	US		The Gender Minority Stress and Resilience Measure: Psychometric Validity of an Adolescent Extension	https:///doi.org/10.1037/cpp0000297
Kolbuck 2019	US		Psychological Functioning, Parenting Stress, and Parental Support among Clinic-Referred Prepubertal Gender Expansive Children	https://psycnet.apa.org/doi/10.1037/cpp0000293
Kuper 2019a	US		Exploring the Gender Development Histories of Children and Adolescents Presenting for Gender Affirming Medical Care	http://dx.doi.org/10.1037/cpp0000290

Kuper 2019b	US		Baseline Mental Health and Psychosocial Functioning of Transgender Adolescents Seeking Gender-Affirming Hormone Therapy	https://doi.org/10.1097/DBP.0000000000000697
Leon 2021	US		Prevalence and Risk Factors for Nonsuicidal Self-Injury in Transgender and Gender-Expansive Youth at a Rural Gender Wellness Clinic	https://doi.org/10.1089/trgh.2020.0031
Lynch 2015	US		Retrospective Study of the Management of Childhood and Adolescent Gender Identity Disorder Using Medroxyprogesterone Acetate	https://doi.org/10.1080/15532739.2015.1080649
McGuire 2021	US		Differences in Patient and Parent Informant Reports of Depression and Anxiety Symptoms in a Clinical Sample of Transgender and Gender Diverse Youth	https://doi.org/10.1089/lgbt.2020.0478
Moyer 2019	US		Using the PHQ-9 and GAD-7 to screen for acute distress in transgender youth: findings from a pediatric endocrinology clinic	https://doi.org/10.1515/jpem-2018-0408
Nahata 2017	US		Mental Health Concerns and Insurance Denials Among Transgender Adolescents	https://doi.org/10.1089/lgbt.2016.0151
O'Bryan 2018	US		Building a Pediatric Patient Registry to Study Health Outcomes Among Transgender and Gender Expansive Youth at a Rural Gender Clinic	https://doi.org/10.1089/trgh.2018.0023
O'Bryan 2020	US		Health-related quality of life among transgender and gender expansive youth at a rural gender wellness clinic	https://doi.org/10.1007/s11136-020-02430-8
Pariseau 2019	US		The relationship between family acceptance-rejection and transgender youth psychosocial functioning	https://psycnet.apa.org/doi/10.1037/cpp0000291
Peterson 2017	US		Suicidality, Self-Harm, and Body Dissatisfaction in Transgender Adolescents and Emerging Adults with Gender Dysphoria	https://doi.org/10.1111/sltb.12289
Peterson 2020b	US		Exploring the Eating Disorder Examination Questionnaire in treatment seeking transgender youth	https://psycnet.apa.org/doi/10.1037/sgd0000386
Poquiz 2021a	US		Comparison of Gender Minority Stress and Resilience Among Transmasculine, Transfeminine, and Nonbinary Adolescents and Young Adults	https://doi.org/10.1016/j.jadohealth.2020.06.014
Poquiz 2021b	US		Gender-affirming care in the midwest: Reaching rural populations	https://psycnet.apa.org/doi/10.1037/rmh0000174
Reguitti 2022	US		Preliminary Factor Structure of the Parental Attitudes of Gender Expansiveness Scale for Parents (PAGES-P)	https://psycnet.apa.org/doi/10.1037/cpp0000384
Shumer 2016	US		Evaluation of Asperger Syndrome in Youth Presenting to a Gender Dysphoria Clinic	https://doi.org/10.1089/lgbt.2015.0070
Shumer 2017	US		Overrepresentation of Adopted Adolescents at a Hospital-Based Gender Dysphoria Clinic	https://doi.org/10.1089/trgh.2016.0042
Spack 2012	US		Children and Adolescents With Gender Identity Disorder Referred to a Pediatric Medical Center	https://doi.org/10.1542/peds.2011-0907
Tordoff 2022	US		Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care	https://doi.org/10.1001/jamanetworkopen.2022.0978
Zou 2018	US		Documenting an epidemic of suffering: low health-related quality of life among transgender youth	https://doi.org/10.1007/s11136-018-1839-y

Supplementary Table S3 - Study details by country

Study ID	Sample description	Service summary	Data collection years	Inclusion/Exclusions	Demographics	Gender status	Mental health problems	Neurodevelopmental conditions (ASC: autism spectrum condition, ADHD: attention deficit hyperactivity disorder)	Adverse childhood experiences
Australia									
Allen 2021	Young people 8-17 who are transgender and gender diverse in Victoria	Royal Children's Hospital Gender Service (RCHGS) in Melbourne, Australia which is a statewide, publicly funded, tertiary referral service that provides gender-affirming clinical care. Introduced a First Assessment Single-Session Triage (FASST) clinic in 2016	January 2017 to January 2019	145 attended FASST and MDC; pre-post FASST study 142	**Age at referral:** Not reported **Age at assessment:** median 15.0 IQR 13.7 to 16.2 **Birth-registered sex:** 105 (73.9%) female and 37 (26.1%) male	**Gender identity:** Transgender male 80 (56.3%), Transgender female 29 (20.4%), Nonbinary 16 (11.3%), Unsure 16 (11.3%), Prefer not to answer 1 (0.7%) **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Full transition - 69/135 (51.9%); Name 83/125 (66.4%); Pronouns 81/133 (60.9%); Look 99/132 (75.0%); At home 83/133 (62.4%); At school 76/128 (59.4%); Online 92/125 (73.6%)	**Depression:** CBCL (carer) mean 68.24 SD 11.79; YSR (child) mean 69.20 SD 11.08 **Anxiety:** CBCL mean 65.97 SD 12.53; YSR mean 64.21 SD 8.36 **Suicide:** Columbia Suicide Severity Rating Scale - High risk 13.4% (16) **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Hilton 2022	Children and adolescents recruited through a gender service located at Westmead with a diagnosis of gender dysphoria based on DSM-5	Single hospital-based multidisciplinary service that provides assessment and treatment for children (<16 years at referral) with gender dysphoria and their families	October 2014 to February 2019	127 initial assessment with adolescent medicine and triaged to appropriate team; 90 referred to gender service for GD assessment; 74 research consent (16 no consent); 10 excluded due to missing data; 64 included in study	**Age at referral:** Not reported **Age at assesment:** mean 12.91 SD 1.90, range 8 to 16 **Birth-registered sex:** 24 (37.5%) male and 40 (62.5%) female	**Gender identity:** Not reported **Gender dysphoria:** The Utrecht Gender Dysphoria Scale (UGDS) - mean 52.89 SD 7.43 range 29 to 60; 60 (94%) scored above 40; all had a diagnosis of gender dysphoria based on DSM-5 **Onset:** Not reported **Social transition:** Not reported	**Depression and anxiety:** DASS-21 - mean 55.57 SD 27.25 range 2 to 112 **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** 4 (6.25%); Austism Spectrum Quotient (AQ) - mean 60.62 SD 18.64 range 18 to 100 **ADHD:** 6 (9.38%) **Combined ASC and ADHD:** 3 (4.69%)	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Kozlowska 2020	Children experiencing dysphoria in relation to their birth-assigned sex were referred by their family doctors to a newly established— but not yet funded—Gender Service	Tertiary care pediatric hospital	December 2013 to June 2017	70 referred to gender service; 65 comprehensive medical assessment with endocrinology or adolescent team; 61 family and individual assessment with psychological team; 60 consented to research study; 57 total study cohort	**Age at referral:** Not reported **Age at assessment:** mean 12.96 SD 1.91 median 13.67 range 8.42 to 15.92 **Birth-registered sex:** 24 (42.1%) male and 33 (57.9%) female	**Gender identity:** 21/24 brm experienced their gender as female, 1 neutral gender, 1 unsure. 31/33 brf experienced their gender as male, 1 liked to wear boy clothes but did not express desire to be a boy in words, 1 gender distressed **Gender dysphoria:** 47 (82.5%), Other Specified Gender Dysphoria 3 (5.3%), Unspecified Gender Dysphoria 4 (7.0%), Does not meet criteria for the above 3 (5.3%); Gender dysphoria (4 point scale): no 0 (0.5%), some 14 (24.6%) very 28 (49.1%) and extreme distress 15 (26.3%) **Onset**: (1) children who had expressed their gender preferences in words, behavior (e.g., refusal to wear dresses), and play from the preschool years onward (n = 32; 56.1%); (2) children who dated their feelings of gender dysphoria from the school-age years (n = 14; 24.6%); (3) children who dated these feelings from the prepubertal time period, when awareness that their own puberty was approaching had triggered their distress (n = 8; 14.0%); and (4) children who dated these feelings from the post-pubertal period (n = 3; 5.3%). Age of disclosure in the four subsets, respectively, was 2.5–14 years (mean = 9.12 years); 8–13.8 years (mean = 11.49), 12.5–14.5 years (mean = 13.34), and 12.0–14.8 years (mean = 13.61). **Social transition:** Not reported	**Depression:** 36 (63.2%) **Anxiety:** 38 (66.7%) **Suicide:** suicidal ideation 28 (49.1%), and suicide attempt 6 (10.5%) **Self-harm:** occurring in the present 7 (12.3%) and self-harm history 30 (52.6%) **Eating disorder:** Not reported	**ASC:** 9 (15.8%) **ADHD:** Not reported	**Neglect or abuse:** Physical abuse 11 (19.3%), Sexual abuse 6 (17.5%), Neglect 6 (10.5%) **Parental mental illness or substance misuse:** Maternal mental illness (most commonly depression) 30 (52.6%), Paternal mental illness 23 (40.4%) **Exposure to domestic violence:** Domestic violence 14 (24.6%) **Household member in prison:** Not reported **Loss of parent:** Placement changes (foster care or between parents) 7 (12.3%)
Mahfouda 2019	Young people under 18 with gender diversity who were invited to take part in the GENTLE cohort	Single gender service located at Perth Children's Hospital in Perth, Western Australia. It is a dedicated tertiary service working with gender diverse children and adolescents and their families. Provides information, consultation, assessment, support, and access to puberty suppression and gender-affirming oestrogen or testosterone hormonal interventions	November 2017 to June 2019	122 contacted; 17 declined to participate, and 1 decided to withdraw from the Cohort. 104 included	**Age at referral:** mean 14.62 SD = 1.72 **Age at assessment**: mean 15.49 SD = 1.67 **Birth-registered sex:** 79 (76%) female and 25 (24%) male	**Gender identity:** male (71), female (23), non-binary/agender (6) and not specified (4) **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression and anxiety:** Internalising mean 67.00 SD 12.83, Externalising mean 54.45 SD 10.19, Total 64.08 10.94 **Suicide and self-harm:** 81/93 (77.9%) reported a history of any mental health problems, deliberate-self harming behaviours and/or suicidal intent or attempts **Eating disorder:** Not reported	**ASC: 10 (9.62%);** Social Responsiveness Scale - Social Awareness n 104 mean 57.88 SD 12.17 normal range 63 (60.6%) mild 15 (14.4%) moderate 18 (17.3%) severe 8 (7.7%), Cognitive n 104 mean 55.95 SD 13.04 normal range 70 (67.3%) mild 10 (9.6%) moderate 14 (13.5%) severe 10 (9.6%), Communication n 104 mean 58.38 SD 13.10 normal range 59 (56.7%) mild 18 (17.3%) moderate 14 (13.5%) severe 13 (12.5%), Motor n 104 mean 63.39 SD 14.52 normal range 41 (39.4%) mild 18 (17.3%) moderate 23 (22.1%) severe 22 (21.2%), Restricted and Repetitive Behaviours n 102 mean 62.24 SD 13.76 normal range 46 (44.2%) mild 21 (20.2%) moderate 13 (12.5%) severe 22 (21.2%), Social Communication n 104 mean 59.83 SD 13.54 normal range 56 (53.8%) mild 14 (13.5%) moderate 17 (16.3%) severe 17 (16.3%), DSM-5 n 100 mean 61.77 SD 14.03 normal range 49 (47.1%) mild 18 (17.3%) moderate 10 (9.6%) severe 23 (22.1%), Total score n 104 mean 60.68 SD 14.06 normal range 53 (51.0%) mild 17 (16.3%) moderate 15 (14.4%) severe 19 (18.3%); Severe indicates ASD. **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Pang 2020*	Young people up to the age of 18 years who are transgender and gender diverse in Victoria	The Royal Children's Hospital Gender Service (RCHGS) in Melbourne, Australia who accept referrals of transgender and gender diverse young people up to the age of 18 years. Serves the state of Victoria (population 6 million) and only specialist service in this area.	January 2009 to December 2016	558 referrals 2009=0 2010=8 2011=14 2012=20 2013=54 2014=100 2015=142 2016=231	**Age at referral:** brm median 11.9 IQR 7 to 15.5, brf median 14.4 IQR 12.7 to 15.8 **Age at assessment:** Not reported **Birth-registered sex:** 250 (44.8%) male and 308 (55.2%) female	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Tollit 2021	Patients needed to have attended their first appointment with RCHGS during this time, and either had a self-reported gender identity which differed from what was presumed for them at birth (as reported during any stage of their clinical assessment) or sought clinical guidance regarding their gender.	Largest multidisciplinary pediatric gender service in Australia providing transgender and gender diverse children and adolescents throughout Victoria with support, assessment and a range of gender affirming treatments to help manage GD.	January 2007 to December 2016	359 patients met inclusion criteria	**Age at referral:** Not reported **Age at assessment:** median 14.3 IQR 5.8 range 3.6 to 18.1; brm age: median 14.8 IQR 3.1 range 3.6 to 18.1; brf age: median 12.4 IQR 8.6 range 3.8 to 17.9 (age at first presentation) **Birth-registered sex:** 193 (53.8%) females and 166 (46.2%) males	**Gender identity:** transgender 313 (87.2%), non-binary 26 (7.2%), cisgender 6 (1.7%), not sure 14 (3.9%) **Gender dysphoria: 81.1% met DSM-5 criteria for GD.** **Onset:** Age at which gender diversity expressed:overall median 3 IQR 8 range 1.5 to 17, brf median 4.8 IQR 9 range 2 to 16.8 and brm 3 IQR 8 range 1.5 to 17; Age at which experiencing GD symptoms: overall median 8 IQR 9 range 1.5 to 17, brf median 11 IQR 10 range 2 to 16.8 and brm median 4 IQR 10 range 1.5 to 17.0. GD symptoms commence age at typical age of pubertal onset: brm (n = 47; 29.6%) and brf (n=104; 54.5%) but 43.6% brm and 40.8% brf had previsouly expressed GD prior to this. **Social transition:** Not reported	**Depression:** Major depressive disorder/history of low mood: 182 (50.7) - males 74 (44.6%) and females 108 (56.0%) **Anxiety:** Not reported **Suicide:** history of suicidal ideation 106 (29.5) - males 36 (21.7%) and females 70 (36.3%) **Self-harm:** history of self-harm 89 (24.8%) - males 25 (15.1%) and females 64 (33.2%) **Eating disorder:** overall 5 (1.4%), males 1 (0.6%) and females 4 (2.1%)	**ASC:** 58 (16.2%); brm 37 (22.3%) and brf 31 (10.9%) **ADHD:** 9 (2.5%); brm 6 (3.6%) and brf 3 (1.6%)	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Kozlowska 2021	Presenting with feelings of dysphoria pertaining to gender that had been assigned to them at birth	The Gender Service is a multidisciplinary service located in a tertiary care children's hospital in New South Wales. Clinic was established in December 2013 in the wake of increased referrals to our hospital Endocrinology Department for children experiencing gender dysphoria. Along with their distressed families, these children (sometimes with court orders in hand) came to Endocrinology typically seeking treatment with puberty-suppressing medications.	December 2013 to November 2018	454 total referrals to gender service, 128 comprehensive medical assessment, 108 family and individual assessment with psychological team, 79consent to take part in research study. 79 children included	**Age at referral:** Not reported **Age at assessment:** 8.42 to 15.92 mean 12.84 SD 1.20 median 13.33 **Birth-registered sex:** 33 (41.8%) males and 46 (58.2%) females	**Gender identity:** Male to female 26 (32.9%), female to male 42 (53.2%), neutral 1 (1.3%), confused 7 (8.9%) **Gender dysphoria:** 41 (51.9%) experienced dysphoria about gender from toddlerhood or preschool, 22 (27.8%) from early primary school, 12 (15.2%) prepubertal, 4 (5.1%) postpubertal; No GD diagnosis given at assessment 4 (5.1%), DSM-5 GD 61 (77.2%), DSM other specified GD (insufficient information) 10 (12.7%), DSM unspecified GD (clear reason why GD criteria were not met) 4 (5.1%); Child gender distress: No distress 1 (1.3%), Some distress 21 (26.9%), Very distressed 35 (44.3%), Extreme distress 22 (27.8%) **Onset**: Age of first disclosure: Preschool years (2.5–5 years) 13 (16.5%), School-age years (7–12.5 years) 30 (38.0%), Adolescent years (13–14.8 years) 28 (35.4%), No verbal disclosure 8 (10.1%) **Social transition:** Not reported	**Depression:** 49 (62.0%) Depression DASS subscale: child (n=54) mean 20.26 clinical cutoff: 41/54 (75.9%), mother (n=40) mean 10.29 clinical cutoff: 21/48 (43.81%), father (n=25) mean 6.24 clinical cutoff: 7/25 (28.0%) **Anxiety:** 50 (63.3%) Anxiety DASS subscale: child (n=54) mean 18.15 clinical cutoff: 46/54 (85.2%), mother (n=40) mean 6.7 clinical cutoff: 17/48 (35.4%), father (n=25) mean 3.04 clinical cutoff: 3/25 (12.0%) **Suicide:** Suicidal ideation (past or current) 33 (41.8%); Suicide attempt 8 (10.1%) **Self-harm:** history 39 (49.4%); current self-harm 13 (16.3%) **Eating disorder:** 2 (2.5%)	**ASC:** (diagnosis by paediatrician or formal testing) 11 (13.9%) **ADHD:** 13 (16.5%)	**Neglect or abuse:** Sexual abuse 15 (19.0%), Physical abuse 12 (15.2%), Emotional abuse 11 (13.9%), Neglect 9 (11.4%) **Parental mental illness or substance misuse:** Maternal mental health 39 (49.4%), Paternal mental health 30 (38.0%), **Exposure to domestic violence:** Domestic violence 18 (22.8%) **Household member in prison:** Not reported **Loss of parent:** Loss death 15 (19.0%), Out-of-home placement (foster care)/change of placements (whom the child lived with) 8 (10.1%)
Tollit 2019	Trans20 is a prospective, longitudinal cohort study, with a sample comprising patients aged 3–17 years when first attending the RCHGS between February 2017 and February 2020. Young people up to age 17 years who reside in Victoria and have concerns regarding their gender identity can be referred to RCHGS by their general practitioner. Patients subsequently enter the service via one of two pathways: the Under 8 clinic for those aged 7 years and below, or the First Assessment Single Session Triage (FASST) clinic for those aged 8 years and older	The RCHGS provides publicly funded assessment and gender affirming care to TGD young people throughout the state of Victoria. With approximately 250 new referrals each year, RCHGS is the largest multidisciplinary gender service for children and adolescents in Australia.	February 2017 to February 2019	397 young people were considered eligible for involvement in Trans20	**Age at referral:** Not reported **Age at assessment:** the large majority of patients (75.3%) were aged 12 years or older, 18.6% were aged 6–11 years and 6.1% were aged 5 years or younger **Birth-registered sex:** Not reported	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Belgium									

de Graf, 2018b*	Adolescents aged 12–18 who were referred to one of the four European specialist gender clinics who completed either the CBCL or the YSR at baseline	Specialist gender service	January 2009 to December 2013	For Belgium, 136 adolescents were referred and data for 71 young people were included in this study (52.2%).	**Age at referral:** Not reported **Age at assessment:** 14.34 (1.65); brf 14.37 (1.83) and brm 14.32 (1.57) **Birth-registered sex:** 47 (66.2%) female and 24 (33.8%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** CBCL internalising N=35, mean 14.63 SD 10.05; Youth Self report internalising N=37, mean 21.14 SD 10.03; Clinical range internalising CBCL N=35, 15 (42.9%); clinical range internalising YSR N=37, 20 (54.1%). **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Van Cauwenberg, 2021	Adolescents between 12 and 18 years, who were referred to pediatric clinic who consented to retrospective chart review and who were eligible for a first session during study period	Pediatric Gender Clinic at Ghent University Hospital for gender variant children and adolescents and their families.	January 2007 to December 2016	235 referrals, 35 excluded whose first session came after 2016, leaving 200 who were eligible for a first session between dates, 12 were referred to adult clinic, 11 did not attend their first session, 177 analysed	**Age at referral:** Not reported **Age at assessment:** 15.01 (1.42) **Birth-registered sex:** overall 1.77 (F:M ratio); Females, Males numbers (ratio) - 2007=0,3; 2008=3,6 (0.5); 2009=4, 5 (0.8); 2010=5,1 (5.00); 2011=6,3 (2.00); 20012=18, 8 (2.25); 2013=20, 8 (2.50); 2014=17, 12 (1.42); 2015=29, 11 (2.64); 2016=21, 7 (3.00) *These were extracted from Figure 2*	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** CBCL internalising N=42, mean 15.98, SD 9.66; T-score 62.24 (10.45) clincial range 52.4%, YSR internalising N=52, mean 19.35, SD 9.26; T-score 59.13 (9.32); clinical range 28.8% **Suicide:** 5 (2.8%); thoughts 21 (40.4%) **Self-harm:** self-harm and/or at least one suicide attempt in last 6 months 17 (32.1%) **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Brazil									
Soll 2019; Soll 2021	Families seeking healthcare at service for gender incongruence using ICD-11 and had response from both parents to questionnaire and consented	Gender Identity Program (PROTIG) at the Hospital de Clínicas de Porto Alegre (HCPA), located in southern Brazil for children aged 8 to 16	May 2014 to December 2018	24	**Age at referral:** Not reported **Age at assessment:** mean 13.88 SD 2.45; range 8 to 16 **Birth-registered sex:** 12 (50%) female and 12 (50%) males	**Gender identity:** Not reported **Gender dysphoria:** All had diagnosis of gender dysphoria (DSM-5) **Onset**: mean 9.25 (min 5 max 15); Male GI 9.5 (5 to 13); Female GI 9.0 (5 to 13) **Social transition:** 79.2% started social transition; age of social transition 14.0 (7 to 16); male GI 13.29 (10 to 15); female GI 12.83 (7 to 16)	**Depression:** major depression 4 (16.6%) **Anxiety:** All said they felt significant sadness and anxiety **Suicide:** attempt 3 (12.5%) **Self-harm:** Not reported **Eating disorder:** anorexia 1 (4.16%) bulimia 1 (4.16%)	**ASC:** 0 (0.0%) **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Canada									
Aitken 2015*	Adolescents (aged 13 years or older) referred for gender dysphoria to specialist gender clinic.	Gender Identity Service housed within the Child, Youth, and Family Services (CYFS) at the Centre for Addiction and Mental Health (CAMH), Toronto	1976 to 2013	n=328 whole period Numbers assessed per year reported Sub-sample of 255 covering 1999-2013 used for some results	**Age at referral:** Not reported **Age at assessment:** Mean age 16.7 (SD 1.7). No significant difference in age between brf and brm. **Birth-registered sex:** 176 (53.7%) female and 152(46.3%) male. From 1999-2005, 17 (32.1%) female and 36 (67.9%) male. M:F ratio 2.11:1. From 2006-2013, 129 (63.9%) female and 73 (36.1%) male. M:F ratio 1:1.76. Study reported significant difference in sex distribution between two time periods.	**Gender identity:** Not reported **Gender dysphoria:** All met criteria for either Gender Identity Disorder (GID) or GID Not Otherwise Specified (GID-NOS). **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Aitken 2016	Consecutive series of children (age 3-12 years) referred to a specialised gender identity clinic.	Specialised gender identity service housed within a child and mental health programme at an academic health science centre. Information in paper suggests it is the Gender Identity Service, Child, Youth, and Family Programme, Centre for Addiction and Mental Health, Toronto.	1976 to 2015	615 referred Excluded 43 as relevant data not available n=572	**Age at referral:** Not reported **Age at assessment:** Age breakdown reported: 3-4= 110, 5= 95, 6= 86, 7= 59, 8= 71, 9= 50, 10= 39, 11= 29, 12= 33. **Birth-registered sex:** 109 (19.1%) female and 463 (80.9%) male	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide or self-harm:** Summed score (range 0-4) for CBCL items 18 (self-harm or suicide attempt) and 91 (ideation) 0.3 (SD 0.7) - same for birth-registered females and males. Percentage rating 1 or 2 for item 18 = 6.6% and for item 91 = 19.1%. Suicide/self-harm data only reported for 6-12 year old participants (n=367). Percentage endorsing (scoring 1-2) item 91 in each age group: 3-4= 0.9%, 5= 7.4%, 6= 9.6%, 7= 10.2%, 8= 18.3%, 9= 26.0%, 10= 33.3%, 11= 27.6%, 12= 27.3%. Percentage endosring Item 18 in each age group: 3-4= 0.0%, 5= 5.3%, 6= 2.3%, 7= 1.7%, 8= 9.9%, 9= 4.0%, 10=12.8%, 11= 17.2%, 12= 6.1% **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Bechard 2017	Adolescents consecutively referred to a specialised gender identity service who had a diagnosis of gender identity disorder (GID)	Specialized gender identity service housed within a child and youth mental health program at an academic health science centre. Information in paper suggests it is the Gender Identity Service, Child, Youth, and Family Programme, Centre for Addiction and Mental Health, Toronto.	February 2011 to June 2012	n=50	**Age at referral:** Not reported **Age at assessment:** Median age 16.9, range 13-20 **Birth-registered sex:** 33 (66%) female and 17 (34%) male	**Gender identity:** Not reported **Gender dysphoria:** All had GID diagnosis (eligibility criteria) **Onset**: Not reported **Social transition:** Not reported	**Depression:** 18 (36%) had DSM diagnosis of Major Depressive Disorder prior to initial assessment (plus 1 with queried MDD diagnosis) and 1 (2%) had DSM diagnosis of Dysthymic Disorder. **Anxiety:** 8 (16%) had DSM diagnosis of Generalised Anxiety Disorder (plus 1 with queried GAD diagnosis), 1 (2%) had Anxiety Disorder Not Otherwise Specified, 2(4%) had Social Phobia (Social Anxiety Disorder), 1 (2%) had Panic Disorder without Agoraphobia. **Suicide:**Ideation 31 (62%). Suicide attempt(s) 13 (26%). **Self-harm:** 18 (36%). **Eating disorder:** 1 had DSM diagnosis of Anorexia Nervosa and 2 of Eating Disorder Not Otherwise Specified. 3/50 (6%)	**ASC:** 2 (4%) had DSM diagnosis of Asperger's Disorder prior to initial assessment. **ADHD:** 9 (19%) had DSM diagnosis of ADHD prior to initial assessment.	**Neglect or abuse:** History of physical abuse coded as present at initial intake interview/from referral information for 10 (20%) and history of sexual abuse for 5 (10%). **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Bradley 1978	Children and adolescents referred to and assessed in a new child and adolescent gender identity service	A child and adolescent section was established within the Clarke Gender Identity Clinic in Toronto in 1975. This consisted of a multi-disciplinary assessment team which starting seeing children in Autumn 1975.	Autumn 1975 to October 1977	n=16	**Age at referral:** Not reported **Age at assessment:** Age range 6-17, 4 children and 12 adolescents. **Birth-registered sex:** 3 (18.8%) female and 13 (81.3%) male. Children: 4 male. Adolescents: 3 female and 9 male.	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

Chiniara 2018	Adolescents (age 12-18) presenting to a transgender clinic. Eligibility included presence of gender dysphoria and desire for medical treatment (those with learning disability or extreme anxiety were excluded) Data from initial vists were used	A large paediatric gender clinic based at the Hospital for Sick Children, Toronto. Described as a medical clinic developed towards meeting the medical needs of transgender adolescents. Opened in October 2013 - rapidly grown to become one of largest in North America.	January 2014 to June 2016	n=203 12 meeting criteria were excluded - did not return to clinic, 3 because initial visit to another clinic. Overall referral / assessed number not reported	**Age at referral:** Not reported **Age at assessment:** Mean age brf 16.3 (SD 1.6), brm 16.1 (1.7). Mean age for first 100 over time period 16.7 (1.6) and for later 100 15.7 (1.6). Significant difference between two time periods reported. **Birth-registered sex:** 156 (76.8%) female, 47 (23.2%) male. M:F ratio: 1:3. Percentage of females among first 100 over time period was 74.7% and 78.8% in later period.	**Gender identity:** Not reported **Gender dysphoria:** Utrecht scale scores (range 12 to 60) indicate presence of gender dysphoria in all participants (mean score brf 56.1 (SD 4.2), brm 50.4 (7.4) - significant difference between groups reported). **Onset**: Not reported **Social transition:** 117 (75.5%) brf and 30 (63.8%) brm had socially transitioned prior to initial visit.	**Depression:** 37.4%; 20.5% brf and 12.6% brm (13.9% brf and 4.0% brm both anxiety and depression). No significant difference between 100 adolescents referred early or later in the time period. 33.9% prescribed medication for a mood disorder (at present or in the past). Mean BDI II scores 23.5 SD (14.8) brf and 19.8 (14.6) brm. Scores indicate severe depression in 41.6% of females and 34.4% of males. **Anxiety:** 28.1%; 12.8% brf and 6.3% brm . No significant difference between 100 adolescents referred early or later in time period. Mean MASC2 scores 63.3 (SD 12.3) brf and 57.4 (12.7) brm - significant anxiety 44.4% brf and 30% brm (significant difference between groups reported). **Suicide:** 67 (33.3%) suicidal thoughts (54, 34.6% brf and 13, 27.7% brm). No significant difference between 100 adolescents referred early or later in the time period. 9.6% brf and 9.7% brm scored positive on the BDI II for suicide risk. **Self-harm:** 62 (30.5%); 52, 33.3% brf and 10, 21.3% brm). No significant difference between 100 adolescents referred early or later in the time period. **Eating disorder:** Not reported	**ASC:** 5.1% brf and 6.4% brm. No significant difference between 100 adolescents referred early or later in the time period. **ADHD:** 14.9% brm, 0% brf	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Chiu 2006	Children referred consecutively to, and then assessed in a gender identity service.	Gender Identity Service, which is housed within the Child, Youth, and Family Program (CYFP) at the Centre for Addiction and Mental Health, Toronto	Not reported	n=65	**Age at referral:** Not reported **Age at assessment:** Mean age 8.1 yrs (SD 2.5), range 3-12 **Birth-registered sex:** 18 (27.7%) female and 47 (72.3%) male	**Gender identity:** Not reported **Gender dysphoria:** 54 (83.1%) met complete DSM criteria for Gender Identity Disorder (GID), and 11 (16.9%) were subthreshold meeting some criteria. **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Cohen-Kettenis 2003*	Children (age 3-12 years) consecutively referred to, and then assessed in a gender identity clinic.	The Child and Adolescent Gender Identity Clinic, which is housed within the Child Psychiatry Program at the Centre for Addiction and Mental Health - Clarke Division (Toronto, Ontario, Canada).	1975 to 2000 Largest number assessed in 1997 (n=28)	n=358	**Age at referral:** % cases: age 3/4=5.9, 4/5=16.8, 5/6=17.9, 6/7=14.7, 7/8=9.7, 8/9=10.9, 9/10=9.2, 10/11=4.4, 11/12=4.4, 12/13=5.9 **Age at assessment:** Mean age 7.2 (SD 2.5), range 3.2-13.0. **Birth-registered sex:** 53 (14.8%) female, 305 (85.2%) male, M:F ratio 5.75:1	**Gender identity:** Reported sum scores (range 0-4) for CBCL item 5 (behaves like opposite sex) and 110 (wishes to be of opposite sex). Mean score 2.8 (SD 1.3) brf and 2.4 (1.3) brm. **Gender dysphoria:** 225 (62.8%) met complete DSM criteria for gender identity disorder. **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** Mean internalising T-score 60.8 (SD 11.0) **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Cohen-Kettenis 2006*	Children (age 2-12) consecutively referred to, and then assessed in a gender identity clinic.	The Child and Adolescent Gender Identity Clinic, which is housed within the Child, Youth and Family Programme at the Centre for Addiction and Mental Health (Toronto, Ontario, Canada).	May 1985 to December 2003	n=338 (GIQC data not available for first 66 children seen for assessment)	**Age at referral:** Not reported **Age at assessment:** Mean age 7.2 (SD 2.5), range 2-12 **Birth-registered sex:** 52 (15.4%) females and 286 (84.6%) males. M:F ratio 5.5:1	**Gender identity:** Gender Identity Questionnaire for Children (GIQC) mean score brf 2.6 (SD 0.6), brm 2.9 (0.6). **Gender dysphoria:** 227 (67.2%) met complete diagnostic criteria for Gender Identity Disorder. GIQC mean score 2.6 (SD 0.5) for those meeting complete criteria, 3.3 (0.5) for those subthreshold (meeting some criteria). **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
de Graaf 2020*	Adolescents aged 13 or older who were referred and assessed at a specialist gender identity clinic (data collected during initial assessment)	Gender Identity Service at the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario	1978 to 2012	n=260	**Age at referral:** Not reported **Age at assessment:** Mean age 16.7 (SD 1.8) **Birth-registered sex:** 131 (50.4%) female and 129 (49.6%) male	**Gender identity:** For CBCL item 110 (wishes to be of the opposite sex), 211 (94.1%) scored 1 or 2 and 13 (5.8%) scored 0. For the YSR, 228 (95.7%) scored 1-2 and 10 (4.2%) scored 0. **Gender dysphoria:** All met DSM criteria for Gender Identity Disorder or Gender Dysphoria **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide and self-harm:** Sum scores for CBCL and YSR item 18 (deliberate self-harm or attempted suicide) and 91 (suicidal ideation) calculated (score range 0-2). Mean scores were 0.8 (SD 1.1) on CBCL and YSR. Percentages scoring 1-2 on CBCL and YSR item 18: 30.8% and 33.6% brf and 29.2% and 23.5% brm. Percentages scoring 1-2 on CBCL and YSR item 91: 32.5% and 40.0% brf and 39.2% and 41.2% brm. **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
de Vries 2016*	Adolescents (age 13–18 years) referred and assessed at specialist gender clinic (baseline assessment data used)	Gender Identity Service at the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario (established in 1975 at the Clarke Institute of Psychiatry, now the Centre for Addiction and Mental Health). Covers large proportion of population in Ontario.	1980 to 2010	n=177 CBCL / YSR data available for 142 / 138 of sample	**Age at referral:** Not reported **Age at assessment:** Mean age 15.2 (SD 1.3) **Birth-registered sex:** 83 (46.9%) female and 94 (53.1%), M:F ratio = 1.13:1	**Gender identity:** Not reported **Gender dysphoria:** 100% met DSM criteria either for Gender Identity Disorder or Gender Identity Disorder Not Otherwise Specified. **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** For CBCL and YSR internalising scale, mean score was 68.8 (SD 9.8) and 62.4 (12.0) for all, 67.5 (10.6) and 60.1 (10.3) for brf, and 70.0 (9.0) and 64.6 (13.0) brm. On the CBCL, 74.5% were in the clinical range for internalising symptoms (69.7% of brf and 78.7% brm). On the YSR, 46.4% were in the clinical range (37.3% brf and 54.9% brm). **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Feder 2007	All adolescents (age 12-18) who were assessed. Those with diagnosis of gender dysphoria (GD) given at assessment were included.	The Gender Diversity Clinic at a Canadian tertiary pediatric care hospital in Ottawa, Ontario. Access is through self-referral or by a primary care provider. Catchment is a moderate size urban centre and surrounding area (population 1.3 million). MDT collaboration between Adolescent Medicine and Endocrinology for those up to age 18.	October 2007 to July 2015	150 assessed Excluded 23 (outside specified age range), and 30 (no GD so discharged) n=97	**Age at referral:** Not reported **Age at assessment:** Mean age 15.7 (SD 1.4) **Birth-registered sex:** 60 (61.9%) female and 37 (38.1%) male	**Gender identity: brf** 58 identified as male and 2 as gender fluid. All 37 brm identified as female. **Gender dysphoria:** Of 150 assessed age 12-18, 120 received diagnosis of gender dysphoria and 30 did not and were discharged from the service. All included sample diagnosed (eligibility criteria). **Onset**: Not reported **Social transition:** At time of assessment, 46 (47%) had completed social transition, 18 (19%) were in the process, and 33 (34%) had not initiated social transition.	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** 5 (5.2%) (3 anorexia nervosa-restrictive subtype, 1 anorexia nervosa-binge/purge subtype, 1 avoidant restrictive food intake disorder). 10 (10.3%) were noted to have eating disorder-related symptoms but no diagnosis. Of the 15 diagnosed / with symptoms 15 (15.5%), 3 (20%) brf and 12 (80%) brm.	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Fridell 2006	Children referred consecutively to, and then assessed in a gender identity service.	The Gender Identity Service, which is housed within the Child, Youth, and Family Program (CYFP) at the Centre for Addiction and Mental Health, Toronto	June 1993 to May 2005	252 started assessment 10 excluded as data not available n=242	**Age at referral:** Not reported **Age at assessment:** Mean age brf 8.0 (SD 2.6) and brm 7.1 (2.4) **Birth-registered sex:** 43 female (17.8%) and 199 male (82.2%)	**Gender identity:** Not reported **Gender dysphoria:** 176 (72.7%) met complete DSM criteria for Gender Identity Disorder (GID) and 66 (27.3%) were subthreshold for diagnosis. **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Heard 2018	All youth who have received care from a gender service (initial assessment data used for specified characteristics). Referrals that were redirected and not followed by the service were only included in the number and demographic of referrals.	Manitoba Gender Dysphoria Assessment and Action for Youth (GDAAY) programme - established in 2011 to provide Manitoba's trans youth with access to trans-specific healthcare. MDT set-up. Prior to establishment there was no comprehensive paediatric gender service for those under 18.	2007 to July 2016	174 referred 13 re-directed to adult service as above age limit Survey data not extracted as selected subsample (n=25) Numbers referred and assessed per year reported	**Age at referral:** Mean age 13.9, range 4.7-17.8 **Age at assessment:** Not reported **Birth-registered sex:** 122 (70.1%) female and 52 (29.9%) male	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression or depression:** 49 of 161 (30.4%) with pre-existing or current anxiety/depression diagnosis (41 (24%) brf and 8 (5%) frm) **Suicide:** Not reported **Self-harm:** behaviours 36 (21%) **Eating disorder:** Not reported	**ASC:** 4 with an ASD diagnosis, 2 with ASD traits not formally meeting diatnostic crieria (total n not reported) **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

Hughes 2017	Children (< age 12) and adolescents (age 12 and over) referred to a gender identity service	Not specified. From information in paper, it is likely to be the Child and Adolescent Gender Identity Service, Toronto	1976 to 2013	n=1023	**Age at referral:** Not reported **Age at assessment:** Mean age brf 12.8 (SD 4.5) and brm 10.4 (4.7). **Birth-registered sex:** 245 (23.9%) female, 778 (76.1%) male	**Gender identity:** Not reported **Gender dysphoria:** Basis of referral: gender dysphoria for 92 brf and 422 brm children, 135 brf and 143 brm adolescents; tranvestic fetishism for 24 and 128 brm; homosexuality for 13 brf and 61 brm adolescents. **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Johnson 2004	Children (age 3-12) referred consecutively, and then assessed in a gender identity clinic	Child and Adolescent Gender Identity Clinic, which is housed within the Child Psychiatry Program at the Centre for Addiction and Mental Health—Clarke Division, Toronto	May 1985 to April 2003	n=325	**Age at referral:** Not reported **Age at assessment:** Mean age 7.1 (SD 2.5), range 3.3-13.0 **Birth-registered sex:** 50 (15.4%) female and 275 (84.6%) male	**Gender identity:** Gender Identity Questionnaire (GIQ) total mean score (range 1-5 with 1 exihibiting most cross-sex behaviour) was 2.8 (SD 0.6), 2.6 (0.6) brf and 2.9 (0.6) brm. Scores for age groups: 3-4 years = 2.7 (0.7), 4.5 = 2.7 (0.6), 5-6 = 2.8 (0.6), 6-7 = 2.8 (0.6), 7-8 = 2.8 (0.6), 8-9 = 2.8 (0.6), 9-10 = 3.0 (0.7), 10-11 = 2.8 (0.6), 11-12 = 2.9 (0.8), 12-13 = 3.2 (0.6). **Gender dysphoria:** 216 (66.5%) (34 (15.7%) brf and 182 (84.3%) brm) DSM for Gender Identity Disorder. 109 (33.5%) (16 (14.7%) brf and 93 (85.3%) brm) were subthreshold, all meeting some criteria. Mean GIQ score was 2.6 (0.5) for those meeting complete DSM criteria and 3.3 (0.5) for those meeting some. Scores for each group by different age brackets are also reported in the paper. **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Khatchadourian 2014	Adolescents referred to a transgender programme for medical therapy. Eligibility criteria are at least Tanner stage 2, assessment by mental health profesional from transgender clinical care group, and confirmed diagnosis of gender dysphoria.	British Columbia (BC) Children's Hospital Transgender Programme - MDT approach providing medical care and psychosocial support. Team was integrated into BC Transgender Clinical Care Group (BCTCCG) in 2003. Youth are assessed by a professional in the BCTCCG and those diagnosed with gender dysphoria are referred to the Transgender Programme (medical team) for medical therapy.	January 1998 to December 2011	n=84 No. of new patients seen per year reported	**Age at referral:** Not reported **Age at assessment:** Mean age at first visit 16.6 (SD 2.2, CI 16.1-17.0). brf 16.4 (2.1, 15.8-17.0) and brm 16.8 (2.4, 16.0-17.5). **Birth-registered sex:** 45 (53.6%) female and 39 (45.4%) male**.** Number of female seen for each year 1998-2011 = 1, 1, 0, 1, 0, 1, 1, 1, 1, 1, 9, 4, 6, 18. Numbers of males seen = 0, 0, 0, 0, 0, 2, 0, 0, 3, 4, 3, 8, 6, 11.	**Gender identity:** 45 identified as female-to-male, 37 as male-to-female, and 2 birth-registered males were undecided **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** 29 (35%) diagnosed with mood disorder; 20 (44%) brf and 8 (19%) brm. **Anxiety:** 20 (24%) diagnosed with anxiety disorder; 15 (33%) brf and 4 (11%) brm. **Suicide:** Suicide attempt / ED visit - before initial assessment 10 (12%); 6 (13%) brf and 2 (5%) brm **Self-harm:** Not reported **Eating disorder:** 4 (5%); 2 (4%) brf and 2 (5%) brm.	**ASC:** 6 (7%) pervasive developmental disorder / ASD; 2 (4%) brf, 4 (11%) brm) **ADHD:** 8 (10%) brf 2 (4%) brm 6 (16%)	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Singh 2010	Adolescents referred consecutively to a Gender Identity Service	Gender Identity Service in the Child, Youth, and Family Programme (CYFP) at the Centre for Addiction and Mental Health (CAMH) in Toronto	February 2005 to February 2008	n=44	**Age at referral:** Not reported **Age at assessment:** Mean age brf 16.8 (SD 1.9), range 13-21 and brm 16.1 (SD 1.4), range 13.18 **Birth-registered sex:** 25 (56.8%) female and 19 (43.2%) male	**Gender identity:** Not reported **Gender dysphoria:** 100% diagnosed with Gender Identity Disorder (GID). Gender Identity/Dysphoria Questionnaire for Adolescents and Adults (GIDYQ-AA) mean score was 2.3 (SD 0.4) brf and 2.6 (0.6) brm. **Onset**: Recalled Childhood Gender Identity/Gender Role Questionnaire (RCGI) Factor 1 mean score 2.1 (0.9) brf, 2.6 (0.9) brm. **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Sorbara 2020	Patients at a Transgender Youth Clinic with initial visits occuring between Oct 2013-June 2016 or Aug 2017-June 2018. Those seeking gender-affirming medical care were included. Those previously strated on medical treatments were excluded. Data from initial clinic and referral documentation used.	Transgender Youth Clinic (TYC) at The Hospital for Sick Children in Toronto, Canada, an interdisciplinary clinic that provides GAMC to youth with gender dysphoria who are in puberty but under 18 years of age. As part of a universal health care system, payment is not required to access the TYC; referals from health care providers are required. Service established in October 2013. Service expanded from Aug 2017 to accommodate increasing referrals.	Cohort 1: October 2013 to June 2016 Cohort 2: August 2017 to June 2018	319 referred 8 excluded as not seeking medical care, 11 excluded due to previous treatment n=300 Cohort 1 = 191 Cohort 2 = 109	**Age at referral:** Not reported **Age at assessment:** Median age at first visit: 15.4 (IQR 14.2-16.4). For n=116 under age 15 years (YPY), median age 13.9 (IQR 12.9-14.5), range 10.5-14.9. For n=184 age 15 years or older (OPY), median 16.3 (15.6-16.8), range 15.0-17.9. In cohort 1, 65 (34.0%) were under 15 and 126 (66.0%) were age 15 or over. In cohort 2, 51 (46.8%) were under 15 and 58 (53.2%) were age 15 or over. **Birth-registered sex:** 229 (76.3%) female (n=87 under 15, n=142 age 15 or over) and 71 (23.7%) male (n=29 under 15, n=42 age 15 or over).	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Median age of recognition of gender incongruence was 5.8 years (IQR 3.0-11.0) for YPY (under 15) and 9.0 years (5.0-13.0) for OPY (15+). Reported significant difference between groups. Time from recognition of gender to first TYC visit was similar between groups. **Social transition:** 76 (65.5%) of those age under 15 socially transitioned before initial visit, 149 (81.0%) of those age 15 or over. Median age of social transition was 13.0 (12.0-13.4) for YPY and 15.0 (14.0-16.0) for OPY. Reported significant difference between groups.	**Depression:** 40.0%; OPY (age 15+) vs YPY (<15) 46% vs 30% **Anxiety:** 44.3%; 44.0% YPY and 44.4% OPY **Suicide:** 12.3% ideation, 47.3% had a history of suicidal ideation, and 14.0% had attempted suicide. OPY vs YPP history (52% vs 40%), attempts (17% vs 9%) and current ideation (13.9% vs. 9.3%). **Self-harm:** 34.7% history; OPY vs YPP (40% vs 28%). **Eating disorder:** Not reported	**ASC:** 18 (6.0%) - 7 (6.0%) of those under age 15 and 11 (6.0%) of those age 15 or over. **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Steensma 2014*	Children (age <12) and adolescents (12 and older) consecutively referred and assessed at a gender identity clinic. All met DSM criteria for Gender Identity Disorder (GID) or GID Not Otherwise Specified (NOS). Data at time of assessment.	Gender Identity Service at the Centre for Addiction and Mental Health in Toronto, Ontario, Canada. The Toronto clinic was established in 1975 at the Clarke Institute of Psychiatry (now the Centre for Addiction and Mental Health).	1986 to 2007	572 referred 176 excluded as data not available n=396	**Age at referral:** Not reported **Age at assessment:** Mean age 9.0 (SD 3.7). Mean age of children 7.4 (2.2) and adolescents 14.8 (1.7). Mean age of 176 excluded: children 5.7 (2.0), adolescents 16.2 (1.6). **Birth-registered sex:** 96 (24.2%) female and 300 (75.8%) male. Of children, 53 (17.0%) female and 259 (83.0%) male. Of adolescents, 43 (51.2%) female and 41 (48.8%) male. In total referred sample, 141 (24.7%) female and 431 (75.3%) male.	**Gender identity:** Not reported **Gender dysphoria:** 100% diagnosed with GID or GID-NOS **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** Internalising mean T-score 58.8 (SD 11.72) - 60.0 (13.5) brf and 58.4 (11.1) brm. For children mean score was 57.6 (11.1) - 58.3 (13.6) brf and 57.5 (10.6) brm. For adolescents mean score was 63.4 (12.9) - 62.2 (13.1) brf and 64.6 (12.7) brm. Percentage in clinical range 35.9% (44.8% brf, 33.0% brm). For children, 30.4% (37.7% brf, 29.0% brm). For adolescents, 56.0% (53.5% brf, 58.5% brm). **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
VanderLaan 2015a	Patients referred consecutively to a gender identity service who had data available for birth weight and ages and sexes of any siblings at time of initial assessment.	Specialty Gender Identity Service within a Child and Adolescent Mental Health Service. Information in paper suggests it is the Gender Identity Service at the Centre for Addiction and Mental Health in Toronto, Ontario, Canada.	Not reported	n=630 497 children, 133 adolescents	**Age at referral:** Not reported **Age at assessment:** Not reported **Birth-registered sex:** 143 (22.7%) female and 487 (77.3%) male	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
VanderLaan 2015c	Children clinically referred for gender dysphoria to a gender identity service	Specialized service housed within a child psychiatry programme at an academic health science centre. Information in paper suggests it is the Gender Identity Service at the Centre for Addiction and Mental Health in Toronto, Ontario, Canada	1976 to 2010	n=534	**Age at referral:** Not reported **Age at assessment:** Age range 3-12 **Birth-registered sex:** 95 (17.8%) female and 439 (82.2%) male	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Used CBCL to measure gender or non-gender related Obsessions (Item 9: "Can't get his/her mind over certain thoughts.") Compulsions (Item 66: "Repeats certain acts over and over." Each item scored 0-2. Number (%) of brf scoring 1-2 for item 9 and 66 was 62 (66.7%) and 20 (21.5%). Number (%) of brm scoring 1-2 for item 9 and 66 was 265 (61.5%) and 114 (26.2%). Of 44 females and 216 males scoring 1-2 on item 9, the nature of obsessions was gender-related in 18 (40.9%) and 118 (54.6%). Of 12 females and 84 males scoring 1-2 on item 66, the nature of compulsions was gender-related in 2 (16.7%) and 14 (16.7%). **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Wallien 2009*	Children consecutively referred to, and then assessed in a gender identity clinic (assessment data used)	The Gender Identity Service, which is housed within the Child, Youth, and Family Program (CYFP) at the Centre for Addiction and Mental Health (Toronto, Ontario, Canada).	March 1992 to July 2008	n=329	**Age at referral:** Not reported **Age at assessment:** Mean age 7.4 (SD 2.5), range 2.9-13.0 **Birth-registered sex:** 63 (19.1%) female and 266 (80.9%) male	**Gender identity:** Not reported **Gender dysphoria:** 234 (71.1%) met complete diagnostic criteria for Gender Identity Disorder. Gender Identity Interview for Children (GIIC) mean sum score (absolute range 0-24) was 6.9 (SD 5.8), 8.0 (5.3) brf and 6.7 (5.9) brm. **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

Wood 2013	Children and adolescents referred for gender dysphoria to a gender identity service.	The Gender Identity Service, which is housed within the Child, Youth, and Family Program (CYFP) at the Centre for Addiction and Mental Health (Toronto, Ontario, Canada).	1976 to 2011 reported in 4 year blocks	830 referred 577 children (age 3-12) 253 adolescents (age 13-20) Numbers per 4-yearly blocks reported	**Age at referral:** Not reported **Age at assessment:** Not reported **Birth-registered sex:** 229 (27.6%) female (105 children, 124 adolescents) and 601 (72.4%) male (472 children, 129 adolescents). Overall M:F sex ratio 2.62:1 (4.49:1 for children and for 1.04:1 for adolescents). M:F ratio for year blocks: 76-79 = 4.57:1, 80-83 = 4.57:1, 84-87 = 4.75:1, 88-91 = 3.20:1, 92-95 = 6.38:1, 96-99 = 4.94:1, 00-03 = 2.5:1, 04-07 = 1.82:1, 08-11 = 1.27:1 (ratios for children and adolescents also reported). Percentage male by age grouping: age 3 = 97.1%, age 4 = 84.8%, age 5 = 83.6%, age 6 = 87.4%, age 7 = 75.8%, age 8 = 82.2%, age 9 = 88.7%, age 10 = 70.1%, age 11 = 70.1%, age 12 = 55.9%, age 13-14 = 54.6%, age 15-16 = 53%, age 17-18 = 39.7%, age 19-20 = 71.4%	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Zucker 1982	All children referred to gender identity clinic for assessment with problems in gender identity development as one of the stated issues of concern	Child and Adolescent Gender Identity Clinic, Child and Family Studies Centre, Clarke Institute of Psychiatry, Toronto	Period of 12 months pre-1980 as results first presented in 1979	15 referred 1 excluded (dropped out) n=14	**Age at referral:** Not reported **Age at assessment:** Mean age 7.4, range 5.1-14.3 **Birth-registered sex:** 4 (28.6%) female and 10 (71.4%) male. Of referred number, 4 were female, 11 male.	**Gender identity:** Not reported **Gender dysphoria:** 7 (50%) brm met full criteria for diagnosis of gender identity disorder in childhood and 3 (30%) showed some of the characteristics. The 4 (100%) brf met criteria associated with Point A, which formed the basis of assessment for diagnosis because of disagreement regarding Point B for brf. **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Zucker 1983 (linked paper Zucker 1984)	Pre-adolescent children referred to gender identity clinic for potential problems in their gender-identity development as one, or the only, issue of concern	Child and Adolescent Gender Identity Clinic, Child and Family Studies Centre, Clarke Institute of Psychiatry, Toronto	3-year period	39 referred 3 excluded (dropped out) n=36	**Age at referral:** Not reported **Age at assessment:** Mean age 7.9 (SD 2.9). Mean age 6.6 (SD 2.2) for children diagnosed with gender identity disorder (GID) (n=21) and 9.7 (2.8) not diagnosed (n=15). **Birth-registered sex:** 5 (13.9%) female and 31 (86.1%) male	**Gender identity:** Not reported **Gender dysphoria:** 21 (58.3%) (5 (100%)brf, 16 (51.6%) brm) met criteria for diagnosis of gender identity disorder in childhood. For females, only point A of the criteria was used. The other 15 brm had some characteristics associated with a diagnosis. **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** CBCL internalising problems mean T score 62.8 (SD 11.3). Score was 60.7 (10.9) for those GID diagnosis and 65.7 (11.6) for those without diagnosis) - difference was not significant. **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Zucker 1985	Consecutive series of children referred to a gender identity service because of concerns about their gender identity development (as one, or the only concern). Initial evaluation data used.	Child and Adolescent Gender Identity Clinic, Child and Family Studies Centre, Clarke Institute of Psychiatry, Toronto	5.5-year period	57 referred 2 excluded (dropped out) n=55	**Age at referral:** Not reported **Age at assessment:** Mean age 7.6 (SD 2.8) **Birth-registered sex:** 7 (12.7%) female and 48 (87.3%) male. Of referred, 7 female and 50 male.	**Gender identity:** Not reported **Gender dysphoria:** 31 (56.4%) met criteria for gender identity disorder of childhood. 24 (50%) brm met full criteria and all 7 (100%) brf met criteria for Point A, which was used for diagnosis due to disagreements about Point B for brf. The other 24 brm manifested at least some characteristics of cross-gender-identification. **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Zucker 1992	Children referred consecutively to a gender identity service	Clinic specialising in gender identity problems in children and adolescents, which is housed within the child psychiatry service of a psychiatric research institute. From information in paper, it is likely to be the Child and Adolescent Gender Identity Clinic, Child and Family Studies Centre, Clarke Institute of Psychiatry, Toronto	Not reported	92 referred 3 excluded (age 3-4) as too young for assessment task; 3 excluded as data lost; 7 excluded as dropped out n=79	**Age at referral:** Not reported **Age at assessment:** Mean age 7.8 (SD 2.7) (6.5 (2.1) for those diagnosed with gender identity disorder and 9.4 (2.5) for those not diagnosed. **Birth-registered sex:** 9 (11.4%) female and 70 (88.6%) male	**Gender identity:** Not reported **Gender dysphoria:** 44 (55.7%) (8 (88.9%) brf and 36 (51.4%)brm) met criteria for diagnosis of gender identity disorder in childhood (only Point A criteria used for brf due to disagreement on Point B). 35 (44.3%) manifested some characteristics of cross-gender identification (met some diagnostic criteria). **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Zucker 1993	Children referred consecutively to a gender identity service. Two other children for whom there was concern about their gender identity development but who were not formally referred.	Clinic specialising in gender identity problems in children and adolescents, which is housed in a children's department within a university's psychiatric research institute. From information in paper, it is likely to be the Child and Adolescent Gender Identity Clinic, Child and Family Studies Centre, Clarke Institute of Psychiatry, Toronto	5-year period	98 referred plus 2 others assessed 15 excluded as dropped out n=85	**Age at referral:** Not reported **Age at assessment:** Mean age 6.8 (SD 2.3) (mean age of those diagnosed with GID was 5.9 (1.7) and those not diagnosed was 8.2 (2.4). **Birth-registered sex:** 14 (16.5%) female and 71 (83.5%) male. Of referred, 16 female and 82 male.	**Gender identity:** Not reported **Gender dysphoria:** 52 met complete criteria for diagnosis of gender identity disorder and 33 did not, although they all manifested some characteristics of cross-gender identification. Group meeting criteria were significantly younger than those who did not. **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Zucker 1997	Children age 3-12 referred to and then assessed in a gender identity service.	Child and Adolescent Gender Identity Clinic, Child and Family Studies Centre, Clarke Institute of Psychiatry, Toronto. Established 1978. Housed in a children's department within a psychiatric research institute.	1978 to 1995	275 referred Excluded 29 (dropped out of assessment) n=246	**Age at referral:** Not reported **Age at assessment:** Of referred, mean age 7.8 (SD 2.9) brf and 7.1 (2.5) brm. **Birth-registered sex:** 32 (13.0%) females and 214 (87.0%) males. Of referred, 36 (13.1%) female and 239 (86.9%) male. M:F sex ratio 6.6:1	**Gender identity:** Reported sum scores for CBCL item 5 (behaves like opposite sex) and 110 (wishes to be of opposite sex) (range 0-4). Mean score 2.8 (SD 1.3) brf and 2.3 (1.3) brm; Gender Identity Questionnaire mean scores (range 1-5) were 3.4 (0.5) brf and 3.1 (0.5) brm. **Gender dysphoria:** 123 (57.5%) brm and 20 brf (64.5%, of 31 assessed) met complete diagnostic criteria for gender identity disorder. **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** CBCL internalising problems mean T score 61.9 (SD 10.9) brf (n=29) and 60.8 (10.6) brm (n=205). **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Zucker 1999	Children referred to, and then assessed in a gender identity service for problems in their gender identity development	Clinic specializing in gender identity problems in children and adolescents, which was housed in a children's department within a psychiatric research institute in Toronto.	1978 to 1995	236 referred 30 excluded (9 data not collected, 20 age 11-12 removed to ensure comparability to controls, 1 no cross-gender identification) n=206	**Age at referral:** Not reported **Age at assessment:** Mean age 6.6 (SD 2.1) **Birth-registered sex:** 22 (10.7%) female and 184 (89.3%) male. Of referred, 29 female and 207 male.	**Gender identity:** Not reported **Gender dysphoria:** 132 (64.1%) met the complete diagnostic criteria for gender identity disorder (GID) of childhood and 74 (35.9%) did not. Of these, all manifested some characteristics of cross-gender identification and were considered subthreshold for the diagnosis of GID.On the Gender constancy gender identity question 9 (Are you a girl or a boy? Are you a (opposite sex of subject's first response)?), 192 (93.2%) responded according to their birth-registered sex (paper reports this as passed) and 14 (6.8%) gave the opposite (paper reports this as failed). **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Zucker 2002	Children (< 13 years) and adolescents (13 years or older) referred consecutively to, and then assessed in a child and adolescent gender identity service. Excluded boys referred for fetishistic cross-dressing who showed no signs of gender identity development problems, and adolescents with co-occuring transvestic fetishism or autogynephilia.	The Child and Adolescent Gender Identity Clinic, which is housed within the Child Psychiatry Program at the Centre for Addiction and Mental Health – Clarke Division (Toronto)	1975 to 2000	n=430 358 children, 72 adolescents Excluded 15 boys referred for fetishistic cross-dressing. Adolescents excluded based on criteria not reported.	**Age at referral:** Not reported **Age at assessment:** Child mean age 7.2 (SD 2.5), range 3.2-12.95. Adolescent mean age 15.8 (1.3), range 13.2-19.9. **Birth-registered sex:** 84 (19.5%) female and 346 (80.5%) male. Among children, 53 female and 305 male (M:F ratio 5.75:1). For adolescents, 31 female and 41 male (M:F ratio 1.32:1)	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** CBCL internalising problems mean T score for children 60.8 (SD 11.0) (n=343), for adolescents 69.2 (66.2) (n=46). **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

Zucker 2010	Adolescents referred consecutively to, and then assessed in, a Gender Identity Service. Adolescent referred for other reasons were excluded: 1) those with transvestic fetishism without co-occurring gender dysphoria, 2) with cross-gender behavior but without explicit desire to be the other sex and no clear sexual orientation, 3) adolescents with a gay/lesbian or bisexual sexual orientation. Baseline assessment data used.	The Gender Identity Service, which is housed within the Child, Youth, and Family Program at the Centre for Addiction and Mental Health, Toronto	2000 to 2009	165 referred Excluded 56 adolescents referred for other reasons as specified (1. n=35, 2. n=6, 3. n=15) n=109	**Age at referral:** Not reported **Age at assessment:** Mean age 16.8 (SD 1.7) **Birth-registered sex:** 55 (50.5%) female and 54 (49.5%) male	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Zucker 2012a	Adolescents referred consecutively to, and then assessed in, a Gender Identity Service. Adolescents referred for gender identity disorder or transvestic fetishism (TF) were included. Excluded 1) adolescents with a homosexual sexual orientation and 2) undifferentiated adolescents.	The Gender Identity Service, which is housed within the Child, Youth, and Family Program at the Centre for Addiction and Mental Health, Toronto	1976 to 2009	417 referred 88 adolescents excluded based on inclusion criteria (1. n=54, 2. 34). n=329 (192 with GID, 137 with TF) n=192 with GID	**Age at referral:** Not reported **Age at assessment:** Mean age brf 16.4 (SD 1.7), range 13.2-21.8. Mean age brm 16.3 (1.7), range 13.4-20.8. **Birth-registered sex:** 87 (45.3%) female and 105 (54.7%) male.	**Gender identity:** CBCL and YSR sum mean scores for item 5 (behaves like opposite sex) and 110 (wishes to be of opposite sex) (range 0-4) were 3.3 (SD 1.0) and 3.7 (0.6) brf (n=69, 71), and 2.8 (1.2) and 3.3 (1.0) brm (n=79, 79). Gender Identity/Gender Role Questionnaire for Adolescents (GIGRQ-Ad) total mean scores were 2.2 (0.7) brf (n=64) and 2.6 (1.0) brm (n=79). Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults (GIQAA) total mean scores were 2.2 (0.4) brf (n=54) and 2.5 (0.5) brm (n=48). **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression and anxiety:** CBCL internalising problems mean T score 67.6 (SD 9.2) brf (n=71) and 69.8 (9.3) brm (n=83). YSR scores 60.3 (10.9) brf (n=72) and 64.8 (12.6) brm (n=81). **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Zucker 2012b	Children (age 2-12) referred to, and then assessed in a gender identity service for problems in gender identity development.	Gender Identity Service, Child, Youth, and Family Program at the Centre for Addiction and Mental Health in Toronto. Since the clinic was established in the mid-1970s, a total of 590 children have been evaluated.	2008	n=26	**Age at referral:** Not reported **Age at assessment:** Mean age 6.5 (SD 2.3, range 3-12 (individual ages reported 10, 7, 5, 6, 9, 5, 3, 7, 6, 8, 12, 8, 7, 6, 7, 6, 4, 10, 6, 3, 10, 6, 4, 5, 4, 5) **Birth-registered sex:** 8 (30.8%) female and 18 (69.2%) male	**Gender identity:** Not reported **Gender dysphoria:** 24 (92.3%) met diagnostic criteria for gender identity disorder, 1 was subthreshold, and 1 showed no signs of gender identity disorder **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Zucker 2017	Children referred for gender dysphoria to and then assessed in a gender identity service for children.	A specialty gender identity service for children, housed within a child psychiatry program at an academic health science center. Information in paper suggests this is Toronto clinic.	1986 to 2013	531 referred or assessed 145 excluded as data not available n=386	**Age at referral:** Not reported **Age at assessment:** Mean age 7.8 (SD 2.4) **Birth-registered sex:** 82 (21.2%) female and 304 (78.8%) male	**Gender identity:** Not reported **Gender dysphoria:** 100% met DSM-III, DSM-IV or DSM-5 criteria for Gender Identity Disorder / Gender Dysphoria or were subthreshold for the diagnosis. **Onset:** Not reported **Social transition:** Not reported	**Depression and anxiety:** CBCL internalising problems mean score for included children (n=386) was 62.1 (SD not reported). For excluded children (n=145), mean score was 56.8. **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Items 9 (obsessions) and 66 (compulsions) on the Teacher's Report Form (TRF) were used to measure intense / obsessional interests. 30 (38.0%) brf scored 1 or 2 for item 9, and 123 (41.7%) brm. For item 66, 8 (10.0%) brf and 55 (18.2%) brm scored 1 or 2. **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Denmark									
Kaltiala 2020	Children and adolescents referred to gender service	Publicly funded, nationally centralised GIDs for minors under 18. A GIDS for minors was established in Copenhagen in 2016.	2016 to 2017	Absolute referral numbers	**Age at referral:** Not reported **Age at assessment:** Not reported **Birth-registered sex:** F:M ratio 2016=2.96 , 2017=3.87	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Finland									
Kaltiala-Heino 2015 (linked paper Sumia 2019)	All adolescents who entered the assessment process for sex reassignment	Specialised multi-disciplinary adolescent gender identity teams at Tampere and Helsinki University Hospitals (these are the only two specialised services for adolescents in Finland)	First two years (2011 to December 2013)	49 referred 2 dropped out n=47	**Age at referral:** Not reported **Age at assessment:** Mean age (SD) 16.04 (0.57) brm and 16.66 (1.07) brf **Birth-registered sex:** 41 (87.2%) female and 6 (12.8%) male	**Gender identity:** Not reported **Gender dysphoria:** All were reported to have gender dysphoria. Gender Identity / Gender Dysphoria Questionnaire for adolescent median score (IQR) = 2.2 (2.0-2.6) brm and 2.1 (1.9-2.3) brf (<3.0 suggest clinically significant GD). **Onset**: 14 (29.8%) reported questioning their gender before age 12, 30 (63.8%) at 12 or later, and 3 (6.4%) applicants could not define this. 5 (10.6%) persistently expressed GD and/or identified with opposite sex during childhood, 3 (6.4%) transient, 9 (19.1%) tomboyish girls but no gender questioning or dysphoria. 30 (63.8%) no recalled GD or cross-gender behaviours during childhood. Recalled Childhood Gender Identity scale scores also reported (female-typical sub-scale mean (sd) brm 15.0 (6.8), brf 13.4 (4.4); male-typical sub-scale brm 9.2 (4.2), brf 11.2 (3.0); gender conformity sub-scale brm 16.0 (6.1), brf 15.6 (4.2); gender nonconformity sub-scale brm 11.7 (4.5), brf 10.8 (3.2). During assessment, 34 (72.3%) were sure about feeling opposite sex to their natal sex (5 (14.7%) reached conclusion before age 12, 27 (79.4%) at 12 or later, 2 (5.9%) unsure) and 13 (27.7%) were not sure about feelings regarding gender identity. No difference between brf anf brm. **Social transition:** 18 (38.3%) were living in desired role when assessment was completed (3 (50%) brm and 15 (36.6%) brf). Mean (SD) / median time of living in desired role was 28.3 (17.9) / 24.0 months brm, and 29.8 (39.2) / 12 months brf.	**Depression:** 30 (64%) Previous or current psychiatric treatment for depression **Anxiety:** 26 (55%) treatment for anxiety disorder **Suicide and self-harm:** 25 (53%) treatment for suicidal and self-harming behaviours **Eating disorder:** 1 severe case of anorexia nervosa was noted (no other data provided)	**ASC:** 12 (26%) previous or current psychiatric treatment for ASD **ADHD:** 5 (11%) treatment for ADHD	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Kaltiala-Heino 2019	Adolescents desiring gender re-assignment who attended for an assessment	One of the two adolescent gender identity services in Finland - Tampere University Hospital	2011 to 2015	107 8 excluded (did not complete assessment) n=99	**Age at referral:** Not reported **Age at assessment:** Mean (SD) age brf 16.86 (0.94) years, and brm 16.91 (0.91) years. Range 14-18 years. **Birth-registered sex:** 84 (84.8%) female and 15 (15.2%) male	**Gender identity:** Not reported **Gender dysphoria:** All reported as having gender dysphoria (no data provided) **Onset:** Age of onset of gender dysphoria - 1 (6.7%) brm and 5 (6.0%) brf <12 years; 12 (80.0%) brm and 79 (94.0%) brf 12 or later. **Social transition:** Not reported	**Depression:** 8 (53.3%) brm and 57 (67.9%) brf with previous or current psychiatric treatment contact due to depression **Anxiety:** 7 (46.7%) brm and 50 (59.5%) brf with previous or current psychiatric treatment contact due to anxiety **Suicide and self-harm:** 6 (40.0%) brm and 47 (56.0%) brf with previous or current psychiatric treatment contact due to suicidality / self-harm **Eating disorder:** Not reported	**ASC:** 2 (13.3%) brm and 15 (17.9%) brf with previous or current psychiatric treatment contact due to ASD **ADHD:** 3 (20.0%) brm and 5 (6.0%) brf with previous or current psychiatric treatment contact due to ADHD	**Neglect or abuse:** 5.2% reported experiences of sexual abuse (no other details provided) **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Kaltiala 2020*	Children and adolescents referred to gender service	Specialised multi-disciplinary adolescent gender identity teams at Tampere and Helsinki University Hospitals (opened in 2011)	2010 to 2017	n=600 Numbers per year reported	**Age:** Not reported **Birth-registered sex:** Female:male ratio 3.7 in 2011, 5.0 in 2012, 6.7 in 2013, 7.4 in 2014, 6.8 in 2015, 7.8 in 2016, 8.3 in 2017. Overal ratio was 0.3 in children (0-12 years), and 7.1 in adolescents (13-17).	**None reported**	**None reported**	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

Vehmas 2021	Adolescents with gender dysphoria seeking hormone interventions who were assessed at a gender service and then referred to an adolescent gynecology clinic (n=124)	Adolescent gynecology clinic at Helsinki University Hospital	January 2011 to December 2018	n=124	**Age at referral:** Not reported **Age at assessment:** Median age (range) at first contact with gender identity service 16.7 years (12.1-18.0). Age at GD diagnosis 18.1 (14.8-20.1). Age at time of assessment at gynecology clinic 17.7 (14.6-19.8). Median ages did not differ between gender groups or change significantly by time during study period. **Birth-registered sex:** 104 (83.9%) female and 20 (16.1%) male. Female: male ratio 1.2 in 2011, 2.3 in 2012, 3.4 in 2013, 4.3 in 2014, 4.9 in 2015, 5.3 in 2016 and 5.6 in 2017	**Gender identity:** Not reported **Gender dysphoria:** All were diagnosed with GD (median (range) age at diagnosis 18.1 (14.8-20.1)) **Onset:** Not reported **Social transition:** Not reported	**Depression:** 36 (29.0%); 31 (29.8%) brf, 5 (25.0%) brm. 31 (25.6%) using anti-depressants (27 (26.2%) brf, 4 (22.2%) brm). Percentage of adolescents with depression did not change with time. **Anxiety:** 24 (19.4%); 20 (19.2%) brf, 4 (20.0%) brm. Percentage of adolescents with anxiety did not change with time. **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** 2 (1.6%); brf 2 (1.9%) brm 0 (0.0%)	**ASC:** 2 (1.6%) brf 1 (1.0%) brm 1 (5.0%) **ADHD:** 5 (4.0%) brf 3 (2.9%) brm 2 (10.0%)	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** 10 (8.4%) had experienced death or permanent hospitalisation of a parent.
Germany									
Becker-Hebly 2020, Nieder 2021	Children and adolescents with gender-variant behaviours and/or experiences who presented at a gender identity service	Hamburg Gender Identity Service, University Medical Center Hamburg-Eppendorf. Established in 2006 and is one of five specialized clinics in Germany for the treatment of children and adolescents with gender dysphoria (GD). Since its establishment, the clinic has provided specialized GD-related diagnostics and treatment for more than 900 referred families.	September 2013 to June 2017	434 children and adolescents referred 270 completed baseline assessment Further sub-sample of 75 were focus of study - data not reported for this selected sub-sample of treated adolescents.	**Age at referral:** Not reported **Age at assessment:** Not reported **Birth-registered sex:** Of referred (n=434), 72% female and 28% male.	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Brecht 2021	Treatment-seeking adolescents (age 12 or over) with gender incongruence according to ICD-11, based on clinical documentation at time of first presentation to a gender identity service.	Gender Identity Special Consultation (GISC) at the Charité Universitätsmedizin Berlin, Germany. Affiliated with Department of Child and Adolescent Psychiatry, specialises in care of children and adolescents with gender incongruence within an inter-disciplinary team. Offers education and treatment ranging from psychological counseling to endocrinological and phoniatric treatment.	December 2018 to November 2020	66 referred 16 excluded as CBCL/YSR data not available n=50	**Age at referral:** Not reported **Age at assessment:** Mean age 15.5 (SD 1.6), range 12–18. **Birth-registered sex:** 39 (78.0%) female and 11 (22.0%) male.	**Gender identity:** 38 (76.0%) transboys, 11 (22.0%) transgirls, 1 (2.0%) non-binary **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression and anxiety:** YSR and CBCL internalising problems mean T-score and percentage in clinical range compared to male norms were 66.82 (SD 12.73), 61.5% and 66.58 (11.66), 56.4% brf and 62.55 (10.85), 54.5% and 66.91 (13.10), 54.5% brm. Compared to female norms, scores were 63.05 (11.78), 48.7% and 64.13 (11.46), 56.4% brf, and 58.27 (9.78), 54.5% and 64.36 (12.04), 45.5% brm. YSR and CBCL anxious / depressed scale mean T-score and percentage in clinical range compared to male norms were 67.05 (10.50), 43.6% and 64.25 (10.51), 35.9% brf and 60.91 (10.62), 18.2% and 63.00 (10.75), 27.3% brm. Compared to female norms, scores were 64.87 (10.13), 35.9% and 64.11 (10.70), 38.5% brf, and 58.91 (9.24), 9.1% and 61.82 (10.73), 27.3% brm. **Suicide:** At initial assessment, 54.0% reported suicidality (suicidal thoughts, intentions, or attempted suicide). **Self-harm:** At initial assessment, 48.0% stated that they had already harmed themselves at least once. **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** YSR and CBCL attention problems mean T-score and percentage in clinical range compared to male norms were 61.33 (11.58), 15.4% and 58.30 (8.26), 10.3% for brf, and 59.36 (6.90), 9.1% and 65.55 (11.30), 36.4% for brm. Compared to female norms, scores were 61.87 (11.40), 28.2% and 59.94 (8.55), 10.3% for brf, and 60.18 (6.79), 18.2% and 67.82 (11.14), 36.4% for brm.	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Hartig 2022	Children (age 5-10) and adolescents (age 11-18) who received a gender dysphoria diagnosis at a specialist service (data collected at initial visit following referral).	Hamburg Gender Identity Service, University Medical Center Hamburg-Eppendorf. MDT providing specialised care to provides specialized care to children and youths.	September 2013 to December 2019	859 referred 278 chose not to participate; 103 dropped out due to missing data; 51 excluded due to having prior treatment; 35 no GD diagnosis n=392 49 children, 343 adolescents In total referred (n=859), 74% were birth-registered female.	**Age at referral:** Not reported **Age at assessment:** Mean age 14.6 (SD 2.9) (brf 15.0 (2.2), brm 12.9 (4.2)). For children age 5-10, mean age 8.2 (1.9) (brf 9.0 (1.7), brm 7.7 (1.9)). For adolescents age 11-18, mean age 15.5 (1.5) (brf 15.4 (1.5), brm 15.7 (1.6). **Birth-registered sex:** 306 (78.1%) female and 86 (21.9%) male. Of those age 5-10, 19 (38.9%) female and 30 (61.2%) male. Of those 11-18, 287 (83.7%) female and 56 (16.3%) male.	**Gender identity:** Not reported **Gender dysphoria:** 316 (80.6%) met complete diagnostic criteria for gender dysphoria, 30 (7.6%) partially fulfilled criteria (subthreshold), 46 (11.7%) missing diagnostic criteria / still ongoing **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide and self-harm:** Children's CBCL for item 18 (deliberate self-harm or attempted suicide) - 3 (6.1%, 95% CI 0.0-9.3) reported any (2 (4.1%, 0.0-9.3) sometimes, 1 (2.0%, 0.0-5.5) often). Adolescent CBCL for item 18 - 100 (29.0%, 6.9-23.9) reported any (67 (19.5%, 15.1-23.9) sometimes, 33 (9.5%, 6.9-12.9) often). Adolescent YSR for item 18 - 155 (45.1%, 15.5-30.9) reported any (89 (25.9%, 21.2-30.9) sometimes, 66 (19.2%, 15.5-23.4) often. Children's CBCL for item 91 (suicidal ideation) - 8 (16.3%, 0.0-27.9) reported any (all of these indicated sometimes, CI 5.9-27.9). Adolescent CBCL for item 91 - 68 (19.8%, 0.8-21.9) reported any (61 (17.8%, 13.8-21.9) sometimes, 7 (2.0%, 0.8-3.7) often). Adolescent YSR for item 91 - 131 (38.2%, 9.3-30.6) reported any (87 (25.4%, 21.3-30.6) sometimes, 44 (12.8%, 9.3-15.9) often. Sum Suicidality Index (sum score of item 18 and 91, range 0-4) mean CBCL score for children 0.25 (SD 0.63); 0.21 (0.54) brf, 0.27 (0.69) brm. Mean CBCL and YSR score for adolescents 0.61 (0.97) and 1.15 (1.35) (YSR brf 1.24 (1.38) brm 0.71 (1.12)). **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Levitan 2019	All families of adolescents (age 11 or older) who attended a first appointment at a gender identity service were invited to take part. Eligibility for study was a diagnosis of gender dysphoria (GD).	Hamburg Gender Identity Service, University Medical Center Hamburg- Eppendorf. Provides specialised services for children and adolescents with gender identity issues with a possibility of a referral to an endocrinology specialist for further medical treatment.	September 13 to June 2017	434 children and adolescents referred, 124 dropped out, 40 missing data Excluded 38 children, 8 adolescents with psychosis, 2 with prior medical treatment, 42 GD criteria not fully met or not determined yet n=180	**Age at referral:** Not reported **Age at assessment:** Mean age 15.53 (SD 1.35). brf 15.54 (1.33) and brm 15.51 (1.47). **Birth-registered sex:** 146 (81.1%) female and 34 (18.9%) male. Of adolescents completing assessment, 79% female and 21% male. Of all referred (n=434), 72% female and 28% male.	**Gender identity:** Mean sum score (range 0-4) for CBCL item 5 (behaves like opposite sex) and 110 (wishes to be of opposite sex) 3.84 (SD 0.41) (3.88 (0.36) for brf, 3.68 (0.54) brm). **Gender dysphoria:** Of 222 adolescents providing data, 180 (81.1%) met full criteria (included sample), 24 (10.8%) partially met criteria (subthreshold), 6 (2.7%) did not meet criteria, 12 (5.4%) diagnostic procedure ongoing **Onset:** Not reported **Social transition:** Social transition status at initial appointment. Mean score 2.90(SD 1.07) (2.99 (1.05) brf and 2.50 (1.08) brm). This was measured on a scale of 1 (no social transition and living in birth-assigned gender role); 2 (partial social transition in at least 1 out of 3 life areas (home, peers, school or in between gender roles); 3 (almost complete social transition, living in new gender role in at least 2 of 3 life areas); 4 (complete social transition in all life areas).	**Depression and anxiety:** YSR internalising problems raw mean score 20.7 (SD 10.38, CI 19.17-22.22). brf 21.1 (10.67, 19.32-22.81) and brm 19.1 (9.01, 15.97-22.26). T-scores were 65.2 (10.64, 63.67-66.80) (brf 64.8 (10.81, 63.07-66.60) brm 66.9 (9.85, 63.51-70.38). **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Roder 2018	Adolescents referred to gender identity service and diagnosed with gender dysphoria who provided consent and data for study.	Hamburg Gender Identity Service, University Medical Center Hamburg- Eppendorf. MDT providing specialised care to provides specialized care to children and youths (age 5-18).	2013 to 2016	203 children and adolescents assessed Excluded 77 on basis of inclusion criteria / missing datat n=126	**Age at referral:** Not reported **Age at assessment:** Mean age 15.6 (SD 1.4), range 11.6 and 18.2. Mean age brf 15.6 (1.3), range 11.6 – 18.2. brm 15.7 (1.6), range 11.8 – 18.0. **Birth-registered sex:** 103 (81.7%) female and 23 (18.3%) male	**Gender identity:** 23 (18.3%) trans females and 103 (81.7%) trans males. **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression and anxiety:** YSR internalising problems mean score brf 21.4 (10.2) and brm 20.6 (7.1). **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Sievert 2021	All families of children (under age 12) who attended a a first appointment at a gender identity service and received a diagnosis of gender dysphoria (GD)	Hamburg Gender Identity Service for Children and Adolescents (Hamburg GIS), University Medical Center Hamburg-Eppendorf. Founded in 2006.	September 2013 to December 2018	680 (age 5-18) referred (89 children, 591 adolescents) 167 dropped out, 65 missing data Excluded 381 adolescents, 13 children not meeting GD criteria n=54	**Age at referral:** Not reported **Age at assessment:** Mean age 9.05 (SD 2.08) (brf 9.98 (1.53), brm 8.25 (2.17)). **Birth-registered sex:** 25 (46.3%) female and 29 53.7%) male. Of children (< age 12), 48% female and 52% male. Of all referred (680), 74% female and 26% male.	**Gender identity:** Not reported **Gender dysphoria:** Of 67 children providing data, 54 (80.6%) met criteria and 13 (19.4%) did not. All included sample (n=54) met criteria (inclusion criteria for analysis sample) **Onset:** Not reported **Social transition:** Social transition status at initial appointment. Mean score 2.60 (SD 1.27) (2.58 (1.32) brf and 2.61 (1.26) brm). This was measured on a scale of 1 (no social transition and living in birth-assigned gender role); 2 (partial social transition in at least 1 out of 3 life areas (home, peers, school or in between gender roles); 3 (almost complete social transition, living in new gender role in at least 2 of 3 life areas); 4 (complete social transition in all life areas).	**Depression and anxiety:** CBCL mean T-scores 59.87 (SD 11.59, CI 56.71-63.03. brf 60.68 (10.20, 56.47-64.89). brm 59.17 (12.80, 54.30-64.04). **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Israel									

Segev-Becker 2020	Children and young people <18 refererred to specialist clinic with GD diangosis (DSMS).	Gender dysphoria clinic ant Dana-Dwek Childrens Hospial , Tel Aviv Medical Centre (estbalished March 2013)	March 2013 to December 2018	106 referred	**Age at referral: mean** 15.5 (range 4.6 to 18.5) **Age at assessment:** Not reported **Birth-registered sex:** (F:M) 2013=1:2, 2014: 0:3, 2015=3:14, 2016=9:11, 2017=23:7, 2018=23:10	**Gender identity:** 59 (56%) identified as transgender males **Gender dysphoria:** All DSM5 GD diagnosis **Onset**: Not stated for full sample **Social transition:** Not stated for full sample	**Depression:** 26 (27%) **Anxiety:** Not reported **Suicide:** thoughts - 11 (11%), attempts - 13 (14%) **Self-harm:** Not reported **Eating disorder:** 5 (5%); brf 2 (3.5%) brm 3 (8%) *These are only reported for pubertal group (n=96)*	**ASC:** 4 (4%) **ADHD:** 26 (27%) *These are only reported for pubertal group (n=96)*	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Italy									
Fisher 2017	Gender-referred adolescents attending several Italian Gender Clinics <18 with diagnosed GD	Sexual Medicine and Andrology Unit of the University of Florence and Gender Clinics of Rome, Milan, and Naples University Hospitals.	September 2014 to February 2016	47 met the parrticipation criteria; 46 included in the analysis	**Age at referral:** Not reported **Age at assessment:** mean 16.35 SD 1.32 **Birth-registered sex:** F:M ratio 1.3:1	**Gender identity:** Transgender female (n=20) and Transgender male (n=26) **Gender dysphoria:** gender dysphoria levels (GIDYQ-AA) mean 2.27 SD 0.40 **Onset**: GD onset <6 years old - 22 (47.8%) **Social transition:** Not reported	**Depression and anxiety:** YSR internalising - mean 62.43 SD 11.18; clinical range - (47.8%) **Suicide:** ideation - 40 (87.0%); attempts - 6 (13.0%) **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Lifetime maltreatment 31 (67.4%) **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Adopted 4 (8.7%)
Mirabella 2022	All adolescents (11 to 18) who had consectively referred to the specialist gender clinics	Specialist gender identity service in Rome and Gender Incongruence Unit of the Careggi Hospital in Florence	April 2019 to June 2021	125 adolescents, 94 referred to the SAIFIP; 31 referred to GI unit	**Age at referral:** Not reported **Age at assessment:** mean 15.37 SD 1.41; 11-14: 32 (26%); 15-18: 93 (74%) **Birth-registered sex:** 85 (68%) female and 40 (32%)	**Gender identity:** 93 (74.4%) trans binary identity, 23 (18.4%) non-binary, 5 (4%) agender, 3 (2.4%) did not identify with any category, and 7 (5.6%) described themselves as undefined. **Gender dysphoria:** Gender Identity/gender dysphoria questionnaire (GIDYQ-AA) brm mean 2.47 SD 0.39 brf mean 2.56 SD 0.88 **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Lving in a foster household 5 (4%)
Ristori 2021	Consecutive series of gender-referred adolescents (11 to 18) on their first day of admission	Gender Clinic of the University of Florence	September 2015 to April 2020	55 referred; 2 not GD/GI, 1 had previous used gender-affirming hormone treatment and 2 refused to participate; 40 included in final sample	**Age at referral:** Not reported **Age at assessment:** Not reported **Birth-registered sex:** 18 males and 21 females, ratio 1:1.8	**Gender identity:** 18 brm and 32 brf **Gender dysphoria:** All DSM5 **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** YSR Anxiety and depression brm mean 12.30 SD 6.39 brf mean 10.71 SD 5.79 **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Netherlands									
Aitken 2015*	Adolescents (aged 13 years or older) referred for gender dysphoria to specialist gender clinic.	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	1989 to 2013	186 from years 1989-2005 234 from years 2006-2013 n=420	**Age at referral:** Not reported **Age at assessment:** Mean age 16.1 (SD 1.6). No significant difference in age between brm and brf. **Birth-registered sex:** From 1989-2005, 77 (41.4%) female and 109 (58.6%) male. M:F ratio 1.41:1. From 2006-2013, 148 (63.3%) female and 86 (36.7%) male. M:F ratio 1:1.72. Study reported significant difference in sex distribution between two time periods.	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Alberse 2019	Children and adolescents (aged 8 years or older) referred for gender dysphoria to specialist gender clinic - data collected during assessment. New referrals only.	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	January 1996 to January 2016 children, January 2004 to January 2016 adolescents	644 children referred, 193 under 8 excluded, 146 missing data excluded, n=305 997 adolescents referred, 190 returning to service excluded, 155 assessed pre 2004 excluded, 283 missing data excluded, n=369 Total n=674	**Age at referral:** Not reported **Age at assessment:** Children: mean age 9.1 (SD 1.5), range 5.9-13.0. Adolescents: mean age 15.3 (SD 1.8), range 10.7-18.0. Significant difference between age of children and adolescents indicated. **Birth-registered sex:** Children: 143 (46.9%) female, 162 (53.1) male. Adolescents 251 (68%) female, 118 (32%) male. Significant difference in sex distribution between children and adolescents indicated.	**Gender identity:** Not reported **Gender dysphoria:** All struggled with gender identity which was reason for referral, but not all may meet DSM criteria for gender dysphoria. Severity of gender dysphoria measured but results not reported. **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Arnoldussen 2020	All consecutively referred adolescents registered at specialist gender clinic (pubertal because all could be eligible for medical interventions - no minimum age reported)	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	2000 to 2016	n=1072 Numbers per year reported	**Age at referral:** Not reported **Age at assessment:** Mean 14.6 (2.2), range 10.1-18.1. **Birth-registered sex:** 668 (62.3%) female and 404 (37.7%) male. No. of males per year from 2000-2016: 11, 10, 9, 15, 18, 19, 7, 17, 14, 20, 17, 17, 18, 52, 53, 48, 60. Female: 1, 10, 4, 9, 6, 13, 16, 21, 36, 17, 22, 24, 30, 60, 88, 137, 173. Year of assessment was significant predictor for birth-registered sex, with females over-represented in later compared to earlier years.	**Gender identity:** Not reported **Gender dysphoria:** 908 (84.7%) diagnosed, 57 (5.3%) not diagnosed, 107 (10%) unknown. Perecentage per year from 2000-2016: 76.6, 84.8, 92.0, 79.1, 74.7, 81.3, 78.2, 81.5, 89.8, 88.8, 97.2, 87.5, 85.1, 81.8, 91.9, 82.7, 81.3. Regression found that proportion diagnosed did not significantly change over time. Analysis found that the intensity of the feeling of gender dysphoria did not significantly change over time (as measured by the Utrecht Gender Dysphoria Scale). **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** Analyses showed no trend over time in the mean internalizing total T-scores or the clinical range total T-scores on the CBCL and the YSR. Data not reported. **Suicide and self-harm:** Analyses showed no trend in time in the Suicidality Scale score for the CBCL and YSR (items 18 and 91). Data not reported. **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Balleur-van Rijn 2013	Children (age 8-12 years) consecutively referred to a gender identity clinic (initial assessment data used)	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	1996 to 2009	n=147	**Age at referral:** Not reported **Age at assessment:** Mean age brf 9.9 (SD 1.2) and brm 9.6 (1.1) **Birth-registered sex:** 57 (38.8%) female and 90 (61.2%) male	**Gender identity:** Not reported **Gender dysphoria:** 90 (61.2%) were diagnosed with Gender Identity Disorder (44 (77.2%) brf, 46 (51.1%) brm). Others were sub-threshold for the diagnosis. **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Bungener 2017	Adolescents consecutively referred to specialist gender clinic who provided data for the study (data collected at initial assessment)	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	June 2011 to December 2013	183 referred 46 excluded (10 dropped out of care, 36 did not complete/return questionnaires) n=137	**Age at referral:** Not reported **Age at assessment:** Mean age 14.7 (SD 2.2), range 10.9-17.7. Mean age brm 14.11 (2.2) range 11.3-17.6, brf 15.14 (2.1) range 10.9-17.7 **Birth-registered sex:** 60 (43.8%) birth-registered males, 77 (56.2%) female	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Cohen 1997	All adolescent patients who attended a gender clinic. All were early age sex reassignment surgery applicants. All were diagnosed as transexuals.	Gender clinic of the Department of Child and Adolescent Psychiatry of the University of Utrecht Hospital, Utrecht - reported as the only gender clinic for adolescents in the Netherlands at the time of the study	Not reported	32 referred 3 excluded due to invalid data n=29	**Age at referral:** Not reported **Age at assessment:** Mean age 17.2 (SD 1.8). **Birth-registered sex:** 20 (69.0%) female, 9 (31.0%) male	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

Cohen-Kettenis 2003*	Children consecutively referred to a gender clinic.	Gender clinic of the Department of Child and Adolescent Psychiatry of the University of Utrecht Hospital, Utrecht - reported as the only gender clinic serving children and adolescents in the Netherlands at the time of the study	1988 to 2000 Largest number assessed in 1997 and 2000 (n=20)	n=130	**Age at referral:** % cases: age 3/4=0, 4/5=2.3, 5/6=9.8, 6/7=18.9, 7/8=18.9, 8/9=16.7, 9/10=11.4, 10/11=9.2, 11/12=9.8, 12/13=3.0 **Age at assessment:** Mean age 8.1 (SD 2.0), range 4.5-12.5 **Birth-registered sex:** 33 (25.4%) female, 97 (74.6%) male, M:F ratio 2.93:1	**Gender identity:** Reported sum scores for CBCL item 5 (behaves like opposite sex) and 110 (wishes to be of opposite sex). Mean score 3.6 (SD 0.9) brf and 2.8 (1.2) brm. **Gender dysphoria:** 102 (78.5%) met complete DSM criteria for gender identity disorder. **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** Mean internalising T-score 64.08 (SD 10.48) **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Cohen-Kettenis 2006*	Children and adolescents consecutively referred to a gender clinic and then assessed in the clinic	Gender clinic of the Department of Child and Adolescent Psychiatry of the University of Utrecht Hospital, Utrecht - established in 1988 and reported as the only gender clinic serving children and adolescents in the Netherlands until 2002 when clinic was tranferred to Amsterdam.	1988 to 2002	n=175 (GIQC not used for first 6 patients in service)	**Age at referral:** Not reported **Age at assessment:** Mean age 8.1 (SD 1.9), range 4-12 **Birth-registered sex:** 43 (24.6%) females and 132 (75.4%) males. M:F ratio 3.1:1	**Gender identity:** Gender Identity Questionnaire for Children (GIQC) mean score brf 2.5 (SD 0.5), brm 2.3 (0.6). **Gender dysphoria:** 122 (69.7%) met complete diagnostic criteria for Gender Identity Disorder. GIQC mean score 2.2 (SD 0.5) for those meeting complete criteria, 2.7 (0.6) for those subthreshold (meeting some criteria). **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
de Graaf 2018b*	All adolescents aged 12-18 who were referred to specialist gender identity clinic (data collected during initial assessment)	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam. Moved from Utrecht to Amsterdam in 2002 - one of longest standing gender services internationally. Only service for children and adolescents in the Netherlands.	January 2009 to December 2013	275 referred 23 excluded as data not available n=252	**Age at referral:** Not reported **Age at assessment:** Mean age 14.3 (SD 2.2), brf 14.8 (2.1) and brm 13.7 (2.2). **Birth-registered sex:** 136 (54.0%) female and 116 (46.0%) male	**Gender identity:** For CBCL and YSR item 110 (wishes to be of the opposite sex), mean sum score (range 0-2) brf was 1.9 (SD 0.3) and 2.0 (0.2), brm 1.7 (0.6) and 1.8 (0.5). **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** For CBCL and YSR internalising scale, mean score was 13.8 (SD 10.0) and 15.8 (9.3) for all, 14.9 (10.4) and 15.5 (9.4) brf, and 12.4 (9.3) and 16.1 (9.3) brm. On the CBCL, 99 (44.2%) were in the clinical range for internalising symptoms (59 (48.4%) brf, 40 (39.2%) brm). On the YSR, 64 (29.1%) were in the clinical range (25 (20.8%) brf, 39 (39.0%) brm). **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
de Graaf 2020*	Adolescents aged 13 or older who were referred and assessed at a specialist gender identity clinic (data collected during initial assessment)	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	1990 to 2012	n=266	**Age at referral:** Not reported **Age at assessment:** Mean age 15.9 (SD 1.4) **Birth-registered sex:** 143 (53.8%) female and 123 (46.2%) male	**Gender identity:** For CBCL item 110 (wishes to be of the opposite sex), 233 (93.5%) scored 1 or 2 and 16 (6.4%) scored 0. For the YSR, 233 (96.6%) scored 1-2 and 8 (3.3%) scored 0. **Gender dysphoria:** All met DSM criteria for Gender Identity Disorder or Gender Dysphoria **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide and self-harm:** Sum scores for CBCL and YSR item 18 (deliberate self-harm or attempted suicide) and 91 (suicidal ideation) calculated (score range 0-2). Mean scores were 0.8 (SD 1.1) on CBCL and YSR. Percentages scoring 1-2 on CBCL and YSR item 18: 17.2% and 25.8% brf and 8.6% and 14.5% brm. Percentages scoring 1-2 on CBCL and YSR item 91: 26.9% and 27.3% brf and 22.4% and 27.3% brm. **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
de Vries 2010	Children (age under 12) and adolescents (age 12-18) referred to a gender identity clinic and consecutively assessed (data collected during initial assessment)	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam. Only multi-disciplinary team-based clinic in the Netherlands examining children and adolescents experiencing gender dysphoria.	April 2004 to October 2007	231 referred 27 excluded due to not completing assessment procedure n=204 (108 children, 96 adolescents)	**Age at referral:** Not reported **Age at assessment:** Mean age 10.8 (SD 3.6). Mean age of children was 8.1 (1.8) and for adolescents 13.9 (2.3). **Birth-registered sex:** 89 (43.6%) female and 115 (56.4%) male	**Gender identity:** Not reported **Gender dysphoria:** Children: 52 (48.1%) Gender Identity Disorder (GID), 45 (41.7%) sub-threshold GID not otherwise specified (GID-NOS), 11 (10.2%) no GID diagnosis. Adolescents: 77 (80.2%) Gender Identity Disorder (GID), 8 (8.3%) sub-threshold GID not otherwise specified (GID-NOS), 11 (11.5%) no GID diagnosis. **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** 16 (7.8%), mean age 10.8 (SD 3.6). Incidence in those with GID diagnosis was 4.7% (n=6) and 17.0% (n=9) in those with GID-NOS diagnosis. 7 (6 birth-registered male and 1 female) of 11 children with suspected ASD on referral. Incidence 7.4% of all 108 children. 1 (1.9%) of those with GID diagnosis, 6 (13%) GID-NOS diagnosis, and 0 no GID diagnosis. Mean age of children with ASD 9.1 (not significantly different to those without (8.0)). 9 (6 male, 3 female) of 15 suspected ASD adolescents. Incidence 9.4% of all 96 adolescents. 5 (6.5%) of those with GID diagnosis, 3 (37.5%) GID-NOS diagnosis, and 1 (1.0%) no GID diagnosis. Mean age of adolescents with ASD 15.4 (significantly higher than those without (13.8)). **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
de Vries 2011a	Adolescents consecutively referred to specialist gender clinic and assessed (assessment data used)	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	April 2002 to December 2009	201 referred, 17 left service, 184 assessed 18 excluded due to previous study participation 166 invited, 66 declined / unable to attend n=105 Characteristics of 79 excluded similar except age at assessment which was older for sample (mean 14.4 vs. 13.9).	**Age at referral:** Not reported **Age at assessment:** Mean age 14.6 (SD 2.2) range 10.5-18.0. brf mean age 14.6 (2.2) range 10.7-18.0, brm 14.5 (2.2) range 10.5-18.0. **Birth-registered sex:** 52 (49.5%) female and 53 (50.5%) male	**Gender identity:** Not reported **Gender dysphoria:** 89 (84.8%) diagnosed with Gender Identity Disorder (GID), 16 (15.2%) were considered subthreshold for GID (met some but not all GID criteria). **Onset**: Not reported **Social transition:** Not reported	**Depression:** 13 (12.4%) any mood disorder; 2 (3.8%) brf and 11 (20.8%)brm. 9 (8.6%) major depression; 2 (3.8%) brf, 7 (13.2%) brm; 4 (3.8%) dysthymia (all brm 7.5% brm). Similar % for those in GID and sub-threshold groups. **Anxiety:** 22 (21.0%) any anxiety disorder; 9 (17.3%) brf and 13 (24.5%) brm. Specific phobia 8 (7.6%); 4 (4.5%) brf, 4 (4.5%) brm. Social phobia 10 (9.5%); 2 (3.8%) brf, 8 (15.1%) brm. Agoraphobia 1 (1.0%) (1 (1.9%) brm). Separation anxiety 4 (3.8%); 3 (5.8%) brf 1 (1.9%) brm. Generalized anxiety 1 (1.0%) (1 (1.9%) brf). Similar % for those in GID and subthreshold groups except for specific phobia (lower in those with GID: 4.5% vs. 25%). **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** 3 (2.9%) (2 (3.8%) brf, 1 (1.9%) brm. 2 (1.9%) diagnosed with ADHD inattentive (1 brf, 1 brm). 1 diagnosed with ADHD hyperactive (1 brm).	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
de Vries 2011b	Adolescents (age 12-18) consecutively referred to specialist gender clinic. Only those fulfilling DSM-IV-TR criteria for Gender Identity Disorder and who were considered eligible for further medical interventions were included.	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	2000 to 2007	90 referred 7 excluded as no gender dysphoria diagnosis n=83	**Age at referral:** Not reported **Age at assessment:** Mean age brf 15.6 (SD 1.6), range 13.1-18.6. Mean age brm 15.7 (1.7), range 13.2–18.7. **Birth-registered sex:** 40 (48.2%) female and 43 (51.8%) male. For referred number, 41 (45.6%) female and 49 (54.4%) male.	**Gender identity:** Not reported **Gender dysphoria:** Of 90 referred, 83 (92.2%) were diagnosed with Gender Identity Disorder and 7 (7.8%) were not diagnosed. **Onset**: Not reported **Social transition:** Not reported	**Depression:** MMPI Depression mean T-score was 54.8 (SD 13.6) brf and 57.9 (11.2) brm. 22.5% brf and 20.9% brm scored in the clinical range. **Anxiety:** MMPI Psychasthenia mean T-score was 52.1 (SD 13.9) brf and 50.1 (9.3) brm. 20.0% brf and 7.0% brm scored in the clinical range. **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
de Vries 2012	Children(age <12 years) and adolescents (age 12 and over) referred to a gender identity clinic.	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	1987 to 2011	465 children referred, 467 adolescents Referral numbers per year reported for children and adolescents	**Age at referral:** Mean age from 1987 to 2011: 16.5, 17.6, 17.9, 17.7, 16.4, 16.6, 17.6, 17.9, 16.8, 17, 15.1, 14.9, 14.2, 15.4, 14.2, 14.7, 14.1, 14.8, 14.1, 14.2, 13.4, 15.1, 13.6, 13.7, 14.2 **Age at assessment:** Not reported **Birth-registered sex:** Not reported	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
de Vries 2016*	Adolescents (age 13–18 years) referred and assessed at specialist gender clinic (baseline assessment data used)	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	1996 to 2008	n=139 CBCL / YSR data available for 112 / 106	**Age at referral:** Not reported **Age at assessment:** Mean age 15.7 (SD 1.5) **Birth-registered sex:** 60 (43.2%) female and 79 (56.8%), M:F ratio = 1.31:1	**Gender identity:** Not reported **Gender dysphoria:** 100% met DSM criteria either for Gender Identity Disorder or Gender Identity Disorder Not Otherwise Specified. **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** For CBCL and YSR internalising scale, mean score was 64.1 (SD 10.9) and 61.5 (12.5) for all, 62.9 (11.2) and 59.7 (11.9) brf, and 65.1 (10.7) and 63.0 (13.0) brm. On the CBCL, 53.6% were in the clinical range for internalising symptoms (38.8%brf and 65.1% brm). On the YSR, 45.3% were in the clinical range (31.2% brf and 56.9% brm). **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

Schagen 2012	Peripubertal children and adolescents experiencing gender dysphoria who attended a gender identity clinic	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	1997 to 2008	n=189	**Age at referral:** Not reported **Age at assessment:** Mean age of 159 diagnosed with Gender Identity Disorder was 13.6 (range 9.1-17.9) brf and 13.4 (range 9.0-17.7) brm. For threshold individuals, mean age was 12.8 (range 9.0-17.0) brf and 12.6 (range 9.2-17.8) brm. **Birth-registered sex:** 95 (50.3%) female and 94 (49.7%) male	**Gender identity:** Not reported **Gender dysphoria:** 159 (84.1%) met complete DSM-IV-TR criteria for Gender Identity Disorder (GID) (85 (89.5%) brf and 74 (78.7%) brm). 30 (15.9%) were subthreshold and showed number of indicators of GID (10 (10.5%) brf and 20 (21.3%) brm). **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Steensma 2013	Children (< 12 years of age) consecutively referred to a gender identity clinic. This study includes a sub-sample of these children followed up as returning adolescents (age 15 and over). Data on this selected sample is not reported.	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	2000 to 2008	225 referred n=124 in study (selected sub-sample so data not used)	**Age at referral:** Not reported **Age at assessment:** Not reported **Birth-registered sex:** 81 (36.0%) female and 144 (64.0%) male	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Steensma 2014*	Children (age <12) and adolescents (12 and older) consecutively referred and assessed at a gender identity clinic. All met DSM criteria for Gender Identity Disorder (GID) or GID Not Otherwise Specified (NOS). Data at time of assessment.	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	1993 to 2007	479 referred 147 excluded as data not available n=332	**Age at referral:** Not reported **Age at assessment:** Mean age 10.0 (SD 3.4). Mean age of children 8.3 (1.9) and adolescents 14.5 (1.9). Mean age of 147 excluded: children 8.2 (2.0), adolescents 15.3 (2.1). **Birth-registered sex:** 123 (37.0%) female and 209 (63.0%) male. Of children, 78 (32.2%) female and 164 (67.8%) male. Of adolescents, 45 (50.0%) female and 45 (50.0%) male. In total referred sample, 180 (37.6%) female and 299 (62.4%) male.	**Gender identity:** Not reported **Gender dysphoria:** 100% diagnosed with GID or GID-NOS **Onset:** Not reported **Social transition:** Not reported	**Depression and anxiety:** Internalising mean T-score 56.6 (SD 10.2) - 56.4 (10.1) brf and 56.7 (10.3) brm. For children mean score was 55.9 (10.0) - 55.1 (9.4) brf and 56.2 (10.2) brf. For adolescents mean score was 58.5 (10.7) - 58.5 (10.8) brf and 58.5 (10.7) brm. Percentage in clinical range 26.5% (27.6% brf, 25.8% brm). For children, 21.9% (21.8% brf, 22.0% brm). For adolescents, 38.9% (37.8% brf, 40.0% brm). **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
van der Miesen 2018	Children and adolescents with gender dysphoria consecutively referred to a gender identity clinic.	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	March 2005 to December 2012	542 referred 52 unable to complete assessment n=490	**Age at referral:** Not reported **Age at assessment:** Mean age 11.1 (SD 3.7) (brf mean age 12.1 (3.4) and brm 10.1 (3.8)). **Birth-registered sex:** 242 (49.4%) females and 248 (50.6%) males	**Gender identity:** Not reported **Gender dysphoria:** All diagnosed with Gender Identity Disorder (GID) **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** 14.5% at threshold score - no differences brf and brm above threshold. CSBQ used to investigate ASD symptoms. Total mean score 20.6 (SD 15.7). Mean subscales scores for Tuned 7.3 (5.5), Social 4.0 (4.5), Orientation 3.0 (3.3), Understanding 3.3 (3.1), Stereotyped 1.6 (2.5), Change 1.3 (1.7). For brf, total mean score 19.6 (14.6) (Tuned 6.9 (5.4), Social 4.4 (4.5), Orientation 2.7 (3.2), Understanding 3.3 (3.1), Stereotyped 0.9 (1.6), Change 1.4 (1.7)). For brm, total mean score 21.5 (16.7) (Tuned 7.7 (5.6), Social 3.7 (4.5), Orientation 3.3 (3.6), Understanding 3.3 (3.1), Stereotyped 2.3 (2.3), Change 1.2 (1.8)). **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
van der Miesen 2020	Adolescents consecutively referred to a specialist gender identity clinic (initial assessment data used)	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	2012 to 2015	504 adolescents seen over period (not just newly referred) 53 excluded as not completed assessment 179 receiving treatment n=272 starting assessment process	**Age at referral:** Not reported **Age at assessment:** Mean age 14.5 (SD 2.2) **Birth-registered sex:** 156 (57.4%) female and 116 (42.6%) male	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression and anxiety:** YSR Internalising problems (score range 0-64) mean score 11.7 (SD 8.4). Mean score brf 11.6 (8.8) and brm 11.7 (7.7). 31.3% had clinical range scores (28.2% brf, 35.3% brm). **Suicide and self-harm:** YSR (item 18 and 91 - score range 0-4) mean score 0.4 (0.8); brf 0.4 (0.8) and brm 0.4 (0.7). 27.2% endorsed the metric of suicadility. **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Verveen 2021	Children (5-12 years) who were referred to specialist gender identity clinic.	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	2010 to 2016	289 children referred 82 excluded (incomplete data or assessment ongoing) n=207	**Age at referral:** Not reported **Age at assessment:** Mean age 8.7 (SD 1.6). brf mean age 8.9 (1.5) and brm 8.3 (1.7). Mean age of those excluded was 8.0 (2.3) (reported as significant difference). **Birth-registered sex:** 124 (60.0%) female and 83 (40.1%) male. Of all referred children, 160 (55.4%) female and 129 (44.6%) male. Reported significant difference in sex ratio between included and excluded children.	**Gender identity:** Not reported **Gender dysphoria:** Gender Identity Questionnaire mean score 1.9 (SD 0.5) (1.9 (0.4) brf and 1.9 (0.5) brm). Gender Identity Interview mean sum score 14.8 (5.6) (15.6 (4.9) brf and 13.8 (6.4) brm. **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Wallien 2007	Children (under age 12) who were referred to a gender identity clinic and received a diagnosis of Gender Identity Disorder (GID) or were subthreshold.	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	March 1998 to December 2004	142 referred 20 excluded - no GID diagnosis n=120	**Age at referral:** Not reported **Age at assessment:** Not reported, age range 4-11 **Birth-registered sex:** 34 (28.3%) female and 86 (71.7%) male. Of referred, 42 (29.6%) female and 100 (70.4%) male.	**Gender identity:** Not reported **Gender dysphoria:** Of referred, 103 (72.5%) met complete diagnostic criteria of Gender Identity Disorder (32 (76.2%)brf and 71 (71.0%) brm). 17 (12.0%) were subthreshold for diagnosis (2 (4.8%) brf and 15 (15.0%) brm). 22 (15.5%) had no GID diagnosis. **Onset:** Not reported **Social transition:** Not reported	**Depression:** Mood disorders 7 (5.8%): 3 (8.9%) brf and 4 (4.7%) brm. 44 (37%) children had internalising psychopathology. **Anxiety:** Anxiety disorders 37 (30.8%): 11 (32.4%) brf and 26 (30.2%) brm. 44 (37%) children had internalising psychopathology. **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** 0 (0.0%)	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Wallien 2008	Total number of children (under age 12) referred to a gender identity clinic. This study includes a sub-sample of adolescents (age 16 and over). Data on this selected sample is not reported.	Gender Identity Clinic of the Department of Child and Adolescent Psychiatry at the University Medical Center Utrecht (which moved to the Department of Medical Psychology of the VU University Medical Center in Amsterdam in 2002).	1989 to 2005	200 referred n=77 in study (selected sub-sample so data not used)	**Age at referral:** Not reported **Age at assessment:** Not reported **Birth-registered sex:** 56 (28%) female and 144 (72%) male	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Wallien 2009*	Children consecutively referred to, and then assessed in a gender identity clinic (assessment data used)	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	December 1988 to January 2006	n=228	**Age at referral:** Not reported **Age at assessment:** Mean age 8.3 (SD 1.9), range 4.5-13.0 **Birth-registered sex:** 58 (25.4%) female and 170 (74.6%) male	**Gender identity:** Not reported **Gender dysphoria:** 163 (71.5%) met complete diagnostic criteria for Gender Identity Disorder. Gender Identity Interview for Children (GIIC) mean sum score (absolute range 0-24) was 10.0 (SD 5.1) for everyone, 11.1 (4.8) brf and 9.6 (5.2) brm. **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Wallien 2010	Cohort of children (age 7 years or older) referred to a gender identity clinic	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	2004 to 2006	44 referred 16 excluded due to lack of parent or school consent n=28	**Age at referral:** Not reported **Age at assessment:** Mean age 10.5 (SD 1.3), range 8.1-12.8 **Birth-registered sex:** Of referred number, 23 (52.3%) female and 21 (47.8%) male.	**Gender identity:** All referred children had clear cross-gender preferences and identified with the other sex **Gender dysphoria:** Of referred, 25 (56.8%) had a Gender Identity Disorder (GID) diagnosis (14 (60.9%) brf and 11 (52.4%) brm). 19 (43.2%) were subthreshold for GID (9 (39.1%) brf and 10 (47.6%) brm). **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Wiepjes 2018	All people who attended a gender identity clinic. Information on first visit presented.	Specialised gender identity clinic - Center of Expertise on Gender Dysphoria at VU University Medical Center in Amsterdam.	1972 to 2015	n=1360 812 adolescents (12-18 years) and 548 children (<12 years). Referral numbers per year provided for children and adolescents.	**Age at referral:** Not reported **Age at assessment:** Adolescent median age 16 (IQR 15-17). Same for both birth-registered sex groups. Children median age 9 (7-10) - for birth-registered females age 9 (8-11) and for males age 8 (7-10). Age at assessment per year provided - fluctuates over the years for children and adolescents. **Birth-registered sex:** 737 (54.2%) female and 623 (45.8%) male. For adolescents, 482 (59.4%) female and 330 (40.6%) male. For children, 255 (46.5%) female and 293 (53.5%) male.	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

Norway									
Kaltiala 2020 - Norway	Children and adolescents referred to gender service	Publicly funded, nationally centralised GIDs for minors under 18. A national GIDS in Oslo was always open to minors but before the 2000s rarely received referrals concerning children and adolescents.	2010 to 2017	Absolute referral numbers	**Age at referral:** Not reported **Age at assessment:** Not reported **Birth-registered sex**:F:M ratio 2012=0.67, 2013=2.02, 2014=0.97, 2015=1.26, 2016=2.84, 2017=1.99	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Scotland									
McCallion 2021	Young people referred to endocrinology clinic for puberty suppression with GnRH analogue (new referrals)	Paediatric Endocrinology, Royal Hospital for Children, Glasgow	2011 to 2019	91 assessed New referrals: 2011=1, 2012=2, 2013=7, 2014=0, 2015=7, 2016=11, 2017=24, 2018=22, 2019=17 Total number: 2011=1, 2012=2, 2013=10, 2014=10, 2015=17, 2016=22, 2017=44, 2018=60, 2019=73 *These were extracted from Figure*	**Age at referral:** Not reported **Age at assessment:** mean 14.6 (range 8.8 to 17.6); 14.1 (range 8.7 to 17.6) brf and 15.1 (range 9.8 to 17.5) brm. **Age at initial assessment each year:** median (range): 2011= 11.55; 2012=14.28 (13.79, 14.28); 2013=14.91 (12.64, 15.64); 2015=14.45 (10.26, 15.57); 2016=13.79 (11.06 to 15.6); 2017=14.43 (8.79, 15.62); 2018=15.06 (9.85, 17.55); 2019=14.91 (10.43, 17.64) *These were extracted from Figure* **Birth-registered sex:** 59 (65%) females and 32 (35%) males; F:M 2011=1:0, ratio 2012=1, 2013=1.50, 2014=1.50, 2015=1.50, 2016=6.14, 2017=2.56, 2018=2.13, 2019=2.03	**Gender identity:** All **Gender dysphoria:** All **Onset**: Not reported **Social transition:** Not reported	**Depression:** 13 (14.3%) **Anxiety:** 19 (20.9%) **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** 1 (1.1%)	**ASC:** 21 (23%); brf 14 (24%) and brm 7 (22%) **ADHD:** 4 (4%)	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Spain									
De Castro 2022	Children and adolescents under the age of 18 who attended the specialist Gender service	Referrals made by pediatricians, general practitioners, mental health specialists or endocrinologists from Catalonia to the Catalonian Gender Identity Unit	January 1999 to December 2016	140 included 1999-2004=6 2005-2010=32 2011-2106=102	**Age at referral:** median (IQR) 15.7 (4.2) transgender n=124 16.0 (2.6); 1999-2004=6 adolescents; 2005-2010=25 adolescents and 7 children; 2011-2016=78 adolescents and 24 children **Age at assessment:** Not reported **Birth-registered sex:** 70 (50%) female and 70 (50%) male; F:M numbers 1999-2004 3:3; 2005-2010 22:10; 2011-2016 57:45	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** 48.5%	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Adopted children 3 (3.3%); living in a child welfare foster placement 1 (1.1%)
Esteva de Antonio 2013	Children and adolescents under the age of 18 who attended the specialist Gender service	Andalusian Gender Team was formed in 1999 and is based at Carlos Haya University Hospital, in Malaga, Spain. 141 children and adolescents with gender dysphoria referred to us in this period.	2000 to 2012	141 referred	**Age at referral:** <12 years 15 and 12-17 126 years; range 5 to 17 **Age at assessment:** Not reported **Birth-registered sex:** F:M 34:107 (ratio 0.32); children 2:13 (ratio 0.15); adolescents 32:94 (ratio 0.34)	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Sweden									
Kaltiala 2020 - Sweden	Children and adolescents referred to gender service	Publicly funded, nationally centralised GIDs for minors under 18. First established in Sweden in Stockholm in the 1990s. This became a part of public child and adolescent healthcare in 2014. Due to increased demand, several other GIDSs in the country also accept referrals of minors.	2010 to 2017	Absolute referral numbers	**Age at referral:** Not reported **Age at assessment:** Not reported **Birth-registered sex:** F:M ratio 2010 =1.91, 2011=1.35, 2012=4.02, 2013=0.62, 2014=2.14,2015=3.05, 2016=3.55, 2017=2.43	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Switzerland									
de Graff 2018b	Adolescents aged 12–18 who were referred to one of the four European specialist gender clinics who completed either the CBCL or the YSR at baseline	Specialist gender clinic (The Department of Child and Adolescent Psychiatry, University Hospital of Psychiatry Zurich, Switzerland). It was founded in 2009 and during the time of the study covered as catchment area the German speaking part of Switzerland	January 2009 to December 2013	32 referred; 26 were included.	**Age at referral:** mean 15.38 SD 1.20; brf 15.09 1.45; brm 15.60 0.99 **Age at assessment:** Not reported **Birth-registered sex:** 15 (57.7%) female and 11 (42.3%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** CBCL Internalising n=23 mean 20.39 SD 10.45; clincial range 16/24 (66.7%); YSR Internalising n=25 mean 22.88 SD 7.92; clinical range 15/26 (57.7%) **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
UK									
Butler 2018	Children and adolescents up to the age of 18 years	Tavistock and Portman NHS Trust in London nationally commissioned by NHS England in 2009 and extended to Leeds in 2012, providing regular outreach clinics in other areas of the UK.	2010 to 2017	Referrals: 2011/12=198, 2012/13=300, 2013/14=465, 2014/15=693, 2015/16=1415, 2016/17=2023	**Age at referral:** 2010 to 2013 data: <5=12, 5=19, 6=24, 7=34, 8=24, 9=36, 10=39, 11=30, 12=45, 13=61, 14=130, 15=229, 16=245, 17=156 **Age at assessment:** Not reported **Birth-registered sex:** F:M (ratio): 2011/12=113:85 (1.33), 2012/13=183:117 (1.56), 2013/14=279:186 (1.50), 2014/15=422:270 (1.56), 2015/16=920:495 (1.86), 2016/17=1396:627 (2.23)	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Costa 2015	A consecutive series of adolescents referred to specialist gender clinic who completed diagnositc procedure (about 6 months) and were invited to take part in the follow-up evaluation.	Gender Identity Development Service (GIDS) in London.	2010 to 2014	436 adolescents referred; 201 completed diagnostic procedure and consented.	**Age at referral:** Not reported **Age at assessment:** Mean 15.52 SD 1.41 years **Birth-registered sex:** male/female ratio = 1:1.6	**Gender identity:** DSM-IV-TR all met criteria **Gender dysphoria:** Utrecht Gender Dysphoria Scale mean 54.7 SD 6.8 **Onset**: Not reported **Social transition:** Living in role completely 117 (62.6%), partly 27 (14.4%), no 43 (23.0%); changed name 107 (57.5%) did not change name 79 (42.5%)	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Living in childrens home or living with other family members 10 (5.3%)
de Graf 2018a	Data extracted for children 12 years of age or younger	Gender Identity Development Service (GIDS) at the Tavistock & Portman National Health Service (NHS) Foundation Trust in London, United Kingdom. The GIDS is the sole specialised service for children and adolescents with gender dysphoria in the United Kingdom that is funded by the NHS.	2000 to 2017	1,215 children were referred to the GIDS	**Age at referral:** brf mean 9.78 SD2.15, brm mean 8.72 SD 2.30 **Age at assessment:** Not reported **Birth-registered sex:** 534 (44%) females and 681 (56%) males; % males 2000-2006=71.6% and 2007-2017=55.0%	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
de Graf 2018b	All adolescents aged 12–18 who were referred to one of the four European specialist gender clinics who completed either the CBCL or the YSR at baseline	Gender Identity Development Service, Tavistock and Portman NHS Foundation Trust, London, United Kingdom, was established in 1989. The GIDS is a national clinic, with a satellite clinic in the north, based on Leeds and a number of other established outreach clinics in the Exeter, Dublin, and Wales.	January 2009 to December 2013	860 adolescents were referred and data were available for 610 (70.9%)	**Age at referral:** Not reported **Age at assessment:** mean 15.54 SD 1.28; brf mean 15.51 SD 1.26 and brm 15.58 SD 1.32 **Birth-registered sex:** 392 (64.3%) females and 218 (35.7%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression and anxiety:** CBCL Internalising n=479 mean 18.79 SD 11.31, clinical range 289/484 (59.7%); YSR n=489 mean 25.36 SD 12.15, clinical range 291/496 (58.7%) **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

de Graf 2018c	Children and adolescents up to the age of 18 years	The national Gender Identity Development Service (GIDS) in the UK	January 2009 to December 2016	4506 referred; 39% children and 60% adolescents had completed CBCL; Referrals (M:F) 2009=34:17=51 2010=63:55=118 2011=70:90=160 2012=107:158=265 2013=151:243=394 2014=140:350=490 2015=396:766=1162 2016=557:1209=1766	**Age at referral:** range 1 to 18; children <12 brm n=408 mean 8.27 SD 2.27, brf n=311 mean 8.97 SD 2.34; adolescents 12-18 brm n=1210 mean 15.59 SD 1.40, brf n=2577 mean 15.45 SD 1.32 **Age at assessment:** Not reported **Birth-registered sex:** 2888 (64.1%) females and 1618 (35.9%) males (ratio 1.78)	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression and anxiety:** CBCL clinical range internalising 1050 (61.9%) **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
de Graf 2019	Children and adolescents up to the age of 18 years	The national Gender Identity Development Service (GIDS) in the UK	April 2012 to April 2015	1444 referrals; 995 (69.2%) included within analysis - 266 ethnicity data not available, 174 data left blank, 7 were referrals for children of trans adults and children not gender diverse	**Age at referral:** brm mean 13.63 and brf mean 14.77 **Age at assessment:** Not reported **Birth-registered sex:** 609 (61.2%) females and 386 (38.8%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
de Graf 2020	Referred and assesed for GD at one of three clinic sites	Gender Identity Development Service at the Tavistock and Portman National Health Service Trust in London, UK	2009 to 2017	2245 adolescents	**Age at referral:** mean 15.93 SD 1.07 **Age at assessment:** Not reported **Birth-registered sex:** 1560 (69.5%) female and 685 (30.5%) male	**Gender identity and gender dysphoria:** all adolescents met DSM-III, DSM III-R, DSM-IV or DSM-5 criteria either for Gender Identity Disorder/Gender Dysphoria or Gender Identity Disorder Not Otherwise Specifed **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** CBCL sum of suicide items n=1562 mean 0.98 SD 1.17; YSR sum of suicide items n=1515 mean 1.29 SD 1.33; CBCL (suicide behviour); CBCL brm 479 (30.3%) brf 1100 (50.8); CBCL ideation brm 479 (31.7%) and brf 1092 (33.4%); YSR behaviour brm 281 (41.3%) and brf 620 (45.2%); YSR ideation brm 283 (49.1%) and brf 619 (55.3%) **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Holt 2016	Referred children and adolescents 0 to 18 years at the London site	Gender Identity Development Service at the Tavistock and Portman National Health Service Trust in London, UK	January 2012 to December 2012	303 referred; 85 excluded as being children who received counselling in relation to having a transsexual parent or were referred to GIDS Leeds base. 218 children and adolescents included.	**Age at referral:** mean 14 SD 3.08 range 5 to 17 **Age at assessment:** Not reported **Birth-registered sex:** 137 (62.8%) females and 81 (37.2%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** n=208, 42.7% had first gender dysphoric feelings between 0 and 6; 34.9% between 7 and 12; 17.9% between 13 and 18. **Social transition:** 47.8% preferred being referred to by a different name from birth name (67.2% brf and 20.8% brm); n=205 54.6% were living in their chosen gender, 9.8% partly and 35.6% were not.	**Depression:** 91 (41.7%) brm 37 (45.7%) and brf 54 (39.4%) **Anxiety:** 49 (22.5%) brm 17 (21.0%) and brf 32 (23.4%) **Suicide:** ideation 76 (34.9%) brm 31 (38.3%) and brf 45 (32.8%); attempts 29 (13.3%) brm 10 (12.3%) and brf 19 (13.9%) **Self-harm:** 84 (38.5%) brm 21 (25.9%) and brf 63 (46%) **Eating disorder:** 29 (13.3%) brm 10 (12.3%) and brf 19 (13.9%)	**ASC:** 29 (13.3%) brm 15 (18.5%) and brf 14 (10.2%) **ADHD:** 18 (8.3%) brm 10 (12.3%) and brf 8 (5.8%)	**Neglect or abuse:** 38 (17.4%) natal males 9 (11.1%) and natal females 29 (21.2%) **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Living in foster care 9 (4.1%), living with adoptive parents 2 (0.9%), living in childrens home 1 (0.5%)
Kaltiala 2020	Children and adolescents up to the age of 18 years	Child and adolescent gender identity development service at the Tavistock Clinic, London and satellite clinics across the UK, in Leeds (North) and Exeter (South), and provides consultation across the country (including Wales, Midlands and Ireland).	2010 to 2017	Referrals 2010=109, 2011=163, 2012=240, 2013=353, 2014=512, 2015=965, 2016=1313, 2017=2197	**Age at referral:** Not reported **Age at assessment:** Not reported **Birth-registered sex:** F:M ratio 2010=0.65, 2011=1.00, 2012=1.73, 2013=1.67, 2014=2.55, 2015=1.85, 2016=2.35, 2017=2.58	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Matthews 2019	Children and adolescents up to the age of 18 years who were referred for an assessment of gender dysphoria	Tavistock and Portman GIDS in London, UK	April 2009 to April 2011	232 referrals; 2 counselling of transgender parents and 45 not first appoitnment or lost to follow up; 185 included	**Age at referral:** 13.70 SD 3.35 range 3 to 17; brm mean 13.03 SD 3.88; bmf mean 14.44 SD 2.45 **Age at assessment:** Not reported **Birth-registered sex:** 52.4% males and 47.6% females	**Gender identity:** Not reported **Gender dysphoria:** 156 (84.3%) met diagnosis of gender dysphoria **Onset:** n=168 mean 6.80 SD 3.96 range 1 to 15 **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** 9 (4.9%) looked after children (7 BR males and 2 BR females), 7 (3.8%) adopted (5 BR males and 2 BR females)
Moriandini 2021	Referred and assessed with completed associated Difficulties form post assessment	Tavistock and Portman GIDS in London, UK	2012 and 2015	782 included; 218/263 referrals in 2012 and 564/1162 referrals in 2015	**Age at referral:** mean 13.94 SD 2.94 range 4 to 17 **Age at assessment:** Not reported **Birth-registered sex:** Not reported	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** full time overall 2012=112 (54.6%) and 2015=228 (55.2%), brf 2012=90 (69.2%) and 2015=150 (57.5%) brm 2012=22 (29.3%) and 2015=78 (51.3%); part time overall 2012=20 (9.8%) and 2015=71 (17.2%), brf 2012=8 (6.2%) and 2015=45 (17.2%) brm 2012=12 (16.0%) and 2015=26 (17.1%); living in birth gender overall 2012=73 (35.6%) and 2015=114 (27.6%), brf 2012=32 (24.6%) and 2015=66 (25.3%) brm 2012=41 (54.7%) and 2015=48 (31.6%); Name change ful time overall 2012=104 (47.7%) and 2015=295 (56.1%), brf 2012=88 (64.2%) and 2015=204 (61.3%) and brm 2012=16 (19.8%) and 2015=91 (47.2%); part time overall 2012=0 (0.0%) and 2015=22 (4.2%), brf 2012=0 (0.0%) and 2015=16 (4.8%), brm 2012=0 (0.0%) and 2015=6 (3.1%)	**Depression:** Not reported **Anxiety:** 2012=49 (22.5%) and 2015=201 (38.6) **Suicide:** attempts 2012=29 (13.3%) and 2015=45 (8.6%) **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** 2012=1.8% and 2015=(15.1%) **ADHD:** Not reported	**Neglect or abuse:** 2012=38 (17.4%) and 2015=62 (11.8%) **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Pang 2020	Children and adolescents up to the age of 18 years	Gender Identity Development Service (GIDS) in London, UK	2009 to 2016	4684 referrals 2009=81 2010=134 2011=194 2012=303 2013=437 2014=642 2015=1175 2016=1799	**Age at referral:** brm meadian 15.3 IQR 12.5 to 16.5 brf median 15.4 IQR 14.0 to 16.4 **Age at assessment:** Not reported **Birth-registered sex:** 2837 (60.6%) females and 1847 (39.4%) male	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Skagerberg 2013a	Adolescents 12-18 who completed Youth Self Report form at the end of the assessment period	Gender Identity Development Service (GIDS) in London, UK	Unclear	141	**Age at referral:** Not reported **Age at assessment:** mean 15.13 SD 1.70 range 12 to 18 **Birth-registered sex:** 84 (59.6) females and 57 (40.4%) males	**Gender identity:** DSM-IV criteria for Gender Identity Disorder **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression and anxiety:** YSR internalising mean 63.23 SD 12.35; brm (n=57) normal range 30% borderline 11% clinical 60%; brf (n=84) normal range 35% borderline 21% clinical 44% **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Skagerberg 2013b	Children and adolescents up to the age of 18 years	Gender Identity Development Service (GIDS) in London, UK	Unclear	135 referrals; 125 included	**Age at referral:** mean 13.56 SD 3.24 **Age at assessment:** Not reported **Birth-registered sex:** 54.8% males and 45.2% females	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** 12 (9.6%) **Self-harm:** 30 (24%) and 18 (14%) thoughts **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

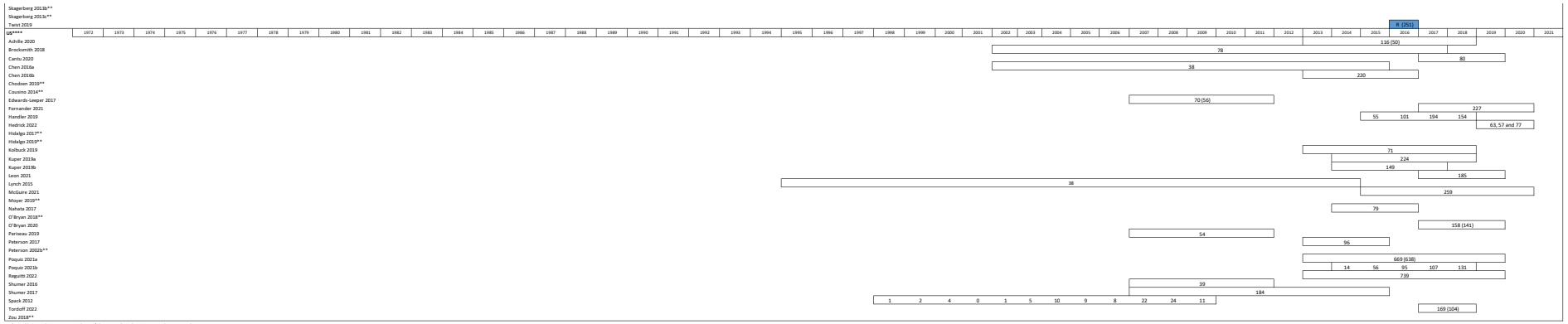
Skagerberg 2015	Children and adolescents up to the age of 18 years presenting with GD	Gender Identity Development Service (GIDS) in London, UK	Unclear	166 included	**Age at referral:** mean 14.26 SD 2.68, range 5 to 18 **Age at assessment:** Not reported **Birth-registered sex:** 104 (62.7%) females and 62 (37.3%)	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** SRS scale brm n=62 mean 60.29 SD 41.41; brf n=104 mean 57.45 SD 35.26; 76 (45.8%) normal - 2.8% had diagnosis of ASD, 45 (27.1%) mild/moderate - 15.6 % had diagnosis of ASD and 45 (27.1%) severe - 24.4% had diagnosis of ASD **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Twist 2019	All clients aged at least 12 years old presenting to GIDS for first assessment completing assessment pack	Gender Identity Development Service (GIDS) in London, UK	June 2016 to February 2017	251 completed questions with some questions	**Age at referral:** aged 12 (n=10), aged 13 (n=17), aged 14 (n=27), aged 15 (n=57), aged 16 (n=70) and aged 17 (n=68). Mean 15.44 SD 1.62 **Age at assessment:** Not reported **Birth-registered sex:** 180 (71%) females and 71 (29%) males	**Gender identity:** Gender Diversity Questionnaire; 140 (56.9%) trans identity, 72 (29.3%) binary identity, 27 (11%) non-binary identity, undefined 4 (1.6%) **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
US									
Achille 2020	Children, adolescents and young adults aged 9–25 years referred for gender dysphoria	Single centre paediatric endocrine department, Stony Brook Children's Hospital, New York	December 2013 to December 2018	Although we do not have exact numbers, the vast majority of eligible subjects agreed to take part in the study. 116 entered the study and 50 are included in the analysis as completed all 3 waves of questionnaires.	**Age at referral:** Not reported **Age at assessment:** mean 16.2 SD 22; brf mean 16.6 SD 2.5; brm mean 15.5 SD 1.6 **Birth-registered sex:** 33 females and 17 males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** in past year 32 (64%); brf 20 (60.6%); brm 12 (70.6%) **Anxiety:** Not reported **Suicide:** 5 (10%); brf 3 (9.1%); brm 2 (11.8%) **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Brocksmith 2018	Patients with gender dysphoria	Pediatric endocrine clinic at Riley Hospital for Children, Indianapolis	2002 to 2017	78 patients	**Age at referral:** mean 14.9 SD 2.37 **Age at assessment:** Not reported **Birth-registered sex:** 49 (63%) female and 29 (27%) male	**Gender identity:** 49 (63%) male and 29 (27%) female **Gender dysphoria:** 100% **Onset:** Not reported **Social transition:** Not reported	**Depression:** 32 (41%) **Anxiety:** 23 (29.5%) **Suicide:** 8 (10.3%) **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** 12 (15.4%)	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Cantu 2020	Transgender and gender-nonconforming youth seeking gender-affirming care 11-18 attending both initial and followup appointment and completed questionnaires at both visits	Academic medical centre in the Northwestern United States	September 2017 to June 2019	80 youth	**Age at referral:** Not reported **Age at assessment:** mean 15.1 SD 1.8 **Birth-registered sex:** Not reported	**Gender identity:** female 15 (18.8%), male 58 (72.5%) and nonbinary 7 (8.8%) **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** PHQ-9 mean 10.5 SD 6.5; PHQ-9>=11 37 (46%) **Anxiety:** GAD-7 mean 9.1 SD 6.1; GAD-7>=6 49 (61%) **Suicide:** 27 (34%) **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Chen 2016a	Not stated	Pediatric endocrine clinic at Riley Hospital for Children, Indianapolis	January 2002 to April 2015	38 patients identified	**Age at referral:** Not reported **Age at assessment:** mean 14.4 SD 3.2 **Birth-registered sex:** 22 females and 16 males	**Gender identity:** 16 female transgender; 22 male transgender; 1 gender fluid **Gender dysphoria:** 29% **Onset:** Not reported **Social transition:** Not reported	**Depression:** 12 (31.6%) **Anxiety:** Not reported **Suicide/self harm:** 5 (13.1%) **Eating disorder:** Not reported	**ASC:** 5 (13.1%) **ADHD:** 6 (15.8%)	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Chen 2016b	Youth under 25 years of age	Gender and Sex Development Program (GSDP) at the Ann & Robert H. Lurie Children's Hospital, Chicago	July 2013 to February 2016	220 patients in GDC with 10–12 new patients seen each month	**Age at referral:** Not reported **Age at assessment:** 54 <=11; 154 12 to 18; 12 19+ **Birth-registered sex:** 120 (54.5%) females and 100 (45.5%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Chodzen 2019	Adolescent patients presenting for the initiation of care at a multidisciplinary gender clinic aged between 12 and 18 years old, self-identified as transgender and gender-nonconforming and who completed behavior health screening questionnaires as standard of care at their first clinical visit	Pediatric academic medical centre in a metropolitan Midwestern city	Unclear	109	**Age at referral:** Not reported **Age at assessment:** mean 15.46 SD 1.55 **Birth-registered sex:** 78 (71.6%) females and 31 (28.4%) males	**Gender identity:** Transgender 94 (86.2%), Gender nonconforming 2 (1.8%), Agender 4 (3.7%), Unsure/questioning 5 (4.6%), Non-binary 3 (2.8%), Gender queer 1 (0.9%) **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Cousino 2014	Children and adolescents	KIDz PRIDE Clinic at MetroHealth Medical Centre is dedicated to the care and support of gender-variant and transgender children, adolescents, and their families (established 2008)	Unclear	20 youth and their families	**Age at referral:** Not reported **Age at assessment:** 7 to 19, mean 14.5 SD 3.0 **Birth-registered sex:** (50%) females and (50%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Edwards-Leeper 2017	Gender-dysphoric adolescents under 18 years of age with a single affirmed gender	Boston GeMS endocrinology clinic	2007 to 2011	70 charts reviewed and 56 included	**Age at referral:** Not reported **Age at assessment:** 8.9 to 17.9 **Birth-registered sex:** 26 (46.4%) females and 30 (53.6%) males	**Gender identity:** All transgender **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression and anxiety:** YSR n=44 internalising problems mean 58.48 SD 13.29; CBCL n=52 mean 60.21 SD 12.44; clinical range YSR (38.6%) and CBCL (48.1%); Depression CDI-child n=50 mean 51.56 SD 11.51; CDI-parent n=52 mean 56.46 SD 11.73; Anxiety RCMAS n=52 mean 9.8 SD 3.5. **Suicide:** YSR 11/46 (23.9%); CBCL 6/51 (11.8%) **Self-harm:** YSR 4/45 (8.9%); CBCL 4/52 (7.7%) **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Fornander 2021	Transgender/gender diverse 9–18 years olds who attended at least one clinic appointment, and completed the patient and caregiver electronic surveys	Academic medical center in a large metropolitan area in the Midwest	2017 to 2020	227 people	**Age at referral:** Not reported **Age at assessment:** mean 14.78 SD 2.06, range: 9 to 18 years **Birth-registered sex:** 219 (79.1%) females and 58 (20.9%) males	**Gender identity:** Masculine 119 (77.8%), Feminine 24 (15.7%), Nonbinary 8 (5.2%), Gender fluid 1 (0.7%), Not sure 1 (0.7%) **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

Handler 2019	<18 years of age at the time of referral	Kaiser Permanente Northern California (KPNC) is a large, integrated health care system that serves >4.2 million members. In 2013, KPNC opened a specialty clinic in Oakland, California, as a referral hub for transition-related services for TGNC members throughout Northern California	February 2015 to June 2018	417 referred to clinic; 2015=55 2016=101 2017=194 2018=154 (6 months data)	**Age at referral:** median 15 range 3 to 17 **Age at assessment:** Not reported **Birth-registered sex:** 303 (73%) females and 114 (27%) males	**Gender identity:** Transmasculine 257 (62%), Transfeminine 102 (24%), Gender nonbinary 56 (13%) **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Hedrick 2022	TGD youth	Doernbecher Gender Clinic (DGC)	3 periods (1) the first 20 weeks of interdisciplinary care provided in person before the pandemic, (2) the first 20 weeks following the initiation of modified operations, and (3) the second 20 weeks of modified operations.	November 2019 to March 2020 = 63 March 2020 to July 2020 = 57 August 2020 to December 2020 = 77	**Age at referral:** Not reported **Age at assessment:** Nov 19 to Mar 20 mean 14.4 range 8 to 18; Mar 20 to Jul 20 mean 14.2 range 7 to 18; Aug 20 to Dec 20 mean 14.4 range 8 to 18 **Birth-registered sex:** Not reported	**Gender identity:** Nov 19 to Mar 20 13 (21%), male 38 (60%), non-binary 12 (19%); Mar 20 to Jul 20 12 (21%), male 39 (68%), non-binary 6 (11%); Aug 20 to Dec 20 20 (26%), male 44 (57%), non-binary 13 (17%) **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Hidalgo 2017	Gender-expansive youth	Outpatients of an interdisciplinary gender-health clinic located within a pediatric academic medical center in a large city within the Midwestern United States	Unclear	341	**Age at referral:** Not reported **Age at assessment:** mean 15.6 SD 1.99, range 12 to 24 **Birth-registered sex:** 228 (66.9%) females and 113 (33.1%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Hidalgo 2019	Gender-expansive youth	Outpatients of an interdisciplinary gender-health clinic located within a pediatric academic medical center in a large city within the Midwestern United States	Unclear	258	**Age at referral:** Not reported **Age at assessment:** mean 15.1 SD 1.4, range 12 to 17.99 **Birth-registered sex:** 185 (71.7%) females and 73 (28.3%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Kolbuck 2019	Prepubertal youth presenting to clinic	Multidisciplinary pediatric gender clinic in the Midwestern US, Ann & Robert H. Lurie Children's Hospital of Chicago	August 2013 to April 2018	71 children	**Age at referral:** Not reported **Age at assessment:** mean 7.79 SD 2.08, range 3 to 11 **Birth-registered sex:** 21 (29.6%) females and 50 (70.4%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** 42 (59%); partially transitioned 3-5: 1 (1%) 6-11: 16 (23%), ST all settings 3-5: 5 (7%) 6-11 20 (28%).	**Depression:** MDD 2 (2.9%) **Anxiety:** GAD 10/68 (14.7%) **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** 12/68 (17.6%)	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Kuper 2019a	Children and youth attending in person assessment and consenting for using data for research	Multidisciplinary gender affirming program in Dallas, Texas	2014 to 2018	224	**Age at referral:** Not reported **Age at assessment:** <=5 0 (0.0%), 6-9 14 (6.2%), 10-13 41 (18.1%), 14+ 171 (75.7%) **Birth-registered sex:** 137 (60.6%) females and 89 (39.4%) males	**Gender identity:** Male/boy/guy 121 (54.0%), Male spectrum 12 (5.3%), Female/girl/woman 82 (36.6%), Female spectrum 4 (1.8%), Nonbinary 5 (2.2%) **Gender dysphoria:** 98.2% DSM-5 for gender dysphoria **Onset**: brf mean 10.7 SD 3.6, brm mean 9.9 SD 4.6 **Social transition:** change in clothing (brf 100% age 8.2 (4.8), brm 85.9% age 12.0 (4.2)), change in appearance (brf 100% age 11.9 (2.7), brm 95.3% age 12.1 (3.4)), change in name/pronoun (brf 99.2% age 13.4 (2.1), brm 87.1% age 12.8 (3.4))	**Depression:** Mean QIDS (Quick Inventory of Depressive Symptoms) 9.5 SD 5.2; 26.7% not elevated range, 31.9% mild range, 24.6% moderate range, and 16.8% severe range. **Anxiety:** Mean Screen for Childhood Anxiety Related Emotional Disorders (SCARED) 30.8 SD 15.8; 60.9% scoring in clinically elevated range **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Kuper 2019b	Adolescents age 12–18 presented for an initial assessment before initiation of gender-affirming medical care (i.e., pubertal suppression and/or cross-sex hormone therapy).	Gender Education and Care Interdisciplinary Support program in Dallas, TX	2014 to 2017	149	**Age at referral:** Not reported **Age at assessment:** mean 15.3 SD 1.52, range 12 to 18 **Birth-registered sex:** (64.4%) females and (35.6%) males	**Gender identity:** 57% male, boy, or guy, 6.0% male spectrum (e.g., "transmasculine"), 34% female, girl, or woman, 1.3% female spectrum (e.g., "mostly female"), and 1.3% different gender identity (e.g., agender) **Gender dysphoria:** All but 1 participant met full criteria for gender dysphoria at the time of assessment. **Onset**: Not reported **Social transition:** Not reported	**Depression:** YSR internalising mean 63.5, clinically elevated 55.2%; DSM orientated mean 66.2, clinically elevated 37.8%; **Anxiety:** DSM orientated mean 64, clinically elevated 32.9% **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** DSM orientated mean 58.9, clinically elevated 10.5%	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Leon 2021	Youth < 18 years of age gave verbal assent to participate, and informed consent was also obtained from a parent or legal guardian. Youth ages 18–25 provided informed consent as legal adults; All pediatric and young adult patients (ages 7–25) receiving gender-affirming care, are eligible for inclusion in the GWC pediatric patient registry	Gender Wellness Center (GWC), a rural clinic providing primary and gender-affirming medical care to TGE youth and adults in Upstate New York	April 2017 to December 2019	185 enrolled in the registry and included in the study	**Age at referral:** Not reported **Age at assessment:** median 16.3 IQR 4.0 range 6.9 to 21.8 **Birth-registered sex:** 131 (71%) females and 53 (29%)males	**Gender identity:** 127 (68.7%) identified on transmale spectrum, 49 (26.5%) identified on transfeminine spectrum and 9 (4.9%) non-binary or gender non-conforming **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** 160 (89.4%)	**Depression:** mood disorder 113 (61.1%) **Anxiety:** 78 (41.2%) **Suicide:** 87 (47.0%) **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** 66 (35.7%) **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Lynch 2015	Patients with gender dysphoria less than 19 years of age	Initially seen at the Gender Identity Clinic at the University of Texas Medical Branch who were treated with MPA	October 1995 to March 2013	38 patients identified	**Age at referral:** Not reported **Age at assessment:** Not reported **Birth-registered sex:** 12:7 (M:F)	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset**: Most know from an early age (1.5–7 years) that they want to be the opposite sex (n=24), while others (n=10) do not make the decision until late childhood or adolescence (8–14 years). Four were not sure when they became aware that they were trans gender. **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
McGuire 2021	Transgender and gender diverse children and young people (8 to 22) at their first visit	Pediatric gender clinic in the southeast United States	2015 to 2020	259	**Age at referral:** Not reported **Age at assessment:** mean 14.9 SD 2.4 **Birth-registered sex:** 149 (69.6%) females and 65 (30.4%) males	**Gender identity:** Boy or man 136 (63.6%), Girl or woman 63 (29.4%), Genderqueer or gender fluid 7 (3.3%), Questioning 6 (2.8%), Agender 2 (0.9%) **Gender dysphoria:** Not reported **Onset**: Not reported **Social transition:** Not reported	**Depression:** PROMIS emotional distress depression scale n=135 mean 60.5 SD 10.3, clinical severity: none to slight 37 (27.4%), mild 29 (21.5%), moderate 43 (31.9%), severe 26 (19.3%) **Anxiety:** PROMIS emotional distress anxiety scale n=94 mean 58.5 SD 11.9, clinical severity: none to slight 35 (37.2%), mild 14 (14.9%), moderate 30 (31.9%), severe 15 (16.0%) **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

Moyer 2019	Transgender and gender nonconforming youth aged 11–18 who presented for an initial appointment with depression and anxiety measures	Pediatric endocrinology clinic	Not reported	79 initial consultation; screening results not documented n=13; under 11s excluded as tools not validated in this group n=19; unsure TGNC n=1 so excluded.	**Age at referral:** Not reported **Age at assessment:** mean 15.5 SD 1.8 **Birth-registered sex:** Not reported	**Gender identity:** Female 18 (22.8%), Male 55 (69.6%), Non-binary 6 (7.6%) **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** PHQ-9 >=11, 38 (48.1%) **Anxiety:** GAD-7>=5, 56 (73.7%) **Suicide/self-harm:** thoughts of death or self-harm - 28 (48.1%) **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Nahata 2017	All referred patients with ICD 9/10 codes for gender dysphoria	Large Mid-western pediatric academic centre, pediatric endocrinology within a multidisciplinary gender program for hormone therapy (gender programme established in 2014)	2014 to 2016	79	**Age at referral:** Not reported **Age at assessment:** median 15 range 9 to 18 **Birth-registered sex:** 51 (64.6%) females and 28 (35.4%) males	**Gender identity:** Transgender females 28 (35.4%), transgender males 51 (64.6%), nonbinary or genderqueer 0 (0.0%) **Gender dysphoria:** 100% **Onset:** Not reported **Social transition:** Not reported	**Depression:** 62 (78.5%); brf 42 (82.4%); brm 20 (71.4%) **Anxiety:** 50 (63.3%); brf 34 (66.6%); brm 16 (57.1%) **Suicide:** 24 (30.4); brf 15 (29.4%); brm 9 (32.1%) **Self-harm:** 44 (55.7%); brf 31 (60.7%); brm 13 (46.4%) **Eating disorder:** 10 (12.7%); brf 5 (9.8%); brm 5 (17.9%)	**ASC:** 5 (6.3%); brf 3 (5.9%); brm 2 (7.1%) **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
O'Bryan 2018	Transgender and gender expansive children, youth and adults (<22 for registry)	The Gender Wellness Center (GWC) is a rural based, multidisciplinary centre that offers gender affirming medical, mental health, and surgical care in Upstate New York (established 2007 for adults and 2012 for youth; registry in 2017)	Not reported	139 have been enrolled in the registry to date (98% recruitment rate). One patient declined to participate, and two patients were interested in participating but unable to obtain informed consent.	**Age at referral:** Not reported **Age at assessment:** mean 16.7 SD 3 **Birth-registered sex:** 97 (69.8%) females and 42 (30.2%) males	**Gender identity:** Trans masculine spectrum 90 (64.7%), Trans feminine spectrum 40 (28.8%), Nonbinary/gender nonconforming 9 (6.5%) **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** 121 (87.8%)	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
O'Bryan 2020	Transgender and gender expansive children, youth and adults (<22 for registry)	The Gender Wellness Center (GWC) is a rural based, multidisciplinary centre that offers gender affirming medical, mental health, and surgical care in Upstate New York (established 2007 for adults and 2012 for youth; registry in 2017)	2017 to January 2019	Of TG/GE youth receiving care at the GWC, 158 were enrolled in the Registry (97%); The HRQOL survey completion rate at baseline for all patients enrolled in the registry was 89% (N=141). 141 included in summaries	**Age at referral:** Not reported **Age at assessment:** mean 16.3 SD 3.2 **Birth-registered sex:** 100 (71.4%) females and 40 (28.6%) males	**Gender identity:** Transmasculine spectrum 95 (67.4%), Transfeminine spectrum 37 (26.2%), Non-binary/gender nonconforming 9 (6.4%) **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Pariseau 2019	Youth attending clinic for psychological assessment prior to receiving possible puberty blocker or gender affirming hormonal intervention	Gender Management Service (GeMS) program at Boston Children's Hospital, a pediatric gender clinic housed in an academic medical center, for psychological assessment	2007 to 2011	54	**Age at referral:** Not reported **Age at assessment:** mean 14.6 SD 2.4 range 8.9 to 17.9 **Birth-registered sex:** 24 (44.4%) females and 30 (55.6%) males	**Gender identity:** transgender female 30 (55.6%), transgender male 24 (44.4%), non binary 0 (0.0%) **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Peterson 2017	Transgender adolescents and emerging adults (aged 12–22) presenting with gender dysphoria	Cincinnati Children's Hospital Medical Center Transgender Clinic (opened in 2013 and served more than 475 patients between ages of 5 and 24)	July 2013 to June 2015	96	**Age at referral:** Not reported **Age at assessment:** mean 17.1 SD 2.3 **Birth-registered sex:** not reported	**Gender identity:** 54 transmale, 31 transfemale, 15 non-binary/gender fluid **Gender dysphoria:** 100% **Onset:** Not reported **Social transition:** Not reported	**Depression:** 36 (38%) **Anxiety:** 26 (27%) **Suicide:** 27 (30.3%) **Self-harm:** (41.8%) **Eating disorder:** 5 (5%)	**ASC:** 3 (3%) **ADHD:** 12 (13%)	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Peterson 2020b	TG youth and young adults meeting diagnostic criteria for gender dysphoria who received medical care	TG clinic within an urban children's hospital in the Midwestern region of the United States	Unclear	249	**Age at referral:** Not reported **Age at assessment:** mean 17.04 SD 2.88, range 11 to 24 **Birth-registered sex:** 180 (72.3%) females and 69 (27.7%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Eating Disorder Examination Questionnaire - brm mean 1.63 SD 1.40; brf mean 1.61 SD 1.33; 23.4% objective binge eating episodes in the last month and 3.9% reported self-induced vomiting episodes in the last month.	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Poquiz 2021a	All patients initiating care within a multidisciplinary gender clinic completing psychosocial forms as standard of care	Ann & Robert H. Lurie Children's Hospital of Chicago	July 2013 to July 2019	669 completed forms 31 who reported "questioning" their gender (n = 28) or an "unknown" gender (n = 3) were removed from analyses; 638 included in the analysis	**Age at referral:** Not reported **Age at assessment:** mean 16.1 years, range 12.03 to 24.11 **Birth-registered sex:** not reported	**Gender identity:** 418 transmasculine (65.5%), 157 transfeminine (24.6%), and 63 nonbinary (9.9%) **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Living as affirmed gender 441 (69.1%)	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Poquiz 2021b	Children and young people referred to the clinic	Children's Mercy Kansas City (CMKC) is a large pediatric medical center serving the Kansas City metro area and the surrounding region, including large rural areas of the Midwest. CMKC offers services at 12 urban and suburban locations and 6 satellite clinics within rural Kansas and Missouri. The Gender Pathway Services (GPS) clinic was developed in 2014.	2014 to 2018	395 patients; 2014=14, 2015=56, 2016=95, 2017=107, 2018=131	**Age at referral:** Not reported **Age at assessment:** mean 15.3, range 3 to 23 **Birth-registered sex:** 269 (68%) females and (%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Reguitti 2022	Children and young people at initial appointment 12-17	Gender health clinic housed in a pediatric academic medical center in the Midwestern United States; Ann & Robert H. Lurie Children's Hospital of Chicago	August 2013 to July 2019	739 parents who completed standard-of-care psychosocial measures during their child's initial appointment	**Age at referral:** Not reported **Age at assessment:** mean 15.4 SD 1.51 range 12.0 to 17.9 **Birth-registered sex:** 542 (73.3%) females and 197 (26.7%) males	**Gender identity:** Boy/man/masculine spectrum 467 (63.2%), Girl/woman/feminine spectrum 169 (22.9%), Nonbinary 66 (8.9%), Questioning 35 (4.7%), Unknown 2 (0.3%) **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Shumer 2016	Children and young people presenting for evluation in the clinic	Multidisciplinary gender clinic in a large U.S. pediatric hospital, Boston Children's Hospital	2007 to 2011	39	**Age at referral:** Not reported **Age at assessment:** mean 15.8 range 8 to 20 **Birth-registered sex:** 17 (43.6%) females and 22 (56.4%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** 1 (2.6%), Aspergers 3 (7.7%); ASQ (>80): Probability of aspergers 9 (23.1%) - 5 (22.7%) BRM and 4 (23.5%) BRF, ; possibly 1 (2.6%), likely 6 (15.4%), very likely 2 (5.1%) **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

Shumer 2017	Children and young people entering the gender programme	Pediatric hospital-based multidisciplinary gender program in Boston, Massachusetts; Boston Children's Hospital	2007 to 2015	184	**Age at referral:** Not reported **Age at assessment:** mean 15.1, range 7.5 to 20.6 **Birth-registered sex:** 105 (57.1%) females and 79 (42.9%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Adopted 15 (8.2%)
Spack 2012	Patients with gender dysphoria	Endocrine division at Children's Hospital Boston and then GeMS clinic	1998 to 2009	1998=1 1999=2 2000=4 2001=0 2002=1 2003=5 2004=10 2005=9 2006=8 2007=22 2008=24 2009=11 97 included	**Age at referral:** Not reported **Age at assessment:** mean 14.8 SD 3.4 median 16 range 4 to 20 **Birth-registered sex:** 54 (55.7%) females and 43 (44.3%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** living full time gender role 89 (91.8%), age mean 13.6 SD 3.8	**Depression:** 25 (58.1%) **Anxiety:** 7 (16.3%) **Suicide:** 9 (9.3%) **Self-harm:** 20 (20.6%) **Eating disorder:** 3 (7.0%)	**ASC:** 1 (2.3%) **ADHD:** 2 (4.7%)	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Adopted 97 (8.2%)
Tordoff 2022	Transgender and nonbinary youths seeking care having a phone intake and in-person appointment	Seattle Children's Gender Clinic, an urban multidisciplinary gender clinic	August 2017 to June 2018	169 youths approached; 161 eligible; 9 declined; 39 did not consent or baseline survey; 9 <13 excluded; 104 in the analysis	**Age at referral:** Not reported **Age at assessment:** mean 15.8 SD 1.6 range 13 to 20 **Birth-registered sex:** 71 (68.3%) females and 33 (31.7%) males	**Gender identity:** transmasculine 63 (60.6%), transfeminine 27 (26.0), nonbinary/gender fluid 10 (2.6%), did not know or did not respond 4 (3.8%) **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** PHQ-9 59 (56.7%); minimal 14 (13.5%), mild 27 (26.0%), moderate 22 (21.2%), moderately severe 11 (0.6%), severe 26 (25.0%) **Anxiety:** GAD-7 52 (50.0%); minimal 20 (19.2%), mild 28 (26.9%), moderate 20 (19.2%), severe 32 (30.8%) **Suicide thoughts or self-harm:** 45 (43.2) **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported
Zou 2018	Eligible participants were aged 4–25 years old TGN, and followed by this clinic	Transgender Clinic of the Division of Adolescent and Transition Medicine in a 629-bed academic pediatric medical center	Unclear	142 enrolled in the study; 134 completed the PedsQL 4.0 generic core scales; one participant did not report age	**Age at referral:** Not reported **Age at assessment:** mean 15.9 SD 3.7 **Birth-registered sex:** 96 (68.3%) females and 45 (31.7%) males	**Gender identity:** Not reported **Gender dysphoria:** Not reported **Onset:** Not reported **Social transition:** Not reported	**Depression:** Not reported **Anxiety:** Not reported **Suicide:** Not reported **Self-harm:** Not reported **Eating disorder:** Not reported	**ASC:** Not reported **ADHD:** Not reported	**Neglect or abuse:** Not reported **Parental mental illness or substance misuse:** Not reported **Exposure to domestic violence:** Not reported **Household member in prison:** Not reported **Loss of parent:** Not reported

* Multiple country study
Abbreviations: brf=birth-registered female, brm=birth-registered male



Coloured bars within a country indicate if the same clinic data is reported across studies
* Multiple countries studies
** Timeline unclear / not reported
*** Provides data from 1972 but specialist clinic established in 1987 so data reported from then
**** US clinics are not differentiated by colour due to limited data reporting

EXHIBIT 94

Gender services for children and adolescents across the EU-15+ countries: an online survey

Ruth Hall, Jo Taylor, Claire Heathcote, Trilby Langton, Catherine Elizabeth Hewitt, Lorna Fraser

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/archdischild-2023-326348).

Department of Health Sciences, University of York, York, UK

Correspondence to
Professor Catherine Elizabeth Hewitt, Department of Health Sciences, University of York, York, UK;
dohs-gender-research@york.ac.uk

Received 22 September 2023
Accepted 25 November 2023

Linked

► http://dx.doi.org/10.1136/archdischild-2023-326347
► http://dx.doi.org/10.1136/archdischild-2023-326112
► http://dx.doi.org/10.1136/archdischild-2023-326500
► http://dx.doi.org/10.1136/archdischild-2023-326499
► http://dx.doi.org/10.1136/archdischild-2023-326760
► http://dx.doi.org/10.1136/archdischild-2023-326670
► http://dx.doi.org/10.1136/archdischild-2023-326681
► http://dx.doi.org/10.1136/archdischild-2023-326669

To cite: Hall R, Taylor J, Heathcote C, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2023-326348

ABSTRACT

Background Over the last 10-15 years, there has been an increase in the number of children and adolescents referred to gender services, particularly among adolescent birth-registered females. This population shows a higher prevalence of co-occurring mental health difficulties and neurodevelopmental conditions. Some countries have recently restricted access to medical treatments in recognition of the uncertain evidence base.

Aim To understand the current provision of gender services for children and adolescents across the EU-15+ countries that have comparable high-income healthcare systems, to inform service development in the UK.

Methods An e-survey of paediatric gender services was conducted between September 2022 and April 2023. It covered service structure, care pathways, interventions and data collection. Data were described and compared to identify similarities and differences among participating services.

Results 15 services in eight countries (Australia, Belgium, Denmark, Norway, Northern Ireland, The Netherlands, Spain and Finland) responded. While a multidisciplinary team was present in all services, its composition and organisation varied. Clinical practice was informed by international guidelines, with four countries following their own national guidelines. Differences were observed in referral criteria, care pathways for prepubertal children and those with co-occurring conditions. Eligibility criteria for medical interventions also varied. Psychosocial support and interventions were limited, and outcome data collection was scarce.

Conclusions This survey revealed both similarities and key variations in the clinical practice of paediatric gender services across eight different countries. The study emphasises the need for service development that both considers the management of co-occurring conditions and embeds routine data collection in practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The number of children and adolescents identifying as a gender different to the sex they were registered at birth have increased markedly over the last 10-15 years.
⇒ Some countries have updated their guidelines and changed gender service provision for children and adolescents.

WHAT THIS STUDY ADDS

⇒ This survey found areas of common practice across gender services for children and adolescents in eight countries, with most using Diagnostic and Statistical Manual fifth edition diagnostic criteria and a multidisciplinary team approach.
⇒ The survey revealed key differences in the composition of teams, the management of co-occurring conditions, prepubertal children and those with a non-binary gender identity, and in the criteria for accessing medical interventions.
⇒ Referral pathways into gender services for children and adolescents varied, and services reported limited provision of psychological care and a reliance on local mental health services.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Gender services needs to consider the provision of psychological care. High-quality standardised data collection should be routinely collected to enable comparison in outcomes for children and adolescents accessing these different services.

INTRODUCTION

Over the last 10-15 years, there has been an increase internationally in the numbers of children and adolescents referred to gender services and a relative increase in referrals for adolescent birth-registered females.[1–7] An over-representation of those with neurodevelopmental conditions, and high rates of co-occurring mental health difficulties have also been reported.[8–10] Addressing the needs of this growing population is a concern for clinicians and policymakers.[11 12]

International clinical practice and guidelines[13 14] have until recently largely been informed by the 'Dutch protocol'[15] entailing psychosocial care and then staged medical interventions. While the main international guideline produced by the World Professional Association for Transgender Health (WPATH) has, over time, relaxed some of the original eligibility criteria for medical interventions,[13] some countries have recently moved away from WPATH. In particular, Sweden[16] and Finland[17] have reviewed the evidence and in response updated their national guidelines, recommending a more cautious approach to providing medical interventions, which in Sweden will only be provided under a research framework and in exceptional cases until this is established. Norway is also considering a review of guidelines.[18 19] In the UK, an independent review[20] has led to the recommendation of a new model of care and the current development of new gender services.[21] Additionally, some professional bodies in

France and Australia have adopted a more cautious approach regarding the medical treatment of adolescents.[22 23]

There has been no recent systematic collection of data on the provision of gender services for children and adolescents in countries with similar healthcare systems. A previous survey of the provision of services internationally focused on North America and Europe and is likely already out of date as this was published in 2018 prior to some countries raising concerns.[24]

This study aimed to understand and describe the current provision of gender services for children and adolescents in the EU-15+ countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden, Australia, Canada, Norway and the UK) which have comparable high-income healthcare systems used in other benchmarking studies,[25] to inform future service development.

METHODS

This was an e-survey of gender services for children and adolescents, reported according to the Checklist for Reporting Results of Internet E-Surveys guidelines.[26] It was confirmed with the University of York Department of Health Sciences Research Governance Committee that ethical approval was not required as this was a service evaluation. The survey was administered according to University of York's data protection and reporting requirements.

Sample

The target sample was gender services for children and adolescents in the EU15+ countries. Contact details for the services were obtained from publicly available data, expert contacts and via snowball sampling.

Recruitment

An email was sent to identified clinicians or managers, explaining the survey aims, confidentiality, data protection and expected completion time. In terms of confidentiality, we stated that data would be reported at country level rather than by naming services or respondents. One reminder email was sent after 3 weeks.

Survey design and administration

An e-survey was created in Qualtrics.[27] It contained 34 questions over five pages on service structure, care pathways, interventions and data collection (see online supplemental file 1). An additional four questions on staffing and waiting lists were optional. The questions were informed by a review of published papers describing service provision (see online supplemental file 2) and the content of clinical guidelines. Items were categorical or free text responses. Adaptive questioning was applied; certain items were conditionally displayed based on responses to other items. Respondents were able to review and change their answers.

The draft survey was reviewed by an advisory committee, which included expert gender clinicians from three European countries in order to check the applicability of the questions to different settings. It was also piloted by one gender clinician, with revisions to the wording and flow of questions made following feedback.

The survey was open between September 2022 and April 2023.

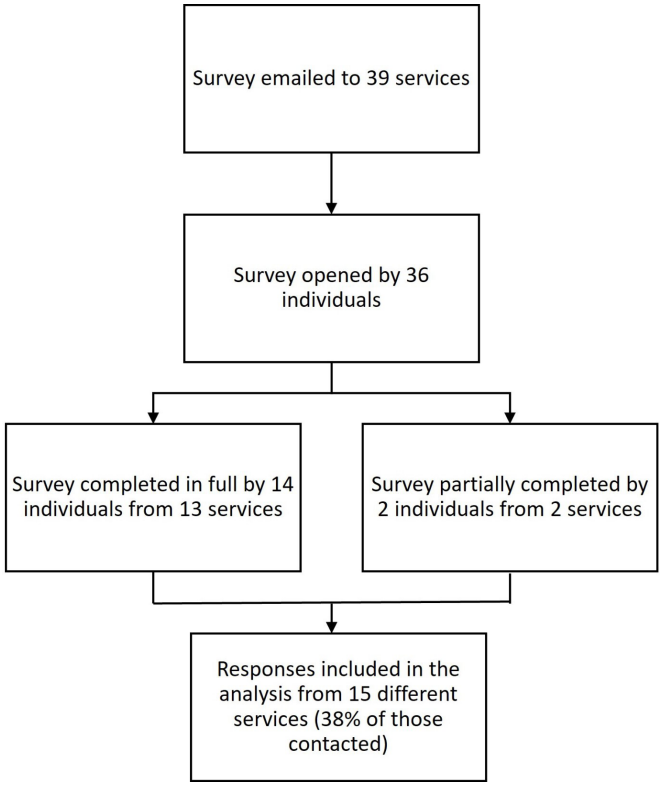


Figure 1 Study flow chart.

Data analysis

Consistency and completeness checks were performed after responses were received; more detail was sought from some services where responses were unclear. As this was a 'closed' survey, it was possible to identify and remove duplicate entries from the same user or service.

All responses were downloaded into Microsoft Excel and descriptively analysed, including those not fully completed. Responses were described, tabulated and compared to assess similarity and variation among the services.

RESULTS

Participation

No services were located in Greece or Luxembourg and Ireland does not have a paediatric provider.[28] Services were identified in Northern Ireland, Scotland and England within the UK. A total of 39 services from 16 countries were contacted. The survey was accessed by 36 individuals from the 39 services and completed in full by 14 individuals. Two respondents partially completed the survey (figure 1). One service was described by two individuals. Responses from 15 different services were submitted, located in eight countries (Australia, Belgium, Denmark, Norway, Northern Ireland, The Netherlands, Spain, Finland), a response rate of 38%.

Structure of services

Countries showed variations in how they structured services for children and adolescents. Most countries had either national gender services (Norway, Denmark, Finland) or regional services (Australia, Northern Ireland, Spain). The Netherlands had a network of both regional and national services with referral pathways between them. All services were publicly funded and mainly located within tertiary or

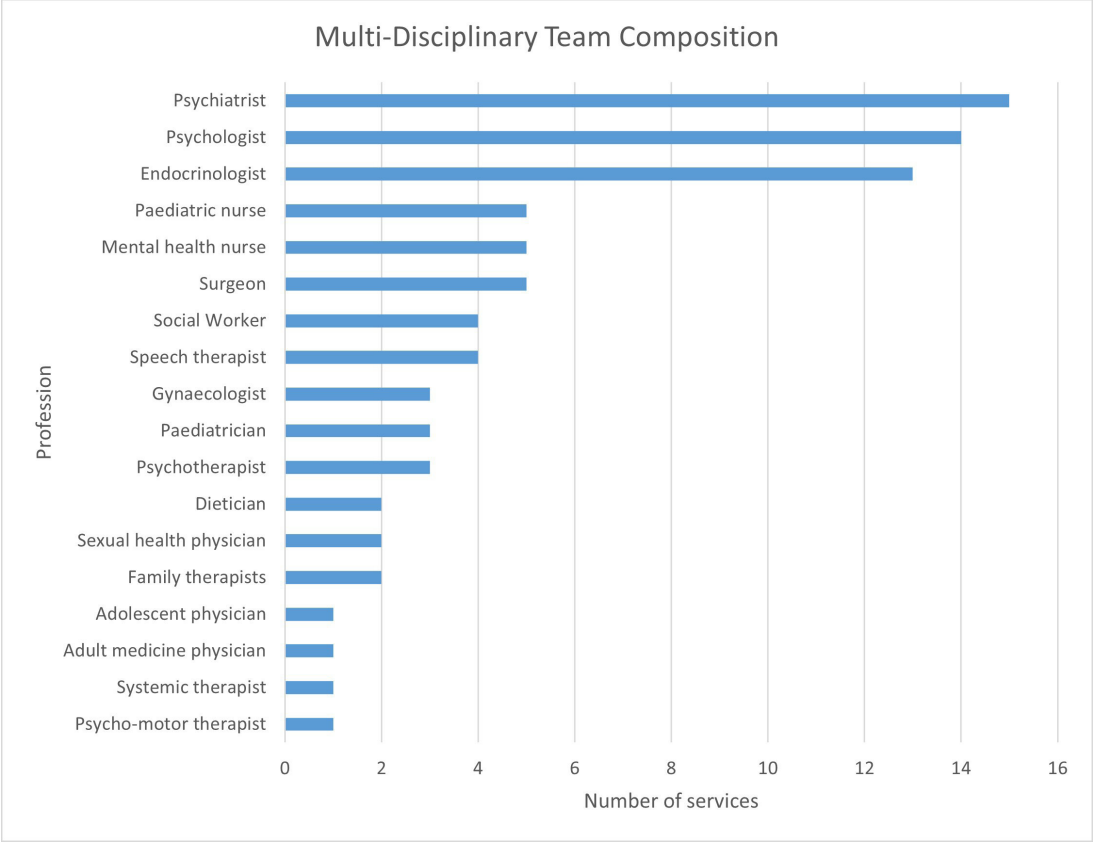


Figure 2 Multi-disciplinary team composition.

secondary care mental health, endocrinology, or paediatric departments.

A minimum age for accessing services existed in three services, ranging from 8 years in Belgium, 9 years in a Netherlands service and 14 years in Spain. Other services did not have a minimum age. Spain reported that their minimum age reflects the legal context in which 14 years is the legal minimum age to access masculinising or feminising hormone interventions. Most (n=9) offered services up to young adulthood (age 17/18). The remainder offered services beyond this age, up to the age of 25 (n=1) or throughout adulthood (n=5).

All services described a multidisciplinary team (MDT) of health professionals, but its composition and organisation varied. Child and adolescent psychologists and/or psychiatrists were present in all services, while most also included paediatricians or endocrinologists. Other professionals were involved in different frequencies (figure 2).

In some services (Finland, Northern Ireland and Denmark), the core MDT consisted of mental health professionals who conducted assessments and facilitated access to other specialties, for example, endocrinology. Conversely, some Australian services described greater integration of disciplines within the MDT, involving different specialties in the assessment phase, and often co-located within the gender clinic instead of separate departments.

Clinical practice was reported as most commonly informed by international guidelines; the WPATH V.7[29] or 8,[13] and Endocrine Society guidelines.[14] Country-specific guidelines were used in Australia[30] and The Netherlands.[31] In Denmark and Finland, national guidelines alone were used.[17 32]

Care pathways

Referral criteria

Referral routes into services varied: some services (Finland, Northern Ireland, Norway) required referrals from child and adolescent mental health services (CAMHS) after assessment, while many others (The Netherlands, Denmark, Belgium, Spain, Australia) had no such requirement. Finland was unique in also having specific referral criteria related to co-occurring conditions; referrals not accepted for children or adolescents with significant mental health, or social concerns. Several services specified that a referral must come from a clinician (Australia). It was unclear if any services accepted self-referrals. Age and residency status were the other main referral criteria.

Assessment processes

Services followed similar assessment pathways with appointments involving psychologists and/or psychiatrists (table 1). Some services with integrated MDT models also included other medical staff (paediatricians and endocrinologists) in the assessment process. The duration and number of appointments varied within and between services and were often described as tailored to individual presentations. Spain was an exception in not routinely offering multiple appointments; a single assessment session was reported and psychologist involvement as being optional.

Core assessment areas were generally aligned among services. Most reported that they evaluate developmental and mental health history as well as gender development (identity, expression, dysphoria/incongruence). Many services conducted a broad psychosocial assessment (Australia, Belgium, Finland,

Table 1 Assessment process

Country	Clinician undertaking assessment	Number of appointments/duration	Areas of assessment	Assessment tools for gender dysphoria*	Assessment tools for other co-occurring conditions*
Australia	Psychologist or Psychiatrist	Multiple appointments depending on clinical need	Gender exploration (history, identity, body) Capacity Mental health Fertility	None used	No screening
Australia	Mental health nurse Psychiatrist Psychologist Endocrinologist *Patient sees all as MDT consensus required*	Minimum 9 appointments of 1–2 hours. 'Fast' pathway 6–7 months.	Mental health Developmental history Family history Drug and alcohol Gender identity development Treatment wishes Fertility Capacity assessment	Perth Gender Picture **Gender Preoccupation and Stability Questionnaire (GPSQ)**	**Social Responsiveness Scale-2** **Child Behaviour Checklist** **Youth Self Report** **Beck Youth Inventory (BYI)** SCOFF: Eating Disorder Screen ESQ quality of life Youth Quality of Life Instrument-short form
Australia	Psychiatrist for diagnosis of Gender Dysphoria Paediatricians or gynaecologists for other assessments	4 appointments over 4–6 months	Gender identity history Developmental history Mental health history Current mental health Aims for gender treatment Medical history Fertility counselling Consent	Gender Diversity Questionnaire	**Spence Children's Anxiety Scale** Mood and Feelings Questionnaire (MFQ) **Columbia Suicide Severity Rating Scale (C-SSRS)**
Australia	Psychiatrists Psychologists Social workers Mental health nurses	Varies depending on age, social support, mental health concerns, social transition status. Ranges from 2 to 3 sessions over 2–3 months to approximately 6 sessions over 6 months.	Developmental history Mental health assessment Bio-psycho-social assessment Gender identity Gender expression Resilience Systemic strengths and challenges	**Gender Preoccupation and Stability Questionnaire** Sometimes also: **Body Image Scale**	Strengths and Difficulties Questionnaire (SDQ) Index of Family Functioning and Change—SCORE-15 **Beck Youth Inventory (BYI)** Sometimes also: Child and Adolescent Trauma Screen (CATS) **Child Behaviour Checklist** **The Wechsler Intelligence Scale for Children (WISC)** No tools for autism spectrum condition assessment used as not accurate in trans population
Australia	Nurse assessment for triage Psychologist or Psychiatrist and Paediatrician	All children over 8 years allocated three initial mental health sessions then a joint paediatric+mental health session. From there; individualised plan devised for ongoing assessment/care/referral elsewhere	Developmental history Mental health assessment Gender identity development Capacity assessment if pursuing medical treatments Assessment of co-occurring mental health conditions or autism Family functioning School functioning	About your gender—gender slider About socially transitioning About your voice **Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults** Single item measuring recent gender distress **Gender Preoccupation and Stability Questionnaire** **Body Image Scale** Chest Dysphoria Scale	**Youth Self Report** **Child Behaviour Checklist** **Spence Children's Anxiety Scale** Branched Eating Disorders test Short mood and feelings questionnaire Depression Anxiety and Stress Scale Social Phobia Scale Gender Minority Stress and Resilience Scale The Brief Resilience Scale **Columbia-Suicide Severity Rating Scale** **Social Responsiveness Scale** About School Psychological Sense of School Membership Survey Gatehouse Bullying Scale Family Assessment Device Child Health Utility 9D Assessment of Quality of Life (AQoL-4D)
Belgium	Psychologist Psychiatrist (in MDT approach)	Average once a month for 6 months	Developmental history Emotional history Social Cognitive Gender resilience Comorbidities Sexual orientation Fertility Peer support	The Genderbread Person **Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults** **Utrecht Gender Dysphoria Scale** **Recalled Childhood Gender Identity scale (RCGI)** **Body Image Scale**	**Child Behaviour Checklist** **Youth Self Report** **Teacher's Report Form** **The Children's Global Assessment Scale**

Continued

Table 1 Continued

Country	Clinician undertaking assessment	Number of appointments/duration	Areas of assessment	Assessment tools for gender dysphoria*	Assessment tools for other co-occurring conditions*
Denmark	Psychologist and Psychiatrist	For adolescents with long standing gender incongruence, stable social and mental health: at least five appointments plus psychiatric assessment.	Gender identity development Gender dysphoria Social support Family relations Sexuality Fertility Cognitive assessment Psychiatric assessment	None	Kiddie-SADS **Social Responsiveness Scale** Behavior Rating Inventory of Executive Function ADHD-Rating Scale **The Wechsler Intelligence Scale for Children (WISC) 4/5** **Autism Diagnostic Observation Schedule** Assessment of Depression Inventory Measures of parental self-efficacy Test of Variables of Attention Rorschach Test **Children's Global Assessment Scale**
Finland	Psychologist and Psychiatrist Information from full MDT team also used Diagnosis always made by Psychiatrist	Approximately 10 appointments over 12 months	Developmental history Mental health history Family history Trauma history Functioning (with peers, at school, in family, leisure time) Gender identity development as situated within broader identity development Current psychiatric or welfare needs Readiness for change Expectations Support needed if proceeding to medical interventions	**Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults** **Recalled Childhood Gender Identity scale (RCGI)** **Utrecht Gender Dysphoria Scale** **Body Image Scale**	**Autism Diagnostic Observation Schedule**
Netherlands	Psychologist Psychiatrist	3–6 appointments	Gender identity Gender dysphoria Social transition Treatment wishes Family history Comorbidities Developmental history Medical history	Gender Unicorn	**Child Behaviour Checklist** **Teacher Report Form** IQ tests if indicated **Autism Diagnostic Observation Schedule** The Anxiety and Related Disorders Interview Schedule
Netherlands	Psychiatrist Psychologist Family therapist	Tailor made but usually starts with three sessions for child, three for parents, one psychiatric evaluation.	Gender feelings Bio-psycho-social assessment of child and family Relation between gender incongruence and other concerns (eg, Autism) Psychiatric evaluation	Yes but not specified	No tools reported
Netherlands	Psychologist Psychiatrist	N/R	N/R	N/R	N/R
Netherlands	Psychologist Psychiatrist	N/R	Broad functioning	Yes but not specified	N/R
Northern Ireland	Psychiatrist and Psychologist and Mental Health nurse in MDT approach	Range 4–20 appointments, average 8. Usually 6 weekly	History of gender identity development Family relations Mental health concerns Neurodevelopmental	**Body Image Scale** **Recalled Childhood Gender Identity scale** **Utrecht Gender Dysphoria Scale**	No tools reported
Norway	Psychiatrist and Psychologist (always meets two clinicians and always team decision)	Prior to gender clinic referral; 4–5 appointments in mental health team over 1–2 years. Within gender clinic; 'several' appointments	Gender incongruence Mental health Somatic health	No tools reported	The Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) **Social Responsiveness Scale**
Spain	Not a diagnostic assessment: Endocrinologist Psychologist only involved if parent or child requests	One day	N/R	N/R	N/R

*Tools in bold used by more than one service.
N/R, not reported.

Netherlands, Northern Ireland). Fewer services discussed fertility preferences (n=5) or sexuality (n=2). In Australia, capacity to consent to treatment was assessed. Finland was the only country to report routinely assessing for any history of trauma.

Services used a variety of measures for assessing gender-related distress and co-occuring conditions. Fourteen tools were used across 10 services to measure gender dysphoria/incongruence. Only five were used by more than one service; Gender Preoccupation and Stability Questionnaire (n=3), Gender Identity Questionnaire (GIDYQ-AA; n=3), Body Image Scale (n=5), Recalled Childhood Gender Identity Scale (n=3), Utrecht Gender Dysphoria Scale (n=3). Thirty-six different measures were used to assess co-occurring conditions; only 10 were used by more than a single service (see table 1).

The DSM-V Gender Dysphoria diagnosis was the most widely used diagnostic criteria (n=13). Three services (Australia,

Netherlands and Norway) also used the International Classification of Diseases 11th revision Gender Incongruence code. Denmark only used the ICD-10 DZ76.8 code ('Persons encountering health services in other specified circumstances').

Pathways for prepubertal children

Prepubertal children usually had a separate care pathway with one-off consultations and local management if needed. Three Australian services offered a unique pathway for those described as 'peri-pubertal' (aged 8–9), prioritised for fast-track entry. They received both psychological support and access to puberty suppression when eligible.

Pathways for those with co-occurring conditions

Most services (n=10) reported that they relied on other providers such as CAMHS for the management of co-occurring mental health concerns or neurodevelopmental conditions. Additionally, nine services reported that they adjusted their assessment processes for these individuals using longer assessment phases, pausing assessments or making additional referrals. Denmark and Finland reported a different pathway for young people with significant psychosocial concerns or short history of gender distress. In Denmark, children and adolescents receive 1–3 reflective sessions instead of a full assessment and are advised to return in adulthood if needed. In Finland, significant mental health concerns must be managed by local teams before assessment by the gender service.

Pathways for children and adolescents with non-binary identities

Only three countries mentioned a different approach for this group. Denmark implemented a delay in assessment and treatment until adulthood, while in Finland and Norway, medical treatments were delayed until adulthood.

Two services in Australia were cautious about the use of interventions to suppress puberty in non-binary adolescents who were unlikely to later want masculinising/feminising hormones, on the basis that these are time-limited treatments.

Interventions

Psychosocial interventions

In-house psychosocial interventions were reported as limited in services. Three services offered psychoeducation support for gender dysphoria/incongruence (Belgium, Australia, Spain). Specific psychosocial interventions offered were family therapy (n=2), psychotherapy (n=2), cognitive behavioural therapy (n=2) and dialectical behavioural therapy (n=1). Five services reported that they did not offer any in-house provision.

Medical interventions

All services routinely offer interventions to suppress puberty and masculinising/feminising hormone interventions except for one regional service (The Netherlands), which referred to a national gender service. Northern Ireland reported halting hormone interventions for new referrals in 2020 due to the length of the corresponding adult service waiting list but continued care for existing patients. Menstrual suppression with progestogens was routine in four services, and one also provided anti-androgens.

Services reported a range of eligibility criteria for medical interventions (figures 3 and 4). There was most consistency across services on requiring a diagnosis of gender dysphoria or incongruence (n=9), reaching Tanner stage 2 (n=8) and stable mental health (n=6) for interventions to suppress puberty. Key differences in criteria were the duration of gender dysphoria/incongruence; while some services did not refer to duration, Belgium, Finland, Norway and Denmark required 'long lasting' or 'since childhood', and Finland specified puberty-intensified distress. Only two services had a minimum age; Finland stated

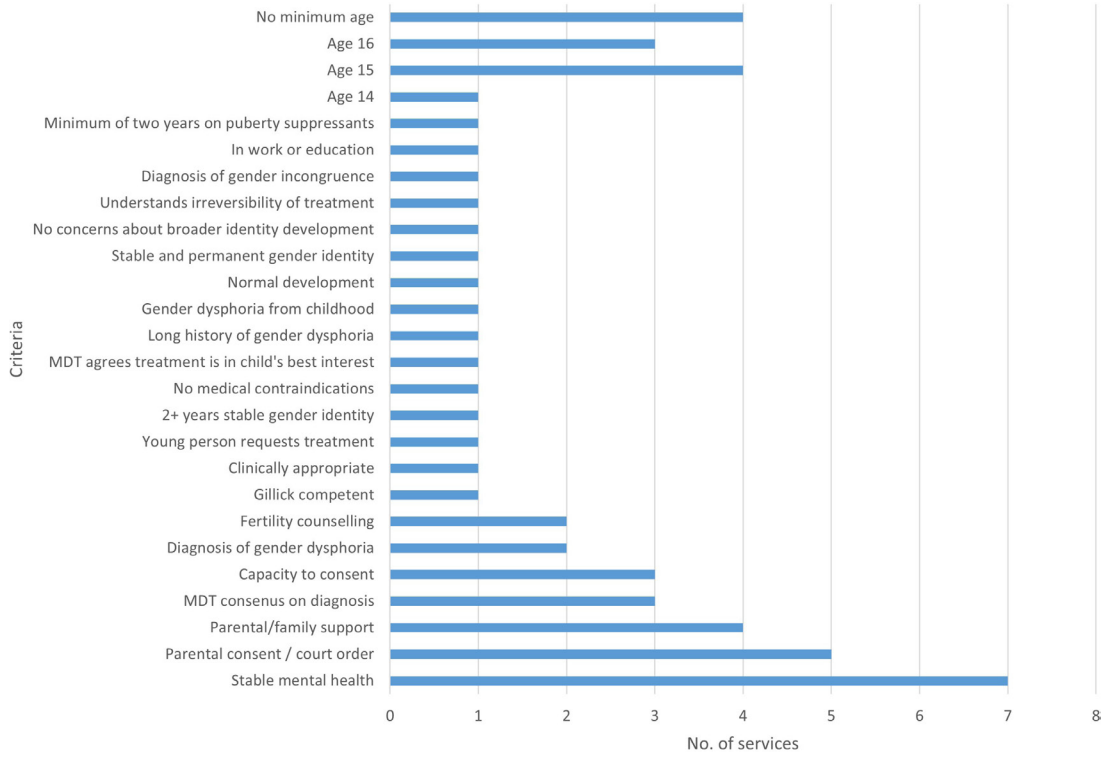


Figure 3 Eligibility criteria for accessing puberty suppressants. MDT, multidisciplinary team.

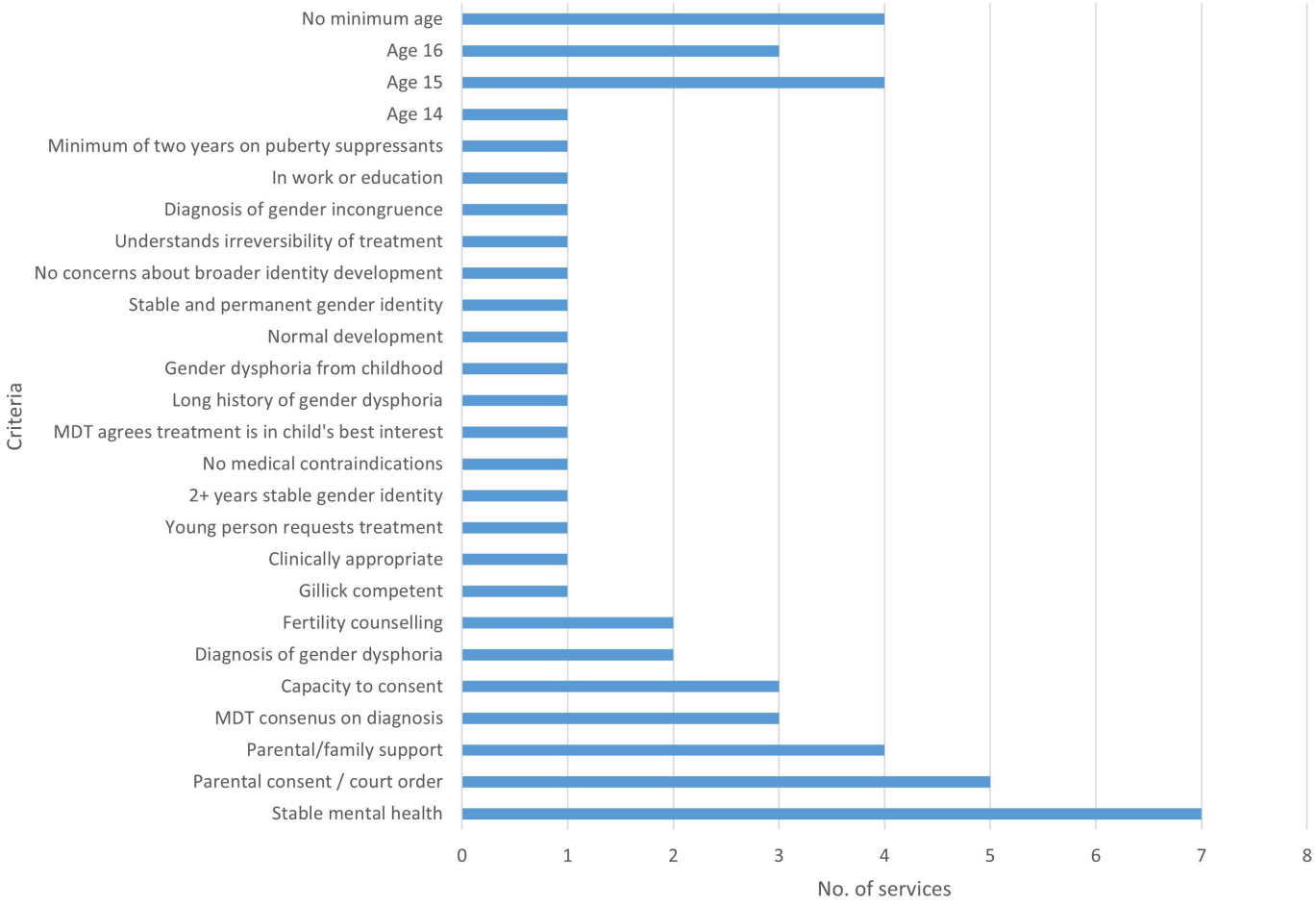


Figure 4 Eligibility criteria for accessing masculinising or feminising hormones. MDT, multidisciplinary team.

age 13, Spain age 12. Five services excluded those in later stages of puberty from puberty suppression (three Australian services, Denmark, Finland).

Criteria for masculinising/feminising hormone interventions also varied with stable mental health mentioned by the majority of services (n=8). However, thresholds differed; some services excluded those in 'acute mental health crisis' and others requiring 'no more than mild mental health problems likely secondary to gender dysphoria'. Variations in clinical practice existed in minimum age requirements for masculinising/feminising hormones; four services had no minimum age, while others specified age 14 (Spain), age 15 (two Australian services, Denmark, one Netherlands service) or age 16 (Finland, Northern Ireland, Norway). The persistence of gender dysphoria/incongruence as criteria for masculinising/feminising hormones also varied; Finland required a 'permanent and stable' identity, Belgium 'long-lasting', Denmark 'since childhood' and one Australian service 'a stable identity for over 2 years'.

Child consent or assent requirements and capacity were infrequently mentioned for both interventions to suppress puberty and masculinising/feminising hormones. Uniquely, the consent of both parents or a court order was legally required in Australia.

Fertility preservation

Access to fertility preservation was offered in nine services across seven countries. Two additional services provided fertility counselling, but access to fertility preservation was via private services.

Surgical treatment

Genital reconstructive surgery was universally reported as accessible only from age 18. Masculinising chest surgery (mastectomy) was accessible at not only different ages in different countries but also different regions within countries. Age 16 was the youngest age reported. Some countries reported limited availability of surgical providers.

Follow-up and outcomes

The 10 gender services exclusively catering for children and adolescents typically provided care until patients reached age 17–18. Afterwards, these services transferred the patients to adult gender services, sexual health services or General Practitioners, depending on the availability of local services. One service provided longer follow-up until age 25 for those expressing regret or discontinuing treatments (Finland).

Six services routinely collected some outcome data; one gave no further details, one recorded the number discontinuing treatment, one used two measures of quality of life, one repeated some baseline assessments and two were involved in cohort studies. The other nine services reported not routinely collecting outcome data.

Operational concerns

Waiting lists

Six services reported both their current caseloads and past 12-month referral numbers; two services (one Australian and

Northern Ireland) reported past 12-month referral numbers greater than their current caseloads. Waiting lists were reported by 11 services (Finland and Denmark had no waiting list). The shortest waiting time reported was 2–3 months for those 'fast-tracked' in an Australian service and the longest 3–4 years (in another Australian service). The majority of services (n=10) had no criteria for triaging waiting lists and prioritising patients according to wait time. Three services in Australia triage according to pubertal stage; one additionally prioritises vulnerable groups.

DISCUSSION

This survey found some similarities across paediatric gender services in eight countries and also some key points of divergence in the management of co-occurring conditions, prepubertal care and criteria for accessing medical interventions. We also found a paucity of in-house psychosocial interventions available and limited routine follow-up data collection across services. These variations in clinical practice could lead to important clinical and demographic differences in the cohorts of children/adolescents accessing treatments and, potentially, in their outcomes in different countries. The local context and guidelines followed likely explain some variation; while some countries to respond are adopting more cautious treatment policies,[17 18 33] others have moved away from psychological assessment in response to the passing of regional laws.[34]

Most services who completed the survey were specialised MDTs serving national or regional populations, providing diagnostic assessments and access to medical interventions for children and adolescents experiencing gender dysphoria/incongruence. Psychologists and/or psychiatrists played central roles in nearly all services. Most but not all gender services showed some similarities to the original Amsterdam gender service,[35] which has influenced international guidelines and practice for many years.[36] The observed differences in service structure mainly centred around the membership and roles of the MDT, and whether an interdisciplinary or a predominantly mental health model underpinned the services. Guidelines typically recommend an interdisciplinary approach though evidence underpinning this is lacking.[37]

The assessment processes shared common elements across services; most offered multiple appointments and covered similar core domains. The use of different tools to assess gender or co-occurring conditions was much less consistent and of the 14 gender-related tools reportedly used, only three are validated for this population[38]: Gender Preoccupation and Stability Questionnaire-2,[39] Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults, [40] and Recalled Childhood Gender Identity Scale.[41]

High rates of co-occurring mental health need and neurodevelopmental conditions in this population are well documented and poses a challenge for gender services.[8 10 42] Participating services reported relying on separate teams, such as CAMHS, for the management of co-occurring mental health concerns. Additionally, some services (Finland, Denmark, Northern Ireland, Norway) either do not accept referrals for those with additional mental health concerns or require a prior CAMHS assessment. Whether this selective approach to who enters the service will, over time, change the outcomes for these children and adolescents is as yet unknown. It may in part, however, explain why Finland and Denmark had no waiting list.

Another notable difference among services is the management of prepubertal children. Traditionally, 'watchful waiting' has been recommended to observe how gender feelings and any distress develops, as the evidence suggests that many children's gender questions or concerns may not persist into adolescence.[15 43 44] Most services still followed this approach for younger children and distinguished between prepubertal and pubertal children in terms of pathways. However, some services described a distinct pathway for 'peripubertal' children. These children are prioritised on the waiting list, so that those who are assessed as likely to benefit, are commenced on interventions to suppress puberty once eligible. The Australian guidelines[30] support this approach in stating that puberty suppression is most effective from Tanner stage 2, however, the impact of this, which might entail longer use of interventions to suppress puberty or earlier commencement of masculinising/feminising hormones, remains unknown as early studies of outcomes of interventions to suppress puberty mandated a minimum age of 12.[45]

The eligibility criteria for medical interventions showed variation across countries, reflecting evolving changes in international and national guidelines over time. The original 'Dutch Protocol' which established specific eligibility criteria for interventions to suppress puberty and masculinising/feminising hormones, required (1) life-long gender dysphoria that had increased around puberty, (2) functioning and psychologically stable and (3) supported by their environment. For puberty suppression, additional criteria were age 12+, at least Tanner stage 2–3 and engaging with psychology or psychiatry for at least 6 months during treatment. For masculinising/feminising hormones, additional criteria were age 16+ and having lived socially in their gender identity prior to treatment ('real-life experience').[46] These criteria have been adapted over time, for instance, WPATH V7[29] removed age requirements, and 'life-long' gender dysphoria became 'long lasting'. The Australian guidelines,[30] in contrast, only adopted the criteria about Tanner stage 2 while requiring a diagnosis of Gender Dysphoria, fertility counselling and MDT agreement that treatment is in the child's best interests. In contrast, the Finnish guidelines[17] have used the original Dutch criteria; this was reflected in the survey response with Finland's criteria most closely resembling the original Dutch protocol.

Data collection practices varied internationally with inconsistency in baseline measures and only a few services routinely collecting follow-up data. Only two services reported systematically collecting data through cohort studies. Similar findings were reported in an earlier survey of gender services where few participated in audits or had a registry.[24] The lack of evidence about short and long-term outcomes, coupled with the evolving demographics of individuals being referred to gender services and the different pathways to accessing psychological care, is particularly concerning in this context. Without high-quality data collection, it is not possible to describe or compare outcomes for children and adolescents seen by gender services internationally.

Strengths and limitations

The survey was designed with input from a range of experts and informed by published literature describing and evaluating gender services for children and adolescents, and clinical guidelines. Analysis and reporting of all survey data prevent selective reporting of results.

Reliance on publicly available information and known experts may mean some services were not identified and contacted. The low response rate means that certain countries are not

represented and other potential differences in gender services are still unknown. Only a partial response was received from the influential Amsterdam gender service and there was no response from the national service for England and Wales. Given one of the purposes of this survey was to inform the service redesign in England this is an important limitation.

Nuanced differences, for instance, in how MDTs make decisions, or how gender is explored during assessments, could not be examined in any depth due to the nature of the survey responses.

CONCLUSIONS

This survey provides valuable insights into the assessment and care provision of gender services for children and adolescents in 15 different services across eight countries. The findings highlight not only some similarities but also key variations in clinical practice. High-quality research and routine data collection are urgently required to understand the impact of these differences in access to services and care pathways. The design of new services needs to consider how best to meet the psychological needs of children and adolescents experiencing gender dysphoria/incongruence.

Contributors LF, CEH and TL contributed to the conception of this study. LF, CH, TL and JT contributed to the design of the study. Data collection was led by RH. Analyses were undertaken by RH and LF. RH drafted the first version of the manuscript. All authors reviewed the manuscript prior to submission. CEH accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was funded by NHS England to inform the Cass Review (Independent review of gender identity services for children and young people). The funder and Cass Review team had a role in commissioning the research programme but no role in the study conduct, interpretation or conclusion.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants but did not require ethical approval as it was classified as service evaluation. Participants gave informed consent to participate in the survey before taking part.

Provenance and peer review Commissioned; externally peer-reviewed.

ORCID iDs
Jo Taylor http://orcid.org/0000-0001-5898-0900
Catherine Elizabeth Hewitt http://orcid.org/0000-0002-0415-3536

REFERENCES

1 Arnoldussen M, Steensma TD, Popma A, *et al*. Re-evaluation of the dutch approach: are recently referred transgender youth different compared to earlier referrals *Eur Child Adolesc Psychiatry* 2020;29:803–11.
2 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender dysphoria literature: 1) epidemiology. *PLOS Glob Public Health* 2022;2:e0000245.
3 Handler T, Hojilla JC, Varghese R, *et al*. Trends in referrals to a pediatric transgender clinic. *Pediatrics* 2019;144:e20191368.
4 Steensma TD, Cohen-Kettenis PT, Zucker KJ. Evidence for a change in the sex ratio of children referred for gender dysphoria: data from the center of expertise on gender dysphoria in amsterdam (1988-2016). *J Sex Marital Ther* 2018;44:713–5.
5 Aitken M, Steensma TD, Blanchard R, *et al*. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. *J Sex Med* 2015;12:756–63.
6 Butler G, De Graaf N, Wren B, *et al*. Assessment and support of children and adolescents with gender dysphoria. *Arch Dis Child* 2018;103:631–6.
7 Kaltiala R, Bergman H, Carmichael P, *et al*. Time trends in referrals to child and adolescent gender identity services: a study in four Nordic countries and in the UK. *Nord J Psychiatry* 2020;74:40–4.
8 Kaltiala-Heino R, Sumia M, Työläjärvi M, *et al*. Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. *Child Adolesc Psychiatry Ment Health* 2015;9:9.
9 Van Der Miesen AIR, Hurley H, De Vries ALC. Gender dysphoria and autism spectrum disorder: a narrative review. *Int Rev Psychiatry* 2016;28:70–80.
10 Thompson L, Sarovic D, Wilson P, *et al*. A PRISMA systematic review of adolescent gender dysphoria literature: 2) mental health. *PLOS Glob Public Health* 2022;2:e0000426.
11 Kozlowska K, McClure G, Chudleigh C, *et al*. Australian children and adolescents with gender dysphoria: clinical presentations and challenges experienced by a multidisciplinary team and gender service. *Human Systems* 2021;1:70–95.
12 Levine SB, Abbruzzese E. Current concerns about gender-affirming therapy in adolescents. *Curr Sex Health Rep* 2023;15:113–23.
13 Coleman E, Radix AE, Bouman WP, *et al*. Standards of care for the health of transgender and gender diverse people, version 8. *Int J Transgend Health* 2022;23:S1–259.
14 Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-dysphoric/gender-Incongruent persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017;102:3869–903.
15 de Vries ALC, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the dutch approach. *J Homosex* 2012;59:301–20.
16 The Swedish National Board of Health and Welfare. Appendix - knowledge base with method description - care of children and young people with gender Dysphoria; 2022. Available: https://www.socialstyrelsen.se/globalassets/sharepointdokument/artikelkatalog/kunskapsstod/2022-12-8302-kunskapsunderlag-medmetodbeskrivning.pdf
17 Council for Choices in Healthcare in Finland. Medical Treatment Methods for Dysphoria Associated with Variations in Gender Identity in Minors – Recommendation; 2020. https://palveluvalikoima.fi/en/recommendations#genderidentity.
18 Norwegian Healthcare Investigation Board (Ukom). Patient safety for children and young people with gender Incongruence; 2023. https://ukom.no/rapporter/pasientsikkerhet-for-barn-og-unge-med-kjonnsinkongruens/sammendrag
19 Block J. Norway's government is "in dialogue" with health services about gender treatments. *BMJ* 2023;382:1572.
20 Cass H. Review of gender identity services for children and young people. *BMJ* 2022:o629.
21 NHS EnglandInterim service specification for specialist gender Incongruence services for children and young people; 2023. https://www.england.nhs.uk/publication/interim-service-specification-for-specialist-gender-incongruence-services-for-children-and-young-people/
22 French National Academy of Medicine. Medical care of children and adolescents with Transgender identity [press release]; 2022. https://www.academie-medecine.fr/la-medecine-face-a-la-transidentite-de-genre-chez-les-enfants-et-les-adolescents/?lang=en
23 The Royal Australian and New Zealand College of Psychiatrists. Recognising and addressing the mental health needs of people experiencing gender Dysphoria: position statement; 2021. https://www.ranzcp.org/clinical-guidelines-publications/clinical-guidelines-publications-library/recognising-and-addressing-the-mental-health-needs-of-the-lgbtiq-population
24 Skordis N, Butler G, de Vries MC, *et al*. ESPE and PES International survey of centers and clinicians delivering specialist care for children and adolescents with gender dysphoria. *Horm Res Paediatr* 2018;90:326–31.
25 Ward JL, Wolfe I, Viner RM. Cause-specific child and adolescent mortality in the UK and Eu15+ countries. *Arch Dis Child* 2020;105:1055–60.
26 Eysenbach G. Improving the quality of web surveys: the checklist for reporting results of Internet E-surveys (CHERRIES). *J Med Internet Res* 2004;6:e34.
27 Qualtrics. 2022 Ed: Qualtrics. Available: https://www.qualtrics.com
28 Review of the implications of the Cass report for the provision of gender identity services for children and young people in Ireland. National Quality and Patient Safety Directorate; 2023.:https://www.hse.ie/eng/services/publications/clinical-strategy-and-programmes/review-of-the-implications-of-the-cass-report-for-the-provision-of-gender-identity-services-for-children-and-young-people-in-ireland-march-2023-published-version.pdf.
29 Coleman E, Bockting W, Botzer M, *et al*. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgend* 2012;13:165–232.

30 Telfer MM, Tollit MA, Pace CC, *et al*. Australian standards of care and treatment guidelines for transgender and gender diverse children and adolescents. *Med J Aust* 2018;209:132–6.
31 Alliance Transgender Care. Quality standard of Transgender mental health care; 2017. https://www.transvisie.nl/wp-content/uploads/2018/01/kwaliteitsstandaard-transgenderzorg-18122017-geautoriseerd.pdf
32 Danish Health AuthorityGuide on Healthcare related to gender identity; 2018. https://www.sst.dk/-/media/English/Publications/2018/Guide-on-healthcare-related-to-gender-identity.ashx?sc_lang=en&hash=0FF626604C50D5EED94852CA5D042A8E
33 Lane B. Doubt in denmark. 2023. Available: https://www.genderclinicnews.com/p/doubt-in-denmark?r=1meqgr&utm_medium=ios&utm_campaign=post [Accessed 20 Aug 2023].
34 Gómez-Gil E, Esteva de Antonio I, Fernández Rodríguez M, *et al*. New care models for transgender people in the Spanish health system: demands, controversies and reflections. *Rev Esp Salud Publica* 2020;94:e202011123.
35 Cohen-Kettenis PT, Steensma TD, de Vries ALC. Treatment of adolescents with gender dysphoria in the Netherlands. *Child Adolesc Psychiatr Clin N Am* 2011;20:689–700.
36 Biggs M. The dutch protocol for juvenile transsexuals: origins and evidence. *J Sex Marital Ther* 2023;49:348–68.
37 Abbruzzese E, Levine SB, Mason JW. The myth of "reliable research" in pediatric gender medicine: a critical evaluation of the dutch studies—and research that has followed. *J Sex Marital Ther* 2023;49:673–99.
38 Bowman SJ, Casey LJ, McAloon J, *et al*. Assessing gender dysphoria: a systematic review of patient-reported outcome measures. *Psychol Sex Orientat Gend Divers* 2021;9:398–409.
39 Bowman SJ, Hakeem A, Demant D, *et al*. Assessing gender dysphoria: development and validation of the gender preoccupation and stability questionnaire - 2(nd) edition (GPSQ-2). *J Homosex* 2024;71:666–90.
40 Deogracias JJ, Johnson LL, Meyer-Bahlburg HFL, *et al*. The gender identity/gender dysphoria questionnaire for adolescents and adults. *J Sex Res* 2007;44:370–9.
41 Zucker KJ, Mitchell JN, Bradley SJ, *et al*. The recalled childhood gender identity/gender role questionnaire: psychometric properties. *Sex Roles* 2006;54:469–83.
42 Holt V, Skagerberg E, Dunsford M. Young people with features of gender dysphoria: demographics and associated difficulties. *Clin Child Psychol Psychiatry* 2016;21:108–18.
43 Zucker KJ. Debate: different strokes for different folks. *Child Adoles Ment Health* 2020;25:36–7.
44 Steensma TD, McGuire JK, Kreukels BPC, *et al*. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry* 2013;52:582–90.
45 de Vries ALC, Steensma TD, Doreleijers TAH, *et al*. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med* 2011;8:2276–83.
46 Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol* 2006;155:S131–7.

Supplementary material: survey questions

Block 1 Clinic Details

Welcome. This survey is intended to be completed by either a senior clinician or service manager within a gender service for children and adolescents. If you are unable to complete it we would be grateful if you could send it on to the most appropriate person in your service. Many thanks.

Name and job title of person completing this survey (this information will not appear in any publication)

Name

Job title

Name, address and country of clinic?

Clinic Name

Address

Country

Block 2 Structure of services

Please broadly describe how gender services for children and adolescents are provided in your country?

Is your gender service publicly funded?

- ○ Yes
- ○ No

Please describe how the service is funded

Do you provide a regional or national service?

- ○ Regional
- ○ National

What is the setting for your service (e.g. paediatric department, mental health department, community setting)?

Block 3 Guidelines

Which national or international guidelines does your service follow?

Block 4 Referral process

Do you have any referral criteria? (e.g. age, pubertal stage, source of referrals)

- ○ Yes
- ○ No

Please describe the referral criteria:

Block 5 Multi-disciplinary team

Which, if any, of the following specialists are employed by your service?

Please tick all that apply:

- ☐ Psychologist
- ☐ Psychiatrist
- ☐ Psychotherapist
- ☐ Endocrinologist
- ☐ Paediatric nurse
- ☐ Mental health nurse
- ☐ Occupational therapist
- ☐ Social worker
- ☐ Speech and Language therapy
- ☐ Surgeons
- ☐ Other: please specify –

Block 6 Assessment Process

Does your service provide a diagnostic assessment for children and adolescents with gender dysphoria?

- ○ Yes
- ○ No

Please say who provides this diagnostic assessment:

Which diagnostic criteria do you use?

Please select all that apply

- ☐ ICD-11 Gender Incongruence of Childhood (code HA61)
- ☐ ICD-11 Gender Incongruence of Adolescence and Adulthood (code HA60)
- ☐ DSM-5 Gender Dysphoria (code 302.85)

Which clinicians undertake assessments (e.g. psychologist, psychiatrist)?

What are the key areas explored in the assessment?

On average, how many appointments do children and adolescents have during the assessment process and over what time period?

Is there a different process for assessing pre-pubertal children as compared to pubertal adolescents?

- ○ Yes
- ○ No

Please describe this process:

Do you routinely use any assessment tools to aid the diagnosis of gender dysphoria?

- ○ Yes
- ○ No

Please list these tools:

Do you routinely screen for any co-occurring conditions (e.g. autism, anxiety, depression, other mental health concerns)?

- ○ Yes
- ○ No

Please state which assessment tools, if any, are used:

Please add any further information to describe the assessment process if not covered above:

Block 7 Psycho-social

Please describe any psycho-social interventions or psychological therapies that your service provides (e.g. for children and adolescents or for parents/families):

Block 8 Medical treatments

Does your service provide medical interventions for Gender Dysphoria?

- ○ Yes
- ○ No

Please say where medical interventions are accessed:

Please describe these interventions

What are your clinic’s inclusion criteria for children and adolescents to access puberty blockers?

What are your clinic's exclusion criteria for children and adolescents to access puberty blockers?

Is there a minimum age that children must be to start puberty blockers?

- ○ Yes
- ○ No

Please state the minimum age:

What are your clinic’s inclusion criteria for children and adolescents to start cross-sex hormones?

What are your clinic's exclusion criteria for children and adolescents to access cross-sex hormones?

What is the minimum age for accessing cross-sex hormones?

Have you made any changes to the accessibility of puberty blockers or cross-sex hormones or do you intend to do so?

- ○ Yes
- ○ No

Please describe the changes and the reasons for them?

Do children and adolescents have access to fertility preservation via your service?

- ○ Yes
- ○ No

Please state at what stage this is accessed:

Please state where fertility preservation is provided:

Block 9 Surgical interventions

What is the minimum age that adolescents can access chest surgery (masculinising or feminising)?

What is the minimum age that adolescents can access genital reconstructive surgery/gender realignment surgery (GRS)?

Block 10 Specific groups

Is there a different care pathway for patients with a non-binary identity compared to those with a binary identity?

Is there a different care pathway for patients presenting with co-occurring autism or mental health concerns compared to those without?

Block 11 Onward care

When are children and adolescents discharged from your clinic?

If children and adolescents transfer to adult gender services when and how does this occur? (e.g. at a specific age, or at a stage of transition?)

Do you routinely collect any outcome data?

- ○ Yes
- ○ No

Please describe what is collected and at what stage:

Block 12 ADDITIONAL / OPTIONAL QUESTIONS

The following questions are optional as we realise this data may not be easily available. If you are able to complete this section then please do.

How many children/adolescents does your service currently have under its care?

How many referrals have been received in the past 12 months?

Do you have a waiting list?

- ○ Yes
- ○ No

Please state how long it is currently:

How do you prioritise those on the waiting list (e.g. length of time waiting, age, level of distress)?

How many staff do you currently employ to provide direct patient care?

Block 13 Close

Thank you for taking the time to complete this survey. We are trying to get as many responses from different clinics as possible so would be grateful if you could either share this survey with your colleagues from other services or provide their contact details for us below.

Study ID	Title of paper	Country of gender clinic	Name of gender clinic(s)	Type of paper
Mahfouda 2019(1)	Mental health correlates of autism spectrum disorder in gender diverse young people: Evidence from a specialised child and adolescent gender clinic in Australia	Australia	Gender Diversity Service, Perth Children's Hospital	Research study containing description of a service
Hilton 2022(2)	The co-occurrence of neurodevelopmental disorders in gender dysphoria: Characteristics within a paediatric treatment-seeking cohort and factors that predict distress pertaining to gender	Australia	Gender Service, Department of psychological Medicine, Children's Hospital Westmead, New South Wales	Research study containing description of a service
Kozlowska 2020(3)	Attachment patterns in children and adolescents with gender dysphoria	Australia	Gender Service, Department of psychological Medicine, Children's Hospital Westmead, New South Wales	Research study containing description of a service
Kozlowska 2021 (4)	Australian children and adolescents with gender dysphoria: Clinical presentations and challenges experienced by a multidisciplinary team and gender service	Australia	Gender Service, Department of psychological Medicine, Children's Hospital Westmead, New South Wales	Research study containing description of a service

1

Tollit 2019(5)	What are the health outcomes of trans and gender diverse young people in Australia? Study protocol for the Trans20 longitudinal cohort study	Australia	The Royal Children's Hospital Gender Service (RCHGS), Melbourne	Research protocol containing description of a service
Hewitt 2012(6)	Hormone treatment of gender identity disorder in a cohort of children and adolescents	Australia	The Royal Children's Hospital Gender Service (RCHGS), Melbourne	Research study containing description of a service
Tollit 2021 (7)	The clinical profile of patients attending a large, Australian pediatric gender service: A 10-year review	Australia	The Royal Children's Hospital Gender Service (RCHGS), Melbourne	Research study containing description of a service
Allen, S. 2021(8)	A waitlist intervention for transgender young people and psychosocial outcomes	Australia	The Royal Children's Hospital Gender Service (RCHGS), Melbourne	Service Evaluation
Eade 2018(9)	Implementing a single-session nurse-led assessment clinic into a gender service	Australia	The Royal Children's Hospital Gender Service (RCHGS), Melbourne	Service Evaluation
Tollit 2018(10)	Patient and parent experiences of care at a paediatric gender service	Australia	The Royal Children's Hospital Gender Service (RCHGS), Melbourne	Service evaluation
VanCauwenberg 2021(11)	Ten years of experience in counselling gender diverse youth in Flanders, Belgium. A clinical overview	Belgium	Pediatric Gender Clinic, Center for Sexology and Gender, Ghent University Hospital, Ghent, Belgium	Research study containing description of a service

Khatchadourian 2014(12)	Clinical management of youth with gender dysphoria in Vancouver	Canada	Gender clinic, British Columbia Children's Hospital	Research study containing description of a service
Feder 2017(13)	Exploring the associations between eating disorders and gender dysphoria in youth	Canada	Gender Diversity Clinic at a Canadian tertiary pediatric care hospital in Ottawa, Ontario	Research study containing description of a service
Zucker 2012(14)	A developmental biopsychosocial model for the treatment of children with gender identity disorder	Canada	Gender Identity Service at the Centre for Addiction and Mental Health in Toronto (formerly Clarke GIC)	Description of a service
Bradley 1978(15)	Gender identity problems of children and adolescents: The establishment of a special clinic	Canada	Clarke Gender Identity Clinic, Clarke Institute of psychiatry, Toronto	Description of a service
Kaltiala-Heino 2015(16)	Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development	Finland	Tampere University Hospital, Department of Adolescent Psychiatry	Research study containing description of a service
Brecht 2021(17)	Assessment of Psychological Distress and Peer Relations among Trans Adolescents—An Examination of the Use of Gender Norms and Parent–Child Congruence of the YSR-R/CBCL-R among a Treatment-Seeking Sample	Germany	Gender Identity Special Consultation (GISC) at the Charité Universitätsmedizin Berlin, Germany	Research study containing description of a service
Becker-Hebly 2020(18)	Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: a descriptive study from the Hamburg Gender Identity Service	Germany	Hamburg Gender Identity Service for children and adolescents (Hamburg GIS).	Research study containing description of a service

Nieder 2021(19)	Individual treatment progress predicts satisfaction with transition-related care for youth with gender dysphoria: A prospective clinical cohort study	Germany	Hamburg Gender Identity Service for children and adolescents (Hamburg GIS).	Research study containing description of a service
Cohen-Kettenis 2011(20)	Treatment of adolescents with gender dysphoria in the Netherlands	Netherlands	Center for Expertise on Gender Dysphoria, VU University Medical Centre, Amsterdam	Description of a service
de Vries 2006(21)	Clinical management of gender dysphoria in adolscents	Netherlands	Center for Expertise on Gender Dysphoria, VU University Medical Centre, Amsterdam	Description of a service
de Vries 2012(22)	Clinical management of gender dysphoria in children and adolescents: the Dutch approach	Netherlands	Center for Expertise on Gender Dysphoria, VU University Medical Centre, Amsterdam	Description of a service
Delemarre - VanDeWaal 2006	Clinical management of gender identity disorder in adolescents: A protocol on psychological and paediatric endocrinology aspects	Netherlands	Center for Expertise on Gender Dysphoria, VU University Medical Centre, Amsterdam	Description of a service

deVries 2010(23)	Autism spectrum disorders in gender dysphoric children and adolescents	Netherlands	Center for Expertise on Gender Dysphoria, VU University Medical Centre, Amsterdam	Research study containing description of a service
Verveen 2021(24)	Body image in children with gender incongruence	Netherlands	Center for Expertise on Gender Dysphoria, VU University Medical Centre, Amsterdam	Research study containing description of a service
Mc Callion 2021(25)	An appraisal of current service delivery and future models of care for young people with gender dypshoria	Scotland	Paediatric Endocrinology Service, Royal Hospital for Children, Glasgow	Research study containing description of service
Churcher Clarke 2019(26)	Taking the lid off the box': The value of extended cinical assessment for adolescents presenting with gender identity difficulties	UK	Gender Identity Development Service	Case review containing a description of a service
Butler 2018(27)	Assessment and support of children and adolescents with gender dysphoria	UK	Gender Identity Development Service	Description of a service
Costa 2015(28)	Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria	UK	Gender Identity Development Service	Research study containing description of a service

Morandini, 2021 (29)	Shift in demographics and mental health co-morbidities among gender dysphoric youth referred to a specialist gender dysphoria service	UK	Gender Identity Development Service	Research study containing description of a service
Denaro 2021(30)	Lessons from Grassroots Efforts to Increase Gender-Affirming Medical Care for Transgender and Gender Diverse Youth in the Community Health Care Setting	US	MultiCare Health System, Washington state	Description of a service
Meyer-Bahlburg 2002(31)	Gender identity disorder in young boys: A parent and peer based treatment protocol	USA	Author at Department of Psychiatry of Columbia University	Description of a service
Warwick, 2021(32)	Gender-affirming multidisciplinary care for transgender and non-binary children and adolescents	USA	Child and Adolescent Gender Services Clinic, C.S. Mott Children's Hospital at the University of Michigan	Description of a service

Poquiz 2021(33)	Gender-affirming care in the midwest: reaching rural populations	USA	Children's Mercy Hospital Gender Pathway Services (GPS) clinic, Kansas	Description of a service
Allen, L. 2019(34)	Wellbeing and suicidality among transgender youth after gender-affirming hormones	USA	Children's Mercy Hospital Gender Pathway Services (GPS) clinic, Kansas	Research study containing description of a service
Allen, L. 2021 (35)	Gender-affirming psychological assessment with youth and families: A mixed methods examination	USA	Children's Mercy Hospital Gender Pathway Services (GPS) clinic, Kansas	Service Evaluation
Chen 2016(36)	Multidisciplinary Care for Gender-Diverse Youth: A Narrative Review and Unique Model of Gender-Affirming Care	USA	Gender and Sex Development Program (GSDP) at the Ann & Robert H. Lurie Children's Hospital of Chicago	Description of a service
Sood 2021(37)	Association of Chest Dysphoria With Anxiety and Depression in Transmasculine and Nonbinary Adolescents Seeking Gender-Affirming Care	USA	Gender and Sex Development Program (GSDP) at the Ann & Robert H. Lurie Children's Hospital of Chicago	Research study containing description of a service

Edwards Leeper 2012(38)	Psychological evaluation and medical treatment of transgender youth in an interdisciplinary "Gender Management Service"(GeMS) in a major pediatric center	USA	Gender Management Service (GEMS) at Children's Hospital Boston	Description of a service
Tishelman 2015(39)	Serving transgender youth: challenges, dilemmas and clinical examples	USA	Gender Management Service (GEMS) at Children's Hospital Boston	Description of a service
Spack 2012(40)	Children and adolscents with gender identity disorder referred to a pediatric medical centre	USA	Gender Management Service (GEMS) at Children's Hospital Boston	Research study containing description of a service
Cousino 2014(41)	An emerging opportunity for pediatric psychologists: Our role in a multidisciplinary clinic for youth with gender dysphoria.	USA	KIDz PRIDE clinic at MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio	Description of a service
Oransky 2019(42)	An interdisciplinary model for meeting the mental health needs of transgender adolescents and young adults: The Mount Sinai Adolescent Health Center approach.	USA	Mount Sinai Adolescent Health Center (MSAHC), NY	Description of a service
Schwartz 2022 (43)	Experiences with menses in transgender and gender nonbinary adolescents	USA	Nemours Children's Hospital Delaware multidisciplinary Gender Wellness Program (GWP)	Research study containing description of a service
Salehi 2018(44)	Review of Current Care Models for Transgender Youth and Application to the Development of a Multidisciplinary Clinic - The Seattle Children's Hospital Experience	USA	Seattle Children's Hospital, Gender clinic	Description of a service

Inwards-Breland 2019(45)	Youth and parent experiences in a multidisciplinary gender clinic	USA	Seattle Children's Hospital, Gender clinic	Service evaluation
Hedrick 2022 (46)	A new virtual reality: benefits and barriers to providing pediatric gender-affirming health care through telehealth	USA	The Doernbecher Gender Clinic (DGC), Portland	Service Evaluation
Menviell e 2012(47)	A comprehensive program for children with gender variant behaviours and gender identity disorders	USA	The Gender and Sexuality Development Program at Children's National Medical Center (CNMC) in Washington, DC	Description of a service
Rodnan 2011(48)	A therapeutic group for parents of transgender adolescents	USA	The Gender and Sexuality Development Program at Children's National Medical Center (CNMC) in Washington, DC	Description of a service
Bates 1975(49)	Intervention with families of gender-disturbed boys	USA	UCLA Department of Psychology	Description of a service
Rosen 1977(50)	Theoretical and diagnostic issues in child gender disturbances	USA	UCLA Department of Psychology	Research study containing description of a service
Olezeski 2017(51)	Development of the Yale Gender Centre: An early progress report	USA	Yale Gender Center	Description of a service

References

1. Mahfouda S, Panos C, Whitehouse AJO, Thomas CS, Maybery M, Strauss P, et al. Mental Health Correlates of Autism Spectrum Disorder in Gender Diverse Young People: Evidence from a Specialised Child and Adolescent Gender Clinic in Australia. J. 2019;8(10):20.
2. Hilton MN, Boulton KA, Kozlowska K, McClure G, Guastella AJ. The co-occurrence of neurodevelopmental disorders in gender dysphoria: Characteristics within a paediatric treatment-seeking cohort and factors that predict distress pertaining to gender. J Psychiatr Res. 2022;149:281-6.
3. Kozlowska K, Chudleigh C, McClure G, Maguire AM, Ambler GR. Attachment Patterns in Children and Adolescents With Gender Dysphoria. Front Psychol. 2020;11:582688.
4. Kozlowska K, McClure G, Chudleigh C, Maguire AM, Gessler D, Scher S, et al. Australian children and adolescents with gender dysphoria: Clinical presentations and challenges experienced by a multidisciplinary team and gender service. Human Systems. 2021;1(1):70-95.
5. Tollit MA, Pace CC, Telfer M, Hoq M, Bryson J, Fulkoski N, et al. What are the health outcomes of trans and gender diverse young people in Australia? Study protocol for the Trans20 longitudinal cohort study. BMJ Open. 2019;9(11):e032151.
6. Hewitt JK, Paul C, Kasiannan P, Grover SR, Newman LK, Warne GL. Hormone treatment of gender identity disorder in a cohort of children and adolescents. Med J Aust. 2012;196(9):578-81.
7. Tollit MA, May T, Maloof T, Telfer MM, Chew D, Engel M, et al. The clinical profile of patients attending a large, Australian pediatric gender service: a 10-year review. Int J Transgend Health.
8. Allen SD, Tollit MA, McDougall R, Eade D, Hoq M, Pang KC. A waitlist intervention for transgender young people and psychosocial outcomes. Pediatrics. 2021;148(2):e2020042762.
9. Eade DM, Telfer MM, Tollit MA. Implementing a Single-Session Nurse-Led Assessment Clinic into a Gender Service. Transgend Health. 2018;3(1):43-6.
10. Tollit MA, Feldman D, McKie G, Telfer MM. Patient and Parent Experiences of Care at a Pediatric Gender Service. Transgend Health. 2018;3(1):251-6.
11. Van Cauwenberg G, Dhondt K, Motmans J. Ten years of experience in counseling gender diverse youth in Flanders, Belgium. A clinical overview. Int J Impot Res. 2021;05:05.
12. Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. J Pediatr. 2014;164(4):906-11.
13. Feder S, Isserlin L, Seale E, Hammond N, Norris ML. Exploring the association between eating disorders and gender dysphoria in youth. Eat. 2017;25(4):310-7.
14. Zucker KJ, Wood H, Singh D, Bradley SJ. A developmental, biopsychosocial model for the treatment of children with gender identity disorder. J Homosex. 2012;59(3):369-97.
15. Bradley SJ, Steiner B, Zucker K, Doering RW, Sullivan J, Finegan JK, et al. Gender identity problems of children and adolescents: the establishment of a special clinic. Can Psychiatr Assoc J. 1978;23(3):175-83.
16. Kaltiala-Heino R, Sumia M, Tyolajarvi M, Lindberg N. Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. Child Adolesc Psychiatry Ment Health. 2015;9:9.

17. Brecht A, Bos S, Ries L, Winter SM, Calvano C. Assessment of Psychological Distress and Peer Relations among Trans Adolescents-An Examination of the Use of Gender Norms and Parent-Child Congruence of the YSR-R/CBCL-R among a Treatment-Seeking Sample. Children (Basel). 2021;8(10):28.
18. Becker-Hebly I, Fahrenkrug S, Campion F, Richter-Appelt H, Schulte-Markwort M, Barkmann C. Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: a descriptive study from the Hamburg Gender Identity Service. Eur Child Adolesc Psychiatry. 2020;29:29.
19. Nieder TO, Mayer TK, Hinz S, Fahrenkrug S, Herrmann L, Becker-Hebly I. Individual Treatment Progress Predicts Satisfaction With Transition-Related Care for Youth With Gender Dysphoria: A Prospective Clinical Cohort Study. J Sex Med. 2021;18(3):632-45.
20. Cohen-Kettenis PT, Steensma TD, de Vries ALC. Treatment of adolescents with gender dysphoria in the Netherlands. Child Adolesc Psychiatr Clin N Am. 2011;20(4):689-700.
21. de Vries ALC, Cohen-Kettenis PT, Delemarre-van de Waal H. Clinical management of gender dysphoria in adolescents. Int J Transgend. 2006;9(3/4):83-94.
22. de Vries ALC, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the Dutch approach. J Homosex. 2012;59(3):301-20.
23. de Vries ALC, Noens ILJ, Cohen-Kettenis PT, van Berckelaer-Onnes IA, Doreleijers TA. Autism spectrum disorders in gender dysphoric children and adolescents. J Autism Dev Disord. 2010;40(8):930-6.
24. Verveen A, Kreukels BP, de Graaf NM, Steensma TD. Body image in children with gender incongruence. Clin. 2021:13591045211000797.
25. McCallion S, Smith S, Kyle H, Shaikh MG, Wilkinson G, Kyriakou A. An appraisal of current service delivery and future models of care for young people with gender dysphoria. Eur J Pediatr. 2021;14:14.
26. Churcher Clarke A, Spiliadis A. 'Taking the lid off the box': The value of extended clinical assessment for adolescents presenting with gender identity difficulties. Clin. 2019;24(2):338-52.
27. Butler G, De Graaf N, Wren B, Carmichael P. Assessment and support of children and adolescents with gender dysphoria. Arch Dis Child. 2018;103(7):631-6.
28. Costa R, Dunsford M, Skagerberg E, Holt V, Carmichael P, Colizzi M. Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria. J Sex Med. 2015;12(11):2206-14.
29. Morandini JS, Kelly A, de Graaf NM, Carmichael P, Dar-Nimrod I. Shifts in demographics and mental health co-morbidities among gender dysphoric youth referred to a specialist gender dysphoria service. Clin. 2021:13591045211046813.
30. Denaro A, Pflugeisen CM, Colglazier T, DeWine D, Thompson B. Lessons from Grassroots Efforts to Increase Gender-Affirming Medical Care for Transgender and Gender Diverse Youth in the Community Health Care Setting. Transgend Health.
31. Meyer-Bahlburg HFL. Gender identity disorder in young boys: A parent- and peer-based treatment protocol. Clinical Child Psychology and Psychiatry. 2002;7(3):360-76.
32. Warwick RM, Shumer DE. Gender-affirming multidisciplinary care for transgender and non-binary children and adolescents. Children's Health Care. 2021.

33. Poquiz J, Moser CN, Grimstad F, Boman K, Sonneville SA, Turpin A, et al. Gender-affirming care in the midwest: Reaching rural populations. Journal of Rural Mental Health. 2021;45(2):121-8.
34. Allen LR. Well-being and suicidality among transgender youth after gender-affirming medical interventions. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2019;80(11-B(E)):No Pagination Specified.
35. Allen LR, Dodd CG, Moser CN. Gender-affirming psychological assessment with youth and families: A mixed-methods examination. Practice Innovations. 2021;6(3):159-70.
36. Chen D, Hidalgo MA, Leibowitz S, Leininger J, Simons L, Finlayson C, et al. Multidisciplinary Care for Gender-Diverse Youth: A Narrative Review and Unique Model of Gender-Affirming Care. Transgend Health. 2016;1(1):117-23.
37. Sood R, Chen D, Muldoon AL, Chen L, Kwasny MJ, Simons LK, et al. Association of Chest Dysphoria With Anxiety and Depression in Transmasculine and Nonbinary Adolescents Seeking Gender-Affirming Care. J Adolesc Health. 2021;10:10.
38. Edwards-Leeper L, Spack NP. Psychological evaluation and medical treatment of transgender youth in an interdisciplinary "Gender Management Service" (GeMS) in a major pediatric center. J Homosex. 2012;59(3):321-36.
39. Tishelman AC, Kaufman R, Edwards-Leeper L, Mandel FH, Shumer DE, Spack NP. Serving Transgender Youth: Challenges, Dilemmas and Clinical Examples. Prof Psychol Res Pr. 2015;46(1):37-45.
40. Spack NP, Edwards-Leeper L, Feldman HA, Leibowitz S, Mandel F, Diamond DA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. Pediatrics. 2012;129(3):418-25.
41. Cousino MK, Davis A, Ng H, Stancin T. An emerging opportunity for pediatric psychologists: Our role in a multidisciplinary clinic for youth with gender dysphoria. Clin. 2014;2(4):400-11.
42. Oransky M, Steever J, Burke EZ. An Interdisciplinary Model for Meeting the Mental Health Needs of Transgender Adolescents and Young Adults: The Mount Sinai Adolescent Health Center Approach. Cognitive and Behavioral Practice. 2019;26(4):603-16.
43. Schwartz BI, Effron A, Bear B, Short VL, Eisenberg J, Felleman S, et al. Experiences with Menses in Transgender and Gender Nonbinary Adolescents. J Pediatr Adolesc Gynecol. 2022;03:03.
44. Salehi P, Divall SA, Crouch JM, Hopkinson RA, Kroon L, Lawrence J, et al. Review of Current Care Models for Transgender Youth and Application to the Development of a Multidisciplinary Clinic - The Seattle Children's Hospital Experience. Pediatr Endocrinol Rev. 2018;15(4):280-90.
45. Inwards-Breland DJ, DiVall S, Salehi P, Crouch JM, Negaard M, Lu A, et al. Youth and Parent Experiences in a Multidisciplinary Gender Clinic. Transgend Health. 2019;4(1):100-6.
46. Hedrick HR, Glover NT, Guerriero JT, Connelly KJ, Moyer DN. A New Virtual Reality: Benefits and Barriers to Providing Pediatric Gender-Affirming Health Care Through Telehealth. Transgend Health. 2022;7(2):144-9.
47. Menvielle E. A comprehensive program for children with gender variant behaviors and gender identity disorders. J Homosex. 2012;59(3):357-68.
48. Rodnan LA, Menvielle EJ. A Therapeutic Group for Parents of Transgender Adolescents. Child and Adolescent Psychiatric Clinics of North America. 2011;20(4):733-43.
49. Bates JE, Skilbeck WM, Smith KV, Bentler P. Intervention with families of gender-disturbed boys. Am J Orthopsychiatry. 1975;45(1):150-7.
50. Rosen AC, Rekers GA, Friar LR. Theoretical and diagnostic issues in child gender disturbances. J Sex Res. 1977;13(2):89-103.

51. Olezeski CL, Boulware SD. Development of the Yale Gender Center: An Early Progress Report. Conn Med. 2017;81(1):41-4.