| | |
|---|---|
| | Alternative measures to the YHC-SUN questionnaire may be used as reported in studies.<br><br>• **Transitioning surgery - Impact on extent of and satisfaction with surgery**<br>This outcome is important because some children and adolescents with gender dysphoria may in adulthood proceed to transitioning surgery. Stated measures of the extent of surgery and satisfaction with surgery in studies may be reported.<br><br>• **De-transition**<br>The proportion of patients who de-transition following the commencement of gender-affirming hormone treatment and the reasons why. This outcome is important to patients because there is uncertainty about the short and long term safety and adverse effects of gender-affirming hormones in children and adolescents with gender dysphoria.<br><br>**B: Safety**<br>• Short and long -term safety and adverse effects of taking gender-affirming hormones is important to assess whether treatment causes acute side effects that may lead to withdrawing the treatment or long term effects that may impact on decisions for transitioning or de-transitioning.<br><br>Aspects to be reported on should include<br>Impact of the drug use such as clinically relevant derangement in renal and liver function tests, lipids, glucose, insulin and glycosylated haemoglobin, cognitive development and functioning.<br><br>The clinical and physical impact of temporary and permanent withdrawal the drug such as when patients decide to de-transition – e.g. delay in the attainment of peak bone mass, attenuation of peak bone mass, permanent physical effects.<br><br>**C: Cost effectiveness**<br><br>Cost effectiveness studies should be reported. |
| **Inclusion criteria** | |
| **Study design** | Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies.<br>If no higher level quality evidence is found, case series can be considered. |
| **Language** | English only |
| **Patients** | Human studies only |
| **Age** | 18 years or less |
| **Date limits** | 2000-2020 |

| Exclusion criteria | |
|---|---|
| **Publication type** | Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-publication prints |
| **Study design** | Case reports, resource utilisation studies |

## Appendix B Search strategy

Medline, Embase, the Cochrane Library, HTA and APA PsycInfo were searched on 21 July 2020, limiting the search to papers published in English language in the last 20 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines, pre-publication prints, case reports and resource utilisation studies were excluded.

**Database: Medline**
Platform: Ovid
Version: Ovid MEDLINE(R) <1946 to July 17, 2020>
Search date: 21 Jul 2020
Number of results retrieved: 650
Search strategy:
Database: Ovid MEDLINE(R) <1946 to July 17, 2020>
Search Strategy:
---
1 Gender Dysphoria/ (485)
2 Gender Identity/ (18431)
3 "Sexual and Gender Disorders"/ (75)
4 Transsexualism/ (3758)
5 Transgender Persons/ (3134)
6 Health Services for Transgender Persons/ (136)
7 exp Sex Reassignment Procedures/ (835)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (7223)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (12665)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (102312)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (6969)
12 (male-to-female or m2f or female-to-male or f2m).tw. (114785)
13 or/1-12 (252562)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (1137237)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (852126)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1912796)
17 Minors/ (2572)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2360626)
19 exp pediatrics/ (58102)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (835833)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2023650)
22 Puberty/ (13277)

23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (424041)
24 Schools/ (38087)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7199)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (468784)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (89314)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (887443)
29 or/14-28 (5532185)
30 13 and 29 (79220)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (7)
32 30 or 31 (79220)
33 Hormones/ad, tu, th (4514)
34 exp Progesterone/ad, tu, th (10899)
35 exp Estrogens/ad, tu, th (28936)
36 exp Gonadal Steroid Hormones/ad, tu, th (34137)
37 (progesteron* or oestrogen* or estrogen*).tw. (196074)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (544)
39 exp Estradiol/ad, tu, th (10823)
40 exp Testosterone/ad, tu, th (8318)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (74936)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (90464)
43 or/33-42 (304239)
44 32 and 43 (3183)
45 limit 44 to yr="2000 -Current" (2019)
46 animals/ not humans/ (4685420)
47 45 not 46 (1194)
48 limit 47 to english language (1155)
49 (MEDLINE or pubmed).tw. (163678)
50 systematic review.tw. (121198)
51 systematic review.pt. (130231)
52 meta-analysis.pt. (117148)
53 intervention$.ti. (123904)
54 or/49-53 (380217)
55 randomized controlled trial.pt. (509468)
56 randomi?ed.mp. (796957)
57 placebo.mp. (194937)
58 or/55-57 (848627)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (5562241)
60 ((control and (group* or study)) or (time and factors)).mp. (3274107)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (4624419)
62 or/59-61 (9030680)
63 Observational Studies as Topic/ (5177)
64 Observational Study/ (81866)
65 Epidemiologic Studies/ (8358)

66 exp Case-Control Studies/ (1090891)
67 exp Cohort Studies/ (2011414)
68 Cross-Sectional Studies/ (332273)
69 Controlled Before-After Studies/ (526)
70 Historically Controlled Study/ (185)
71 Interrupted Time Series Analysis/ (913)
72 Comparative Study.pt. (1866044)
73 case control$.tw. (112152)
74 case series.tw. (59119)
75 (cohort adj (study or studies)).tw. (170281)
76 cohort analy$.tw. (6758)
77 (follow up adj (study or studies)).tw. (45131)
78 (observational adj (study or studies)).tw. (86247)
79 longitudinal.tw. (204239)
80 prospective.tw. (495367)
81 retrospective.tw. (442876)
82 cross sectional.tw. (284856)
83 or/63-82 (4368140)
84 54 or 58 or 62 or 83 (9402123)
85 48 and 84 (683)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (33)
87 85 not 86 (650)

**Database: Medline in-process**
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 17, 2020>
Search date: 21 July 2020
Number of results retrieved: 122
Search strategy:
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 17, 2020>
Search Strategy:
---
1 Gender Dysphoria/ (0)
2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (1473)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (2315)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (20821)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (963)
12 (male-to-female or m2f or female-to-male or f2m).tw. (15453)
13 or/1-12 (39735)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (80295)

16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (320315)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (119124)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (59969)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (68979)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (10287)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (112220)
29 or/14-28 (523053)
30 13 and 29 (9143)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (3)
32 30 or 31 (9144)
33 Hormones/ad, tu, th (0)
34 exp Progesterone/ad, tu, th (0)
35 exp Estrogens/ad, tu, th (0)
36 exp Gonadal Steroid Hormones/ad, tu, th (0)
37 (progesteron* or oestrogen* or estrogen*).tw. (13291)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (241)
39 exp Estradiol/ad, tu, th (0)
40 exp Testosterone/ad, tu, th (0)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (5458)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (4772)
43 or/33-42 (19706)
44 32 and 43 (316)
45 limit 44 to yr="2000 -Current" (303)
46 animals/ not humans/ (1)
47 45 not 46 (303)
48 limit 47 to english language (303)
49 (MEDLINE or pubmed).tw. (36030)
50 systematic review.tw. (29830)
51 systematic review.pt. (1007)
52 meta-analysis.pt. (49)
53 intervention$.ti. (21354)
54 or/49-53 (68976)
55 randomized controlled trial.pt. (277)
56 randomi?ed.mp. (74978)
57 placebo.mp. (18290)
58 or/55-57 (81427)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (455)

60 ((control and (group* or study)) or (time and factors)).mp. (214372)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (339764)
62 or/59-61 (507046)
63 Observational Studies as Topic/ (0)
64 Observational Study/ (91)
65 Epidemiologic Studies/ (0)
66 exp Case-Control Studies/ (1)
67 exp Cohort Studies/ (1)
68 Cross-Sectional Studies/ (0)
69 Controlled Before-After Studies/ (0)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (0)
72 Comparative Study.pt. (46)
73 case control$.tw. (14451)
74 case series.tw. (13070)
75 (cohort adj (study or studies)).tw. (29119)
76 cohort analy$.tw. (1039)
77 (follow up adj (study or studies)).tw. (3540)
78 (observational adj (study or studies)).tw. (17421)
79 longitudinal.tw. (34485)
80 prospective.tw. (63689)
81 retrospective.tw. (73761)
82 cross sectional.tw. (60195)
83 or/63-82 (250805)
84 54 or 58 or 62 or 83 (687622)
85 48 and 84 (126)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (4)
87 85 not 86 (122)

**Database: Medline epubs ahead of print**
Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <July 17, 2020>
Search date: 21 July 2020
Number of results retrieved: 32
Search strategy:
Database: Ovid MEDLINE(R) Epub Ahead of Print <July 17, 2020>
Search Strategy:
---
1 Gender Dysphoria/ (0)
2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (430)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (637)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (1499)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (179)
12 (male-to-female or m2f or female-to-male or f2m).tw. (2460)

13 or/1-12 (4883)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (15416)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (53285)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (22649)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (13005)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (12420)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (1407)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (20083)
29 or/14-28 (87968)
30 13 and 29 (1618)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (1)
32 30 or 31 (1618)
33 Hormones/ad, tu, th (0)
34 exp Progesterone/ad, tu, th (0)
35 exp Estrogens/ad, tu, th (0)
36 exp Gonadal Steroid Hormones/ad, tu, th (0)
37 (progesteron* or oestrogen* or estrogen*).tw. (1876)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (63)
39 exp Estradiol/ad, tu, th (0)
40 exp Testosterone/ad, tu, th (0)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (846)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (665)
43 or/33-42 (2850)
44 32 and 43 (64)
45 limit 44 to yr="2000 -Current" (61)
46 animals/ not humans/ (0)
47 45 not 46 (61)
48 limit 47 to english language (61)
49 (MEDLINE or pubmed).tw. (7948)
50 systematic review.tw. (7508)
51 systematic review.pt. (28)
52 meta-analysis.pt. (37)
53 intervention$.ti. (4267)
54 or/49-53 (15048)
55 randomized controlled trial.pt. (1)

56 randomi?ed.mp. (14113)
57 placebo.mp. (3097)
58 or/55-57 (15128)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (34)
60 ((control and (group* or study)) or (time and factors)).mp. (31615)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (65735)
62 or/59-61 (88222)
63 Observational Studies as Topic/ (0)
64 Observational Study/ (4)
65 Epidemiologic Studies/ (0)
66 exp Case-Control Studies/ (0)
67 exp Cohort Studies/ (0)
68 Cross-Sectional Studies/ (0)
69 Controlled Before-After Studies/ (0)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (0)
72 Comparative Study.pt. (0)
73 case control$.tw. (2577)
74 case series.tw. (2480)
75 (cohort adj (study or studies)).tw. (7959)
76 cohort analy$.tw. (287)
77 (follow up adj (study or studies)).tw. (632)
78 (observational adj (study or studies)).tw. (3763)
79 longitudinal.tw. (7079)
80 prospective.tw. (12148)
81 retrospective.tw. (16600)
82 cross sectional.tw. (9459)
83 or/63-82 (48534)
84 54 or 58 or 62 or 83 (119752)
85 48 and 84 (32)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (0)
87 85 not 86 (32)

**Database: Medline daily update**
Platform: Ovid
Version: Ovid MEDLINE(R) Daily Update <July 21, 2020>
Search date: 22 July 2020
Number of results retrieved: 3
Search strategy

Database: Ovid MEDLINE(R) Daily Update <July 21, 2020>
Search Strategy:
---
1 Gender Dysphoria/ (4)
2 Gender Identity/ (38)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (2)
5 Transgender Persons/ (26)
6 Health Services for Transgender Persons/ (1)
7 exp Sex Reassignment Procedures/ (3)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (22)

9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (39)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (87)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (15)
12 (male-to-female or m2f or female-to-male or f2m).tw. (181)
13 or/1-12 (358)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (932)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (981)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1756)
17 Minors/ (3)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3672)
19 exp pediatrics/ (75)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1658)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2006)
22 Puberty/ (8)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (732)
24 Schools/ (56)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (5)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (622)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (98)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1301)
29 or/14-28 (6705)
30 13 and 29 (130)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (0)
32 30 or 31 (130)
33 Hormones/ad, tu, th (3)
34 exp Progesterone/ad, tu, th (3)
35 exp Estrogens/ad, tu, th (8)
36 exp Gonadal Steroid Hormones/ad, tu, th (22)
37 (progesteron* or oestrogen* or estrogen*).tw. (161)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (3)
39 exp Estradiol/ad, tu, th (8)
40 exp Testosterone/ad, tu, th (8)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (79)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (61)
43 or/33-42 (261)
44 32 and 43 (7)
45 limit 44 to yr="2000 -Current" (7)
46 animals/ not humans/ (3647)
47 45 not 46 (6)
48 limit 47 to english language (6)
49 (MEDLINE or pubmed).tw. (529)
50 systematic review.tw. (512)

51 systematic review.pt. (522)
52 meta-analysis.pt. (370)
53 intervention$.ti. (247)
54 or/49-53 (1065)
55 randomized controlled trial.pt. (595)
56 randomi?ed.mp. (1203)
57 placebo.mp. (219)
58 or/55-57 (1234)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (7958)
60 ((control and (group* or study)) or (time and factors)).mp. (4307)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (5828)
62 or/59-61 (11814)
63 Observational Studies as Topic/ (27)
64 Observational Study/ (449)
65 Epidemiologic Studies/ (7)
66 exp Case-Control Studies/ (2173)
67 exp Cohort Studies/ (3287)
68 Cross-Sectional Studies/ (837)
69 Controlled Before-After Studies/ (1)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (6)
72 Comparative Study.pt. (768)
73 case control$.tw. (182)
74 case series.tw. (139)
75 (cohort adj (study or studies)).tw. (561)
76 cohort analy$.tw. (22)
77 (follow up adj (study or studies)).tw. (40)
78 (observational adj (study or studies)).tw. (253)
79 longitudinal.tw. (429)
80 prospective.tw. (778)
81 retrospective.tw. (1032)
82 cross sectional.tw. (739)
83 or/63-82 (5471)
84 54 or 58 or 62 or 83 (12581)
85 48 and 84 (3)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (0)
87 85 not 86 (3)

**Database: Embase**
Platform: Ovid
Version: Embase <1974 to 2020 July 22>
Search date: 23 July 2020
Number of results retrieved: 1207
Search strategy:

Database: Embase <1974 to 2020 July 22>
Search Strategy:
---
1 exp Gender Dysphoria/ (5399)
2 Gender Identity/ (16820)
3 "Sexual and Gender Disorders"/ (24689)
4 Transsexualism/ (3869)
5 exp Transgender/ (6597)

6 Health Services for Transgender Persons/ (158848)
7 exp Sex Reassignment Procedures/ (1108)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (12470)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (22509)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (154446)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (10327)
12 (male-to-female or m2f or female-to-male or f2m).tw. (200166)
13 or/1-12 (581748)
14 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ or adolescent health/ or middle school student/ or high school student/ (3440943)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1186161)
16 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3586795)
17 exp pediatrics/ (106214)
18 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1491597)
19 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (105108)
20 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (641660)
21 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (103791)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (687437)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (138908)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1562903)
25 or/14-24 (7130881)
26 13 and 25 (181778)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (17)
28 26 or 27 (181778)
29 hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (5160)
30 exp progesterone derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (23479)
31 exp estrogen/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (57641)
32 steroid hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (372)
33 sex hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (1984)
34 hormonal therapy/ (42222)
35 (progesteron* or oestrogen* or estrogen*).tw. (254142)
36 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (1224)
37 exp estradiol derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (30740)

38 exp testosterone derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (15868)
39 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (99596)
40 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (114290)
41 or/29-40 (438737)
42 28 and 41 (6053)
43 limit 42 to yr="2000 -Current" (4741)
44 nonhuman/ not human/ (4649157)
45 43 not 44 (3636)
46 limit 45 to english language (3513)
47 (MEDLINE or pubmed).tw. (261145)
48 exp systematic review/ or systematic review.tw. (302985)
49 meta-analysis/ (191173)
50 intervention$.ti. (200041)
51 or/47-50 (660206)
52 random:.tw. (1552336)
53 placebo:.mp. (455979)
54 double-blind:.tw. (210671)
55 or/52-54 (1807280)
56 cohort analysis/ (596360)
57 exp epidemiology/ (3434332)
58 exp clinical trial/ (1504711)
59 evaluation study/ (45870)
60 statistics/ (301181)
61 ((control and (group* or study)) or (time and factors)).mp. (3324555)
62 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (6067112)
63 or/56-62 (11048972)
64 Clinical study/ (155444)
65 Case control study/ (157943)
66 Family study/ (26047)
67 Longitudinal study/ (141660)
68 Retrospective study/ (937696)
69 comparative study/ (859061)
70 Prospective study/ (613138)
71 Randomized controlled trials/ (182542)
72 70 not 71 (606604)
73 Cohort analysis/ (596360)
74 cohort analy$.tw. (13020)
75 (Cohort adj (study or studies)).tw. (302159)
76 (Case control$ adj (study or studies)).tw. (137432)
77 (follow up adj (study or studies)).tw. (63423)
78 (observational adj (study or studies)).tw. (168428)
79 (epidemiologic$ adj (study or studies)).tw. (106448)
80 (cross sectional adj (study or studies)).tw. (220073)
81 case series.tw. (104089)
82 prospective.tw. (861922)
83 retrospective.tw. (886445)
84 or/64-69,72-83 (4047788)
85 51 or 55 or 63 or 84 (12494560)
86 46 and 85 (2151)
87 86 not (letter or editorial).pt. (2137)

88 87 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (1207)

**Database: APA PsycInfo**

Platform: Ovid
Version: APA PsycInfo <1806 to July Week 2 2020>
Search date: 22 July 2020
Number of results retrieved: 581
Search strategy:

Database: APA PsycInfo <1806 to July Week 2 2020>
Search Strategy:
---
1 Gender Dysphoria/ (936)
2 Gender Identity/ (8648)
3 Transsexualism/ (2825)
4 Transgender/ (5257)
5 exp Gender Reassignment/ (568)
6 (gender* adj3 (dysphori* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (15276)
7 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (13028)
8 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (7679)
9 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (5796)
10 (male-to-female or m2f or female-to-male or f2m).tw. (63688)
11 or/1-10 (99498)
12 exp Infant Development/ (21841)
13 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (150219)
14 Child Characteristics/ or exp Child Behavior/ or Child Psychology/ or exp Child Welfare/ or Child Psychiatry/ (23423)
15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (984230)
16 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (78962)
17 Adolescent Psychiatry/ or Adolescent Behavior/ or Adolescent Development/ or Adolescent Psychology/ or Adolescent Characteristics/ or Adolescent Health/ (62142)
18 Puberty/ (2753)
19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (347604)
20 Schools/ (29181)
21 Child Day Care/ or Nursery Schools/ (2836)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (772814)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (21475)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (285697)
25 or/12-24 (1765408)
26 11 and 25 (49560)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (14)

28 26 or 27 (49561)
29 hormones/ (8408)
30 sex hormones/ (1777)
31 exp progestational hormones/ (2409)
32 estrogens/ (3889)
33 steroids/ (3797)
34 (progesteron* or oestrogen* or estrogen*).tw. (11188)
35 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (457)
36 estradiol/ (3120)
37 testosterone/ (5606)
38 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (9625)
39 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (6741)
40 or/29-39 (30344)
41 28 and 40 (1005)
42 limit 41 to yr="2000 -Current" (749)
43 limit 42 to english language (692)
44 limit 43 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract") (111)
45 43 not 44 (581)

**Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL**

Platform: Wiley
Version:
CDSR –Issue 7 of 12, July 2020
CENTRAL – Issue 7 of 12, July 2020
Search date: 22 July 2020
Number of results retrieved: CDSR 0 ; CENTRAL 67.

ID Search Hits
#1 MeSH descriptor: [Gender Dysphoria] this term only 3
#2 MeSH descriptor: [Gender Identity] this term only 227
#3 MeSH descriptor: [Sexual and Gender Disorders] this term only 2
#4 MeSH descriptor: [Transsexualism] this term only 27
#5 MeSH descriptor: [Transgender Persons] this term only 36
#6 MeSH descriptor: [Health Services for Transgender Persons] this term only 0
#7 MeSH descriptor: [Sex Reassignment Procedures] explode all trees 4
#8 (gender* near/3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)):ti,ab,kw 702
#9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*):ti,ab,kw 959
#10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*):ti,ab,kw 3969
#11 ((sex or gender*) near/3 (reassign* or chang* or transform* or transition*)):ti,ab,kw 524
#12 (male-to-female or m2f or female-to-male or f2m):ti,ab,kw 516
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 6413
#14 MeSH descriptor: [Infant] explode all trees 28440
#15 MeSH descriptor: [Infant Health] this term only 49
#16 MeSH descriptor: [Infant Welfare] this term only 82

#17 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*):ti,ab,kw,so 89530
#18 MeSH descriptor: [Child] explode all trees 44089
#19 MeSH descriptor: [Child Behavior] explode all trees 2061
#20 MeSH descriptor: [Child Health] this term only 98
#21 MeSH descriptor: [Child Welfare] this term only 325
#22 MeSH descriptor: [Minors] this term only 8
#23 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab,kw,so 265417
#24 MeSH descriptor: [Pediatrics] explode all trees 661
#25 (pediatric* or paediatric* or peadiatric*):ti,ab,kw,so 57725
#26 MeSH descriptor: [Adolescent] this term only 102154
#27 MeSH descriptor: [Adolescent Behavior] this term only 1358
#28 MeSH descriptor: [Adolescent Health] this term only29
#29 MeSH descriptor: [Puberty] this term only 295
#30 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*):ti,ab,kw,so 140927
#31 MeSH descriptor: [Schools] this term only 1914
#32 MeSH descriptor: [Child Day Care Centers] this term only 231
#33 MeSH descriptor: [Nurseries, Infant] explode all trees 17
#34 MeSH descriptor: [Schools, Nursery] this term only 37
#35 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab,kw,so 97810
#36 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") near/2 (year or years or age or ages or aged)):ti,ab 6710
#37 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") near/2 (year or years or age or ages or aged)):ti,ab 196881
#38 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 516067
#39 #13 and #38 2488
#40 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*):ti,ab,kw 0
#41 #39 or #40 2488
#42 MeSH descriptor: [Hormones] this term only 2241
#43 MeSH descriptor: [Progesterone] explode all trees 3135
#44 MeSH descriptor: [Estrogens] explode all trees 1841
#45 MeSH descriptor: [Gonadal Steroid Hormones] explode all trees 10747
#46 (progesteron* or oestrogen* or estrogen*):ti,ab,kw 18387
#47 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)):ti,ab,kw 24
#48 MeSH descriptor: [Estradiol] explode all trees 4434
#49 MeSH descriptor: [Testosterone] explode all trees 2945
#50 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan):ti,ab,kw 7386
#51 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle):ti,ab,kw 11410
#52 #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 31870
#53 #41 and #52 121
#54 "conference":pt or (clinicaltrials or trialsearch):so 492465
#55 #53 not #54 72

**Database: HTA**

Platform: Wiley
Version: up to 2018
Search date: 22nd July 2020
Number of results retrieved: 4
Search strategy:

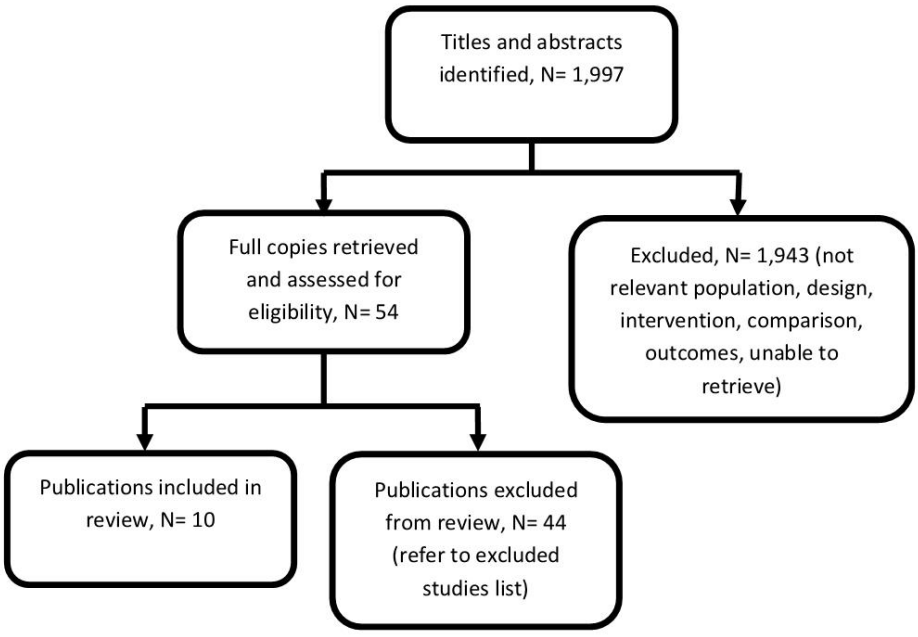
#1 MeSH DESCRIPTOR Gender Dysphoria 0
#2 MeSH DESCRIPTOR Gender Identity 12
#3 MeSH DESCRIPTOR Sexual and Gender Disorders 2
#4 MeSH DESCRIPTOR Transsexualism 12
#5 MeSH DESCRIPTOR Transgender Persons 3
#6 MeSH DESCRIPTOR Health Services for Transgender Persons 0
#7 MeSH DESCRIPTOR Sex Reassignment Procedures EXPLODE ALL TREES 1
#8 ((gender* near3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*))) 28
#9 ((transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*)) 76
#10 ((trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*)) 83
#11 (((sex or gender*) near3 (reassign* or chang* or transform* or transition*))) 24
#12 ((male-to-female or m2f or female-to-male or f2m)) 86
#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 261
#14 MeSH DESCRIPTOR Infant EXPLODE ALL TREES 2964
#15 MeSH DESCRIPTOR Infant Health 0
#16 MeSH DESCRIPTOR Infant Welfare 22
#17 ((prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*)) 5510
#18 MeSH DESCRIPTOR Child EXPLODE ALL TREES4935
#19 MeSH DESCRIPTOR Child Behavior EXPLODE ALL TREES 64
#20 MeSH DESCRIPTOR Child Health 2
#21 MeSH DESCRIPTOR Child Welfare 80
#22 MeSH DESCRIPTOR Minors 2
#23 ((child* or minor or minors or boy* or girl* or kid or kids or young*)) 13575
#24 MeSH DESCRIPTOR Pediatrics EXPLODE ALL TREES 119
#25 ((pediatric* or paediatric* or peadiatric*)) 2842
#26 MeSH DESCRIPTOR Adolescent 4594
#27 MeSH DESCRIPTOR Adolescent Behavior 94
#28 MeSH DESCRIPTOR Adolescent Health 0
#29 MeSH DESCRIPTOR Puberty 3
#30 ((adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*)) 5621
#31 MeSH DESCRIPTOR Schools 168
#32 MeSH DESCRIPTOR Child Day Care Centers 12
#33 MeSH DESCRIPTOR Schools, Nursery 3
#34 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*)) 4454
#35 ((("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") near2 (year or years or age or ages or aged))) 380
#36 ((("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") near2 (year or years or age or ages or aged)))7996

#37 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 22640
#38 #13 AND #37 116
#39 (#13 AND #37) IN HTA 4

## Appendix C Evidence selection

The literature searches identified 1,997 references. These were screened using their titles and abstracts and 54 references were obtained and assessed for relevance. Of these, 10 references are included in the evidence review. The remaining 44 references were excluded and are listed in appendix D.

**Figure 1 – Study selection flow diagram**




## References submitted with Preliminary Policy Proposal

There is no preliminary policy proposal for this policy.

## Appendix D Excluded studies table

| Study reference | Reason for exclusion |
|---|---|
| Aranda G, Mora M, Hanzu FA et al. (2019) Effects of sex steroids on cardiovascular risk profile in transgender men under gender affirming hormone therapy. Endocrinologia, diabetes y nutricion 66(6): 385–392 | Excluded on population – adult study, participants not 18 years or less (mean age 27.1 years). |
| Arnold, Justin D, Sarkodie, Eleanor P, Coleman, Megan E et al. (2016) Incidence of Venous Thromboembolism in Transgender Women | Excluded on population – adult study, participants not 18 years or less (mean age 33.2 years). |

| Study reference | Reason for exclusion |
|---|---|
| Receiving Oral Estradiol. The journal of sexual medicine 13(11): 1773–1777 | |
| Asscheman, Henk, Giltay, Erik J, Megens, Jos A J et al. (2011) A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. European journal of endocrinology 164(4): 635–42 | Excluded on population – although some participants started gender-affirming hormones when young, the study does not report the proportion who started treatment when 18 years or less. Mean ages at start of treatment were 31.4 years (transfemales) and 26.1 years (transmales), suggesting the majority of participants were older than 18 years at the start of treatment. Outcomes not reported separately for people aged 18 years or less. |
| Author not, found (2014) Hormone therapy for the treatment of gender dysphoria. Lansdale, PA: HAYES, Inc | Full text paper not available. |
| Baba, T., Endo, T., Honnma, H. et al. (2007) Association between polycystic ovary syndrome and female-to-male transsexuality. Human Reproduction 22(4): 1011–1016 | Excluded on population – although study included some younger people (age range 17 to 47), most participants were adults (mean age around 25 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less. |
| Becerra-Fernandez A, Perez-Lopez G, Roman MM et al. (2014) Prevalence of hyperandrogenism and polycystic ovary syndrome in female to male transsexuals. Endocrinologia y Nutricion: Organo de la Sociedad Espanola de Endocrinologia y Nutricion 61(7): 351–8 | Excluded on population – although study included some younger people (age range 18 to 45), most participants were adults (mean age around 25 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less. |
| Becker I, Auer M, Barkmann C et al. (2018) A Cross-Sectional Multicenter Study of Multidimensional Body Image in Adolescents and Adults with Gender Dysphoria Before and After Transition-Related Medical Interventions. Archives of Sexual Behavior 47(8): 2335–2347 | Excluded on population – study included people aged 14 to 21 years. Outcomes not reported separately for people aged 18 years or less.<br>Better evidence available – only 11 participants received gender-affirming hormones. The majority of the study cohort were either pre-treatment, received puberty suppression alone, or received hormones and underwent surgery. |
| Chew D, Anderson J, Williams K et al. (2018) Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics 141(4): e20173742 | Excluded on better available evidence - systematic review did not meta-analyse results from. Individual studies from this systematic review are either |

| Study reference | Reason for exclusion |
|---|---|
| | included, or excluded because they did not meet the PICO criteria. |
| Connolly MD, Zervos MJ, Barone CJ 2nd et al. (2016) The Mental Health of Transgender Youth: Advances in Understanding. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 59(5): 489–495 | Excluded on intervention - review did not investigate gender-affirming hormones |
| de Vries ALC, McGuire JK, Steensma TD et al. (2014) Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 134(4): 696–704 | Exclude on intervention – all participants had surgery after gender-affirming hormones. Unable to determine whether changes were due to hormones or surgery. Complete data only available for 40 patients. Details of gender-affirming hormones are poorly reported. Outcomes reported in other study (with a population that more closely matches PICO) |
| Elamin MB, Garcia MZ, Murad MH et al. (2010) Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clinical Endocrinology 72(1): 1–10 | Exclude on population – all included studies conducted in adult population. Unclear whether hormones were started when participants were aged 18 years or less. Outcomes not reported by age at treatment initiation. |
| Fernandez JD and Tannock LR (2016) Metabolic effects of hormone therapy in transgender patients. Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 22(4): 383–8 | Excluded on population – adult study, participants not 18 years or less (mean ages 31 and 27 years). |
| Fighera TM, Ziegelmann PK, Da Silva TR et al. (2019) Bone mass effects of cross-sex hormone therapy in transgender people: Updated systematic review and meta-analysis. Journal of the Endocrine Society 3(5): 943–964 | Excluded on population – all included studies conducted in adult population. Unclear whether hormones were started when participants were aged 18 years or less. Outcomes not reported by age at treatment initiation. |
| Getahun D, Nash R, Flanders WD et al. (2018) Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study. Annals of Internal Medicine 169(4): 205–213 | Excluded on population – adult study, participants not 18 years or less. |
| Gomez-Gil E, Zubiaurre-Elorza L, de Antonio IE et al. (2014) Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Quality of Life Research: an International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation 23(2): 669–76 | Excluded on population – although study included some younger people (age range 16 to 67), most participants were adults (mean age 31.2 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less. |
| Gomez-Gil E, Zubiaurre-Elorza L, Esteva I et al. (2012) Hormone-treated transsexuals report less | Excluded on population – adult study, participants not 18 years or less (mean age 24.6 years). |

| Study reference | Reason for exclusion |
|---|---|
| social distress, anxiety and depression. Psychoneuroendocrinology 37(5): 662–70 | |
| Gooren LJ, van Trotsenburg MAA, Giltay EJ et al. (2013) Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. The Journal of Sexual Medicine 10(12): 3129–34 | Excluded on population – study reports on cancer rates in people aged 18-80 years. The 3 cases of cancer all started gender-affirming hormone treatment >18 years. |
| Grimstad FW, Boskey E, Grey M (2020) New-Onset Abdominopelvic Pain After Initiation of Testosterone Therapy Among TransMasculine Persons: A Community-Based Exploratory Survey. LGBT health 7(5): Published Online:13 Jul 2020https://doi.org/10.1089/lgbt.2019.0258 | Excluded on population – adult study, participants not 18 years or less. |
| Hannema SE, Schagen SEE, Cohen-Kettenis PT et al. (2017) Efficacy and Safety of Pubertal Induction Using 17beta-Estradiol in Transgirls. The Journal of Clinical Endocrinology and Metabolism 102(7): 2356–2363 | Excluded on better evidence available – small study (n=28) with high drop-out rate (n=16 at final follow-up). Same outcomes reported in larger studies. |
| Jarin J, Pine-Twaddell E, Trotman G et al. (2017) Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. Pediatrics 139(5) | Excluded on population and better evidence available. Although the study included some younger people (age range 13 to 25; mean age 16 and 18), the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less. Outcomes were limited to physiological results (including haemoglobin, lipids and BMI). Follow-up only 6 months, other included studies report same outcomes with longer follow-up (12 to 31 months). |
| Keo-Meier CL, Herman LI, Reisner SL et al. (2015) Testosterone treatment and MMPI-2 improvement in transgender men: a prospective controlled study. Journal of consulting and clinical psychology 83(1): 143–56 | Excluded on population – although study included some younger people (age range 18 to 54), most participants were adults (mean age 26.6 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less. |
| Klaver M, de Mutsert R, Wiepjes CM et al. (2018) Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. The Journal of Sexual Medicine 15(2): 251–260 | Excluded on outcomes – reported outcomes not included in PICO document. The risk of obesity with gender-affirmed hormones was reported in an included study. |
| McFarlane T, Zajac JD, Cheung AS (2018) Gender-affirming hormone therapy and the risk of sex hormone-dependent tumours in transgender individuals-A systematic review. Clinical Endocrinology 89(6): 700-711 | Exclude on population – all included studies conducted in adult population. |

| Study reference | Reason for exclusion |
|---|---|
| Meriggiola MC, Armillotta F, Costantino A et al. (2008) Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. The Journal of Sexual Medicine 5(10): 2442–53 | Excluded on population – adult study, participants not 18 years or less. |
| Nota NM, Wiepjes CM, de Blok, CJM et al. (2018) The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment. Brain: A Journal of Neurology 141(7): 2047–2054 | Excluded on population – adult study, participants not 18 years or less. |
| Oda H and Kinoshita T (2017) Efficacy of hormonal and mental treatments with MMPI in FtM individuals: Cross-sectional and longitudinal studies. BMC Psychiatry 17(1): 256 | Excluded on population – although study included some younger people (age range 15 to 43), most participants were adults (mean age around 25.6 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less. |
| Olson-Kennedy J, Okonta V, Clark LF et al. (2018) Physiologic Response to Gender-Affirming Hormones Among Transgender Youth. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 62(4): 397–401 | Excluded on population – although study included some younger people (age range 12 to 23; mean age 18 years). Outcomes not reported separately for people aged 18 years or less. Outcomes limited to physiological results (including haemoglobin, lipids, liver enzymes and BMI). Same outcomes reported in included studies that had a less indirect population and a longer follow-up. |
| Ott J, Kaufmann U, Bentz K et al. (2010) Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. Fertility and sterility 93(4): 1267–72 | Excluded on population – adult study, participants not 18 years or less. |
| Pakpoor J, Wotton CJ, Schmierer K et al. (2016) Gender identity disorders and multiple sclerosis risk: A national record-linkage study. Multiple sclerosis. Multiple Sclerosis Journal. 22(13): 1759–1762 | Excluded on population – although study included some younger people, outcomes not reported separately for people aged 18 years or less. Also exclude for intervention – unclear if people received gender-affirming hormones. |
| Pyra M, Casimiro I, Rusie L et al. (2020) An Observational Study of Hypertension and Thromboembolism among Transgender Patients Using Gender-Affirming Hormone Therapy. Transgender Health 5(1): 1–9 | Excluded on population – adult study (age range 20-70). Age at which gender-affirming hormones started not reported. |
| Quiros C, Patrascioiu I, Mora M et al. (2015) Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. Endocrinologia y nutricion : organo de la Sociedad Espanola de Endocrinologia y Nutricion 62(5): 210–6 | Excluded on population – adult study, participants not 18 years or less. |

| Study reference | Reason for exclusion |
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| Rowniak S, Bolt L, Sharifi C (2019) Effect of cross-sex hormones on the quality of life, depression and anxiety of transgender individuals: A quantitative systematic review. JBI Database of Systematic Reviews and Implementation Reports 17(9): 1826–1854 | Exclude on population – all included studies conducted in adult population. |
| Sequeira GM, Kidd K, El Nokali NE et al. (2019) Early Effects of Testosterone Initiation on Body Mass Index in Transmasculine Adolescents. Journal of Adolescent Health 65(6): 818–820 | Exclude on outcome - study only reports BMI z-score over 12 month testosterone treatment. BMI not listed as an outcome of interest in the PICO document. Other included studies have investigated the impact of gender-affirming hormone treatment on CV risk profile, including longer term obesity rates, with a longer follow-up and more participants. |
| Shim JY, Laufer MR, Grimstad FW (2020) Dysmenorrhea and Endometriosis in Transgender Adolescents. Journal of Pediatric and Adolescent Gynecology. Available online 11 June 2020. https://doi.org/10.1016/j.jpag.2020.06.001 | Exclude on population – only 2 participants taking testosterone before diagnosis of dysmenorrhea. |
| Slabbekoorn D, Van Goozen SHM, Gooren, LJG et al. (2001) Effects of cross-sex hormone treatment on emotionality in transsexuals. International Journal of Transgenderism 5(3): http://www.symposion.com/ijt/ijtvo05no03_02.htm | Excluded on population – adult study (age range 21 to 28 years) |
| Smith YLS., Van Goozen SHM, Kuiper AJ et al. (2005) Sex reassignment: Outcomes and predictors of treatment for adolescent and adult transsexuals. Psychological Medicine 35(1): 89–99 | Excluded on population – results on adults only used to assess hormone treatment. |
| Sutherland N, Espinel W, Grotzke M et al. (2020) Unanswered Questions: Hereditary breast and gynecological cancer risk assessment in transgender adolescents and young adults. Journal of Genetic Counseling 29(4): 625–633 | Excluded on study type – narrative review of 3 case reports. |
| van Velzen DM, Paldino A, Klaver M et al. (2019) Cardiometabolic Effects of Testosterone in Transmen and Estrogen Plus Cyproterone Acetate in Transwomen. The Journal of Clinical Endocrinology and Metabolism 104(6): 1937–1947 | Excluded on population – adult study, participants not 18 years or less. |
| White Hughto JM and Reisner SL (2016) A Systematic Review of the Effects of Hormone Therapy on Psychological Functioning and Quality of Life in Transgender Individuals. Transgender Health 1(1): 21–31 | Exclude on population – all included studies conducted in adult population. |
| Wiepjes CM, de Blok CJM, Staphorsius AS et al. (2020) Fracture Risk in Trans Women and Trans Men Using Long-Term Gender-Affirming Hormonal Treatment: A Nationwide Cohort Study. Journal of Bone and Mineral Research 35(1): 64–70 | Excluded on population – adult study, all participants started gender-affirming hormones after 18 years. |
| Wierckx K, Mueller S, Weyers S et al. (2012) Long-term evaluation of cross-sex hormone treatment in | Excluded on population – adult study, participants not 18 years or less. |

| Study reference | Reason for exclusion |
|---|---|
| transsexual persons. The Journal of Sexual Medicine 9(10): 2641–51 | |
| Wierckx K, Van Caenegem E, Schreiner T et al. (2014) Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. The journal of sexual medicine 11(8): 1999–2011 | Excluded on population – adult study, participants not 18 years or less. |
| Wilson R, Jenkins C, Miller H et al. (2006) The effect of oestrogen on cytokine and antioxidant levels in male to female transsexual patients. Maturitas 55(1): 14–8 | Excluded on population – adult study, participants not 18 years or less. |
| Witcomb GL, Bouman WP, Claes L et al. (2018) Levels of depression in transgender people and its predictors: Results of a large matched control study with transgender people accessing clinical services. Journal of Affective Disorders 235: 308–315 | Excluded on population – although study included some younger people (age range 15 to 79), most participants were adults (mean age around 30.4 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less. |

## Appendix E Evidence tables

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| **Full citation**<br>Achille, C., Taggart, T., Eaton, N.R. et al. (2020) Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. International Journal of Pediatric Endocrinology 2020(1): 8<br><br>**Study location**<br>Single centre, New York, United States<br><br>**Study type**<br>Prospective longitudinal study<br><br>**Study aim**<br>To assess the psychological wellbeing and quality of life in children and adolescents who have sought endocrine | Inclusion and exclusion not reported- it appears from the description in the publication that all people referred for gender dysphoria were invited to participate, and the vast majority agreed. Of the 95 treatment naïve people who entered the study, 50 people completed all follow-up questionnaires and were included in the analysis. No description of the 45 people without follow-up data reported.<br><br>The study included 50 children, adolescents and young adults with gender dysphoria. | **Intervention**<br><br>Endocrine interventions (the collective term used by authors for puberty suppression and gender-affirming hormones) were introduced as per Endocrine Society and the World Professional Association for | **Critical Outcomes**<br>***Impact on mental health***<br>Depression symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CESD-R). Statistically significant improvements in CESD-R score were observed from baseline (initial assessment; 21.4 points) to about 12 months follow-up (13.9 points; p<0.001).<br>Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found no statistically significant change from baseline in transfemales (p=0.27) and transmales (p=0.43).<br><br>The Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) was also used to assess depression symptoms. Depression scores improved from baseline (p< 0.001; absolute scores not reported numerically).<br>Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found no statistically significant change from baseline in transfemales (p=0.07) and transmales (p=0.67).<br><br>Suicidal ideation measured using the additional questions from the PHQ 9_Modified for Teens, was presented in 10% (5/50) of participants at baseline and 6% (3/50) at | This study was appraised using the Newcastle-Ottawa tool for cohort studies.<br><br>**Domain 1: Selection domain**<br>1. b) somewhat representative<br>2. c) no-non exposed cohort<br>3. a) secure record<br>4. b) no<br>**Domain 2: Comparability**<br>1. c) no comparator<br>**Domain 3: Outcome**<br>1. c) self-report<br>2. a) yes – 6 monthly assessment up to 12 months (preliminary results from an ongoing study)<br>3. c) Follow up rate less than 80% and no description of those lost<br><br>**Overall quality is assessed as poor**<br><br>Other comments: Although regression analysis results for some outcomes were controlled for use of medicines for mental health problems, details of these is not |

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| intervention to help with gender dysphoria.<br><br>**Study dates**<br>Study recruitment ran from December 2013 to December 2018; study is ongoing | 17 transfemales and 33 transmales.<br><br>Diagnostic criteria for gender dysphoria not reported.<br><br>Mean age at baseline was 16.2 years (SD 2.2).<br><br>Mean age at the start of gender-affirming hormone treatment not reported. | Transgender Health (WPATH) guidelines.<br><br>Puberty suppression was:<br>• GnRH agonist and/or anti-androgens (transfemales)<br>• GnRH agonist or medroxyprogesterone (transmales)<br><br>Average duration of GnRH analogue treatment not reported.<br><br>Once eligible, gender-affirming hormones were offered, these were:<br>• Oestradiol (transfemales)<br>• Testosterone (transmales)<br>Doses and route of administration not reported.<br><br>After about 12-months treatment ('wave 3' in the study):<br>• 24 people (48%) were on gender-affirming hormones alone<br>• 12 people (24%) were on puberty suppression alone | about 12-month follow-up, no statistical analysis reported.<br>The study also reported results by gender:<br>In transfemales, 11.8% (2/17) had suicidal ideation at baseline compared with 5.9% (1/17) at 12-month follow-up (no statistically analysis reported)<br>In transmales, 9.1% (3/33) had suicidal ideation at baseline compared with 6.1% (2/33) at 12-month follow-up (no statistically analysis reported)<br><br>***Impact on quality of life***<br>Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF) scores: there was no statistically significant change in score from baseline to about 12-months (p=0.085; absolute scores not reported numerically).<br>Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found not statistically significant change from baseline in transfemales (p=0.06) and transmales (p=0.08).<br><br>*No other critical or important outcomes reported* | reported. Other co-morbidities not reported.<br><br>Source of funding: None |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| | | • 11 people (22%) were on both gender-affirming hormones and puberty suppression<br>• 3 people (6%) were on no endocrine intervention<br>Results not represented separately for the sub-group of people who received gender-affirming hormones.<br><br>Average duration of treatment with gender-affirming hormones not reported.<br><br>**Comparison**<br><br>No comparison group. Change overtime reported. | | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| **Full citation**<br>Allen, LR, Watson, LB, Egan, AM et al. (2019) Well-being and suicidality among transgender youth after gender-affirming hormones. Clinical Practice in Pediatric Psychology 7(3): 302-311 | The study included adolescents and young adults (age range 13-20 years) who received services for gender dysphoria in a clinic in the United States. Participants were required to have received gender-affirming hormones for | 39 participants received gender-affirming hormones only<br><br>8 participants received a GnRH analogue followed by gender-affirming hormones.<br><br>Mean duration of treatment in the gender- | **Critical Outcomes**<br>***Impact on mental health***<br>The Ask Suicide-Screening Questions (ASQ) instrument was used to assess suicidality. Following an average of about 12 months treatment with gender-affirming hormones, adjusted mean ASQ score was statistically significantly lower (from 1.11 [standard error | This study was appraised using the Newcastle-Ottawa tool for cohort studies.<br><br>**Domain 1: Selection domain**<br>1. b) somewhat representative<br>2. c) no-non exposed cohort |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| **Study location**<br>Single centre, Kansas City, United States<br><br>**Study type**<br>Retrospective longitudinal study<br><br>**Study aim**<br>To examine suicidality and general well-being following administration of gender-affirming hormones.<br><br>**Study dates**<br>Participants first presented to the clinic between 2015 and 2018. | at least 3 months, and have pre-test and final assessment data points. No exclusion criteria reported.<br><br>In total 47 adolescents and young adults with gender dysphoria were included: 14 transfemales (sex assigned at birth male) and 33 transmales (sex assigned at birth female).<br><br>Diagnostic criteria for gender dysphoria not reported.<br><br>Mean age at pre-test (before administration of gender-affirming hormones) was 16.59 years (range 13.73 to 19.04).<br><br>Mean age at the start of treatment in the sub-group who received gender-affirming hormones-only was 16.72 years.<br><br>Mean age at the start of treatment with gender-affirming hormones in people who previously received a GnRH | affirming hormones only subgroup was 366 days.<br><br>Mean duration of gender-affirming hormone treatment in people who had previously received a GnRH analogue was not reported.<br><br>Mean duration of treatment with a GnRH analogue was not reported.<br><br>Participants were assessed at the start of treatment and at least 3 months after treatment. | (SE) 0.22] at baseline to 0.27 [SE 0.12] at final assessment; p<0.001).<br><br>The authors also reported change in ASQ separately for transfemales (from 1.21 [SE 0.36] at baseline to 0.24 [SE 0.19] at final assessment) and transmales (from 1.01 [SE 0.36] at baseline to 0.29 [0.13] at final assessment). There was no statistically significant difference in change from baseline between transfemales and transmales (p=0.79)<br><br>***Impact on quality of life***<br>Assessed using the General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory. Following an average of about 12 months treatment with gender-affirming hormones, adjusted mean GWBS score was statistically significantly higher (from 61.7 [SE 2.43] at baseline to 70.23 [2.15] at final assessment; p<0.002).<br><br>The authors also reported change in GWBS of the Pediatric Quality of Life Inventory for transfemales (from 58.44 [SE 4.09] at baseline to 69.52 [SE 3.62] at final assessment) and transmales (from 64.95 [SE 2.66] at baseline to 70.94 [2.35] at final assessment). There was no statistically significant difference in change from baseline between transfemales and transmales (p=0.32)<br><br>*No other critical or important outcomes reported* | 3. a) secure record<br>4. b) no<br>**Domain 2: Comparability**<br>2. c) no comparator<br>**Domain 3: Outcome**<br>1. b) record linkage<br>2. a) yes – mean duration of treatment was 366 days<br>3. a) complete follow up - all subjects accounted for<br><br>**Overall quality is assessed as poor**<br><br>Other comments: None<br><br>Source of funding: Not reported |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| | analogue was not reported. | | | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| **Full citation**<br>Kaltiala, R., Heino, E., Tyolajarvi, M. et al. (2020) Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. Nordic Journal of Psychiatry 74(3): 213-219<br><br>**Study location**<br>Single centre, Tampere, Finland<br><br>**Study type**<br>Retrospective chart review<br><br>**Study aim**<br>To evaluate the psychosocial functioning and need for mental health treatment during the gender identity diagnostic phase and after about a year on gender-affirming hormones. | The study included adolescents who were referred to the gender identity service before they 18 years old, were diagnosed with gender dysphoria, received gender-affirming hormones and completed a follow-up of approximately 12 months after starting hormones.<br><br>In total 52 adolescents were included, comprising of 11 transfemales and 41 transmales.<br><br>Gender dysphoria was diagnosed according to International Classification of Disease 10 (ICD-10). The authors state that the corresponding diagnosis to 'gender dysphoria' in | Intervention referred to as 'hormonal sex reassignment treatment' – details of intervention not reported, although gender-affirming hormones were prescribed to all participants. It is not clear from the study whether additional interventions were prescribed.<br><br>Medical records reviewed for the 'real-life phase' – the approximately 12 months follow-up period for this population in Finland. | **Critical Outcomes**<br>***Impact on mental health***<br>Of the 52 people who received gender-affirming hormones, 50% (26/52) needed mental health treatment before or during the assessment and 46% (24/51) needed mental health treatment during the 12-month 'real life' phase (no statistically significant difference).<br>For specific symptoms / conditions:<br>• depression: 54% (28/52) needed treatment before or during the assessment and 15% (8/52) needed treatment during the 12-month 'real life' phase (statistically significant reduction, p<0.001)<br>• anxiety: 48% (25/52) needed treatment before or during the assessment and 15% (8/52) needed treatment during the 12-month 'real life' phase (statistically significant reduction, p<0.001)<br>• suicidality/self-harm: 35% (18/52) needed treatment before or during the assessment and 4% (2/52) needed treatment during the 12-month 'real life' phase (statistically significant reduction, p<0.001)<br>• conduct problems/antisocial: 14% (7/52) needed treatment before or during the assessment and 6% (3/52) needed treatment during the 12-month 'real life' | This study was appraised using the Newcastle-Ottawa tool for cohort studies.<br><br>**Domain 1: Selection domain**<br>1. b) somewhat representative<br>2. c) no-non exposed cohort<br>3. a) secure record<br>4. b) no<br>**Domain 2: Comparability**<br>1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders<br>**Domain 3: Outcome**<br>1. b) record linkage<br>2. a) yes – 12 month follow-up<br>3. a) complete follow up - all subjects accounted for<br><br>**Overall quality is assessed as poor** |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| **Study dates**<br>2011 to 2017 | the ICD-10 is 'transsexualism'.<br><br>Mean age at diagnosis 18.1 years (range 15.2 to 19.9) | | phase (no statistically significant difference, p= 0.18)<br>• psychotic symptoms/psychosis: 2% (1/52) needed treatment before or during the assessment and 4% (2/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.56)<br>• substance abuse: 4% (2/52) needed treatment before or during the assessment and 2% (1/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.56)<br>• autism: 12% (6/52) needed treatment before or during the assessment and 6% (3/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.30)<br>• ADHD: 10% (5/52) needed treatment before or during the assessment and 2% (1/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.09)<br>• eating disorder: 2% (1/52) needed treatment before or during the assessment and 2% (1/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 1.0).<br>No details of actual treatment reported.<br><br>**Important Outcomes**<br>***Psychosocial Impact***<br>Study reported on measures of functioning in different domains of adolescent development, reported over the approximately 12-month period after starting gender-affirming | Other comments: None<br><br>Source of funding: No source of funding reported |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| | | | hormones (referred to as the 'real-life phase' in Finland)<br><br>Significantly fewer participants were living with parent(s)/ guardians during the real-life phase (40%; 21/50) compared with during gender identity assessment (73%; 38/52; p=0.001))<br><br>There was a statistically significant reduction in the number of participants with normative peer contacts, from gender identity assessment (89%; 46/52) to the real-life phase (81%; 42/52; p<0.001).<br><br>There was no significant difference in the number of participants who were progressing normally in school or work during gender identity assessment (64%; 33/52) compared with the real-life phase (60%; 31/52).<br><br>There was no significant difference in the number of participants who have been dating or were in steady relationships during gender identity assessment (62%; 32/50) compared with the real-life phase (58%; 30/52).<br><br>There was no significant difference in the number of participants who were able to deal with matters outside of the home in an age-appropriate manner during gender identity assessment (81% (42/52) compared with the real-life phase (81%; 42/52)<br><br>*No other critical or important outcomes reported* | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| **Full citation**<br>Khatchadourian K, Amed S, Metzger DL (2014) Clinical management of youth with gender dysphoria in Vancouver. The Journal of pediatrics 164(4): 906-11<br><br>**Study location**<br>Single centre study, Vancouver, Canada<br><br>**Study type**<br>Retrospective chart review<br><br>**Study aim**<br>To describe the patient characteristics, clinical management, and response to treatment in a cohort of people seen in a single clinic.<br><br>**Study dates**<br>1998 to 2011 | Inclusion criteria were at least Tanner stage 2 pubertal development, previous assessment by a mental health professional and a confirmed diagnosis of gender dysphoria (diagnostic criteria not specified). No exclusion criteria are specified.<br><br>63 children, adolescents and young people with gender dysphoria who started gender-affirming hormones, out of 84 young people seen in the unit between 1998 and 2011.<br>39 transfemales and 24 transmales.<br><br>Diagnostic criteria for gender dysphoria not reported.<br><br>Mean age at the start of gender-affirming hormone treatment was 17.4 years (SD 1.9). | **Intervention**<br>Transfemales: Oestrogen (oral micronized 17β-oestradiol)<br>Transmales: Testosterone (injectable testosterone enanthate and/or cypionate)<br><br>19 participants (30%) had previously received a GnRH analogue. The median time from start of GnRH analogue to start of gender-affirming hormones was 11.3 months (range 2.2 to 42.0). 11 participants continued GnRH analogues after starting gender-affirming hormones.<br><br>Average duration of treatment with a GnRH analogue not reported<br><br>**Comparison**<br>No comparator | **Critical Outcomes**<br><br>No critical outcomes assessed.<br><br>**Important outcomes**<br><br>***Safety***<br>Of the 63 participants who received gender-affirming hormones:<br>• No participants permanently discontinued gender-affirming hormones<br>• 3 participants (5%) temporarily discontinued treatment:<br>○ 2 transmales due to concomitant mental health comorbidities<br>○ 1 transmale due to androgenic alopecia.<br>○ No transfemale stopped treatment.<br>The authors report that all patients eventually restarted gender-affirming hormones, although they do not report how long treatment was | This study was appraised using the Newcastle-Ottawa tool for cohort studies.<br><br>**Domain 1: Selection domain**<br>1. b) somewhat representative<br>2. c) no-non exposed cohort<br>3. a) secure record*<br>4. b) no<br>**Domain 2: Comparability**<br>1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders<br>**Domain 3: Outcome**<br>1. b) record linkage<br>2. b) no – although follow-up time is reported for patients with more than 1 clinic visit, duration of treatment with gender-affirming hormones is not reported<br>3. c) incomplete - missing data<br><br>**Overall quality is assessed as poor**<br><br>Other comments: Mental health comorbidity was reported for all participants but not for the gender-affirming hormone cohort separately. |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| | | | stopped for, or what the effect of stopped treatment was.<br>• No participants reported major complications<br>• 12 participants (19%) had minor complications:<br>○ 7 transmales had severe acne (requiring isotretinoin)<br>○ 1 transmale had andogenic alopecia<br>○ 3 transmales had mild dyslipidaemia (levels not reported)<br>○ 1 transmale had significant mood swings<br>○ No transfemales had minor complications | Concomitant use of other medicines was not reported.<br><br>Source of funding: No source of funding identified. |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| **Full citation**<br>Klaver, Maartje, de Mutsert, Renee, van der Loos, Maria A T C et al. (2020) Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents. Pediatrics 145(3)<br><br>**Study location**<br>Single centre, Amsterdam, Netherlands<br><br>**Study type** | Participants were included if i) they had started GnRH analogue treatment before 18 years, ii) if whole body dual-energy radiograph absorptiometry was performed at least once during treatment (4 months before or after the start of GnRH analogues or gender-affirming hormones, or within 1.5 years before or after the 22nd birthday), iii) if | Transfemales: Oestrogen (17-β oestradiol [E2]) orally, starting with 5 mcg/kg body weight per day, which was increased every 6 months until the maintenance dose of 2 mg per day was reached.<br><br>Transmales: mixed testosterone esters (Sustanon), 25 mg/m$^2$ body surface area every 2 weeks intramuscularly, | **Critical Outcomes**<br><br>No critical outcomes assessed.<br><br>**Important outcomes**<br><br>***Safety***<br>Safety outcomes reported separately for transfemales and transmales.<br><br>**For transfemales**, from the start of gender-affirming hormone treatment to age 22 years:<br>• Mean BMI statistically significantly increased (mean change +1.9, 95% CI 0.6 to 3.2, p<0.005; mean BMI at 22 years= 23.2, 95% CI 21.6 to 24.8). At age 22 years, 9.9% of the cohort were | This study was appraised using the Newcastle-Ottawa tool for cohort studies.<br><br>**Domain 1: Selection domain**<br>1. b) somewhat representative<br>2. c) no-non exposed cohort<br>3. a) secure record*<br>4. b) no<br>**Domain 2: Comparability**<br>1. c) cohorts are not comparable on the basis |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
|---|---|---|---|---|
| Retrospective chart review<br><br>**Study aim**<br>To examine the effects of treatment on changes in cardiovascular risk factors, including BMI, blood pressure, insulin sensitivity, and lipid levels.<br><br>**Study dates**<br>1998-2015 | they were likely to have had at least 1 medical consultation in young adulthood.<br><br>The study included 192 young people with dysphoria who met the above inclusion criteria: 71 transfemales and 121 transmales.<br><br>Gender dysphoria was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria.<br><br>Mean age at the start of gender-affirming hormones was 16.4 years (SD 1.1) for transfemales and 16.9 years (SD 0.9) for transmales. | increased every 6 months to maintenance dose of 250 mg every 3 to 4 weeks.<br><br>When GnRH analogues were started after the age of 16 years a different hormone starter dose was used (1 mg oestrogen daily and 75 mg testosterone weekly).<br><br>Median (IQR) duration of GnRH analogue (monotherapy) was 2.1 years (1.0 to 2.7) in transfemales and 1.0 (0.5 to 2.9) for transmales. | obese, compared with 3.0% in reference cisgender population[1].<br>• Mean systolic blood pressure (SBP) did not significantly change (mean change -3 mmHg, 95% CI -8 to 2; mean SBP at 22 years= 117 mmHg, 95% CI 113 to 122)<br>• Mean diastolic blood pressure (DBP) statistically significantly increased (mean change +6 mmHg, 95% CI 3 to 10, p<0.001; mean DBP at 22 years= 75 mmHg, 95% CI 72 to 78)<br>• Mean glucose level did not significantly change (mean change +0.1 mmol/L, 95% CI -0.1 to 0.2; mean glucose level at 22 years= 5.0 mmol/L, 95% CI 4.8 to 5.1)<br>• Mean insulin level did not significantly change (mean change +2.7 mU/L, 95% CI -1.7 to 7.1; mean insulin level at 22 years= 5.0 mU/L (4.8 to 5.1)<br>• Insulin resistance (mean Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]) did not significantly change (mean change +0.7, 95% CI -0.2 to 1.5; mean HOMA-IR at 22 years 2.9, 95% CI 1.9 to 3.9)<br>• Mean total cholesterol did not significantly change (mean change +0.1 mmol/L, 95% CI -0.2 to 0.4; mean total cholesterol at 22 years 4.1 mmol/L, 95% CI 3.8 to 4.4)<br>• Mean HDL cholesterol did not significantly change (mean change +0.0 mmol/L, 95% CI -0.1 to 0.2; mean HDL cholesterol at 22 years 1.6 mmol/L, 95% CI 1.4 to 1.7)<br>• Mean LDL cholesterol did not significantly change (mean change +0.0 mmol/L, 95% | of the design or analysis controlled for confounders<br>**Domain 3: Outcome**<br>1. b) record linkage<br>2. a) yes- follow-up from start of gender-affirming hormones to age 22 years, around 5 years<br>3. a) complete follow up - all subjects accounted for<br><br>**Overall quality is assessed as poor**<br><br>Other comments: None<br><br>Source of funding: No external funding |

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| | | | CI -0.3 to 0.2; mean LDL cholesterol at 22 years 2.0 mmol/L, 95% CI 1.8 to 2.3)<br>• Mean triglycerides statistically significantly increased (mean change +0.2 mmol/L, 95% CI 0.0 to 0.5, p<0.05; triglyceride level at 22 years 1.1 mmol/L, 95% CI 0.9 to 1.4)<br><br>**For transmales**, from the start of gender-affirming hormone treatment to age 22 years:<br>• Mean BMI statistically significantly increased (mean change +1.4, 95% CI 0.8 to 2.0, p<0.005; mean BMI at 22 years= 23.9, 95% CI 23.0 to 24.7). At age 22 years, 6.6% of the cohort were obese, compared with 2.2% in reference cisgender population[1].<br>• Mean systolic blood pressure (SBP) statistically significantly increased (mean change +5 mmHg, 95% CI 1 to 9; mean SBP at 22 years= 126 mmHg, 95% CI 122 to 130)<br>• Mean diastolic blood pressure (DBP) statistically significantly increased (mean change +6 mmHg, 95% CI 4 to 9, p<0.001; mean DBP at 22 years= 74 mmHg, 95% CI 72 to 77)<br>• Mean glucose level did not significantly change (mean change 0.0 mmol/L, 95% CI -0.2 to 0.2; mean glucose level at 22 years= 4.8 mmol/L, 95% CI 4.7 to 5.0)<br>• Mean insulin level statistically significantly decreased (mean change -2.1 mU/L, 95% CI -3.9 to -0.3, p<0.05; mean insulin level at 22 years= 8.6 mU/L (6.9 to 10.2)<br>• Insulin resistance (mean Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]) statistically significantly decreased (mean change -0.5, 95% CI - | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
|---|---|---|---|---|
| | | | 1.0 to -0.1, p<0.05; mean HOMA-IR at 22 years 1.8, 95% CI 1.4 to 2.2)<br>• Mean total cholesterol statistically significantly increased (mean change +0.4 mmol/L, 95% CI 0.2 to 0.6, p<0.001; mean total cholesterol at 22 years 4.6 mmol/L, 95% CI 4.3 to 4.8)<br>• Mean HDL cholesterol statistically significantly decreased (mean change -0.3 mmol/L, 95% CI -0.4 to -0.2, p<0.001; mean HDL cholesterol at 22 years 1.3 mmol/L, 95% CI 1.2 to 1.3)<br>• Mean LDL cholesterol statistically significantly increased (mean change +0.4 mmol/L, 95% CI 0.2 to 0.6, p<0.001; mean LDL cholesterol at 22 years 2.6 mmol/L, 95% CI 2.4 to 2.8)<br>• Mean triglycerides statistically significantly increased (mean change +0.5 mmol/L, 95% CI 0.3 to 0.7, p<0.001; triglyceride level at 22 years 1.3 mmol/L, 95% CI 1.1 to 1.5) | |

[1] Reference population taken from Fredriks et al. (2000)

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| **Full citation**<br>Klink D, Caris M, Heijboer A et al. (2015) Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. The Journal of Clinical Endocrinology and Metabolism 100(2): e270-5<br><br>**Study location**<br>Single centre, Amsterdam, Netherlands<br><br>**Study type**<br>Retrospective longitudinal study<br><br>**Study aim**<br>To assess peak bone mass in young adults with gender dysphoria who had received GnRH analogues and gender-affirming hormones during their pubertal years.<br><br>**Study dates** | 34 young people with gender dysphoria who received GnRH analogues, gender-affirming hormones and gonadectomy.<br><br>The study included 15 transfemales and 19 transmales; mean age at start of gender-affirming hormones was 16.6 years (SD 1.4) and 16.4 years (SD 2.3) respectively.<br><br>Participants were required to meet the DSM-IV-TR criteria for gender identity disorder of adolescence. Participants were included if they had undergone gonadectomy between June 1998 and August 2012, and they were at least 21 years old when they had the surgery. Bone mineral density data were also required at the start of GnRH analogue, gender-affirming hormones and at the age of 22 years.<br><br>No concomitant treatments were reported. | **Intervention**<br><br>Transfemales - oral 17-β oestradiol<br>(incremental dosing)<br><br>Transmales – IM testosterone (Sustanon 250 mg/ml; incremental dosing)<br><br>Median duration of treatment with gender-affirming hormones for transfemales was 5.8 years (range 3.0 to 8.0) and for transmales was 5.4 years (range 2.8 to 7.8).<br><br>The GnRH analogue was SC triptorelin 3.75 mg every 4 weeks.<br><br>No details of gonadectomy reported.<br><br>**Comparison**<br><br>No comparison group. Comparison over time reported. | **Critical outcomes**<br><br>No critical outcomes reported<br><br>**Important outcomes**<br><br>**Safety**<br><br>***Bone density: lumbar spine***<br><br>**Lumbar spine bone mineral apparent density (BMAD)**<br>Change from starting gender-affirming hormones to age 22 years in transfemales- Mean (SD); g/m$^3$<br>• Start of gender-affirming hormones: 0.22 (0.02)<br>• Age 22 years: 0.23 (0.03)<br>• p=0.003<br>z-score (range)<br>• Start of gender-affirming hormones: -0.90 (0.80)<br>• Age 22 years: -0.78 (1.03)<br>• No statistically significant difference<br>Change from starting gender-affirming hormones to age 22 years in transmales- Mean (SD); g/m$^3$<br>• Start of gender-affirming hormones: 0.24 (0.02)<br>• Age 22 years: 0.25 (0.28<br>• p=0.001<br>z-score (SD)<br>• Start of gender-affirming hormones: -0.50 (0.81)<br>• Age 22 years: -0.033 (0.95)<br>• p=0.002 | This study was appraised using the Newcastle-Ottawa tool for cohort studies.<br><br>**Domain 1: Selection domain**<br>1. b) somewhat representative<br>2. c) no-non exposed cohort<br>3. a) secure record*<br>4. b) no<br>**Domain 2: Comparability**<br>1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders<br>**Domain 3: Outcome**<br>1. b) record linkage<br>2. a) yes – mean duration of gender-affirming hormone treatment was 5.8 and 5.4 years.<br>3. c) follow-up rate variable across timepoints and no description of those lost<br><br>**Overall quality is assessed as poor**<br><br>Other comments: Within person comparison. Small numbers of participants in each subgroup. No |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| Gonadectomy took place between June 1998 and August 2012 | At the start of gender-affirming hormone treatment, in the transfemale subgroup the median Tanner P was 4 (IQR 2) and the median Tanner G was 12 (IQR 11). In the transmale subgroup the median Tanner B was 5 (IQR 2) and the median Tanner P was 5 (IQR 0). | | **Lumbar spine bone mineral density (BMD)**<br>Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m$^2$<br>• Start of gender-affirming hormones: 0.84 (0.11)<br>• Age 22 years: 0.93 (0.10)<br>• p<0.001<br>z-score (range)<br>• Start of gender-affirming hormones: -1.01 (0.98)<br>• Age 22 years: -1.36 (0.83)<br>• No statistically significant difference<br>Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m$^2$<br>• Start of gender-affirming hormones: 0.91 (0.10)<br>• Age 22 years: 0.99 (0.13)<br>• P<0.001<br>z-score (range)<br>• Start of gender-affirming hormones: -0.72 (0.99)<br>• Age 22 years: -0.33 (1.12)<br>• No statistically significant difference<br><br>***Bone density: femoral region, nondominant side***<br><br>**Femoral region, nondominant side BMAD**<br>Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m$^3$<br>• Start of gender-affirming hormones: 0.26 (0.04)<br>• Age 22 years: 0.28 (0.05)<br>• No statistically significant difference<br>z-score (SD) | concomitant treatments or comorbidities were reported.<br><br>Source of funding: None disclosed |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| | | | • Start of gender-affirming hormones: -1.57 (1.74)<br>• Age 22 years: Not reported<br>• No statistical analysis reported<br>Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m$^3$<br>• Start of gender-affirming hormones: 0.31 (0.04)<br>• Age 22 years: 0.33 (0.05)<br>• p=0.010<br>z-score (SD)<br>• Start of gender-affirming hormones: -0.28 (0.74)<br>• Age 22 years: Not reported<br>• No statistical analysis reported<br><br>**Femoral region, nondominant side BMD**<br>Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m$^2$<br>• Start of gender-affirming hormones: 0.87 (0.08)<br>• Age 22 years: 0.94 (0.11)<br>• P=0.009<br>z-score (SD)<br>• Start of gender-affirming hormones: -0.95 (0.63)<br>• Age 22 years: -0.69 (0.74)<br>• No statistically significant difference<br>Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m$^2$<br>• Start of gender-affirming hormones: 0.88 (0.09)<br>• Age 22 years: 0.95 (0.10)<br>• P<0.001<br>z-score (SD) | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| | | | • Start of gender-affirming hormones: -0.35 (0.79)<br>• Age 22 years: -0.35 (0.74)<br>• p=0.006 | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| **Full citation**<br>Kuper, Laura E, Stewart, Sunita, Preston, Stephanie et al. (2020) Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. Pediatrics 145(4)<br><br>**Study location**<br>Single centre, Texas, USA<br><br>**Study type**<br>Prospective longitudinal study<br><br>**Study aim**<br>To:<br>• explore how baseline body dissatisfaction, depression, and anxiety symptoms vary by gender, age at initial assessment, and | 148 children and adolescents with gender dysphoria, n=148, of whom:<br>• 25 received puberty suppression only<br>• 93 received gender-affirming hormone therapy only<br>• 30 received both<br>Results for treatments reported separately.<br><br>Mean age at initial assessment was 15.4 years (range 9 to 18).<br><br>Mean age at start of gender-affirming hormone therapy was 16.2 years (range 13.2 to 18.6).<br><br>All participants met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for gender | Hormone therapy, guided by Endocrine Society Clinical Practice Guidelines<br><br>Follow-up at least 18 months from initial assessment at the clinic.<br><br>Mean duration of gender-affirming hormone therapy before follow-up was 10.9 months (range 1 to 18; SD 3.3) | **Critical Outcomes**<br><br>***Impact on mental health***<br>Mean depression score, assessed using the Quick Inventory of Depressive Symptoms (QIDS), self-reported was 9.6 (SD 5.0) at baseline and 7.4 (SD 4.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant.<br><br>Mean depression score, assessed using the QIDS, clinician-reported was 5.9 (SD 4.1) at baseline and 6.0 (SD 3.8) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant.<br><br>Mean anxiety score, assessed using the Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire was 32.6 (SD 16.3) at baseline and 28.4 (SD 15.9) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming | This study was appraised using the Newcastle-Ottawa tool for cohort studies.<br><br>**Domain 1: Selection domain**<br>1. b) somewhat representative<br>2. c) no-non exposed cohort<br>3. a) secure record<br>4. b) no<br>**Domain 2: Comparability**<br>1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders<br>**Domain 3: Outcome**<br>1. d) assessors not blinded to treatment<br>2. a) yes – follow-up at least 18 months from initial assessment. Mean duration of gender-affirming hormone |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| Tanner stage at first medical visit<br>• examine how body dissatisfaction, depression, and anxiety symptoms change over the first year of gender-affirming hormone treatment<br>• explore how any changes vary by affirmed gender, Tanner stage, age, type of treatment, months on gender-affirming hormone therapy, mental health treatment received, and whether chest surgery was also obtained (among transmales).<br><br>**Study dates**<br>Initial participant assessments took place between August 2014 and March 2018. | dysphoria.<br><br>Specific inclusion and exclusion criteria for the study are not reported. It would appear that all children and adolescents eligible for gender-affirming hormones were considered eligible for the study. The authors state that before initial assessment with a psychologist, psychiatrist, and/or clinical therapist, parents completed a phone intake survey. Around one-third of families did not follow-up after the phone intake. | | hormones and it is unclear whether the change in score was statistically significant.<br><br>Mean panic score, assessed using specific questions from the SCARED questionnaire was 8.1 (SD 6.3) at baseline and 7.1 (SD 6.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant.<br><br>Mean generalised anxiety score, assessed using specific questions from the SCARED questionnaire was 10.0 (SD 5.1) at baseline and 8.8 (SD 6.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant.<br><br>Mean social anxiety score, assessed using specific questions from the SCARED questionnaire was 8.5 (SD 4.1) at baseline and 7.7 (SD 4.2) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant.<br><br>Mean separation anxiety score, assessed using specific questions from the SCARED questionnaire was 3.5 (SD 3.0) at baseline and 3.1 (SD 2.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender- | treatment was 10.9 months.<br>3. c) patient numbers vary by outcome with no explanation<br><br>**Overall quality is assessed as poor**<br><br>Other comments: None<br><br>Source of funding: Supported by Children's Health. The Research Electronic Data Capture database was funded by the Clinical and Translational Science Awards program |

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| | | | affirming hormones and it is unclear whether the change in score was statistically significant.<br><br>Mean school avoidance score, assessed using specific questions from the SCARED questionnaire was 2.6 (SD 2.1) at baseline and 2.0 (SD 2.0) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant.<br><br>The authors also reported results separately for transfemales and transmales:<br><br>**Transfemales** No statistical analyses were reported for this sub-group and it is unclear whether any changes in score were statistically significant.<br>• Mean depression symptoms, assessed using the QIDS, self-reported was 7.5 (SD 4.9) at baseline and 6.6 (SD 4.4) at follow-up.<br>• Mean depression symptoms, assessed using the QIDS, clinician-reported was 4.2 (SD 3.2) at baseline and 5.4 (SD 3.4) at follow-up.<br>• Mean anxiety symptoms, assessed using the SCARED questionnaire was 26.4 (SD 14.2) at baseline and 24.3 (SD 15.4) at follow-up.<br>• Mean panic symptoms, assessed using specific questions from the SCARED questionnaire was 5.7 (SD 4.9) at baseline and 5.1 (SD 4.9) at follow-up.<br>• Mean generalised anxiety symptoms, assessed using specific questions from | |

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| | | | the SCARED questionnaire was 8.6 (SD 5.1) at baseline and 8.0 (SD 5.1) at follow-up.<br>• Mean social anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 7.1 (SD 3.9) at baseline and 6.8 (SD 4.4) at follow-up.<br>• Mean separation anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 3.4 (SD 3.3) at baseline and 2.7 (SD 2.3) at follow-up.<br>• Mean school avoidance symptoms, assessed using specific questions from the SCARED questionnaire was 1.8 (SD 1.7) at baseline and 1.9 (SD 2.1) at follow-up.<br><br>**Transmales** No statistical analyses were reported for this sub-group and it is unclear whether any changes in score were statistically significant.<br>• Mean depression symptoms, assessed using the QIDS, self-reported was 10.4 (SD 5.0) at baseline and 7.5 (SD 4.5) at follow-up.<br>• Mean depression symptoms, assessed using the QIDS, clinician-reported was 6.7 (SD 4.4) at baseline and 6.2 (SD 4.1) at follow-up.<br>• Mean anxiety symptoms, assessed using the SCARED questionnaire was 35.4 (SD 16.5) at baseline and 29.8 (SD 15.5) at follow-up.<br>• Mean panic symptoms, assessed using specific questions from the SCARED questionnaire was 9.3 (SD 6.5) at baseline and 7.9 (SD 6.5) at follow-up. | |

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| | | | • Mean generalised anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 10.4 (SD 5.0) at baseline and 9.0 (SD 5.1) at follow-up.<br>• Mean social anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 8.5 (SD 4.0) at baseline and 7.8 (SD 4.1) at follow-up.<br>• Mean separation anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 4.2 (SD 3.4) at baseline and 3.4 (SD 2.6) at follow-up.<br>• Mean school avoidance symptoms, assessed using specific questions from the SCARED questionnaire was 2.6 (SD 2.1) at baseline and 2.0 (SD 2.0) at follow-up.<br><br>No difference in impact on mental health found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint.<br><br>**Important Outcomes**<br>***Impact on body image***<br>Mean Body Image Scale (BIS) score was 70.7 (SD 15.2) at baseline and 51.4 (SD 18.3) at follow-up. The authors do not present statistical analysis for this population and it is unclear whether the change in score was statistically significant. | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
|---|---|---|---|---|
| | | | The authors also reported body image results separately for transfemales and transmales. No statistical analyses were reported for this sub-groups and it is unclear whether changes in score were statistically significant.<br>• In transfemales, BIS score was 67.5 (SD 19.5) at baseline and 49.0 (SD 21.6) at follow-up.<br>• In transmales, BIS score was 71.1 (SD 13.4) at baseline and 52.9 (SD 16.8) at follow-up.<br><br>No difference in body image score found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint.<br><br>*No other critical or important outcomes reported* | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
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| **Study dates**<br>Lopez de Lara, D., Perez Rodriguez, O., Cuellar Flores, I. et al. (2020) Psychosocial assessment in transgender adolescents. Anales de Pediatria | 23 adolescents with gender dysphoria; 16 transmale and 7 transfemale.<br><br>Participants were required to be at a stage of pubertal development of Tanner 2 or higher. People with mental | Gender-affirming hormones-<br>• Oral oestradiol<br>• Intramuscular testosterone<br><br>Participants had previously received gonadotropin-releasing | **Critical Outcomes**<br>***Impact on gender dysphoria***<br>Following gender-affirming hormones for 12 months, mean (±SD) Utrecht Gender Dysphoria Scale (UGDS) score statistically | This study was appraised using the Newcastle-Ottawa tool for cohort studies.<br><br>**Domain 1: Selection domain**<br>1. b) somewhat representative<br>2. Not applicable – although a control group is reported |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
|---|---|---|---|---|
| **Study location**<br>Single centre in Madrid, Spain<br><br>**Study type**<br>Prospective analytical study<br><br>**Study aim**<br>To assess the psychosocial status of patients seeking care in the paediatric endocrinology clinic for gender dysphoria, and the impact on psychosocial status of gender-affirming hormone therapy at 12 months of treatment<br><br>**Study dates**<br>Not reported | health comorbidity that could affect the experience of gender dysphoria were excluded.<br><br>Mean age at baseline was 16 years (range 14 to 18).<br><br>30 cisgender controls, matched for age, ethnicity, and socioeconomic status | hormone (GnRH) analogues in the intermediate pubertal stages (Tanner 2---3). | significantly improved, from 57.1 (±4.1) at baseline to 14.7 (±3.2; p<0.001)<br><br>***Impact on mental health***<br>Mean depression score statistically significantly improved following treatment with gender-affirming hormones. Mean Beck Depression Inventory II (BDI-II) score (±SD) reduced from 19.3 points (±5.5) at baseline to 9.7 points (±3.9) at 12 months (p<0.001).<br><br>Mean anxiety scores statistically significantly improved following treatment with gender-affirming hormones. Mean (±SD) State-Trait Anxiety Inventory (STAI) State subscale score improved from 33.3 points (±9.1) at baseline to 16.8 points (±8.1) at 12 months (p<0.001). Mean (±SD) State-Trait Anxiety Inventory (STAI) Trait subscale score improved from 33.0 points (±7.2) at baseline to 18.5 points (±8.4) at 12 months (p<0.001).<br><br>**Important Outcomes**<br>***Psychosocial Impact***<br>There was not change in family functioning, measured using the Family APGAR test, from baseline (17.9 points) to 1 year after starting gender-affirming hormones (18.0 points; no statistical analysis reported).<br><br>Results from the Strengths and Difficulties Questionnaire, Spanish Version (SDQ-Cas) showed statistically significant improvements from baseline (14.7 points; SD±3.3) to 12 | on, people in this group did not have gender dysphoria.<br>3. a) secure record*<br>4. b) no<br>**Domain 2: Comparability**<br>1. Not applicable – although a control group is reported on, people in this group did not have gender dysphoria.<br>**Domain 3: Outcome**<br>1. d) assessors not blinded to treatment<br>2. a) yes – 12 months treatment with gender-affirming hormones<br>3. a) complete follow up - all subjects accounted for<br><br>**Overall quality is assessed as poor**<br><br>Other comments: None<br><br>Source of funding: Not reported |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
|---|---|---|---|---|
| | | | months after gender-affirming hormones (10.3 points; SD±2.9; p<0.001)<br><br>*No other critical or important outcomes reported* | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
|---|---|---|---|---|
| **Full citation**<br>Stoffers, Iris E; de Vries, Martine C; Hannema, Sabine E (2019) Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. The journal of sexual medicine 16(9): 1459-1468<br><br>**Study location**<br>Single centre, Leiden, Netherlands<br><br>**Study type**<br>Retrospective chart review<br><br>**Study aim**<br>To report changes in height, BMI, blood pressure, laboratory parameters and bone density.<br><br>**Study dates**<br>November 2010 to August 2018 | 62 transmales with gender dysphoria. participants were required to have been receiving testosterone therapy for at least 6 months. Further inclusion or exclusion criteria not reported.<br><br>Gender dysphoria was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria.<br>. | Testosterone intramuscular injection (Sustanon 250 mg). Dose escalated every 6 months up to the standard adult dose of 125 mg every 2 weeks or 250 mg every 3-4 weeks. A more rapid dose escalation was using in patients who started GnRH analogue treatment at 16 years or older.<br><br>Median age at start of testosterone treatment was 17.2 years (range 14.9 to 18.4)<br><br>Median duration of testosterone treatment was 12 months (range 5 to 33)<br><br>Median duration of GnRH analogue treatment was 8 months (range 3 to 39) | **Critical Outcomes**<br><br>No critical outcomes assessed.<br><br>**Important outcomes**<br><br>***Safety***<br><br>***Bone mineral density (BMD): lumbar spine***<br>There was no statistically significant difference in lumber spine bone mineral density (BMD) from start of testosterone treatment to any timepoint, up to 24 months follow-up.<br>Mean (±SD), g/cm$^2$:<br>• Start of testosterone: 0.90 (±0.11)<br>• 6 months: 0.94 (±0.10)<br>• 12 months: 0.95 (±0.09)<br>• 24 months: 0.95 (±0.11)<br>z-score (±SD):<br>• Start of testosterone: -0.81 (±1.02)<br>• 6 months: -0.67 (±0.95)<br>• 12 months: -0.66 (±0.81)<br>• 24 months: -0.74 (±1.17)<br><br>***Bone mineral density (BMD): femoral neck (hip)***<br>There was no statistically significant difference in right or left femoral neck (hip) bone mineral density (BMD) from start of | This study was appraised using the Newcastle-Ottawa tool for cohort studies.<br><br>**Domain 1: Selection domain**<br>1. b) somewhat representative<br>2. c) no-non exposed cohort<br>3. a) secure record*<br>4. b) no<br>**Domain 2: Comparability**<br>1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders<br>**Domain 3: Outcome**<br>1. b) record linkage<br>2. a) yes – mean duration of gender-affirming hormone treatment was 5.8 and 5.4 years.<br>3. a) complete follow up - all subjects accounted for<br><br>**Overall quality is assessed as poor**<br><br>Other comments: None<br><br>Source of funding: None |

| | | | | |
|---|---|---|---|---|
| | | | testosterone treatment to any timepoint, up to 24 months follow-up.<br>**Right**<br>Mean (±SD), g/cm$^2$:<br>• Start of testosterone: 0.77 (±0.08)<br>• 6 months: 0.84 (±0.11)<br>• 12 months: 0.82 (±0.08)<br>• 24 months: 0.85 (±0.11)<br>z-score (±SD):<br>• Start of testosterone: -0.97 (0.79)<br>• 6 months: -0.54 (±0.96)<br>• 12 months: -0.80 (±0.69)<br>• 24 months: -0.31 (±0.84)<br>**Left**<br>Mean (±SD), g/cm$^2$:<br>• Start of testosterone: 0.76 (±0.09)<br>• 6 months: 0.83 (±0.12)<br>• 12 months: 0.81 (±0.08)<br>• 24 months: 0.86 (±0.09)<br>z-score (±SD):<br>• Start of testosterone: -1.07 (0.85)<br>• 6 months: -0.62 (±1.12)<br>• 12 months: -0.93 (±0.63)<br>• 24 months: -0.20 (±0.70)<br><br>***Other safety-related outcomes***<br>• Alkaline phosphatase: statistically significant increases observed from start of testosterone treatment to 6 months and 12 months ($p<0.001$), although difference at 24 months was not statistically significant. Median (IQR), U/L<br>○ Start of testosterone: 102 (78 to 136)<br>○ 6 months: 115 (102 to 147)<br>○ 12 months: 112 (88 to 143)<br>○ 24 months: 81 (range 69 to 98)<br>• Creatinine: statistically significant increases observed from start of testosterone treatment to 6, 12 and | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
|---|---|---|---|---|
| | | | 24 months (p<0.001). Mean (±SD), umol/L<br>○ Start of testosterone: 62 (±7)<br>○ 6 months: 70 (±9)<br>○ 12 months: 74 (±10)<br>○ 24 months: 81 (±10)<br><br>There was no statistically significant change from start of testosterone treatment in:<br>• HbA1c<br>• Aspartate aminotransferase (AST)<br>• Alanine aminotransferase (ALT)<br>• Gamma-glutamyl transferase<br>• Urea<br>Numerical results, follow-up duration and further details of statistical analysis not reported. | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
|---|---|---|---|---|
| **Full citation**<br>Vlot MC, Klink DT, den Heijer M et al. (2017) Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone 95: 11-19<br><br>**Study location**<br>Single centre, Amsterdam, Netherlands<br><br>**Study type**<br>Retrospective chart review<br><br>**Study aim**<br>To investigate the impact of GnRH analogues and gender-affirming hormones on bone mineral apparent density (BMAD) in transgender adolescents. The study also report on levels of bone turnover markers, although the authors concluded that the | 70 adolescents with gender dysphoria (42 transmales and 28 transfemales).<br><br>Median age (range) at the start of gender-affirming hormones was 16.3 years (15.9 to 19.5) for transmales and 16.0 years (14.0 to 18.9) for transfemales.<br><br>Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who received GnRH analogues and then gender-affirming hormones.<br><br>No concomitant treatments were reported.<br><br>The study categorised participants into a young and old pubertal group, based on their bone age. The young transmales had a bone age of <14 years and the old transmales had a bone age of ≥14 years. The young transfemales group had a bone age of | Transfemales:<br>Oestradiol oral<br>Dose escalated every 6 months until standard adult dose of 2 mg daily was reached<br><br>Transmales:<br>Testosterone intramuscular injection (Sustanon 250 mg).<br>Dose escalated every 6 months up to the standard adult dose of 250 mg every 4 weeks or 250 mg every 3-4 weeks.<br><br>All participants previously received a GnRH analogue (triptorelin 3.75 mg subcutaneously every 4 weeks)<br><br>Median duration of GnRH analogue therapy not reported. | **Critical outcomes**<br><br>No critical outcomes reported<br><br>**Important outcomes**<br><br>***Bone density: lumbar spine***<br><br>**Lumbar spine bone mineral apparent density (BMAD)**<br><br>Transfemales (bone age <15 years), change from starting gender-affirming hormones to 24 months follow-up.<br>Median (range), g/m$^3$<br>• Start of gender-affirming hormones (C0): 0.20 (0.18 to 0.24)<br>• 24-month follow-up (C24): 0.22 (0.19 to 0.27)<br>• Statistically significant increase (p≤0.01)<br>z-score (range)<br>• Start of gender-affirming hormones (C0): -1.52 (-2.36 to 0.42)<br>• 24-month follow-up (C24):<br>• Statistically significant increase (p≤0.05)<br><br>Transfemales (bone age ≥15 years), change from starting gender-affirming hormones to 24 months follow-up.<br>Median (range), g/m$^3$<br>• Start of gender-affirming hormones: 0.22 (0.19 to 0.24)<br>• 24-months: 0.23 (0.21 to 0.26)<br>• Statistically significant increase (p≤0.05)<br>z-score (range)<br>• Start of gender-affirming hormones: -1.15 (-2.21 to 0.08)<br>• 24-months: -0.66 (-1.66 to 0.54) | This study was appraised using the Newcastle-Ottawa tool for cohort studies.<br><br>**Domain 1: Selection domain**<br>1. b) somewhat representative<br>2. c) no-non exposed cohort<br>3. a) secure record*<br>4. b) no<br>**Domain 2: Comparability**<br>1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders<br>**Domain 3: Outcome**<br>1. b) record linkage<br>2. a) yes- 24 month follow-up<br>3. a) complete follow up - all subjects accounted for<br><br>**Overall quality is assessed as poor.**<br><br>Other comments: None<br><br>Source of funding: grant from Abbott diagnostics |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
|---|---|---|---|---|
| added value of these seems to be limited.<br><br>**Study dates**<br>Participants started gender-affirming therapy between 2001 and 2011 | <15 years and the old transfemales group ≥15 years. | | Statistically significant increase (p≤0.05)<br><br>Transmales (bone age <14 years), change from starting gender-affirming hormones to 24 months follow-up.<br>Median (range), g/m$^3$<br>• Start of gender-affirming hormones: 0.23 (0.19 to 0.28)<br>• 24-months: 0.25 (0.22 to 0.28)<br>• Statistically significant increase (p≤0.01)<br>z-score (range)<br>• Start of gender-affirming hormones: -0.84 (-2.2 to 0.87)<br>• 24-months: -0.15 (-1.38 to 0.94)<br>Statistically significant increase (p≤0.01)<br><br>Transmales (bone age ≥14 years), change from starting gender-affirming hormones to 24 months follow-up.<br>Median (range), g/m$^3$<br>• Start of gender-affirming hormones: 0.24 (0.20 to 0.28)<br>• 24-months: 0.25 (0.21 to 0.30)<br>• Statistically significant increase (p≤0.01)<br>z-score (range)<br>• Start of gender-affirming hormones: -0.29 (-2.28 to 0.90)<br>• 24-months: -0.06 (-1.75 to 1.61)<br>Statistically significant increase (p≤0.01)<br><br>***Bone density: femoral neck***<br><br>**Femoral neck BMAD**<br><br>Transfemales (bone age <15 years), change from starting gender-affirming hormones to 24 months follow-up.<br>Median (range), g/m$^3$ | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
|---|---|---|---|---|
| | | | • Start of gender-affirming hormones: 0.27 (0.20 to 0.33)<br>• 24-months: 0.27 (0.20 to 0.36)<br>• No statistically significant change<br>z-score (range)<br>• Start of gender-affirming hormones: -1.32 (-3.39 to 0.21)<br>• 24-months: -1.30 (-3.51 to 0.92)<br>• No statistically significant change<br><br>Transfemales (bone age ≥15 years), change from starting gender-affirming hormones to 24 months follow-up.<br>Median (range), g/m$^3$<br>• Start of gender-affirming hormones: 0.30 (0.26 to 0.34)<br>• 24-months: 0.29 (0.24 to 0.38)<br>• No statistically significant change<br>z-score (range)<br>• Start of gender-affirming hormones: -0.36 (-1.50 to 0.46)<br>• 24-months: -0.56 (-2.17 to 1.29)<br>• No statistically significant change<br><br>Transmales (bone age <14 years), change from starting gender-affirming hormones to 24 months follow-up.<br>Median (range), g/m$^3$<br>• Start of gender-affirming hormones: 0.30 (0.22 to 0.35)<br>• 24-months: 0.33 (0.23 to 0.37)<br>• Statistically significant increase (p≤0.01)<br>z-score (range)<br>• Start of gender-affirming hormones: -0.37 (-2.28 to 0.47)<br>• 24-months: -0.37 (-2.03 to 0.85) | |

| Study details | Population | Interventions | Study outcomes | Appraisal and Funding |
|---|---|---|---|---|
| | | | • Statistically significant increase (p≤0.01)<br><br>Transmales (bone age ≥14 years), change from starting gender-affirming hormones to 24 months follow-up.<br>• Start of gender-affirming hormones: 0.30 (0.23 to 0.41)<br>• 24-months: 0.32 (0.23 to 0.41)<br>• Statistically significant increase (p≤0.01)<br>z-score (range)<br>• Start of gender-affirming hormones: -0.27 ((-1.91 to 1.29)<br>• 24-months: 0.02 (-2.1 to 1.35)<br>• Statistically significant increase (p≤0.05) | |

## Appendix F Quality appraisal checklists

### *Newcastle-Ottawa Quality Assessment Form for Cohort Studies*

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

**Selection**

1) Representativeness of the exposed cohort
    a) Truly representative (one star)
    b) Somewhat representative (one star)
    c) Selected group
    d) No description of the derivation of the cohort
2) Selection of the non-exposed cohort
    a) Drawn from the same community as the exposed cohort (one star)
    b) Drawn from a different source
    c) No description of the derivation of the non exposed cohort
3) Ascertainment of exposure
    a) Secure record (e.g., surgical record) (one star)
    b) Structured interview (one star)
    c) Written self report
    d) No description
    e) Other
4) Demonstration that outcome of interest was not present at start of study
    a) Yes (one star)
    b) No

**Comparability**

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
    a) The study controls for age, sex and marital status (one star)
    b) Study controls for other factors (list) _____ (one star)
    c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

**Outcome**

1) Assessment of outcome
    a) Independent blind assessment (one star)
    b) Record linkage (one star)
    c) Self report
    d) No description
    e) Other
2) Was follow-up long enough for outcomes to occur
    a) Yes (one star)
    b) No
    Indicate the median duration of follow-up and a brief rationale for the assessment above:_____
3) Adequacy of follow-up of cohorts
    a) Complete follow up- all subject accounted for (one star)

b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one star)
c) Follow up rate less than 80% and no description of those lost
d) No statement

*Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):*
**Good quality:** 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
**Fair quality**: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
**Poor quality:** 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

## Appendix G Grade profiles

**Table 2: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? - Gender dysphoria**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| ***Impact on gender dysphoria (1 uncontrolled, prospective observational study)*** | | | | | | | | | |
| ***Change from baseline in mean gender dysphoria score, measured using the UGDS (duration of treatment 12 months). Higher scores indicate greater gender dysphoria.*** | | | | | | | | | |
| 1 cohort study Lopez de Lara et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=23 | None | T0 (baseline) = 57.1 (SD 4.1) T1 (12 months) = 14.7 (SD 3.2) Statistically significant improvement, p<0.001 | Critical | VERY LOW |

**Abbreviations:** p: p-value; SD: standard deviation; UGDS: Utrecht Gender Dysphoria Scale

*1 Downgraded 1 level - the cohort study by Lopez de Lara et al. 2020 was assessed at high risk of bias (poor quality overall; lack of blinding and no control group)*

**Table 3: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Mental health**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of events | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| ***Impact on mental health (3 uncontrolled, prospective observational studies and 2 uncontrolled, retrospective observational studies)*** | | | | | | | | | |
| ***Change from baseline in mean depression score, measured using the BDI-II (duration of treatment 12 months). Higher scores indicate more severe depression.*** | | | | | | | | | |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of events | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| 1 cohort study Lopez de Lara et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=23 | None | T0 (baseline) = 19.3 (SD 5.5)<br>T1 (12 months) = 9.7 (SD 3.9)<br>Statistically significant improvement, p<0.001 | Critical | VERY LOW |
| ***Change from baseline in mean depression score, measured using the CESD-R (approximately 12-month follow-up). Higher scores indicate more severe depression.*** | | | | | | | | | |
| 1 cohort study Achille et al. 2020 | Serious limitations[2] | Serious indirectness[3] | No serious inconsistency | Not calculable | N=50 | None | Wave 1 (baseline) = 21.4<br>Wave 3 (approx. 12 months) = 13.9<br>Statistically significant improvement (p<0.001) | Critical | VERY LOW |
| ***Change from baseline in depression score, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up). Higher scores indicate more severe depression.*** | | | | | | | | | |
| 1 cohort study Achille et al. 2020 | Serious limitations[2] | Serious indirectness[3] | No serious inconsistency | Not calculable | N=50 | None | Statistically significant reductions in mean score, p<0.001<br>Results presented diagrammatically, numerical results for mean score not reported | Critical | VERY LOW |
| ***Change from baseline in depression symptoms, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[4] | No serious indirectness | No serious inconsistency | Not calculable | N=105 | None | Baseline = 9.6 (SD 5.0)<br>Follow-up = 7.4 (SD 4.5)<br>No statistical analysis reported for the sub-group of participants receiving gender-affirming hormones | Critical | VERY LOW |
| ***Change from baseline in depression symptoms, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.*** | | | | | | | | | |
| 1 cohort study | Serious limitations[4] | No serious indirectness | No serious inconsistency | Not calculable | N=106 | None | Baseline = 5.9 (SD 4.1)<br>Follow-up = 6.0 (SD 3.8) | Critical | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of events | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| Kuper et al. 2020 | | | | | | | No statistical analysis reported for the sub-group of participants who received gender-affirming hormones | | |
| ***Need for treatment due to depression, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[7] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During and before gender identity assessment 54% (28/52) During real life phase 15% (8/52) Statistically significant reduction (p<0.001) | Critical | VERY LOW |
| ***Change from baseline in anxiety score, measured using the STAI-State subscale (duration of treatment 12 months). Higher scores indicate more severe anxiety.*** | | | | | | | | | |
| 1 cohort study Lopez de Lara et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=23 | None | T0 (baseline) = 33.3 (SD 9.1) T1 (12 months) = 16.8 (SD 8.1) Statistically significant improvement, p<0.001 | Critical | VERY LOW |
| ***Change from baseline in anxiety score, measured using the STAI-Trait subscale (duration of treatment 12 months). Higher scores indicate more severe anxiety.*** | | | | | | | | | |
| 1 cohort study Lopez de Lara et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=23 | None | T0 (baseline) = 33.0 (SD 7.2) T1 (12 months) = 18.5 (SD 8.4) Statistically significant improvement, p<0.001 | Critical | VERY LOW |
| ***Change from baseline in anxiety symptoms, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[4] | No serious indirectness | No serious inconsistency | Not calculable | N=80 | None | Baseline = 32.6 (SD 16.3) Follow-up = 28.4 (SD 15.9) No statistical analysis reported for the sub-group of participants | Critical | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of events | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| | | | | | | | who received gender-affirming hormones | | |
| ***Change from baseline in panic symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[4] | No serious indirectness | No serious inconsistency | Not calculable | N=82 | None | Baseline = 8.1 (SD 6.3)<br>Follow-up = 7.1 (SD 6.5)<br>No statistical analysis reported for the sub-group of participants who received gender-affirming hormones | Critical | VERY LOW |
| ***Change from baseline in generalised anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[4] | No serious indirectness | No serious inconsistency | Not calculable | N=82 | None | Baseline = 10.0 (SD 5.1)<br>Follow-up = 8.8 (SD 5.0)<br>No statistical analysis reported for the sub-group of participants who received gender-affirming hormones | Critical | VERY LOW |
| ***Change from baseline in social anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[4] | No serious indirectness | No serious inconsistency | Not calculable | N=82 | None | Baseline = 8.5 (SD 4.1)<br>Follow-up = 7.7 (SD 4.2)<br>No statistical analysis reported for the sub-group of participants who received gender-affirming hormones | Critical | VERY LOW |
| ***Change from baseline in separation anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[4] | No serious indirectness | No serious inconsistency | Not calculable | N=81 | None | Baseline = 3.5 (SD 3.0)<br>Follow-up = 3.1 (SD 2.5)<br>No statistical analysis reported for the sub-group of participants | Critical | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of events | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| | | | | | | | who received gender-affirming hormones | | |
| ***Change from baseline in school avoidance, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[4] | No serious indirectness | No serious inconsistency | Not calculable | N=80 | None | Baseline = 2.6 (SD 2.1) Follow-up = 2.0 (SD 2.0) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones | Critical | VERY LOW |
| ***Need for treatment due to anxiety, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[7] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During and before gender identity assessment 48% (25/52) During real life phase 15% (8/52) Statistically significant reduction (p<0.001) | Critical | VERY LOW |
| ***Change from baseline in adjusted mean suicidality score, measured using the ASQ instrument (mean treatment duration 349 days). Higher scores indicate a greater degree of suicidality.*** | | | | | | | | | |
| 1 cohort study Allen et al. 2019 | Serious limitations[5] | No serious indirectness | No serious inconsistency | Not calculable | N=39 | None | T0 (baseline) = 1.11 (SE 0.22) T1 (final assessment) = 0.27 (SE 0.12) Statistically significant improvement in score from T0 to T1, p<0.001 | Critical | VERY LOW |
| ***Change from baseline in percentage of participants with suicidal ideation, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)*** | | | | | | | | | |
| 1 cohort study Achille et al. 2020 | Serious limitations[2] | Serious indirectness[3] | No serious inconsistency | Not calculable | N=50 | None | Wave 1 (baseline) = 10% (5/50) Wave 3 (approx. 12 months) = 6% (3/50) | Critical | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of events | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| | | | | | | | No statistical analysis reported | | |
| ***Change from baseline in suicidal ideation (passive), information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[4] | Serious indirectness [6] | No serious inconsistency | Not calculable | N=130 | None | Lifetime = 81% (105 people) 1 month before initial assessment = 25% (33 people) Follow-up period = 38% (51 people) No statistical analysis reported | Critical | VERY LOW |
| ***Change from baseline in suicide attempts, information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[4] | Serious indirectness[6] | No serious inconsistency | Not calculable | N=130 | None | Lifetime = 15% (20 people) 3 months before initial assessment = 2% (3 people) Follow-up period = 5% (6 people) No statistical analysis reported | Critical | VERY LOW |
| ***Change from baseline in non-suicidal self-injury, information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[4] | Serious indirectness[6] | No serious inconsistency | Not calculable | N=130 | None | Lifetime = 52% (68 people) 3 months before initial assessment = 10% (13 people) Follow-up period = 17% (23 people) No statistical analysis reported | Critical | VERY LOW |
| ***Need for treatment due to suicidality / self-harm, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[7] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During and before gender identity assessment 35% (18/52) During real life phase | Critical | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of events | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| | | | | | | | 4% (2/52)<br>Statistically significant reduction (p<0.001) | | |
| ***Need for mental health treatment, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[7] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During and before gender identity assessment<br>50% (26/52)<br>During real life phase<br>46% (24/51)<br>No statistically significant difference (p= 0.77) | Critical | VERY LOW |
| ***Need for treatment due to conduct problems / antisocial, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[7] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During and before gender identity assessment<br>14% (7/52)<br>During real life phase<br>6% (3/52)<br>No statistically significant difference (p= 0.18) | Critical | VERY LOW |
| ***Need for treatment due to psychotic symptoms or psychosis, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[7] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During and before gender identity assessment<br>2% (1/52)<br>During real life phase<br>4% (2/52)<br>No statistically significant difference (p= 0.56) | Critical | VERY LOW |
| ***Need for treatment due to substance abuse, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)*** | | | | | | | | | |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of events | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[7] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During and before gender identity assessment 4% (2/52) During real life phase 2% (1/52) No statistically significant difference (p= 0.56) | Critical | VERY LOW |
| ***Need for treatment due to autism, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[7] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During and before gender identity assessment 12% (6/52) During real life phase 6% (3/52) No statistically significant difference (p= 0.30) | Critical | VERY LOW |
| ***Need for treatment due to ADHD, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[7] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During and before gender identity assessment 10% (5/52) During real life phase 2% (1/52) No statistically significant difference (p= 0.09) | Critical | VERY LOW |
| ***Need for treatment due to eating disorder, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[7] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During and before gender identity assessment 2% (1/52) | Critical | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of events | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| | | | | | | | During real life phase<br>2% (1/52)<br><br>No statistically significant difference (p=1.0) | | |

**Abbreviations:** ADHD: attention deficit hyperactivity disorder; ASQ: Ask Suicide-Screening Questions; CESD-R: Center for Epidemiologic Studies Depression Scale; BDI-II: Beck Depression Inventory II (BDI-II); p: p-value; PHQ 9_Modified for Teens: Patient Health Questionnaire Modified for Teens; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation; STAI: State-Trait Anxiety Inventory

*1 Downgraded 1 level - the cohort study by Lopez de Lara et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).*
*2 Downgraded 1 level - the cohort study by Achille et al (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).*
*3 Serious indirectness in Achille 2020- Outcome reported for full study cohort, of whom 30% were taking no treatment or puberty suppression alone at follow-up. Results for people taking gender-affirming hormones not reported separately.[4] Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality).*
*5 Downgraded 1 level - the cohort study by Allen et al. (2019) was assessed at high risk of bias (poor quality; lack of blinding and no control group).*
*6 Serious indirectness in Kuper et al. 2020- Outcome reported for full study cohort, of whom approximately 17% received puberty suppression alone and did not receive gender-affirming hormones*
*7 Downgraded 1 level - the cohort study by Kaltiala et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).*

**Table 4: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Quality of life**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| ***Impact on quality of life (1 uncontrolled, prospective observational study and 1 uncontrolled, retrospective observational study)*** | | | | | | | | | |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| ***Change from baseline in mean quality of life score, measured using the QLES-Q-SF) (approximately 12-month follow-up). Higher scores indicated better quality of life.*** | | | | | | | | | |
| 1 cohort study Achille et al. 2020 | Serious limitations[1] | Serious indirectness[2] | No serious inconsistency | Not calculable | N=50 | None | Numerical improvements in mean score reported from wave 1 (baseline) to wave 3 (approx. 12 months), but difference not statistically significant (p = 0.085)<br>Results presented diagrammatically, numerical results for mean score not reported | Critical | VERY LOW |
| ***Change from baseline in adjusted mean well-being score, measured using the GWBS of the Pediatric Quality of Life Inventory (mean treatment duration 349 days). Higher scores indicated better well-being.*** | | | | | | | | | |
| 1 cohort study Allen et al. 2019 | Serious limitations[3] | No serious indirectness | No serious inconsistency | Not calculable | N=39 | None | T0 (baseline) = 61.70 (SE 2.43)<br>T1 (final assessment) = 70.23 (SE 2.15)<br>Statistically significant improvement in well-being score, p<0.002 | Critical | VERY LOW |

**Abbreviations:** GWBS: General Well-Being Scale; p: p-value; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire; SE: standard error

*1 Downgraded 1 level - the cohort study by Achille et al (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).*
*2 Serious indirectness in Achille et al. 2020 - Outcome reported for full study cohort, of whom 30% were taking no treatment or puberty suppression alone at follow-up. Results for people taking gender-affirming hormones not reported separately.*
*3 Downgraded 1 level - the cohort study by Allen et al. (2019) was assessed at high risk of bias (poor quality; lack of blinding and no control group).*

**Table 5: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Body image**

| QUALITY | Summary of findings | IMPORTANCE | CERTAINTY |
|---|---|---|---|

| | | | | | No of patients | | Effect | | |
|---|---|---|---|---|---|---|---|---|---|
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result | | |
| **Impact on body image *(1 uncontrolled, prospective observational study)*** | | | | | | | | | |
| ***Change from baseline in mean body image, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=86 | None | Baseline = 70.7 (SD 15.2)<br>Follow-up = 51.4 (SD 18.3)<br>No statistical analysis reported for the sub-group of participants who received gender-affirming hormones | Important | VERY LOW |

**Abbreviations:** BIS: Body Image Scale; p: p-value; SD: standard deviation

*1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).*

**Table 6: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Psychological impact**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Psychosocial Impact (1 uncontrolled, prospective observational study and 1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Change from baseline in family functioning, measured using the Family APGAR test. Higher scores suggest more family dysfunction.*** | | | | | | | | | |
| 1 cohort study Lopez de Lara et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=23 | None | T0 (baseline) = 17.9<br>T1 (12 months) = 18.0<br>No statistical analysis reported | Important | VERY LOW |
| ***Change from baseline in mean patient strengths and difficulties score, measured using the SDQ, Spanish Version (total difficulties score) (duration of treatment 12 months). Higher scores suggest the presence of a behavioural disorder.*** | | | | | | | | | |
| 1 cohort study | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=23 | None | T0 (baseline) = 14.7 (SD 3.3)<br>T1 (12 months) = 10.3 (SD 2.9) | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| Lopez de Lara et al. 2020 | | | | | | | Statistically significant improvement p<0.001 | | |
| ***Functioning in adolescent development: Living with parent(s)/ guardians[2] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland). Not living with parent(s) or guardian in your early 20s is a marker of age-appropriate functioning in Finnish culture.*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[3] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During gender identity assessment = 73% (38/52) During real life phase = 40% (21/50) Statistically significant reduction (p=0.001) | Important | VERY LOW |
| ***Functioning in adolescent development: Normative peer contacts[4] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[3] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During gender identity assessment = 89% (46/52) During real life phase = 81% (42/52) Statistically significant reduction (p<0.001) | Important | VERY LOW |
| ***Functioning in adolescent development: Progresses normatively in school/ work[5] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[3] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During gender identity assessment = 64% (33/52) During real life phase = 60% (31/52) No statistically significant difference (p=0.69) | Important | VERY LOW |
| ***Functioning in adolescent development: Has been dating or had steady relationships[6] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)*** | | | | | | | | | |
| 1 cohort study | Serious limitations[3] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During gender identity assessment = 62% (32/50) | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| Kaltiala et al. 2020 | | | | | | | During real life phase = 58% (30/52)<br>No statistically significant difference (p=0.51) | | |
| ***Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home[7] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[2] | No serious indirectness | No serious inconsistency | Not calculable | N=52 | None | During gender identity assessment = 81% (42/52)<br>During real life phase = 81% (42/52)<br>No statistically significant difference (p=1.00) | Important | VERY LOW |

**Abbreviations:** APGAR: Adaptability, Partnership, Growth, Affection and Resolve; p: p-value; SD: standard deviation; SDQ: Strengths and Difficulties Questionnaire

*1 Downgraded 1 level - the cohort study by Lopez de Lara et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).*
*2 Living arrangements were classified as (1) living with at least one parent/guardian, (2) living in a boarding school, with an adult relative, in some form of supported accommodation or the like, where supervision and guidance by a responsible adult is provided, (3) independently alone or in a shared household with a peer, (4) with a romantic partner. In the analyses dichotomised living arrangements as (a) parent(s)/guardian(s) vs. in other arrangements.*
*3 Downgraded 1 level - the cohort study by Kaltiala et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).*
*4 Peer relationships were classified as: (1) socialises with friends in leisure time, outside of activities supervised by adults, (2) socialises with peers only at school or in the context of rehabilitative activity, (3) spends time close to peers, for example in school or rehabilitative activity, but does not connect with them, (4) does not meet peers at all. In the analyses, peer relationships during (a) gender identity assessment and (b) the real-life phase were dichotomized to age-appropriate (normative) (1) vs. restricted or lacking (2–4).*
*5 School/work participation was classified as (1) age appropriate participation in mainstream curriculum, progresses without difficulties, (2) participates in mainstream curriculum with difficulty, (3) participates in rehabilitative educational or work activity, (4) not involved in education and working life. Age-appropriate participation during (1) was recorded if the adolescent attended mainstream secondary education or upper secondary education at a regular rate (a class per year in comprehensive school; has not changed more than once between tracks in upper secondary education) or had proceeded to work life after completing vocational education. Participation with difficulty (2) was recorded if the adolescent was enrolled in mainstream education but had to repeat a class, studied with special arrangements (for example, in a special small group), or followed some form of adjusted curriculum. In the analyses, school/work life during (a) gender identity assessment and (b) real-life phase was dichotomised to normative (1) vs. any other (2, 3 or 4).*
*6 Romantic involvement was recorded (1) has or has had a dating or steady relationship, not only online, (2) has had a romantic relationship only online, (3) has not had dating or steady relationships. In the analyses we compared has or has had (1) vs. has not had (2,3) a dating or steady relationship during (a) gender identity assessment and (b) real-life phase. Sexual history was recorded in more detail in case histories during gender identity assessment, and for this period we also collected the experiences of (French) kissing (yes/no), intercourse (yes/no) and experience of any genitally intimate contact with a partner (petting under clothes or naked, intercourse, oral sex) (yes/no).*

*7 In recording age-appropriate competence in managing everyday matters it was expected that early adolescents (up to 14 years) would be able, for example, to do shopping and travel alone on local public transport, and to help with household duties assigned by their parents. Middle adolescents (15–17 years) were further assumed, for example, to be able make telephone calls in matters important to them (for example, when seeking a summer job), to deal with school-related issues with school personnel without parental participation, to select and start new hobbies independently and to fulfil their role in summer jobs and in similar responsibilities of young people. Late adolescents (18 years and over), legally adults, were expected to have, in addition to the above, competence to talk to authorities such as professionals in health and social services, employment or educational institutions, to deal with banks or health insurance, to manage their financial issues and to manage their housekeeping if they chose to move to live independently of parents/guardians. Competence in managing everyday matters was recorded as follows: (1) the adolescent is able to cope age appropriately outside home, (2) the adolescent needs support in age-appropriate matters outside home but functions age-appropriately in the home (manages her/his own hygiene, clothing and nutrition, participates in (younger subjects) or takes responsibility for (older subjects) housekeeping) and (3) the adolescent's functioning is inadequate both at home and outside home. For the analyses, participants were determined to be able to age-appropriately able cope with matters outside of the home (1) vs. not (2,3).*

**Table 7: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Bone density**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Lumbar spine bone mineral apparent density (BMAD) (2 uncontrolled, retrospective observational studies)*** | | | | | | | | | |
| ***Change from start of gender-affirming hormones to age 22 years in lumber spine BMAD in transfemales*** | | | | | | | | | |
| 1 cohort study Klink et al. 2015 | Serious limitations[1] | Serious indirectness[2] | Not applicable | Not calculable | N=13 (Mean)<br>N=14 (z-score) | None | Mean (SD), g/m$^3$<br>Start of gender-affirming hormones: 0.22 (0.02)<br>Age 22 years: 0.23 (0.03)<br>P=0.003<br><br>z-score (SD)<br>Start of gender-affirming hormones: -0.90 (0.80)<br>Age 22 years: -0.78 (1.03)<br>No statistically significant difference | Important | VERY LOW |
| ***Change from baseline in lumbar spine BMAD in transfemales with a bone age less than 15 years ('young'; 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study Vlot et al. 2017 | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=15 | None | Median (range), g/m$^3$<br>Start of gender-affirming hormones (C0): 0.20 (0.18 to 0.24) | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| | | | | | | | 24-month follow-up (C24): 0.22 (0.19 to 0.27)<br>Statistically significant increase (p≤0.01)<br><br>z-score (range)<br>Start of gender-affirming hormones (C0): -1.52 (-2.36 to 0.42)<br>24-month follow-up (C24): -1.10 (-2.44 to 0.69)<br>Statistically significant increase (p≤0.05) | | |
| ***Change from baseline in lumbar spine BMAD in transfemales with a bone age of 15 years or more ('old'; 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study<br>Vlot et al. 2017 | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=5 | None | Median (range), g/m$^3$<br>Start of gender-affirming hormones (C0): 0.22 (0.19 to 0.24)<br>24-month follow-up (C24): 0.23 (0.21 to 0.26)<br>Statistically significant increase (p≤0.05)<br><br>z-score (range)<br>Start of gender-affirming hormones (C0): -1.15 (-2.21 to 0.08)<br>24-month follow-up (C24): -0.66 (-1.66 to 0.54)<br>Statistically significant increase (p≤0.05) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in lumber spine BMAD in transmales*** | | | | | | | | | |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| 1 cohort study Klink et al. 2015 | Serious limitations[1] | Serious indirectness[2] | Not applicable | Not calculable | N=19 (Mean and z-score) | None | Mean (SD), g/m$^3$<br>Start of gender-affirming hormones: 0.24 (0.02)<br>Age 22 years: 0.25 (0.28)<br>P=0.001<br><br>z-score<br>Start of gender-affirming hormones: -0.50 (0.81)<br>Age 22 years: -0.033 (0.95)<br>P=0.002 | Important | VERY LOW |
| ***Change from baseline in lumbar spine BMAD in transmales with a bone age of less than 14 years ('young'; 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study Vlot et al. 2017 | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=11 | None | Median (range), g/m$^3$<br>Start of gender-affirming hormones (C0): 0.23 (0.19 to 0.28)<br>24-month follow-up (C24): 0.25 (0.22 to 0.28)<br>Statistically significant increase (p≤0.01)<br><br>z-score (range)<br>Start of gender-affirming hormones (C0): -0.84 (-2.2 to 0.87)<br>24-month follow-up (C24): -0.15 (-1.38 to 0.94)<br>Statistically significant increase (p≤0.01) | Important | VERY LOW |
| ***Change from baseline in lumbar spine BMAD in transmales with a bone age of 14 years or more ('old'; 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=23 | None | Median (range), g/m$^3$ | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| Vlot et al. 2017 | | | | | | | Start of gender-affirming hormones (C0): 0.24 (0.20 to 0.28)<br>24-month follow-up (C24): 0.25 (0.21 to 0.30)<br>Statistically significant increase (p≤0.01)<br><br>z-score (range)<br>Start of gender-affirming hormones (C0): -0.29 (-2.28 to 0.90)<br>24-month follow-up (C24): -0.06 (-1.75 to 1.61)<br>Statistically significant increase (p≤0.01) | | |
| ***Change in femoral neck BMAD (2 uncontrolled, retrospective observational studies)*** | | | | | | | | | |
| ***Change from start of gender-affirming hormones to age 22 years in femoral neck BMAD in transfemales*** | | | | | | | | | |
| 1 cohort study Klink et al. 2015 | Serious limitations[1] | Serious indirectness[2] | Not applicable | Not calculable | N=14 (Mean)<br><br>N=10 (z-score) | None | Mean (SD), g/m$^3$<br>Start of gender-affirming hormones: 0.26 (0.04)<br>Age 22 years: 0.28 (0.05)<br>No statistically significant difference<br><br>z-score (SD)<br>Start of gender-affirming hormones: -1.57 (1.74)<br>Age 22 years: Not reported | Important | VERY LOW |
| ***Change from baseline in femoral neck BMAD in transfemales with a bone age less than 15 years ('young'; 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study Vlot et al. 2017 | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=16 | None | Median (range), g/m$^3$<br>C0: 0.27 (0.20 to 0.33)<br>C24: 0.27 (0.20 to 0.36) | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| | | | | | | | No statistically significant change<br><br>z-score (range)<br>C0: -1.32 (-3.39 to 0.21)<br>C24: -1.30 (-3.51 to 0.92)<br>No statistically significant change | | |
| ***Change from baseline in femoral neck BMAD in transfemales with a bone age of 15 years or more ('old'; 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study<br>Vlot et al. 2017 | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=6 | None | Median (range), g/m$^3$<br>C0: 0.30 (0.26 to 0.34)<br>C24: 0.29 (0.24 to 0.38)<br>No statistically significant change<br><br>z-score (range)<br>C0: -0.36 (-1.50 to 0.46)<br>C24: -0.56 (-2.17 to 1.29)<br>No statistically significant change | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in femoral neck BMAD in transmales*** | | | | | | | | | |
| 1 cohort study<br>Klink et al. 2015 | Serious limitations[1] | Serious indirectness[2] | Not applicable | Not calculable | N=19 (Mean)<br><br>N=18 (z-score) | None | Mean (SD), g/m$^3$<br>Start of gender-affirming hormones: 0.31 (0.04)<br>Age 22 years: 0.33 (0.05)<br>P=0.010<br><br>z-score (SD)<br>Start of gender-affirming hormones: -0.28 (0.74)<br>Age 22 years: Not reported | Important | VERY LOW |
| ***Change from baseline in femoral neck BMAD in transmales with a bone age of less than 14 years ('young'; 24 months follow-up)*** | | | | | | | | | |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| 1 cohort study Vlot et al. 2017 | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=10 | None | Median (range), g/m$^3$<br>C0: 0.30 (0.22 to 0.35)<br>C24: 0.33 (0.23 to 0.37)<br>Statistically significant increase (p≤0.01)<br><br>z-score (range)<br>C0: -0.37 (-2.28 to 0.47)<br>C24: -0.37 (-2.03 to 0.85)<br>Statistically significant increase (p≤0.01) | Important | VERY LOW |
| ***Change from baseline in femoral neck BMAD in transmales with a bone age of 14 years or more ('old'; 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study Vlot et al. 2017 | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=23 | None | Median (range), g/m$^3$<br>C0: 0.30 (0.23 to 0.41)<br>C24: 0.32 (0.23 to 0.41)<br>Statistically significant increase (p≤0.01)<br><br>z-score (range)<br>C0: -0.27 ((-1.91 to 1.29)<br>C24: 0.02 (-2.1 to 1.35)<br>Statistically significant increase (p≤0.05) | Important | VERY LOW |
| ***Change in lumbar spine BMD (2 uncontrolled, retrospective observational studies)*** | | | | | | | | | |
| ***Change from start of gender-affirming hormones to age 22 years in lumbar spine BMD in transfemales*** | | | | | | | | | |
| 1 cohort study Klink et al. 2015 | Serious limitations[1] | Serious indirectness[2] | Not applicable | Not calculable | N=15 (Mean)<br>N=13 (z-score) | None | Mean (SD), g/m$^2$<br>Start of gender-affirming hormones: 0.84 (0.11)<br>Age 22 years: 0.93 (0.10)<br>P<0.001<br><br>z-score (SD) | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| | | | | | | | Start of gender-affirming hormones: -1.01 (0.98)<br>Age 22 years: -1.36 (0.83)<br>No statistically significant difference | | |
| ***Change from start of gender-affirming hormones to age 22 years in lumbar spine BMD in transmales*** | | | | | | | | | |
| 1 cohort study<br>Klink et al. 2015 | Serious limitations[1] | Serious indirectness[2] | Not applicable | Not calculable | N=19 (Mean and z-score) | None | Mean (SD), g/m$^2$<br>Start of gender-affirming hormones: 0.91 (0.10)<br>Age 22 years: 0.99 (0.13)<br>P<0.001<br><br>z-score (SD)<br>Start of gender-affirming hormones: -0.72 (0.99)<br>Age 22 years: -0.33 (1.12)<br>No statistically significant difference | Important | VERY LOW |
| ***Change from start of testosterone treatment in lumbar spine BMD in transmen (follow-up 6 to 24 months)*** | | | | | | | | | |
| 1 cohort study<br>Stoffers et al. 2019 | Serious limitations[4] | No serious indirectness | Not applicable | Not calculable | N=62 (T0 and T6)<br><br>N=37 (T12)<br><br>N=15 (T24) | None | Mean (SD), g/cm$^2$<br>T0: 0.90 (0.11)<br>T6: 0.94 (0.10)<br>T12: 0.95 (0.09)<br>T24: 0.95 (0.11)<br>No statistically significant difference from T0 to any timepoint<br><br>z-score (SD)<br>T0: -0.81 (1.02)<br>T6: -0.67 (0.95)<br>T12: -0.66 (0.81)<br>T24: -0.74 (1.17) | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| | | | | | | | No statistically significant difference from T0 to any timepoint | | |
| ***Change in femoral neck BMD (2 uncontrolled, retrospective observational studies)*** | | | | | | | | | |
| ***Change from start of gender-affirming hormones to age 22 years in femoral neck BMD in transfemales*** | | | | | | | | | |
| 1 cohort study Klink et al. 2015 | Serious limitations[1] | Serious indirectness[2] | Not applicable | Not calculable | N=15 (Mean)<br>N=11 (z-score) | None | Mean (SD), g/m$^2$<br>Start of gender-affirming hormones: 0.87 (0.08)<br>Age 22 years: 0.94 (0.11)<br>P=0.009<br>z-score (SD)<br>Start of gender-affirming hormones: -0.95 (0.63)<br>Age 22 years: -0.69 (0.74)<br>No statistically significant difference | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in femoral neck BMD in transmales*** | | | | | | | | | |
| 1 cohort study Klink et al. 2015 | Serious limitations[1] | Serious indirectness[2] | Not applicable | Not calculable | N=19 (Mean)<br>N=16 (z-score) | None | Mean (SD), g/m$^2$<br>Start of gender-affirming hormones: 0.88 (0.09)<br>Age 22 years: 0.95 (0.10)<br>P<0.001<br>z-score (SD)<br>Start of gender-affirming hormones: -0.35 (0.79)<br>Age 22 years: -0.35 (0.74)<br>P=0.006 | Important | VERY LOW |
| ***Change from start of testosterone treatment in right femoral neck (hip) BMD in transmales (follow-up 6 to 24 months)*** | | | | | | | | | |
| 1 cohort study | Serious limitations[4] | No serious indirectness | Not applicable | Not calculable | N=62 (T0 and T6) | None | Mean (SD), g/cm$^2$<br>T0: 0.77 (0.08) | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| Stoffers et al. 2019 | | | | | N=37 (T12)<br><br>N=15 (T24) | | T6: 0.84 (0.11)<br>T12: 0.82 (0.08)<br>T24: 0.85 (0.11)<br>No statistically significant difference from T0 to any timepoint<br><br>z-score (SD)<br>T0: -0.97 (0.79)<br>T6: -0.54 (0.96)<br>T12: -0.80 (0.69)<br>T24: -0.31 (0.84)<br>No statistically significant difference from T0 to any timepoint | | |
| ***Change from start of testosterone treatment in left femoral neck (hip) BMD in transmales (follow-up 6 to 24 months)*** | | | | | | | | | |
| 1 cohort study Stoffers et al. 2019 | Serious limitations[4] | No serious indirectness | Not applicable | Not calculable | N=62 (T0 and T6)<br><br>N=37 (T12)<br><br>N=15 (T24) | None | Mean (SD), g/cm$^2$<br>T0: 0.76 (0.09)<br>T6: 0.83 (0.12)<br>T12: 0.81 (0.08)<br>T24: 0.86 (0.09)<br>No statistically significant difference from T0 to any timepoint<br><br>z-score (SD)<br>T0: -1.07 (0.85)<br>T6: -0.62 (1.12)<br>T12: -0.93 (0.63)<br>T24: -0.20 (0.70)<br>No statistically significant difference from T0 to any timepoint | Important | VERY LOW |

**Abbreviations:** BMAD: bone mineral apparent density; BMD: bone mineral density; g: grams; m: metre; SD: standard deviation

*1 Downgraded 1 level - the cohort study by Klink et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up)*
*2 Outcomes reported after gender reassignment surgery and not after gender-affirming hormones alone. Unclear whether observed changes are due to hormones or surgery*
*3 Downgraded 1 level - the cohort study by Vlot et al. (2017) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control)*
*4 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)*

**Table 8: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Cardiovascular risk factors**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Change in body mass index (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Change from start of gender-affirming hormones to age 22 years in BMI in transfemales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=71 | None | Mean change (95% CI) +1.9 (0.6 to 3.2) Statistically significant increase (p<0.005)<br><br>Mean BMI at 22 years (95% CI): 23.2 (21.6 to 24.8) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in BMI in transmales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=121 | None | Mean change (95% CI) +1.4 (0.8 to 2.0) Statistically significant increase (p<0.005)<br><br>Mean BMI at 22 years (95% CI): 23.9 (23.0 to 24.7) | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Obesity rates at age 22 years (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Obesity rates at age 22 years in transfemales who started gender-affirming hormones as adolescents (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=71 | None | At 22 years, 9.9% of transfemales were obese, compared with 3.0% in reference cisgender population<br><br>No statistically analysis reported | Important | VERY LOW |
| ***Obesity rates at age 22 years in transfemales who started gender-affirming hormones as adolescents (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=121 | None | At 22 years, 6.6% of transmales were obese, compared with 2.2% in reference cisgender population<br><br>No statistically analysis reported | Important | VERY LOW |
| ***Change in blood pressure (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Change from start of gender-affirming hormones to age 22 years in systolic blood pressure (SBP) in transfemales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=71 | None | Mean change (95% CI)<br>-3 (-8 to 2)<br>No statistically significant difference<br><br>Mean SBP at 22 years (95% CI): 117 (113 to 122) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in diastolic blood pressure (DBP) in transfemales*** | | | | | | | | | |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=71 | None | Mean change (95% CI) +6 (3 to 10) Statistically significant increase (p<0.001)<br><br>Mean DBP at 22 years (95% CI): 75 (72 to 78) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in systolic blood pressure (SBP) in transmales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=121 | None | Mean change (95% CI): +5 (1 to 9) Statistically significant increase (p<0.05)<br><br>Mean SBP at 22 years (95% CI): 126 (122 to 130) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in diastolic blood pressure (DBP) in transmales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=121 | None | Mean change (95% CI): +6 (4 to 9) Statistically significant increase (p<0.001)<br><br>Mean DBP at 22 years (95% CI): 74 (72 to 77) | Important | VERY LOW |
| ***Change in glucose levels, insulin levels, insulin resistance and HbA1c (2 uncontrolled, retrospective observational studies)*** | | | | | | | | | |
| ***Change from start of gender-affirming hormones to age 22 years in glucose level (mmol/L) in transfemales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=71 | None | Mean change (95% CI): +0.1 (-0.1 to 0.2) | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| | | | | | | | No statistically significant difference<br><br>Mean glucose level at 22 years (95% CI): 5.0 (4.8 to 5.1) | | |
| ***Change from start of gender-affirming hormones to age 22 years in insulin level (mU/L) in transfemales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=71 | None | Mean change (95% CI) +2.7 (-1.7 to 7.1) No statistically significant difference<br><br>Mean insulin level at 22 years (95% CI): 13.0 (8.4 to 17.6) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in insulin resistance (HOMA-IR) in transfemales. Higher scores indicate more insulin resistance.*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=71 | None | Mean change (95% CI) +0.7 (-0.2 to 1.5) No statistically significant difference<br><br>Mean HOMA-IR at 22 years (95% CI): 2.9 (1.9 to 3.9) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in glucose level (mmol/L) in transmales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=121 | None | Mean change (95% CI) 0.0 (-0.2 to 0.2) No statistically significant difference | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| | | | | | | | Mean glucose level at 22 years (95% CI): 4.8 (4.7 to 5.0) | | |
| ***Change from start of gender-affirming hormones to age 22 years in insulin level (mU/L) in transmales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=121 | None | Mean change (95% CI) -2.1 (-3.9 to -0.3) Statistically significant decrease (p<0.05)<br><br>Mean insulin level at 22 years (95% CI): 8.6 (6.9 to 10.2) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in insulin resistance (HOMA-IR) in transmales. Higher scores indicate more insulin resistance.*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=121 | None | Mean change (95% CI): -0.5 (-1.0 to -0.1) Statistically significant decrease (p<0.05)<br><br>Mean HOMA-IR at 22 years (95% CI): 1.8 (1.4 to 2.2) | Important | VERY LOW |
| ***Change from start of testosterone in HbA1c in transmales (up to 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study Stoffers et al. 2019 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N= Not reported | None | No statistically significant change from start of testosterone treatment<br><br>Numerical results, follow-up duration and further details of statistical analysis not reported. | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Change in lipid profile (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Change from start of gender-affirming hormones to age 22 years in total cholesterol (mmol/L) in transfemales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=71 | None | Mean change (95% CI): +0.1 (-0.2 to 0.4) No statistically significant difference<br><br>Mean total cholesterol at 22 years (95% CI): 4.1 (3.8 to 4.4) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in HDL cholesterol (mmol/L) in transfemales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=71 | None | Mean change (95% CI): 0.0 (-0.1 to 0.2) No statistically significant difference<br><br>Mean HDL cholesterol at 22 years (95% CI): 1.6 (1.4 to 1.7) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in LDL cholesterol (mmol/L) in transfemales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=71 | None | Mean change (95% CI): 0.0 (-0.3 to 0.2) No statistically significant difference<br><br>Mean LDL cholesterol at 22 years (95% CI): 2.0 (1.8 to 2.3) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in triglycerides (mmol/L) in transfemales*** | | | | | | | | | |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=71 | None | Mean change (95% CI): +0.2 (0.0 to 0.5) Statistically significant increase (p<0.05)<br><br>Mean triglycerides at 22 years (95% CI): 1.1 (0.9 to 1.4) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in total cholesterol (mmol/L) in transmales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=121 | None | Mean change (95% CI): +0.4 (0.2 to 0.6) Statistically significant increase (p<0.001)<br><br>Mean total cholesterol at 22 years (95% CI): 4.6 (4.3 to 4.8) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in HDL cholesterol (mmol/L) in transmales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=121 | None | Mean change (95% CI) -0.3 (-0.4 to -0.2) Statistically significant decrease (p<0.001)<br><br>Mean HDL cholesterol at 22 years (95% CI): 1.3 (1.2 to 1.3) | Important | VERY LOW |
| ***Change from start of gender-affirming hormones to age 22 years in LDL cholesterol (mmol/L) in transmales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=121 | None | Mean change (95% CI): +0.4 (0.2 to 0.6) Statistically significant increase (p<0.001) | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| | | | | | | | Mean LDL cholesterol at 22 years (95% CI): 2.6 (2.4 to 2.8) | | |
| ***Change from start of gender-affirming hormones to age 22 years in triglycerides (mmol/L) in transmales*** | | | | | | | | | |
| 1 cohort study Klaver et al. 2020 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=121 | None | Mean change (95% CI) +0.5 (0.3 to 0.7) Statistically significant increase (p<0.001)<br><br>Mean triglycerides at 22 years (95% CI): 1.3 (1.1 to 1.5) | Important | VERY LOW |

**Abbreviations:** BMI: boss mass index; CI: confidence interval; DBP: diastolic blood pressure; HbA1c: glycated haemoglobin; HDL: high-density lipoproteins; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; LDL: low-density lipoproteins; mmol/L: millimoles per litre; mU/L: milliunits per litre; SBP: systolic blood pressure; SD: standard deviation

*1 Downgraded 1 level - the cohort study by Klaver et al. (2020) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)*
*2 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)*

**Table 9: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Other safety outcomes**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Liver enzymes (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Change from start of testosterone in aspartate aminotransferase (AST) level in transmales (up to 24 months follow-up)*** | | | | | | | | | |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| 1 cohort study Stoffers et al. 2019 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N= Not reported | None | No statistically significant change from start of testosterone treatment<br><br>Numerical results, follow-up duration and further details of statistical analysis not reported. | Important | VERY LOW |
| ***Change from start of testosterone in alanine aminotransferase (ALT) level in transmales (up to 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study Stoffers et al. 2019 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N= Not reported | None | No statistically significant change from start of testosterone treatment<br><br>Numerical results, follow-up duration and further details of statistical analysis not reported. | Important | VERY LOW |
| ***Change from start of testosterone in gamma-glutamyl transferase (GGT) level in transmales (up to 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study Stoffers et al. 2019 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N= Not reported | None | No statistically significant change from start of testosterone treatment<br><br>Numerical results, follow-up duration and further details of statistical analysis not reported. | Important | VERY LOW |
| ***Change from start of testosterone in alkaline phosphatase (ALP) level in transmales (up to 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study Stoffers et al. 2019 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=62 (T0 and T1)<br><br>N=37 (T12)<br><br>N-15 (T24) | None | Median (IQR), U/L<br>T0: 102 (78 to 136)<br>T6: 115 (102 to 147)<br>T12: 112 (88 to 143)<br>T24: 81 (range 69 to 98)<br>Statistically significant increase from T0 at T6 and T12 (p<0.001) | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Kidney markers (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Change from start of testosterone in serum creatinine level in transmales (up to 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study Stoffers et al. 2019 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N=62 (T0 and T1)<br>N=37 (T12)<br>N=15 (T24) | None | Mean (SD), umol/L<br>T0: 62 (7)<br>T6: 70 (9)<br>T12: 74 (10)<br>T24: 81 (10)<br>Statistically significant increase from T0 at all timepoints (p<0.001) | Important | VERY LOW |
| ***Change from start of testosterone in serum urea[2] level in transmales (up to 24 months follow-up)*** | | | | | | | | | |
| 1 cohort study Stoffers et al. 2019 | Serious limitations[1] | No serious indirectness | Not applicable | Not calculable | N= Not reported | None | No statistically significant change from start of testosterone treatment<br>Numerical results, follow-up duration and further details of statistical analysis not reported. | Important | VERY LOW |
| ***Adverse effects (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Permanent discontinuation of gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)*** | | | | | | | | | |
| 1 cohort study Khatchadourian et al. 2014 | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=63 | None | No participants permanently discontinued gender-affirming hormones. | Important | VERY LOW |
| ***Temporary discontinuation of gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)*** | | | | | | | | | |
| 1 cohort study Khatchadourian et al. 2014 | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=63 | None | 3/37 transmales receiving testosterone temporarily discontinued treatment, 2 due to concomitant mental health | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| | | | | | | | comorbidities and 1 due to androgenic alopecia. All eventually resumed treatment.<br><br>No transfemales receiving oestrogen temporarily discontinued treatment | | |
| ***Minor complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)*** | | | | | | | | | |
| 1 cohort study Khatchadourian et al. 2014 | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=63 | None | 12/63 participants had minor complications during treatment with gender-affirming hormones<br><br>All 12 were transmales receiving testosterone. Complications were severe acne (n=7), androgenic alopecia (n=1) mild dyslipidaemia (n=3) and significant mood swings (n=1)<br><br>No transfemales receiving oestrogen had minor complications | Important | VERY LOW |
| ***Severe complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)*** | | | | | | | | | |
| 1 cohort study Khatchadourian et al. 2014 | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=63 | None | No severe complications reported during gender-affirming treatment | Important | VERY LOW |

**Abbreviations:** ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; IQR: interquartile range; SD: standard deviation; U/L: units per litre; umol/L: micromole per litre

*1 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)*
*2 Referred to as 'ureum' in original publication*
*3 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up)*

**Table 10: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Transfemales compared with transmales**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Transfemales | Transmales | Result (95% CI) | | |
| ***Impact on mental health (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Change from baseline in adjusted mean suicidality score, measured using the ASQ tool (mean treatment duration 349 days). Higher scores indicate a greater degree of suicidality.*** | | | | | | | | | |
| 1 cohort study Allen et al. 2019 | Serious limitations[4] | No serious indirectness | No serious inconsistency | Not calculable | N=14 | N=33 | **Transfemales**<br>T0 (baseline) = 1.21 (SE 0.36)<br>T1 (final assessment) = 0.24 (SE 0.19)<br><br>**Transmales**<br>T0 (baseline) = 1.01 (SE 0.23)<br>T1 (final assessment) = 0.29 (SE 0.13)<br><br>No statistically significant difference in change from baseline between transfemales and transmales (p=0.79) | Critical | VERY LOW |
| ***Impact on quality of life (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Change from baseline in adjusted mean well-being score, measured using the GWBS of the Pediatric Quality of Life Inventory (mean treatment duration 349 days). Higher scores indicate better well-being.*** | | | | | | | | | |
| 1 cohort study Allen et al. 2019 | Serious limitations[4] | No serious indirectness | No serious inconsistency | Not calculable | N=14 | N=33 | **Transfemales**<br>T0 (baseline) = 58.44 (SE 4.09)<br>T1 (final assessment) = 69.52 (SE 3.62)<br><br>**Transmales**<br>T0 (baseline) = 64.95 (SE 2.66) | Critical | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Transfemales | Transmales | Result (95% CI) | | |
| | | | | | | | T1 (final assessment) = 70.94 (SE 2.35)<br><br>No statistically significant difference in change from baseline between transfemales and transmales (p=0.32) | | |

**Abbreviations:** ASQ: Ask Suicide-Screening Questions; GWBS: General Well-Being Scale; SE: standard error

*1 The cohort study by Allen et al. 2019 was assessed at high risk of bias (poor quality; lack of blinding and no control group).*

**Table 11: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Sex assigned at birth males (transfemales)**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of events/No of patients% (n/N%) | | Effect | | |
| Study type and number of studies Author year | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Change from baseline in mean depression symptoms in transfemales, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more depression.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=40 | None | Baseline = 7.5 (SD 4.9)<br>Follow-up = 6.6 (SD 4.4)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in mean depression symptoms in transfemales, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=45 | None | Baseline = 4.2 (SD 3.2)<br>Follow-up = 5.4 (SD 3.4)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of events/No of patients% (n/N%) | | Effect | | |
| Study type and number of studies Author year | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Change from baseline in mean anxiety symptoms in transfemales, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=33 | None | Baseline = 26.4 (SD 14.2)<br>Follow-up = 24.3 (SD 15.4)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in mean panic symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=34 | None | Baseline = 5.7 (SD 4.9)<br>Follow-up = 5.1 (SD 4.9)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in mean generalised anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=34 | None | Baseline = 8.6 (SD 5.1)<br>Follow-up = 8.0 (SD 5.1)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in mean social anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=34 | None | Baseline = 7.1 (SD 3.9)<br>Follow-up = 6.8 (SD 4.4)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in mean separation anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=34 | None | Baseline = 3.4 (SD 3.3)<br>Follow-up = 2.7 (SD 2.3)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in mean school avoidance symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of events/No of patients% (n/N%) | | Effect | | |
| Study type and number of studies Author year | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=33 | None | Baseline = 1.8 (SD 1.7)<br>Follow-up = 1.9 (SD 2.1)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in percentage of participants with suicidal ideation in transfemales, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)*** | | | | | | | | | |
| 1 cohort study Achille et al. 2020 | Serious limitations[2] | Serious indirectness[2] | No serious inconsistency | Not calculable | N=17 | None | Wave 1 (baseline) = 11.8% (2/17)<br>Wave 2 (approx. 12 months) = 5.9% (1/17)<br>No statistical analysis reported | Critical | VERY LOW |
| ***Impact on body image (1 uncontrolled, prospective observational study)*** | | | | | | | | | |
| ***Change from baseline in mean body image in transfemales, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=30 | None | Baseline = 67.5 (SD 19.5)<br>Follow-up = 49.0 (SD 21.6)<br>No statistical analysis reported for this sub-group | Important | VERY LOW |

**Abbreviations:** BIS: Body Image Scale; PHQ 9: Patient Health Questionnaire 9; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation

*1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).*
*2 Downgraded 1 level - the cohort study by Achille et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).*
*3 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.*

**Table 12: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Sex assigned at birth females (transmales)**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Change from baseline in mean depression symptoms in transmales, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=76 | None | Baseline = 10.4 (SD 5.0)<br>Follow-up = 7.5 (SD 4.5)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in mean depression symptoms in transmales, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=78 | None | Baseline = 6.7 (SD 4.4)<br>Follow-up = 6.2 (SD 4.1)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in mean anxiety symptoms in transmales, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=65 | None | Baseline = 35.4 (SD 16.5)<br>Follow-up = 29.8 (SD 15.5)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in mean panic symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=66 | None | Baseline = 9.3 (SD 6.5)<br>Follow-up = 7.9 (SD 6.5)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in mean generalised anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=66 | None | Baseline = 10.4 (SD 5.0)<br>Follow-up = 9.0 (SD 5.1)<br>No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in mean social anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=66 | None | Baseline = 8.5 (SD 4.0)<br>Follow-up = 7.8 (SD 4.1) | Critical | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| Kuper et al. 2020 | | | | | | | No statistical analysis reported for this sub-group | | |
| ***Change from baseline in mean separation anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=65 | None | Baseline = 4.2 (SD 3.4) Follow-up = 3.4 (SD 2.6) No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in mean school avoidance symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=65 | None | Baseline = 2.9 (SD 2.3) Follow-up = 2.0 (SD 2.3) No statistical analysis reported for this sub-group | Critical | VERY LOW |
| ***Change from baseline in percentage of participants with suicidal ideation in transmales, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)*** | | | | | | | | | |
| 1 cohort study Achille et al. 2020 | Serious limitations[2] | Serious indirectness[3] | No serious inconsistency | Not calculable | N=33 | None | Wave 1 (baseline) = 9.1% (3/33) Wave 2 (approx. 12 months) = 6.1% (2/33) No statistical analysis reported | Critical | VERY LOW |
| ***Impact on body image (1 uncontrolled, prospective observational study)*** | | | | | | | | | |
| ***Change from baseline in mean body image in transmales, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=66 | None | Baseline = 71.1 (SD 13.4) Follow-up = 52.9 (SD 16.8) No statistical analysis reported for this sub-group | Important | VERY LOW |

**Abbreviations:** BIS: Body Image Scale; PHQ 9: Patient Health Questionnaire 9; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation

*1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).*

*2 Downgraded 1 level - the cohort study by Achille et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).*
*3 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.*

**Table 14: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Outcomes controlled for concurrent counselling and medicines for mental health problems**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Impact on mental health (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Change from baseline in mean depression score in transfemales, measured using the CESD-R (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more depression.*** | | | | | | | | | |
| 1 cohort study Achille et al. 2020 | Serious limitations[1] | Serious indirectness[2] | No serious inconsistency | Not calculable | N=17 | None | No statistically significant change from baseline (p=0.27) Numerical scores not reported | Critical | VERY LOW |
| ***Change from baseline in mean depression score in transmales, measured using the CESD-R (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.*** | | | | | | | | | |
| 1 cohort study Achille et al. 2020 | Serious limitations[1] | Serious indirectness[2] | No serious inconsistency | Not calculable | N=33 | None | No statistically significant change from baseline (p=0.43) Numerical scores not reported | Critical | VERY LOW |
| ***Change from baseline in depression score in transfemales, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.*** | | | | | | | | | |
| 1 cohort study Achille et al. 2020 | Serious limitations[1] | Serious indirectness[2] | No serious inconsistency | Not calculable | N=17 | None | No statistically significant change from baseline (p=0.07) Numerical scores not reported | Critical | VERY LOW |
| ***Change from baseline in depression score in transmales, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.*** | | | | | | | | | |
| 1 cohort study Achille et al. 2020 | Serious limitations[1] | Serious indirectness[2] | No serious inconsistency | Not calculable | N=33 | None | No statistically significant change from baseline (p=0.67) Numerical scores not reported | Critical | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Impact on quality of life (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Change from baseline in mean quality of life score in transfemales, measured using the QLES-Q-SF (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicated better quality of life.*** | | | | | | | | | |
| 1 cohort study Achille et al. 2020 | Serious limitations[1] | Serious indirectness[2] | No serious inconsistency | Not calculable | N=17 | None | No statistically significant change from baseline (p=0.06) | Critical | VERY LOW |
| ***Change from baseline in mean quality of life score in transmales, measured using the QLES-Q-SF (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicated better quality of life.*** | | | | | | | | | |
| 1 cohort study Achille et al. 2020 | Serious limitations[1] | Serious indirectness[2] | No serious inconsistency | Not calculable | N=33 | None | No statistically significant change from baseline (p=0.08) | Critical | VERY LOW |
| ***Psychosocial Impact (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Functioning in adolescent development: Progresses normatively in school/ work during the real-life phase – impact on need for mental health treatment before or during gender identity assessment*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[3] | No serious indirectness | No serious inconsistency | Not calculable | N=49 | None | Needed mental health treatment:<br>47% (15/32) functioning well<br><br>Did not need mental health treatment:<br>82% (14/17) functioning well<br><br>Statistically significant difference p=0.02 | Important | VERY LOW |
| ***Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home during the real-life phase – impact on need for mental health treatment before or during gender identity assessment*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[3] | No serious indirectness | No serious inconsistency | Not calculable | N=49 | None | Needed mental health treatment:<br>72% (23/32) managing well<br><br>Did not need mental health treatment:<br>94% (16/17) managing well | Important | VERY LOW |

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| | | | | | | | No statistically significant difference p=0.06 | | |
| ***Functioning in adolescent development: Progresses normatively in school/ work during the real-life phase – impact on need for mental health treatment during the real-life phase*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[3] | No serious indirectness | No serious inconsistency | Not calculable | N=51 | None | Needed mental health treatment: 42% (10/24) functioning well<br><br>Did not need mental health treatment: 74% (20/27) functioning well<br><br>Statistically significant difference p=0.02 | Important | VERY LOW |
| ***Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home during the real-life phase – impact on need for mental health treatment during the real-life phase*** | | | | | | | | | |
| 1 cohort study Kaltiala et al. 2020 | Serious limitations[3] | No serious indirectness | No serious inconsistency | Not calculable | N=51 | None | Needed mental health treatment: 67% (16/24) managing well<br><br>Did not need mental health treatment: 93% (25/27) managing well<br><br>Statistically significant difference p=0.02 | Important | VERY LOW |

**Abbreviations:** CESD-R: Center for Epidemiologic Studies Depression; p: p-value; PHQ 9: Patient Health Questionnaire 9; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire

*1 Downgraded 1 level - the cohort study by Achille et al 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).*
*2 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.*
*3 Downgraded 1 level - the cohort study by Kaltiala et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding and no control).*

**Table 15: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Tanner age**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | Intervention | Comparator | Result (95% CI) | | |
| ***Impact on mental health (1 uncontrolled, retrospective observational study)*** | | | | | | | | | |
| ***Change from baseline in mental health problems – depression, anxiety and anxiety-related symptoms (mean duration of gender-affirming hormone treatment was 10.9 months)*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=105 | None | No difference in outcomes found by Tanner age.<br><br>Numerical results, statistical analysis and information on specific outcomes not reported.<br><br>It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint | Critical | VERY LOW |
| ***Impact on body image (1 uncontrolled, prospective observational study)*** | | | | | | | | | |
| ***Change from baseline in mean body image, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.*** | | | | | | | | | |
| 1 cohort study Kuper et al. 2020 | Serious limitations[1] | No serious indirectness | No serious inconsistency | Not calculable | N=105 | None | No difference in body image score found by Tanner age.<br><br>Numerical results, statistical analysis and information on specific outcomes not reported.<br><br>It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint | Important | VERY LOW |

**Abbreviations:** BIS: Body Image Scale

*1 Downgraded 1 level - the cohort study by Kuper et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).*

## Glossary

| | |
|---|---|
| Ask Suicide-Screening Questions (ASQ) | ASQ is a four-item dichotomous (yes, no) response measure with high sensitivity, designed to identify risk of suicide. A patient is considered to have screened positive if they answered yes to any item. The authors of Allen et al. 2019 altered the fourth item of the ASQ ("Have you ever tried to kill yourself?") and prefaced it with "In the past few weeks . . ." as they were not investigating lifetime suicidality. A response of 'no' was scored as 0 and a response of 'yes' was scored as 1; each item was summed, generating an overall score for suicidality on a scale ranging from 0 to 4, with higher scores indicating greater levels of suicidal ideation. |
| Beck Depression Inventory-II (BDI-II) | The BDI-II is a tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63. |
| Body Image Scale (BIS) | The BIS is used to measure body satisfaction. The scale consists of 30 body features, which the person rates on a 5-point scale. Each of the 30 items falls into one of 3 basic groups based on its relative importance as a gender-defining body feature: primary sex characteristics, secondary sex characteristics, and neutral body characteristics. A higher score indicates more dissatisfaction. |
| Bone mineral apparent density (BMAD) | BMAD is a size adjusted value of bone mineral density (BMD) incorporating bone size measurements using UK norms in growing adolescents. |
| Center for Epidemiologic Studies Depression scale (CESD-R) | The CESD-R is a valid, widely used tool to access depressive symptoms. The CESD-R asks about how frequently a person has felt or behaved in a certain way; with 20 questions scored from 0 score is calculated as a sum of 20 questions, ranging from 0 ("not at all or less than one day") to 3 ("5–7 days" and/or "nearly every day for 2 weeks"). Total score ranges from 0 to 60, with higher scores indicating more depressive symptoms. |
| Cisgender | Cisgender is a term for someone whose gender identity matches their birth-registered sex. |
| Family APGAR (Adaptability, Partnership, Growth, Affection and Resolve) test | The Family APGAR test is a 5-item questionnaire, with higher scores indicating better family functioning. The authors reported the following interpretation of the score: functional, 17-20 points; mildly dysfunctional, 16-13 points; moderately dysfunctional, 12-10 point; severely dysfunctional, <9 points. |
| Gender | The roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men. |
| Gender dysphoria | Discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves regarding their gender) and that person's sex assigned at birth (and the associated gender role, and/or primary and secondary sex characteristics). |