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TITLE PAGE

A systematic review of hormone treatment for children with gender dysphoria and recommendations for research

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/apa.16791

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Word count: Abstract: 199, Manuscript: 3073, References: 42, Tables: 5, Figures: 1.

Abbreviations: *All full terms lower cases except for the ICD full term. Journal policy is to reduce abbreviations to the bare minimum and to those that will be familiar to readers. Please see detailed guidance*
BMD, Bone Mineral Density.
CSHT, Cross-sex hormone treatment
DXA, Dual-Energy X-ray Absorptiometry.
GnRHa, Gonadotropin-releasing hormone agonist (analogues).
GRADE, Grades of Recommendation, Assessment, Development and Evaluation
ICD, International Classification of Diseases.
MRI, Magnetic Resonance Imaging.
SBU, Swedish Agency for Health Technology Assessment and Assessment of Social Services.

Key Notes

- This systematic review assessed psychosocial effects, bone health, body composition and metabolism, and therapy persistence in children (<18 years of age) with gender dysphoria undergoing treatment with gonadotropin-releasing hormone analogues (GnRHa)).
- Long-term effects of hormone therapy on psychosocial health are unknown. GnRHa treatment delays bone maturation and gain in bone mineral density.
- GnRHa treatment in children with gender dysphoria should be considered experimental treatment of individual cases rather than standard procedure.

Abstract

Aim: The aim of this systematic review was to assess the effects on psychosocial and mental health, cognition, body composition, and metabolic markers of hormone treatment in children with gender dysphoria.

Methods: Systematic review essentially following PRISMA. We searched PubMed, EMBASE and thirteen other databases until 9 November 2021 for English-language studies of hormone therapy in children with gender dysphoria. Of 9,934 potential studies identified with abstracts reviewed, 195 were assessed in full text, and 24 were relevant.

Results: In 21 studies, adolescents were given Gonadotropin-releasing hormone analogues (GnRHa) treatment. In three studies, cross-sex hormone treatment (CSHT) was given without previous GnRHa treatment. No randomised controlled trials were identified. The few longitudinal observational studies were hampered by small numbers, and high attrition rates. Hence, the long-term effects of hormone therapy on psychosocial health could not be evaluated. Concerning bone health, GnRHa treatment delays bone maturation and bone mineral density gain, however found to partially recover during CSHT when studied at age 22 years.

Conclusion: Evidence to assess the effects of hormone treatment on the above fields in children with gender dysphoria are insufficient. To improve future research, we present the GENDHOR checklist, a checklist for studies in gender dysphoria.

Key words: adolescent; bone density; gender dysphoria; gonadotropin-releasing hormone agonist; psychosocial functioning.

Introduction

Gender incongruence refers to a mismatch between the biological sex at birth and perceived gender identity. When gender incongruence causes significant discomfort, it is called gender dysphoria. When gender dysphoria causes clinically significant distress, the condition might meet the diagnostic criteria for transsexualism according to the (international classification of disease) ICD-10 guidelines,[1] or gender dysphoria according to the DSM-5.[2] Gender identity-affirming health care is provided to ease gender dysphoria.[3] The treatment aims to align bodily characteristics with the individual's gender identity, and usually includes cross-sex hormone treatment (CSHT), as well as chest and genital surgery.

In youth with gender dysphoria, gonadotropin-releasing hormone analogues (GnRHa) have been used to inhibit spontaneous puberty development. The rationale is to prevent irreversible bodily changes and give young individuals time to explore their gender identity. Following the first case report in which a GnRHa was used to suppress puberty in a female-to-male transsexual individual,[4] the '"Dutch protocol" was developed.[5] According to this protocol, young pubertal people presenting with gender dysphoria should first undergo a thorough psychological evaluation. If the diagnosis gender dysphoria is confirmed, GnRHa treatment is recommended to start during the early stages of puberty (Tanner stages 2–3). If gender dysphoria subsides, the individual may discontinue GnRHa treatment, at which point spontaneous puberty will restart. If gender dysphoria persists, CSHT might start at age 16 years and sex-reassignment surgery at 18 years. Gender dysphoria in youth was a rare phenomenon when the Dutch multidisciplinary protocol for the treatment of gender dysphoria was introduced. Seeking care for gender dysphoria has since become increasingly common in younger people in many parts of the western world, [6] [7] with an exponential rise among children born female.[8] Although not all children with gender dysphoria receive gender identity affirming treatment, there has been an ensuing increase in hormones to treat children with gender dysphoria, of which data on the effects and side effects are limited. There is no previous systematic review or meta-analysis of hormone treatment for children with gender dysphoria.

This systematic review aimed at assessing a) psychosocial effects, b) effects on bone health, c) effects on body composition and metabolism, and d) satisfaction and therapy persistence in children aged <18 years with gender dysphoria undergoing hormone therapy. In this review, trans women are referred to as male-to-female and trans men as female-to-male.

Methods

Preregistration

This systematic review originated from a 2-year commissioned work from the governmental body the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). Ongoing SBU reviews are registered on the SBU website (https://www.sbu.se/en/ongoing-projects/) but not recorded in external databases.

Selection criteria

The search was restricted to children aged <18 years with reported gender dysphoria. We included observational studies, randomised controlled trials, and systematic reviews according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] Case reports, editorials, and non-human studies were excluded from further review. The search was limited to English-language publications.

Search strategy

Two professional information specialists at the Swedish Agency for Health Technology Assessment and Assessment for Social Services (SBU) performed a comprehensive search of the following medical databases up until 9 November 2021: CINAHL (EBSCO), Cochrane Library (Wiley), EMBASE (Embase.com), PsycINFO (EBSCO), PubMed (NLM), Scopus (Elsevier), and SocINDEX (EBSCO). They also searched the Campbell Library, Epistemonikos, Evidence Search, International HTA database, as well as three NIHR Centre for Reviews and Dissemination (CRD) databases: Database of Abstracts of Reviews of Effects (DARE), Health, and Technology Assessment (HTA), and NHS Economic Evaluation Database (EED). Finally, we searched PROSPERO, an international prospective register for systematic reviews, to identify any relevant ongoing systematic reviews but found none. The search, selection, and assessment were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses) guidelines.[9] The search and selection processes are outlined in **Figure 1**. Only studies of low or moderate bias were eligible for this review. Full literature search strategy is provided at the SBU web page (https://www.sbu.se/contentassets/4062b596a35c4e1383405766b7365076/bilaga-1-litteratursokning.pdf).

Relevance, risk of bias, and quality of evidence

Two independent experts checked all hits for relevance. Relevant studies (based on a pre-defined PICO) were then evaluated for risk of bias, also by two independent experts, according to ROBINS-I (Risk of bias in non-randomised studies of interventions) [10 11] . Robins-I assesses possible bias in seven domains: confounding; bias due to selection, measurement classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.

If the two reviewers did not agree on content or quality, the paper was discussed in the larger research team of four experts (JFL, PR, BK, ML). Randomized controlled trials were planned to be assessed by RoB-2 [10 11]. To rate the quality of evidence for specific outcomes, we used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system.[12] GRADE has four levels of evidence (very low, low, moderate, high) and considers five domains that can decrease the level of certainty one or two levels (risk of bias, imprecision, inconsistency, indirectness (similar to 'external validity'), and publication bias).

Data extraction

Two reviewers (MH, JA) retrieved data from the included studies. The data extracted included the outcomes mental and psychosocial health including suicidality, anthropometric measures and metabolism, bone health, adverse events, and the characteristics of each study including age at referral or intake, age at start of GnRHa treatment, age at start of CSHT, number of participants enrolled in study, number of transgender participants, number of hormone treated

transgender participants, number of non-transgender participants, number of participants evaluated, treatment type (drugs, dosages, type of administration, treatment frequency), total treatment duration, and total follow-up time. The full data extraction of included studies is provided at the SBU web page (https://www.sbu.se/contentassets/4062b596a35c4e1383405766b7365076/bilaga-3-tabellverk-over-inkluderade-studier.pdf).

Statistics

No statistical analyses were performed.

Ethics

Ethical approval is not applicable for this systematic review.

Results

Identified studies

After duplicate removal, the search yielded 9,934 potential studies (Figure 1). Of these, 195 were selected for thorough reading. Of these, 36 were relevant and assessed for risk of bias. Twelve studies were excluded because of high risk for bias, leaving 24 studies with low or moderate, moderate to high, or high risk of bias reviewed in this paper. A list of excluded studies is provided at the SBU web page (https://www.sbu.se/contentassets/4062b596a35c4e1383405766b7365076/bilaga-2-exkluderade-studier-med-hog-risk-for-bias.pdf).

Characteristics of the 24 studies

All 24 relevant studies had been published since 2014 (Table 1). Study participant age at the start of GnRHa therapy was typically between 11 and 15 years (range 9-18.6 years), with CSHT

rarely being introduced before age 15. Except for the Hisle-Gorman et al. [6] (n=3754 participants) and Mullins et al. [13] (n=611) papers, few studies included >200 individuals. GnRHa treatment often continued for around two years, sometimes up to four years, and similar treatment durations were observed or reported for CSHT as observations were usually not reported after age 18 years. Full details of included studies are given at the SBU web page. Overall, there were eight studies on GnRH alone, 13 studies on GnRH + CSHT, and three studies on CSHT alone.

Psychosocial and mental health

Table 2 outlines the six studies that examined psychosocial outcomes and cognitive effects.[14 15 16 17 18 19] Three of these studies found significantly improved overall psychosocial function after GnRHa treatment as measured by the Children's Global Assessment Scale (CGAS).[14-16] Two of these studies observed no statistically significant change in gender dysphoria.[15 16] Two of these studies reported significantly improved self-rated quality of life after treatment measured through Kidscreen-27, Short Form-8 (SF-8), Child Behaviour Checklist (CBCL) (parent report), and Youth Self Report (YSR),[16 17] while another study reported no statistically significant differences in anxiety and depression between those who started and not started hormone therapy.[18]

Because these studies were hampered by small number of participants and substantial risk of selection bias, the long-term effects of hormone treatment on psychosocial health could not be evaluated. Of note, the above studies do not allow separation of potential effects of psychological intervention independent of hormonal effects.

Cognitive outcomes

We could only identify one study of low-moderate bias on cognitive outcomes in children with gender dysphoria receiving GnRHa therapy.[19] This cross-sectional study from the USA comprised 20 treated (8 male-to-female and 12 female-to-male) and 20 untreated (10 male-to-female and 10 female-to-male) young transgender persons and a control group (n=45). Controls were identified from age-matched family members and friends. The Tower of London task was administered to assess executive functioning. The study neither found differences in cognitive function between treated and untreated transgender persons, nor between treated transgender persons and controls. However, because no before-after GnRHa therapy analyses were performed, the study could not investigate potential cognitive effects of hormone therapy.

Bone health outcomes

Six longitudinal studies used dual-energy X-ray absorptiometry (DXA) scan technology to explore bone health before and again after some time with GnRHa treatment (**Table 3**). The second DXA scan usually coincided with CSHT initiation leading to different follow-up durations. The third DXA scan was performed after variable time with CSHT, performed with variable dosing and administration. The lumbar spine and hip were most often examined. One study investigated bone geometry .[26] Six studies were retrospective [20-25] and one study was prospective.[26] An additional study was cross-sectional where study participants in early puberty (Tanner stages 2–3) were examined only once, before the start of GnRHa therapy.[27]

Three studies reported a lower bone mineral density (BMD) in patients before or at start of GnRHa treatment compared with the general population of the same biological sex and age.[20 22 27] During GnRHa treatment, BMD estimated through area or volume, and expressed in z-scores increased less compared with general population reference values. However, the mean absolute BMD remained unchanged up to 2–3 years of GnRHa treatment.[22 26] The initiation of CSHT stimulated bone maturation and mineral accrual, increasing BMD.[20 21] After a median CSHT duration of 5.4 years in in female-to-male and 5.8 years in male-to-female, the lumbar spine mean areal BMD z-score was still significantly lower than at the start of GnRH therapy,

while the other volume BMD and femoral neck estimates had normalised.[20] In another study, female-to-male receiving testosterone replacement therapy for 1–2 years had not regained their group mean BMD z-score registered at the start of GnRHa therapy.[23]

Bone geometry, estimated as subperiosteal width and endocortical diameter, was studied on DXA scans before start of GnRHa treatment and after at least two years on CSHT and compared with reference values of the general population: the bone geometry resembled the reference curve for the experienced sex only when GnRHa was started during early puberty. Bone geometry estimates in those who started GnRHa treatment during mid and late puberty remained within the reference curve of the biological sex.[25]

Body composition and metabolic markers

GnRHa treatment effectively reduced endogenous sex hormone serum levels **(Table 4)**. DXA scans after one year of GnRHa treatment revealed increased fat mass and reduced lean body mass [28]. Longitudinal growth depends on bone maturity (bone age) of those in the study group. Ongoing pubertal growth spurt will be arrested when GnRHa therapy is started, reducing the growth velocity to the prepubertal rate.[29]

Nokoff et al studied body composition and insulin sensitivity during one year of GnRHa therapy.[30] In addition to body composition, metabolic effects as insulin sensitivity during CSHT, and changes in blood pressure during testosterone therapy were examined.[31-33] Of these studies, three originated from Amsterdam.[29, 32, 33] The Amsterdam studies included observations during GnRHa therapy,[28] one year after starting CSHT,[32] as well as after a group median >5 years with CSHT in a cohort of 22-year-old adolescents.[31, 33] The studies from Amsterdam were generally larger than the other studies. CSHT changed body composition towards the affirmed sex.[31,32] Obesity (defined as BMI >30 at age 22 years) was more prevalent in the transgender population[33] **(Table 4).**

CSHT in children without prior GnRHa treatment

We were able to identify three studies of low-to-moderate bias examining CSHT in children without prior GnRHa treatment.[13 34 35] All were retrospective longitudinal studies. Because the number of study participants was small, studies were deemed to have low external validity, and because the studies examined different outcomes (e.g., lipid serum levels, Hb, blood pressure, metrorrhagia), it was not possible to draw any overall conclusions from these studies. Although the Mullins et al. paper [13] included several individuals at elevated risk of arterial or venous thrombosis, no cases of thrombosis were reported.

Discussion

We performed an extensive literature search to examine psychosocial and cognitive outcomes as well as metabolic and bone health in children with gender dysphoria taking hormone therapy. No randomised controlled trials were found, but we could identify 24 relevant observational studies. However, these were limited by methodological weaknesses, for instance lack of or inappropriate control group, lack of intra-individual analyses, high attrition rates that precluded conclusion to be drawn. The exception being that children with gender dysphoria often had lower group mean values for BMD already prior to GnRHa-treatment, and that GnRHa treatment delays the physiologically occurring BMD gain during pubertal sex hormone stimulation. However, this GnRHa-induced delay in BMD gain is almost fully compensated for by later ensuing CSHT. Although study participants were followed up to 22 years of age, the observed remaining deficit may depend on the limited study group size or on too short observation time.[20]

Our review highlights several specific knowledge gaps in gender dysphoria that are important to bridge not least given the recent increased incidence in many countries.[6 7] First, randomised controlled trials are lacking in gender dysphoria research. We call for such studies, which may be the only way to address biases that we have noted in the field. Given the current lack of evidence for hormonal therapy improving gender dysphoria, another ethically feasible option would be to randomise individuals to hormone therapy with all study participants, independent of intervention status receive psychological and psychosocial support. However, controlled trials do not necessarily require placebo treatment, but could for example build on the date or time of starting hormonal therapy to generate comparison groups. However, it should also be noted that this is a highly vulnerable population.

A second limitation concerns the statistical management of data. In the reviewed studies, observational data have frequently been analysed at a group level where intra-individual changes would have been more appropriate. Intra-individual analyses would allow for a better understanding of how subgroups of individuals respond (both positively and negatively) to hormone therapy. Group-level analyses are sensitive to selection bias because of high drop-out

rates: The group studied at the end of the study is a selection of the group studied at baseline, which increases indirectness (reduces external validity). Moreover, it is important to analyse the distribution of individual data to be able to identify outliers who may be at risk for severe consequences of treatment.

Third, many studies only present data on chronological age but fail to account for puberty stage and biological age. This is a concern because the main purpose of GnRHa treatment is to suppress puberty and, with that, biological ageing.

Fourth, long-term studies are lacking. The duration of GnRHa treatment and CSHT was rarely >4 years. The absence of long-term studies is worrying because many individuals start treatment as minors (<18 years) and CSHT is lifelong. Fifth, individuals who stop GnRHa treatment before the start of CSHT need to be described and followed up. Sixth, some of the findings underlying this review are old, and there are inherent limitations of the ROBINS-I and GRADE instruments *per se*. Seventh, we did not evaluate the use of GnRHa for other indications such as precocious puberty, or in adults with prostate cancer, endometriosis or infertility.

Finally, we could not evaluate the frequency of individuals who drop out from GnRHa treatment and no longer wish to continue with gender transition, or who regret initiating CSHT. However, a follow up study was published after our literature search.[36] Of 720 children (31% born male and 69% born female) who started GnRHa treatment in adolescence, 98% continued to use hormone treatment into adulthood, which suggests that children generally continue with gender transition once they have started GnRHa treatment. We know from internet-based surveys that detransitioning exists,[37] but such studies cannot provide reliable estimates of detransitioning frequency because of selection bias. Studies that closely follow individuals who start GnRHa therapy and/or CSHT until at least age 30 are urgently needed. We also acknowledge there are other potential side effects from GnRHa therapy or CSHT that were not included in our review such as alopecia and abscesses from injections [38].

Due to limitations in reporting of data, previous published studies in this field repeatedly contain insufficient details on drug administration and dosages, treatment duration, and the type of surgery performed. Some of these limitations will be partly remedied by the

introduction of the new ICD version 11, and the Utrecht criteria [39], but the field also urgently needs high quality longitudinal studies that not only assess medical outcomes but also those outcomes that matter most for affected individuals. Building on the identified limitations in previous research, we compiled a checklist to improve gender dysphoria research ("GENDHOR", Table 5). The aim of this checklist is not to replace existing research guidelines, but using it together with existing guidelines might support researchers and peer reviewers, and ultimately benefit patients and their families.

Last, there have been studies in this field published after the date of our literature search (9 November 2021). These have not been added to this study in order to not depart from the systematic approach. We nevertheless wish to comment on some of the publications. First, the National Institute for Health and Care Excellence in England (NICE) conducted evidence reviews of GnRHa[40] as well as CSHT[41] for children with gender dysphoria, which were independent from our work. The conclusions generally align with our findings. Second, Chien et al[42] recently published a prospective study of psychosocial functioning during two years after initiation of CSHT in youths (12 to 20 years of age) with gender dysphoria. Of 315 participants, 162 completed that study. Life satisfaction increased, and depression and anxiety scores decreased, among biological females but not biological males. The strongest finding was a moderately improved appearance congruence. No information on concomitant psychological or psychopharmacological therapy was provided.

CONCLUSION

This systematic review of almost 10,000 screened abstracts suggests that long-term effects of hormone therapy on psychosocial and somatic health are unknown, except that GnRHa treatment seems to delay bone maturation and gain in bone mineral density.

Acknowledgements

Information specialists Klas Moberg and Hanna Olofsson designed and performed the literature search.

Conflict of Interest

JFL coordinated an unrelated study on behalf of the Swedish inflammatory bowel disease quality register (SWIBREG) that received funding from the Janssen Corporation. JFL has also received financial support from Merck Sharp & Dohme developing a paper reviewing national healthcare registers in China. JFL is currently discussing potential research collaboration with Takeda. ML has received lecture honoraria for Lundbeck pharmaceuticals and served as consultant for AstraZeneca. The other authors report no conflict of interest.

The data collection of this study was funded by the Swedish agency for technology assessment and assessment for social services. JA and MH are employees at this agency.

Funding

This study received funding from the Swedish Agency for Health Technology Assessment and Assessment of Social Services.

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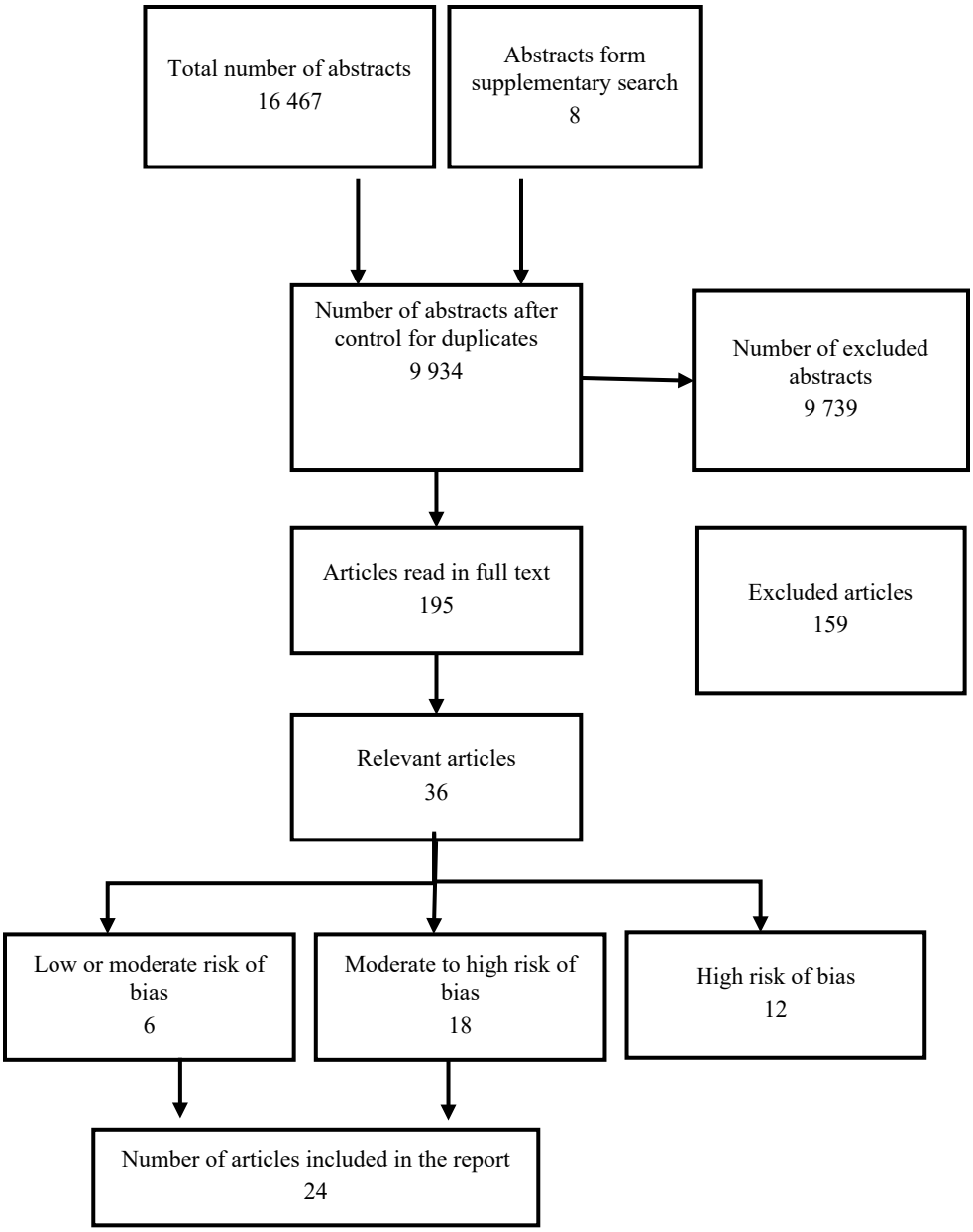

Figure 1. PRISMA flow diagram.

Table 1. Overview of 24 included studies

	Ages of patients (years)			**Numbers of patients**						**Interventions**			**Time:** Duration and Follow-Up			**Outcomes extracted**
Reference	Age at intake range (mean)	Age at start of GnRH range (mean)	Age at start of CSHT range (mean)	n referred	n TG enrolled	**n TG HT**	n TG non-HT	n non-TG	**n TG HT at last FU**	GnRH	CSHT	Surgery #	GnRH duration range (mean)	CSHT duration range (mean)	Follow-Up time range (mean)	**Mental health** **Bone health** **Anthropometrics** **Metabolism**
MENTAL HEALTH																
de Vries 2014 (14)	11–17 (13.6)	11.5–18.5 (14.8)	13.9–19 (16.7)	196	111	**55**			**32**	x	x	x	1 y*	4 y*		UGDS, global functioning (CGAS), depression (BDI), anxiety (STAI), anger (TPI)
Costa 2015 (15)	12-17 (15.5)	13-17 (16.5)		436	201	**101**	100		**35**	x			1 y		**1.5 y**	UGDS, psychosocial functioning (CGAS)
Becker-Hebly 2020 (17)		11-17 (15.5)	13-17 (15.5)	434	75	**54**	21		**54**	x	x	x	0.5-4 y*	0.5-4 y*	**7-49 mo**	Global functioning (CGAS), psychosocial functioning (YSR/ASR)
Cantu 2020 (18)		11-xx (15)	xx-18 (15)		80	**42**	38		**28**	x	x		NR	NR	**1-11 mo (5 mo)**	Psychosocial functioning (PHQ-9, GAD-7), acute distress, suicidality
Carmichael 2021 (16)		12.0-15.3 (13.6)			44	**44**			**14**	x			12-59 mo (31 mo)		**12-36 mo**	UGDS, CGAS, psychological functioning (CBCL, YSR), Self-harm, BIS, HRQoL (Kidscreen52)
Hisle-Gorman 2021 (6)	8-13 (10)		16.6-19.8 (18.2)		3754	**963**		6603	**963**	x	x		0.7-2.7 y (1.5)	0.7-2.7 y (1.5)	**8.5 y**	Mental health diagnosis, psychotropic medication use, medication days, service use
Staphorsius 2015 (19)		min 12			41	**20**	20	45		x			0.6-2.6 y (1.6)			Psychological functioning (CBCL), cognitive function (executive function task)
BONE HEALTH																
Joseph 2019 (22)		12-14 (13)				**70**			**70**	x			1-xx y		**up to 2.8 y**	height, weight, BMI BMD, BMAD, Z-score
Klink 2015 (20)		11.4-18.3 (15)	15.6-19 (16)			**34**			**34**	x	x	x	0.25-8 y	xx - 8 y	**up to age 22**	height, BMD, aBMD, Z-score, T-score (femoral neck, lumbar spine)
Vlot 2017 (21)		11.5-18.6 (14)	14.0-19.5 (16)		215	**70**			**57**	x	x		1-xx y		**up to 2 y**	height, BMAD, Z-score (hip, lumbar spine), bone markers (P1NP, OC, ICTP)
Schagen 2020 (26)		12.2-16.5 (14)	15.0-17.9 (16)			**127**			**121**	x	x		1.5-4 y	3 y		aBMD, Z-score (hip)
Stoffers 2019 (23)		11.8-18.0 (16)	14.9-18.4 (17.2)		64	**62**			**15**	x	x		3 mo - 3 y	5 mo -3 y	**2 y**	height, BP, BMD, Z-score (femoral neck, lumbar spine)
Navabi 2021 (24)		13.4-17.4 (15)			198	**172**			**116**	x			6 mo - 2 y		**1.5 y**	BMD, aBMAD, Z-score (hip, lumbar spine)
van der Loos 2021 (25)		11-17	15-17			**322**			**322**	x	x	x	1- 3 y	2-6 y	**up to 4 y**	subperiostal width, endocortical diameter

Lee 2020 (27)		9.6-13.4 (11.5)			95	**63**			**63**	x			2 mo			BMD, aBMAD, Z-score (hip, lumbar spine)
ANTHROPOMETRICS and METABOLISM																
Schagen 2016 (28)		11.1-18.6 (14)			138	**116**			**77**	x			3-12 mo		**1 y**	height, weight, BMI, lean body mass, liver enzymes, creatinine
Klaver 2018 (31)		12.7-17.3* (15)	15.3-17.8* (16)	489	192	**192**			**192**	x	x	x	0.5-2.9 y (1.5*)	1.6-3.4 y (2.9*)	**age 22**	weight, BMI, total body %, WHR
Klaver 2020 (32)		12.8-17.2* (14.9)	15.3-17.8* (16.6)		192	**192**			**192**	x	x	x	0.5–2.9 y (1.5)*	1.1-3.4 y (2.5*)	**age 22**	BMI, SBP, DBP, glucose, insulin, HOMA-IR, cholesterol, triglycerides
Perl 2020 (33)		13.4-15.4 (14)	14.2-16.0 (15)		48	**15**			**15**	x	x		2-4 mo	2-6 mo		BMI, BP
Schulmeister 2021 (29)		9.0-14.5 (11.5)			92	**55**	226		**55**	x			10-14 mo		**1 y**	height velocity, BMI, z-score
Nokoff 2021 (30)		10.2-14.1 (12)			17	**17**	31		**17**	x			0.5 - 5.8 y			insulin, glucose HbA1c, HOMA-IR, body fat, % lean mass
Tack 2016 (34)			NR (15-17)		45	**43**			**43**		x			6-18 mo (12)	**1.5 y**	height, weight, BMI, triglycerides, cholesterol, suicide, side effects
Jarin 2017 (35)		13-xx	xx-25 (16-18)		116	**116**			**116**	(x)	x				**2 y**	BMI, BP, haematocrit, Hb, cholesterol
Mullins 2021 (13)			13-24 (17)	1406	611	**611**			**611**		x			0.8-2.8 y (1.5y)	**3 y**	haematology, thrombosis, BMI

Number of patients:

n referred	number of patients referred to gender clinic for evaluation of gender dysphoria (not same at number of patients receiving GD diagnosis)
n TG enrolled	number of patients enrolled in the study at start
n TG	number of patients with gender dysphoria
n TG HT	number of patients with gender dysphoria treated with hormones (GnRH alone, GnRH + CSHT, or CSHT only)
n TG non-HT	number of patients with gender dysphoria treated NOT with hormones
n TG HT at last FU	number of patients with gender dysphoria treated with hormones (GnRH alone, GnRH + CSHT, or CSHT only) evaluated at last follow-up time
n non-TG	number of subjects in study without gender dysphoria (reference population)
*	calculated by SBU
# surgery	any kind of gender reassignment surgery (gonadectomy, mastectomy, hysterectomy, laryngeal surgery, hair removal, phalloplasty, vaginoplasty)

Abbreviations:

BDI: Beck Depression Inventory; BIS: Body Image Scale; BMAD: Bone Mineral Apparent Density; BMD: Bone Mineral Density; BMI: Body Mass Index; BP: Blood pressure; CBCL: Child Behaviour Checklist; CGAS: Global functioning Children's Global Assessment Scale: [higher scores (> 80) indicating better global functioning]; CSHT: Cross-Sex Hormone Treatment/ gender-affirming treatment: testosterone, oestradiol, cyproterone acetate (CA), spironolactone, lynestrenol; GAD-7: Generalized Anxiety Disorder-7; GnRH: Gonadotropin Releasing Hormone analogue: triptorelin; HRQoL: Health Related Quality of Life; HT: Hormone treatment: either GnRH, CSHT, or both; PHQ-9: Patient Health Questionnaire-9; SF-8: Short Form-8: (<18 y); STAI: Spielberger's Trait Anxiety; TG: Transgender; TPI: Anger Spielberger's Trait Anger; UGDS: Utrecht Gender Dysphoria Scale: score range 12-60 points [high score = high level of GD]; WHR: Waist-hip ratio; YSR: Youth Self Report: YSR (ages 11-18y); Adult version (ASR, >18y): [higher scores reflect higher degree of problems]; NR: not reported.

Table 2. Summary of findings on psychosocial outcomes of puberty-blocking treatment (GnRHa) treatment in children with gender dysphoria[14 15 16 17 18 19]

Outcome measures	Number of study participants, description of studies	Main result	"Certainty of evidence"	Deduction in GRADE*
Global function	n on hormones = 254 n evaluated = 113 Four observational cohort studies: one prospective and three retrospective studies [14-17]	Improved global function as assessed with the CGAS	Cannot be assessed	-2 risk of overall bias[a] -2 precision[b]
Suicide ideation	n on hormones = 42 n evaluated = 28 One prospective observational cohort study with mixed treatment (38 subjects with no pharmacological treatment) [18]	No change in suicide ideation	Cannot be assessed	-2 risk of overall bias[a] -2 precision[b]
Gender dysphoria	n on hormones = 145 n evaluated =49 Two prospective observational cohort studies [15 16]	No change in gender dysphoria	Cannot be assessed	-2 risk of overall bias[a] -2 precision[b]
Depression	n on hormones = 97 n evaluated = 60 Two prospective observational cohort studies of which one included mixed treatment [14 18]	No change in depression	Cannot be assessed	-2 risk of overall bias[a] -2 precision[b]
Anxiety	n on hormones = 97 n evaluated = 60 Two prospective observational cohort studies [14 18]	No change in anxiety	Cannot be assessed	-2 risk of overall bias[a] -2 precision[b]
Cognition	n on hormones = 20 n evaluated = 20 One study [19]	No change in cognition compared with matched controls	Cannot be assessed	-2 risk of overall bias[a] -2 precision[b]
Quality of life	n on hormones = 98 n evaluated = 46 Two observational cohort studies, whereof one retrospective [16 17]	1. Improvement in quality of life most pronounced in subjects receiving puberty-blocking hormones, followed by gender-affirming hormone treatment [17] 2. Some improvement [16]	Cannot be assessed	-2 risk of overall bias[a] -2 precision[b]

*Starting at 4 for optimal studies in each study type. [a] Selection of study participants is difficult to assess, analysis not based on stage in puberty development [b] Few study subjects in each study, heterogeneity in outcome and analyses. CGAS=Children's Global Assessment Scale

Table 3. Summary of effects on bone development by puberty-blocking treatment (GnRHa) followed by CSHT in children with gender dysphoria. [20-24 26]

Outcome measures	Number of study participants, description of studies	Main Result	"Certainty of Evidence"	Deduction in GRADE*
Bone density during puberty-blocking hormonal treatment (g/cm^2, g/cm^3)	n on hormones = 363 n evaluated = 297 Five observational cohort studies (four retrospective and one prospective) [22 20 23 21 26]	Unchanged bone density (DXA measurement)	⊕⊕◯◯ Low certainty	-1 risk of overall bias[a] -1 precision
Bone density during puberty blocking hormonal treatment in relation to reference data in the literature (z-score)	n on hormones = 408 n evaluated = 292 Five observational cohort studies (four retrospective, and one prospective) [20-24]	Decreased increase in bone density over time	⊕⊕◯◯ Low certainty	-1 risk of overall bias [a] -1 precision
Bone density after 1-3 years (up to 22 years of age) of CSHT, which had been preceded by puberty-blocking hormonal treatment in relation to reference data in the literature	n on hormones = 268 n evaluated = 165 Three observational cohort studies (two retrospective and one prospective) [20 23 24]	After group median five years with CSHT, bone density recovered in hip but not in lumbar spine compared to data at start of treatment (z-score)	⊕⊕◯◯ Low certainty	-1 risk of overall bias [a] -1 precision

*Starting at 4 for optimal studies in each study type. [a] Analysis not based on stage in puberty development. CSHT, Cross-sex hormone treatment. DXA, Dual-Energy X-ray Absorptiometry.

Table 4. Summary of findings of puberty-blocking (GnRHa) hormone treatment on anthropometric measures, body composition, and metabolism in children with gender dysphoria. [28 30 31 29 33 33]

Outcome measures	Number of study participants, description of studies	Main result	"Certainty of Evidence"	Deduction in GRADE*
Anthropometric measures	n on hormones = 192 n evaluated = 192 One retrospective observational cohort study [31]	Increased weight and body mass index	Cannot be assessed	-2 risk for overall bias[a] -1 precision[b] -1 indirectness[c]
Body composition	n on hormones = 325 n evaluated = 286 Two prospective observational cohort studies and one controlled cross-sectional study [28 30 31]	Decreased lean body mass	Cannot be assessed	-2 risk for overall bias[a] -1 precision[b] -1 indirectness[c]
Metabolic measures	n on hormones = 209 n evaluated = 209 One retrospective observational cohort study and one controlled cross-sectional study [30 32]	No change in serum lipids or blood pressure Increased insulin level in MtF Decreased insulin sensitivity	Cannot be assessed	-2 risk for overall bias[a] -1 precision[b] -1 indirectness[c]
Blood pressure	n on hormones = 15 n evaluated =15 One retrospective observational cohort study [33]	Change in blood pressure	Cannot be assessed	-2 risk for overall bias[a] -1 precision[b] -1 indirectness[c]
Growth (cm/year)	n on hormones = 55 n evaluated = 55 One prospective multicentre observational GnRHa treatment cohort study [29]	Reduced growth velocity	Cannot be assessed	-2 risk for overall bias[a] -1 precision[b] -1 indirectness[c]

*Starting at 4 for optimal studies in each study type. [a] Selection of study participants is difficult to assess. Analysis not based on stage in puberty development. [b] Few study subjects in each study, hence there is heterogeneity in outcome and analyses. [c] Single study. In this context, 'indirectness' is similar to 'external validity'.

Table 5. the GEnder Dysphoria HORmone treatment (GENDHOR) checklist

	Recommendations
Aim	Describe the aim of the study
Study participants: cases/ exposed	Define gender dysphoria in your study, including the assessment tools used. Define eligibility criteria for your study (including chronological age, bone age or puberty stage, according to Tanner or Prader (when study concerns adolescents), biological sex, perceived gender identity, psychiatric and somatic comorbidities, medications at baseline). List exclusion criteria (diagnoses). List ages of participants at the start of each treatment (including absolute age ranges).
Comparators/ unexposed	Clarify how controls were selected (were controls recruited from the general population?) or whether national/ regional reference data (for instance, Z-scores) were used instead of individual controls.
Study design	Describe the study design: Cross-sectional, retrospective, prospective; case-control (and if nested), cohort study, randomised clinical trial.
Setting	Describe the setting of the study. Were study participants included at a tertiary centre or from the general population? Describe the catchment area/population of participating centres.
Intervention	Hormone treatment Describe whether GnRHa, anti-androgens, CSHT, or a combination was used. List generic names, mode of administration, and dosages of all treatments. Specify the treatment duration of each treatment. If hormone serum concentrations are studied, include the standard procedure for the timing of blood samples to hormone intake. If patients undergo surgery, clarify the type of surgery and number of participants undergoing each surgical procedure (gonadectomy, mastectomy, laryngeal surgery, vaginoplasty/phalloplasty, etc.).
	Clarify if any participant received psychiatric counselling before, or during the study, including total duration and frequency of counselling.
Variables	Define each variable (including co-variates) and its source. If possible, mention any effort to validate the variables.
Data measurement	Clarify who collected the data on study participants. Present time between first and second measurements if your study is longitudinal and includes “before-after” measurements in relation to the intervention. Mention if study participants had previously been included in other studies with a different aim or examining other outcomes.
Blinding	Describe if the data collectors were blinded to participant status/treatment or not.
Loss to follow-up	Indicate the number of participants discontinuing GnRHa/ CSHT and the reason(s) for discontinuation, including no longer wish to pursue gender reassignment treatment. Describe loss to follow-up/missing data
Statistical methods	Describe statistics according to a relevant checklist. Consider when applicable: Intra-individual changes (mean, SD, median, range) vs. between-group differences.
Descriptive data	In addition to usual demographic, clinical, social/socioeconomic information, report body mass index (BMI), smoking, use of oral contraceptives (type) or other hormonal treatment, puberty stage.
	Report any psychiatric illness at baseline, as well as the use of psychotropic medication.

	Describe other comorbidities, including disorders that could be considered contraindications for either hormone treatment or surgery.
	Specify follow-up time (median, mean) since the start of the intervention and since start of hormone treatment (define intervention start).
Outcome data	Specify main outcome of the study. Indicate all secondary outcomes, including adverse events.
Adverse events/ complications	Describe all adverse events.
Main results	Present absolute numbers. Calculate absolute and relative risks/Intraindividual effects/change and group mean/ median. Present incidence data. Describe any adjustment for potential confounders.
Limitations	Discuss limitations of your study, including limitations of the measurements used (e.g., DXA) and sources of potential bias or imprecision.
Generalisability/ external validity	Can data be generalised to individuals with gender dysphoria outside your study centre and the study country?
Conflict of interest	Report any conflict of interest.

Based on our literature review, we created a *GEnder Dysphoria HORmone treatment checklist* (GENDHOR).

This list consists of recommendations that researchers may consider when planning a study of gender dysphoria, whether observational or interventional.

CSHT, Cross-sex hormone treatment. DXA, Dual-Energy X-ray Absorptiometry. GnRHa, Gonadotropin-releasing hormone agonist (analogues).