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

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ABSTRACT

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

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

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

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

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

PROSPERO registration number CRD42021289659.

WHAT IS ALREADY KNOWN ON THIS TOPIC

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

WHAT THIS STUDY ADDS

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

HOW THIS STUDY MIGHT AFFECT RESEARCH, POLICY OR PRACTICE

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

INTRODUCTION

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

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

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

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

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

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

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

METHODS

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

Search strategy

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

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

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

Table 1 Inclusion and exclusion criteria

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

GnRH-a, gonadotropin-releasing hormone analogues.

Inclusion criteria

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

Selection process

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

Data extraction

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

Study quality

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

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

Synthesis

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

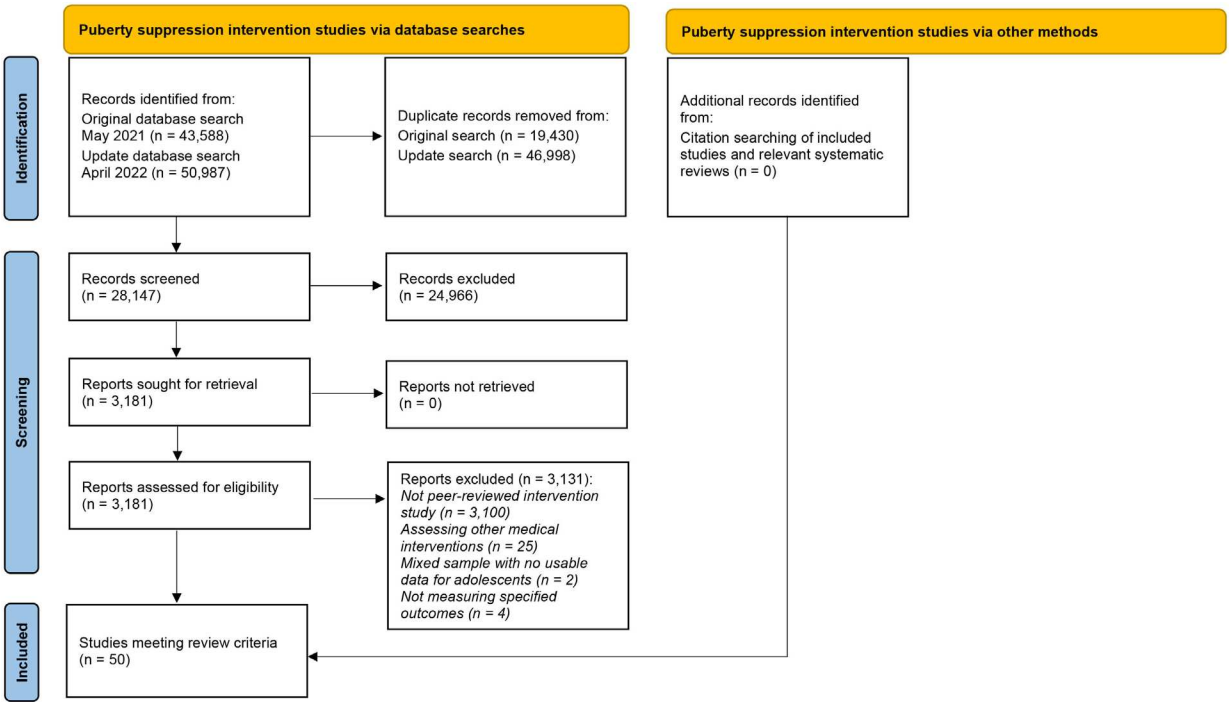

Figure 1 Study flow diagram.

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

RESULTS

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

Study characteristics

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

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

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

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

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

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

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

Study quality

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

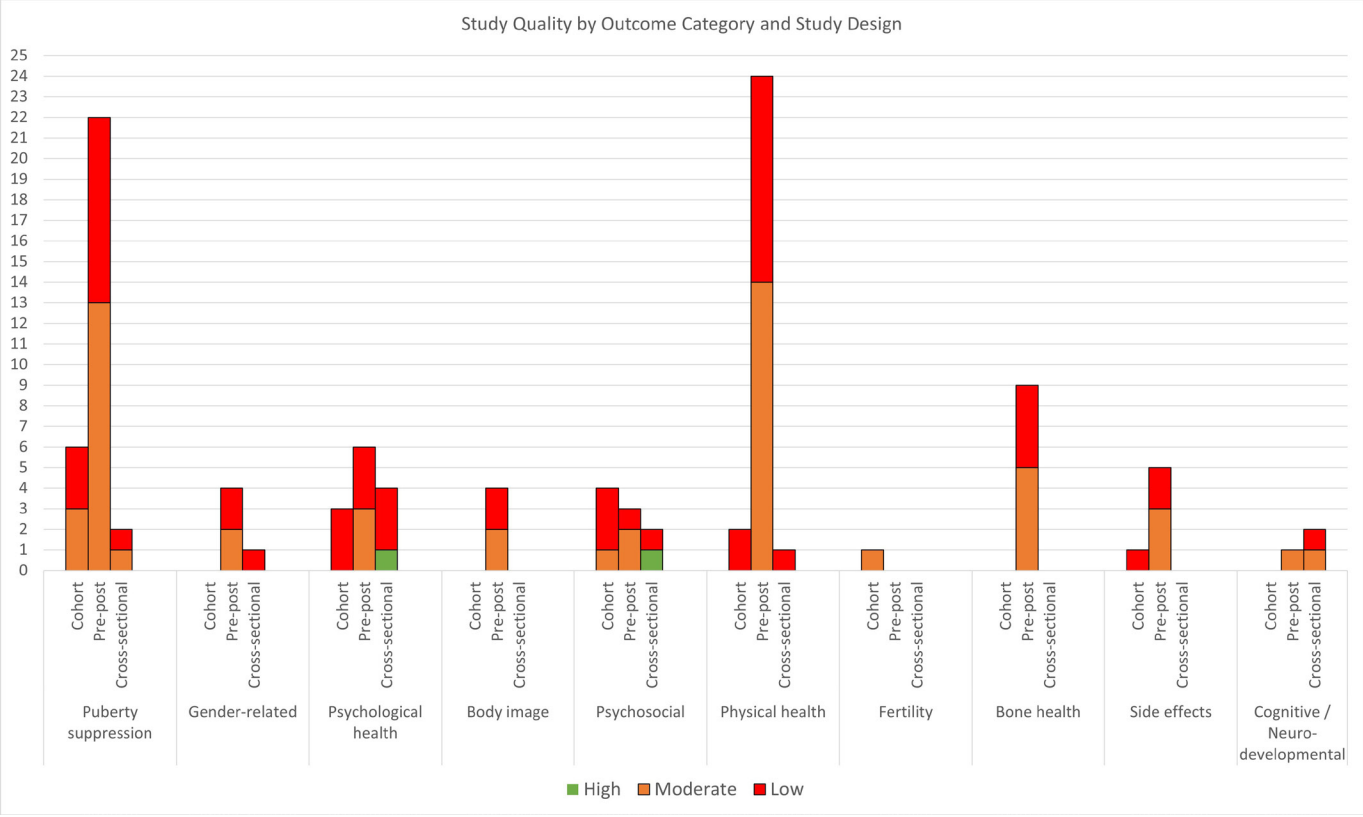

Figure 2 Outcome categories by study quality and design.

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

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

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

Synthesis of outcomes

Gender dysphoria and body satisfaction

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

Psychological health

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

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

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

Psychosocial outcomes

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

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

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

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

Continued

Table 2 Continued

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

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

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

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

Cognitive/neurodevelopmental outcomes

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

Physical health outcomes

Bone health

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

Cardiometabolic health

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

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

Other physiological parameters

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

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

Side effects

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

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

Puberty suppression

Hormone levels

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

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

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

Pubertal progression

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

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

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

Table 3 Physical health outcomes and side effects

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

Continued

Table 3 Continued

Study	Country	Study design	Study quality	Treated sample	Intervention	Outcome (measure)	Follow-up specific to outcome	Summary of study results
Perl *et al*[68]	Israel	Pre-post	Moderate	19 brm	GnRH-a	Systolic and diastolic blood pressure	Single (end of GnRH-a, mean 9 m SD 6)	Systolic and diastolic blood pressure remained the same.
Stoffers *et al*[34]	The Netherlands	Pre-post	Moderate	62 brf	GnRH-a	Systolic and diastolic blood pressure	Before CSH start (median 8 m, range 3–39)	Systolic and diastolic blood pressure remained the same.
Metabolic measures								
Stoffers *et al*[34]	The Netherlands	Pre-post	Moderate	62 brf	GnRH-a	Total cholesterol, HDL, LDL, triglycerides	Before CSH start (median 8 m, range 3–39)	No evidence for a change in any measure.
Tack *et al*[65]	Belgium	Pre-post	Moderate	38 brf	Lynestrenol	Total cholesterol, triglycerides, HDL, LDL, fasting insulin, HbA1c	6 m, 12 m	No evidence for a change in any measure, except for a decrease in HDL and increase in LDL.
Tack *et al*[67]	Belgium	Pre-post	Moderate	27 brm	Cyproterone acetate	Triglycerides, total cholesterol, HDL, LDL, HbA1c, glucose, insulin	6 m, 12 m	There was a decrease in HDL and triglycerides.
Other physical parameters								
Schagen *et al*[30]	The Netherlands	Pre-post	Moderate	116 (67 brf, 49 brm)	GnRH-a	ALT, AST, ALP, γ-glutamyl transferase, creatinine	3 m, 6 m, 12 m	There was a decrease in alkaline phosphate (both sexes) and creatinine (brf only). No changes were reported in AST, γ-glutamyl and ALT (narrative—no data).
Stoffers *et al*[34]	The Netherlands	Pre-post	Moderate	62 brf	GnRH-a	SHBG, TSH, prolactin, free thyroxine, DHEAS, A4, haemoglobin, haematocrit, creatinine, ALP, vitamin D, ureum	Before CSH start (median 8 m, range 3–39)	There was an increase in vitamin D levels and a decrease in prolactin levels—no change for other measures.
Tack *et al*[65]	Belgium	Pre-post	Moderate	38 brf	Lynestrenol	Haemoglobin, haematocrit, creatinine, ALT, AST, TSH, free thyroxine, anti-Müllerian hormone, SHBG	6 m, 12 m	There were increases in haemoglobin and haematocrit and a decrease in SHBG. Increases in free thyroxine levels, creatinine and ALT were reported.
Tack *et al*[67]	Belgium	Pre-post	Moderate	27 brm	Cyproterone acetate	DHEAS, haemoglobin, haematocrit, creatinine, AST, ALT, prolactin, TSH, free thyroxine, SHBG	6 m, 12 m	There was an increase in prolactin and free thyroxine levels, and a decrease in haemoglobin and haematocrit. No change in other measures.
Schagen *et al*[31]	The Netherlands	Pre-post	Moderate	127 (73 brf, 54 brm)	GnRH-a	DHEAS and A4	12 m, 24 m	DHEAS increased in brf and increased slightly in brm. A4 decreased in brf and remained constant in brm.
Waldner *et al*[64]	Canada	Pre-post	Moderate	33 (23 brf, 10 brm)	GnRH-a	Proportion with clinically significant QTc prolongation (defined as QTc >460 ms)	Single (>6 weeks after initiation of treatment)	There was no change in the mean QTc over time. At follow-up, no participants were in the clinical range >(460 ms). Just under 25% had a QTc between 440 and 460 ms.
Side effects								
Carmichael *et al*[55]	UK	Pre-post	Moderate	44 (19 brf, 25 brm)	GnRH-a	Patient-reported side effects	12 m, 24 m, 36 m	Mild headaches or hot flushes common (~20%). Moderate/Severe headaches or hot flushes, mild fatigue, mood swings, weight gain, sleep problems less common (<10%).
Tack *et al*[65]	Belgium	Pre-post	Moderate	38 brf	Lynestrenol	Patient-reported side effects	6 m, 12 m	Headaches and hot flushes were common, reported increase in acne and metrorrhagia was also reported—no numbers given.
Tack *et al*[67]	Belgium	Pre-post	Moderate	27 brm	Cyproterone acetate	Patient-reported side effects	6 m, 12 m	Complaints of fatigue in 37% and emotionality in ~10%.

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

Table 4 Puberty suppression outcomes

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

Continued

Table 4 Continued

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

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

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

Menstrual suppression

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

Height/Growth

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

Body composition

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

Bone geometry

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

DISCUSSION

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

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

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

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

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

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

Strengths and limitations

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

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

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

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

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

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

Conclusions

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

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