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Evidence Check

# Evidence for effective interventions for children and young people with gender dysphoria—update

An Evidence Check rapid review brokered by the Sax Institute for the NSW Ministry of Health—February 2024

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This report was prepared by: Bragge, P, Ngo C, Delafosse V, Goldberg E, Temple-Smith M, Sanci L.

February 2024


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# Evidence Check: Evidence for effective interventions for children and young people with gender dysphoria—update

## Supporting the statewide Specialist Trans and Gender Diverse Health Service to deliver best practice care and treatment

**An Evidence Check rapid review brokered by the Sax Institute for the NSW Ministry of Health. February 2024.**

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# Contents

# List of Abbreviations

| | | | |
|---|---|---|---|
| AFAB | assigned female at birth | Hb | haemoglobin |
| AMAB | assigned male at birth | HbA1c | haemoglobin A1c |
| ALT | alanine aminotransferase | Hct | haematocrit |
| ALP | alkaline phosphatase | HDL | high-density lipoprotein |
| AST | aspartate aminotransferase | K+ | potassium |
| BC | Bicalutamide | L | lynestrenol |
| BMAD | bone mineral apparent density | LDL | low-density lipoprotein |
| BMD | bone mineral density | LH | luteinising hormone |
| BMI | body mass index | LS | lumbar spine |
| BP | blood pressure | MPA | medroxyprogesterone acetate |
| CA | cyproterone acetate | NHMRC | National Health and Medical Research Council |
| CASP | Critical Appraisal Skills Program | NOS | not otherwise specified |
| CGAS | Children's Global Assessment Scale | OC | oral contraceptive pill |
| CSHT | cross-sex hormone treatment | QtC | heart-rate corrected QT interval (time taken for ventricular depolarisation and repolarisation) on an electrocardiogram |
| DEXA | dual-energy X-ray absorptiometry | PS | puberty suppression treatment |
| ED | eating disorder | RCHGS | Royal Children's Hospital Melbourne Gender Service |
| FA | fractional anisotropy | RCT | Randomised controlled trial |
| FN | femoral neck | SSC | spermatogonial stem cell |
| FP | fertility preservation | TAYAs | transgender adolescents and young adults |
| FSH | follicle-stimulating hormone | TE | testosterone esters |
| GAC | gender-affirming care | TESE | testicular sperm extraction |
| GAHT | gender-affirming hormone therapy | TG | transgender |

| | | | |
|---|---|---|---|
| GAS | gender-affirming surgery | TGD | trans and gender diverse |
| GD | gender dysphoria | TGNB | transgender and nonbinary |
| GICT | gender identity conversion therapy | TSH | thyroid-stimulating hormone |
| GID | gender identity disorder | TTC | testicular tissue cryopreservation |
| GnRH | gonadotropin-releasing hormone | TVQ | Transsexual Voice Questionnaire |
| GnRHa | gonadotropin-releasing hormone agonist | UGDS | Utrecht GD Scale |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation | WM | white matter |
| GRS | gender reassignment surgery | WPATH | World Professional Association for Transgender Health |

# Foreword

This Evidence Check report, commissioned by the NSW Ministry of Health through the Sax Institute, provides a comprehensive update of research evidence pertaining to interventions for young people aged under 18 experiencing gender dysphoria and published between 2019 and 2023. The purpose of this review is to provide an objective summary of the available literature on this topic.

The review builds on a previous Evidence Check, also commissioned by the NSW Ministry of Health through the Sax Institute, which covered the years 2000–2019. The research team that conducted this Evidence Check includes members involved in the previous Evidence Check.

This Evidence Check identified 82 new studies encompassing five gender dysphoria interventions—puberty suppression treatment, gender-affirming hormone therapy, gender-affirming chest ('top') surgery, fertility preservation and psychosocial therapies.

The increased volume of research evidence identified in this Evidence Check compared with the previous Evidence Check of the same topic (which identified 46 studies) reflects considerable growth in research in this field.

This Evidence Check systematically identified, tabulated, evaluated and described research regarding the effectiveness, risks and key characteristics of research on gender dysphoria interventions. Recommended best practice approaches to research evidence synthesis were consistently applied and transparently reported. As is standard practice for research evidence synthesis, we summarised the strengths and limitations of the body of research identified based on findings from analysis and the reported conclusions of authors of the research papers reviewed. This information informed recommendations for further research in this field.

**This report does not make recommendations for policy and clinical practice.**

Although knowledge of the state of the research evidence is an important input, policy decision making and the development of clinical practice guidelines are separate activities requiring a range of other inputs and consultation activities that were not within the scope of this project.

**Therefore, this report is not designed to support policy or clinical practice decision making in isolation from other inputs and consultation activities.**

We encourage readers of the report to consider its findings alongside credible policy, health service, clinical and other information sources relevant to their setting.

# Definitions used in this Evidence Check

The language used in this field is evolving. Consequently, terms used in past research will vary. Additionally, terms preferred by members of the community and clinicians may vary and carry different meanings. As such, we provide the following summary of the definitions used in this report.

**Transgender / trans and gender diverse** are umbrella terms referring to people whose assigned sex at birth does not match their internal gender identity. Transgender / trans or gender diverse people may identify as nonbinary (that is, not exclusively as either gender); as both genders; as neither gender; they may move between the gender binary; or they may reject the idea of gender altogether. Transgender / trans or gender diverse people may or may not modify their body, dress or legal status, and may or may not seek medical treatment.[1]

**Gender dysphoria** is defined as *"clinically significant distress arising from the incongruence between birth-assigned sex and gender identity"*.[2(p3)]

**Gender-affirmative healthcare** refers to a broad array of psychological, social, behavioural and medical interventions that aim to support and affirm an individual's gender identity. These interventions include, but are not limited to, interventions provided to people with gender dysphoria.

**Gender-affirming chest surgery ('top surgery')** is the surgical alteration of physical characteristics of the chest, including breast reduction (mammoplasty), breast augmentation or other types of chest reconstruction such as alterations to the chest wall. Additionally, both transgender men and women may have facial masculinisation or feminisation surgery as well as surgery to alter their vocal cords and related organs.[3]

**Gender-affirming hormone therapy (GAHT)** refers to medicines prescribed to help a person gain the outward characteristics that match their gender identity.

**Puberty suppression treatment** involves medicines that delay the physical and physiological changes associated with puberty.

**Fertility preservation** is the process of saving or protecting eggs, sperm or reproductive tissue so that a person can use them to have biological children in the future.

# Executive summary

## Background

Transgender and gender diverse healthcare is an emerging and complex area. In 2020, the Sax Institute published an Evidence Check review commissioned by the NSW Ministry of Health on the effectiveness of interventions for children and young people under 18 years old with gender dysphoria[2], defined as *"clinically significant distress arising from the incongruence between birth-assigned sex and gender identity"*.[2(p3)] In 2023, the NSW Ministry of Health commissioned the Sax Institute to provide a comprehensive update of the research evidence on this topic published between 2019 and 2023. This updated review followed the same research questions as the previous Evidence Check. This Evidence Check synthesises and appraises the newly identified evidence about the effectiveness of a range of gender dysphoria interventions that can be delivered in public hospitals and community settings in NSW, as well as any risks or safety issues associated with each component of care. This report does not make recommendations for policy and clinical practice. Information provided in this report on the state of the available research evidence will inform a range of activities and consultations to be undertaken by the NSW Ministry of Health.

## Research questions

This Evidence Check update aimed to address the following set of umbrella and sub-questions, developed in consultation with the NSW Ministry of Health:

**Question 1—Effective clinical medical interventions for transgender and gender diverse young people under 18 years old with gender dysphoria**

**Question 2—Effective psychosocial interventions for transgender and gender diverse young people under 18 years old with gender dysphoria**

**a:** What have been shown to be the most effective medical interventions and psychosocial interventions for treating transgender and gender diverse young people **under 18 years old** with gender dysphoria?

**b:** What have been shown to be the risks or potential harms from medical interventions and psychosocial interventions for treating transgender and gender diverse young people **under 18 years old** with gender dysphoria?

**c:** Is there variation in the effectiveness or risks associated with medical interventions and psychosocial interventions for treating transgender and gender diverse young people with gender dysphoria?

## Summary of methods

Our team undertook a search and selection process to identify peer-reviewed literature that responded to the research questions and was published between January 2019 and September 2023. We selected 82 eligible studies for inclusion in the Evidence Check update. All citations were ranked according to the established National Health and Medical Research Council (NHMRC) Levels of Evidence to assess the robustness of the included studies. We critically appraised all included studies using appraisal tools appropriate for the study design type. The proportionate levels of evidence identified were:

- 16 studies (20% of 82 included studies) Level I evidence (systematic reviews of level II studies—noting that although this is the technical NHMRC classification, the included systematic reviews did NOT review level II studies)
- 1 study (1%) Level II evidence (a randomised controlled trial)
- 12 studies (15%) Level III-2 evidence (comparative studies with concurrent controls)
- 5 studies (7%) Level III-3 evidence (comparative studies without concurrent controls)
- 48 studies (57%) Level IV evidence (case series or cross-sectional studies).

We performed a narrative synthesis of the results. In this process we mapped the updated review outputs against the findings of the first Evidence Check.[2] Studies examining multiple interventions for gender dysphoria were categorised based on their stated primary aim.

## Key findings

### Results of searching and study characteristics

Eighty-two studies met criteria for inclusion in this update review, comprising the following proportionate volumes of research by intervention type:

- 39 studies (48%) pertaining to gender-affirming hormone therapy (GAHT)
- 17 studies (21%) relevant to puberty suppression treatment
- 8 studies (9%) focusing on gender-affirming chest surgery
- 7 studies (8%) relevant to psychosocial therapies
- 6 studies (7%) relevant to fertility preservation.

There were also five studies (6%) that reported on care use (the proportion of participants who discontinued gender-affirming medical treatment); however, no firm conclusions can be drawn from this evidence about care use as it was an incomplete set of studies and was not a primary focus of this review. This section is therefore contained in Appendix 1.

The 82 eligible studies represented a considerable increase in volume of research examining gender dysphoria interventions from 2019–2023 with only 46 studies eligible for the previous review covering the years 2000–2019. Overall, the evidence about gender dysphoria interventions remains weak due to poor study designs, low participant numbers and single-centre recruitment. Additionally, there was variability in study characteristics such as included populations, specifics of interventions and outcome measures used. Therefore, readers with specific interests are encouraged to access the relevant evidence tables detailing individual study characteristics. While studies in this Evidence Check update generally report favourable outcomes for gender-affirming care initiatives, the limitations in the evidence need to be borne in mind when interpreting these findings. Notwithstanding these caveats the findings for key interventions of interest showed general congruence with those of the previous review of this topic.

## Key findings by intervention

### Question 1—Effective clinical medical interventions for transgender and gender diverse young people under 18 years old with gender dysphoria

As in the 2020 Evidence Check, the following clinical interventions were evaluated: two types of pharmaceutical intervention (puberty suppression and gender-affirming hormone therapy), surgical intervention (chest or breast surgery), and cryopreservation of gametes (sperm or oocytes).

#### *Puberty suppression treatment (PS)*

*(Number of studies by level of evidence: 3x Level I, 4x Level III-2, 1x Level III-3, 9x Level IV; total 17 studies)*

We identified 17 studies pertaining to puberty suppression treatment (PS) in this Evidence Check update. Broadly, the newly identified evidence reinforced the finding of the previous Evidence Check regarding benefits and effectiveness. That is, PS agents (generally referred to as GnRHa) were reported to be safe, effective and reversible. As a counterpoint, this update identified one study describing differential implications of PS for later surgery, with reduced need for mastectomy in trans men but potential complications for genital surgery in trans women as penile inversion may be compromised. Psychological effects of PS on conditions such as depression and anxiety appear modest in comparison with GAHT, with the primary impact being reduction of distress associated with unwanted secondary sexual characteristics; two Level IV studies reflected positive impacts on gender dysphoria.

With regard to risks and potential harms, reductions in bone density remain the primary concern with PS and monitoring of bone mineral density is recommended. However, some newly identified studies suggest maintenance of bone mineral density during PS treatment. Studies reported no indications to monitor liver or renal function in the PS setting. Other reported side effects of PS were also relatively minor. Instances of insufficient suppression of puberty (known as ‘pubertal escape’) were reported, but satisfaction with PS treatment was reported as good overall. In summary, this Evidence Check update predominantly reinforces the findings of the previous review and adds to the evidence base underpinning these findings; with the qualification that the strength of the evidence remains low.

### *Gender-affirming hormone therapy (GAHT)*

*(Number of studies by level of evidence: 7x Level I, 5x Level III-2, 2x Level III-3, 25x Level IV; total 39 studies)*

This Evidence Check update identified a considerable volume of evidence (39 studies) pertaining to GAHT, reflecting an overall rise in research into interventions for gender dysphoria since 2019–20. The newly identified studies support the conclusions of the previous review, which reported that GAHT was effective in producing changes in body composition that align with the desired sex. Increases in BMI were reported; however, this remained in the healthy range and did not appear to be long term. There does not appear to be a significant impact on adult height and it appears that GAHT recovers the bone mineral density losses that occur during PS.

Additionally, there were mixed results on menstrual suppression (albeit in Level IV studies) with some studies reporting good achievement of amenorrhea and others reporting breakthrough bleeding. A number of studies provided new evidence pertaining to the psychological benefits of GAHT. The identified studies reported positive results across the domains of body image, gender dysphoria, depression, anxiety, suicide risk, quality of life and cognitive function. However, neutral and some negative findings were also reported in these domains. Additionally, two Level IV studies reported no changes in mental health care use following gender-affirming pharmaceutical care. Although studies reporting positive mental health outcomes following GAHT outnumber those with neutral or negative findings, considerable flaws remain in the evidence because of generally low participation rates of target groups, inadequate representation of young people and / or poor study designs and conduct. The relevant systematic reviews identified underline this observation. Several studies support the finding of the previous review, which reported that GAHT appears to increase bone density following the negative impact of puberty suppression treatment on bone density.

We observed similar increases in research volume in studies reporting on the risks and potential harms of GAHT. Findings on overall safety, cardiometabolic risk, kidney and physiological parameters support the previous review's findings that serious adverse outcomes associated with GAHT are rare. One Level I study flagged risk of meningioma associated with cumulative dose exposures of cyproterone acetate greater than 3g and therefore quoted recommendations that daily doses should be 10mg or less. This study also reported increased prolactinoma risk, which may reflect increased monitoring, with symptomatic prolactinoma risk not elevated. Minor changes in physiological parameters were reported, for example, blood pressure and elevated potassium—in the case of potassium, none of the subjects had symptoms of hyperkalaemia, and all elevated measurements were normal when repeated. Newly identified primary studies reported a range of less serious side effects (for example, headaches, nausea and vomiting), consistent with the previous review. There was some evidence regarding fertility impacts of GAHT, although only from two Level IV studies. Overall, despite increases in research volume, the conclusions of the previous review with respect to GAHT are largely unchanged as the increased number of studies is offset by generally poor study designs.

### *Gender-affirming chest surgery ('top surgery')*

*(Number of studies by level of evidence: 1x Level I, 3x Level III-2, 4x Level IV; total 8 studies)*

This update identified eight studies evaluating surgery including one systematic review, therefore expanding the evidence base from the previous review. With regards to benefits / effectiveness, the

updated evidence reports generally positive findings for gender dysphoria, psychosocial outcomes and sexual function and quality of life. However, there were neutral findings on psychosocial outcomes in transgender men as well as mixed positive / negative findings on quality of life.

The irreversible nature of surgery remains a key risk / potential harm, although regret rates were low where reported. Complication rates for chest surgery were also reported to be low. In contrast with the previous review, several studies reported on outcomes in adolescents referred for chest surgery at 16–17 years of age. Findings were generally positive across these studies on sexual function, gender incongruence and chest dysphoria. One Level I study reported low regret rates and two Level III-2 studies reported low complication rates. Although the evidence base is expanded and generally supports chest surgery, confidence in findings is low because of a lack of studies and / or poor study quality, use of mixed surgery populations and the confounding effect of hormone and other therapies, which almost always precede surgery. Offsetting these limitations are three high quality comparative studies with positive findings specific to adolescents. In summary, this update provides some additional evidence that supports chest surgery; however, further studies are required that focus on the effect of surgery in adolescents.

### *Fertility preservation (cryopreservation)*

*(Number of studies by level of evidence: 2x Level I, 2x Level III-2, 3x Level IV; total 6 studies)*

This update has added two systematic reviews and a further four primary studies to the evidence base pertaining to cryopreservation (noting that three of the four primary studies were included in the two Level I reviews). Desire to have children among transgender adolescents is relatively high; however, uptake of fertility preservation treatment remains low because of cost barriers, late referral and low awareness. One Level I review found evidence for another factor contributing to low uptake of fertility preservation, identifying that most people who expressed an interest in having children did not see biological offspring as their preferred option. Although the newly identified evidence generally reports favourable benefits and effectiveness outcomes for both semen and oocyte cryopreservation, some risks or potential harms warrant mention. Studies consistently reported that semen was of lower quality if patients had received puberty suppression and / or GAHT. Furthermore, harvesting semen can be challenging in early puberty and / or due to discomfort with masturbation. There is emerging evidence that testicular sperm extraction can mitigate these limitations, although this research is in its infancy and semen cryopreservation remains the dominant approach. Oocyte preservation was reported as generally effective with no adverse events; however, cryopreservation procedures are invasive and psychologically challenging and can worsen gender dysphoria.

In summary, while additional evidence supporting fertility preservation was identified, both reviews and primary studies remain limited by small sample sizes, single centre recruitment, study design limitations and variation in use of hormones in participant cohorts. Notwithstanding this, outcomes reported are predominantly positive and very few adverse effects were described in identified studies.

## Question 2—Effective psychosocial interventions for transgender and gender diverse young people under 18 years old with gender dysphoria

### *Psychosocial therapies*

*(Number of studies by level of evidence: 3x Level I, 1x Level II, 1x Level III-3, 2x Level IV; total 7 studies)*

This Evidence Check update has added considerably to the volume of evidence evaluating psychosocial interventions such as such as psychotherapy, family therapy and mental health / crisis support. The previous review identified only three studies, with one a single case study; this Evidence Check has identified three systematic reviews and four primary studies including a randomised controlled trial. The newly identified studies report benefits and effectiveness across numerous outcome domains including suicidal ideation, psychological distress, depression, anxiety and gender minority stress. Furthermore, most studies report that interventions are both acceptable and safe, with no risks or potential harms reported.

Although the existence of an RCT is unique to this intervention category, it should be noted it was of a mixed population of sexual and gender-minority youth—the number of people experiencing gender dysphoria is not reported and no subgroup analysis of this group is presented. Furthermore, considerable limitations were identified in this body of literature. In addition to the previously observed limitations of small sample sizes and lack of diversity in participant cohorts, these included a large number of psychological interventions with additional variability in delivery mode; and studies of mixed populations with no subgroup analysis of adolescents and / or transgender participants. Therefore, although study designs are stronger relative to other intervention areas in this Evidence Check update, a number of limitations that are applicable to studies of psychological therapies should be borne in mind when interpreting findings of studies of psychological interventions.

## Gaps in evidence

We assessed the extent to which gaps in the evidence base reported in the previous Evidence Check[2] have been addressed by newly identified studies, with the following observations:

- The studies examining the characteristics of transgender and gender diverse young people within the context of treatment interventions in Australia are limited to descriptions of those attending a Melbourne-based gender-affirming care clinic. Knowledge of characteristics of cohorts in other Australian jurisdictions remains limited to poor.
- The evidence base was dominated by studies without control or reference group comparisons. This limitation was compounded by the complex nature of gender-affirming models of care for people experiencing gender dysphoria, which may involve multifaceted interventions that are often concurrent and/or delivered over a long period of time. This makes evaluation of specific treatment effects for individual therapies challenging. Hence the gap remains (as previously identified) for proof of effectiveness of the discrete interventions, medical or psychosocial. While it is acknowledged that ethical limitations preclude the conduct of randomised controlled trials for many gender dysphoria interventions, further comparative studies (i.e. Level III-2 and III-3 designs) would be of more value than uncontrolled (Level IV) studies in addressing this gap.
- The previous review noted that further studies were needed to explore the potential for the TGD child undergoing puberty suppression to experience the (increasing) social isolation proposed by some authors. As we found no newly identified evidence pertaining to social isolation during puberty suppression in this update, this gap in the evidence base remains.
- This Evidence Check update identified only one study targeting the relationship between puberty suppression, GAHT and surgical outcomes—confirming a persisting lack of research attention.

- Studies examining the effects of exercise and diet on bone density inadequately controlled for confounding (for example, due to exercise and vitamin D levels) and this remains a gap in knowledge.

There was a welcome increase in the volume of studies identified in this Evidence Check update, with a wide breadth of outcomes examined; however, there was inconsistent to low use of validated measures.

Likewise, the evidence base for psychosocial interventions has been augmented by a number of newly identified studies, although confidence in the findings remains low. Further research is required to explore specific effects of therapies at different ages and to expand the evidence beyond association (correlation) to firmer conclusions regarding causation and factoring in the influence of mediating variables.

## Recommendations for further research

Analysis of persisting research gaps indicated three main recommendations for research directions:

1. **Long-term follow-up and cohort tracking:**
   Existing identified cohorts from longitudinal studies should continue regular periodic follow-up to improve understanding of longer-term outcomes, including risks, benefits and potential economic-related insights.
2. **Collaboration and multicentre cohorts:**
   Newly established research studies in Australia should collaborate as much as practicable with established research teams to build multicentre cohorts. Such multisite cohorts may also harness the power and promise of data linkage to understand, for example, service use behaviours and best investments for models of care.
3. **Generalisability and bias reduction**
   Innovative study designs are needed that offer controls via appropriately recruited reference groups. The traditional RCT approach is unlikely to be feasible and ethically acceptable for many of the key intervention areas; however, in addition to other comparative study designs, one promising direction may be the application of hybrid designs emerging in the field of implementation science.

## Discussion and conclusion

Gender-affirming medical and psychosocial interventions can be considered a complex intervention, defined as comprising numerous interacting components; a corresponding number and variability of outcomes; and requiring flexibility and tailoring in delivery.[4] Complex interventions are resource-intensive to deliver and evaluate.

It can be challenging in the field of research into interventions for gender dysphoria to design studies that compare those receiving treatment with a well matched control group to ascertain the effect of the treatment. Ethical concerns arise regarding withholding of treatment to people experiencing gender dysphoria because of perceptions that this may cause greater distress. In addition, the nature of some gender dysphoria treatments themselves can make the selection of control groups difficult. It is

therefore not surprising that Level IV studies account for 57% of the total research volume in this Evidence Check update, with proportionally fewer comparative studies than in the previous Evidence Check. It is likely that these differences in part reflect dedicated efforts to report outcomes or 'snapshots' of clinical interest for cohorts over time as they progress through management at specialist gender dysphoria clinics. Examples include the programs led by the Royal Children's Hospital in Melbourne[5,6] and in Amsterdam.[7,8]

Moreover, the inherent limitation of research into interventions for gender dysphoria, independent of study design, is that gender dysphoria management is undertaken over a long treatment period during which various interventions may overlap. This makes it difficult to study the differential effect of individual interventions, even when a control group is used. For example, PS and GAHT, two interventions in 70% of all included studies in this Evidence Check update, often overlap; of the 57 primary studies examining these therapies, 40 contained cohorts that had received both therapies during the period of the study, including 21 of the 23 Level IV studies examining GAHT. The complex nature of gender dysphoria treatment, in addition to these factors, should be considered when interpreting the findings of this Evidence Check.

Notwithstanding the above considerations, there was some consistency in the findings between the original Evidence Check and this update. Several newly identified studies, including reviews and controlled empirical studies, supported previous conclusions that gonadotropin-releasing hormone agonists are the most effective treatment for puberty suppression. Similarly, a relatively large number of studies reported positive impacts of GAHT on a range of psychosocial outcomes including gender dysphoria, depression, anxiety and suicide risk. Evidence identified in this Evidence Check update also reported that both semen and oocyte cryopreservation were successful approaches to fertility preservation.

This update added considerably to the evidence base about psychosocial therapies from the previous Evidence Check. Newly identified studies reported a range of benefits across suicidal ideation, depression and anxiety. Both the confounding effects of hormonal therapies and the wide range of disparate psychological therapies evaluated should be borne in mind when interpreting findings of psychological interventions.

While there has not been a rapid growth in the conventionally accepted gold standard designs of RCTs in this field, this Evidence Check offers important insights into the effectiveness and risks associated with gender dysphoria interventions. The combined total of 128 studies (of varying quality) provides a platform for engaging patients and carers in dialogue on key issues, including defining directions for future research investment.

Finally, it is important to emphasise that this Evidence Check provides a synthesis of reported findings of eligible studies, the strength of the study design and how each study has been conducted. This review is not designed to guide policy or clinical practice. Although knowledge of the state of the research evidence is an important input into policy and clinical practice guideline development, these activities involve considerable additional processes, consultations and inputs. Therefore, this report should not be used in isolation to guide policy or practice.

# Background

Not all people who identify as transgender / trans or gender diverse experience gender dysphoria.[9] However, people who do experience persistent gender dysphoria are a uniquely vulnerable group at high risk of harm from discrimination, bullying, social exclusion and physical assault, which can contribute to poorer health outcomes.[10] Transgender individuals experience an elevated prevalence of mental health problems that negatively impact wellbeing and quality of life[11], including higher suicidal ideation and suicide rates than the general population.[12]

To address these impacts, it is important that transgender and gender diverse people, including those experiencing gender dysphoria, have access to supports and services that are informed by the best available research evidence. NSW Health's current LGBTIQ+ Health Strategy 2022–2027 reflects this principle with a stated vision that *"LGBTIQ+ people in NSW receive high quality, safe, inclusive and responsive healthcare that delivers outcomes that matter to them"*.[13] Accordingly, a Framework for the Specialist Trans and Gender Diverse Health Service for People Under 25 Years was published by NSW Health in July 2023. This is designed to guide *"how evidence-based trans and gender diverse health care will be delivered through the Specialist Trans and Gender Diverse Health Service (the TGD Health Service) to NSW Local Health Districts (LHDs) and Speciality Health Networks (SHNs)"*.[1]

A previous review of evidence pertaining to the effectiveness of interventions for children and young people with gender dysphoria commissioned by NSW Health through the Sax Institute was published in 2020.[2] It identified 46 papers, comprising 34 empirical studies, six reviews and six guidelines or consensus statements.

The previous Evidence Check concluded that *"the available evidence of the benefits and harms of treatment for this age group is of low quality"*.[2(p11)] Specific limitations highlighted included small sample sizes, an absence of RCTs from ethical concerns, lack of standardised outcome measures and failure to control for confounders (variables that can influence measured outcomes). Although the quality of evidence was described as low, the review outlined a range of benefits and risks associated with puberty suppression treatment and gender-affirming hormone therapy (GAHT). In contrast, the review reported very little evidence for either benefits or risks associated with gender-affirming surgery or psychosocial interventions.[2]

The current Evidence Check was commissioned by NSW Health through the Sax Institute to inform a range of projects to ensure delivery of high quality responsive services, including but not limited to:

- Development of clinical guidance for the TGD Health Service by a Clinical Advisory Group to support consistent and high-quality care
- Development and implementation of monitoring and evaluation mechanisms to track outcomes, embed quality improvement and contribute to the wider evidence base
- Development of accessible resources to ensure young people and families have the information they need to make informed decisions about treatment and care options.

The questions for this Evidence Check are:

**Question 1—Effective clinical medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria**

1. Question 1a—What have been shown to be the most effective medical interventions for trans and gender diverse young people **under 18 years old** with gender dysphoria?
2. Question 1b—What have been shown to be the risks or potential harms from medical interventions for trans and gender diverse young people **under 18 years old** with gender dysphoria?
3. Question 1c—Is there variation in the effectiveness and risks associated with medical interventions for trans and gender diverse young people **under 18 years old** with gender dysphoria by factors listed below?

**Question 2—Effective psychosocial interventions for trans and gender diverse young people under 18 years old with gender dysphoria**

1. Question 2a—What have been shown to be the most effective psychosocial interventions for treating trans and gender diverse young people **under 18 years old** with gender dysphoria?
2. Question 2b—What have been shown to be the risks or potential harms from psychosocial interventions for treating trans and gender diverse young people **under 18 years old** with gender dysphoria?
3. Question 2c—Is there variation in the effectiveness or risks associated with psychosocial interventions for treating trans and gender diverse young people **under 18 years old** with gender dysphoria?

The Evidence Check was undertaken between August 2023 and February 2024 and focused on research on this topic published since the previous Evidence Check. We therefore limited searches for evidence to the years 2019–2023. All searches were conducted on **19 September 2023.**

In reporting the results of this Evidence Check, we made reference to the key conclusions from the previous 2020 review[2]; the commentary focused on what the new evidence from 2019 onwards has added to these previous conclusions. Readers interested in the evidence tables and further details from the 2020 review are encouraged to access the previous report.[2]

# Methods

The methodology of the Evidence Check update included:

- Identifying peer-reviewed articles for each research question
- Screening for relevant studies
- Characterising the studies
- Grading the level of evidence of peer-reviewed articles for selected questions (strength of study design) and evaluating their methodological quality (conduct of study)
- Reporting the results of selected studies and summarising key findings for each question by intervention
- Identifying evidence gaps and providing recommendations for future research that might address the gaps.

## Peer-reviewed literature search

As this is an update of a previous review, an *a priori* review protocol was developed based on the parameters of the original Evidence Check, with testing and refinement in consultation with the NSW Ministry of Health and the Sax Institute.

The peer-reviewed literature search was conducted using electronic databases including the Cochrane Library, Joanna Briggs Institute, Medline, Embase, PsycINFO, CINAHL and Scopus. All databases were searched on September 19, 2023. Following screening and selection of relevant articles from the database search, references cited in five clinical practice guidelines supplied by the NSW Ministry of Health (listed in Appendix 2) were cross-checked against the yield from the database search for eligible articles not captured in the search[*].

## Eligibility criteria

Citations, abstracts and full-text articles were screened independently by two members of the research team, with disagreements resolved via consensus discussion. The study inclusion and exclusion criteria were co-developed with the NSW Ministry of Health based on the previous Evidence Check (Table 1).

[*] Note the inclusion of the clinical practice guidelines was not within the scope of this review Evidence Check update as the focus of the review was on the underlying evidence rather than clinical practice recommendations.

## Table 1—Study selection: Inclusion and exclusion criteria

| | Include | Exclude |
|---|---|---|
| **Publication type** | • Systematic reviews focused on gender dysphoria or contained a section focused on gender dysphoria<br>• Primary studies conducted in Australia and countries with comparable health services: New Zealand, Canada, US, UK, Western Europe [Luxembourg, Germany, Netherlands, Spain, Portugal, Ireland, Monaco, Switzerland, Belgium, Liechtenstein, Andorra, UK, France, Gibraltar, Isle of Man] and Scandinavia [Denmark, Sweden, Norway, Iceland, Finland, the Faroe Islands]. | • Systematic reviews without a focus or specific section on gender dysphoria—for example, more broadly focused on LGBTQI+<br>• Non-systematic reviews, as these are subject to article selection bias<br>• Clinical practice guidelines are out of scope for the review, which focuses on the evidence base rather than clinical practice recommendations<br>• Qualitative studies, as these focus on care experience rather than effectiveness of interventions<br>• Primary studies not conducted in Australia or the listed countries with comparable health services<br>• Book chapters<br>• Theses<br>• Conference presentations that are not full peer-reviewed papers<br>• Expert or consensus opinion papers, commentaries<br>• Case reports / small case series with fewer than 10 participants as these are not generalisable<br>• Preprints as these are not peer-reviewed. |
| **Language** | English | Non-English |
| **Population** | • Children and young people (including prepubertal) ⩽ 18 years of age experiencing gender dysphoria, defined as *"clinically significant distress arising from the incongruence between birth-assigned sex and gender identity"*.[14] This includes those with variations of sex characteristics or differences in sex development at birth who were assigned a gender that differs from their gender identity | • Adults aged over 18, unless treatment was received when ⩽ 18 years of age<br>• Mixed-age populations with no sub-analysis of people ⩽ 18 years of age or where the proportion of participants ⩽ 18 cannot be determined<br>• *Studies of mixed age populations ⩽ 25 years of age will be tagged as 'of interest' as this is the relevant age range of the sponsoring health service; however, the search strategy will not capture all such studies* |

| | Include | Exclude |
|---|---|---|
| | • Studies reporting on interventions for transgender adolescents up to the age of 25 where the mean age was 17 years or younger and mean age is reported in the study, or if more than 50% of the sample was 17 years or younger<br>• Studies of mixed age groups where there is sub-analysis of children ⩽ 18 years of age<br>• Where participant follow-up was reported beyond 18 years, studies in which the intervention was commenced at 18 years or younger. | • Studies of stakeholder and community views, including those of parents of children and young people (including prepubertal) ⩽ 18 years of age experiencing gender dysphoria, as the primary focus is the effects of treatment on this group rather than wider impacts and perceptions. |
| **Study focus** | • All studies evaluating interventions for gender dysphoria including:<br>• Fertility preservation<br>• Psychological and psychosocial interventions<br>• Puberty suppression treatment<br>• Contraception in the context of management of gender dysphoria<br>• Gender-affirming hormone therapy, sometimes referred to as cross-sex hormone therapy<br>• 'Top' surgery. | • Non-interventional studies<br>• Contraception outside of the context of gender dysphoria (for example, to manage menstruation problems in cisgender adolescents)<br>• Conversion therapy<br>• HIV prophylaxis<br>• Ethics papers, e.g. regarding consent practices<br>• Legal papers regarding gender dysphoria laws / rulings<br>• 'Bottom' surgery (genital surgery). |
| **Outcomes** | All outcomes including costs, side effects, adverse outcomes, harms of not providing treatment, non-deterioration and benefits. | |
| **Date Range** | 2019–2023 | Studies published before 2019. |

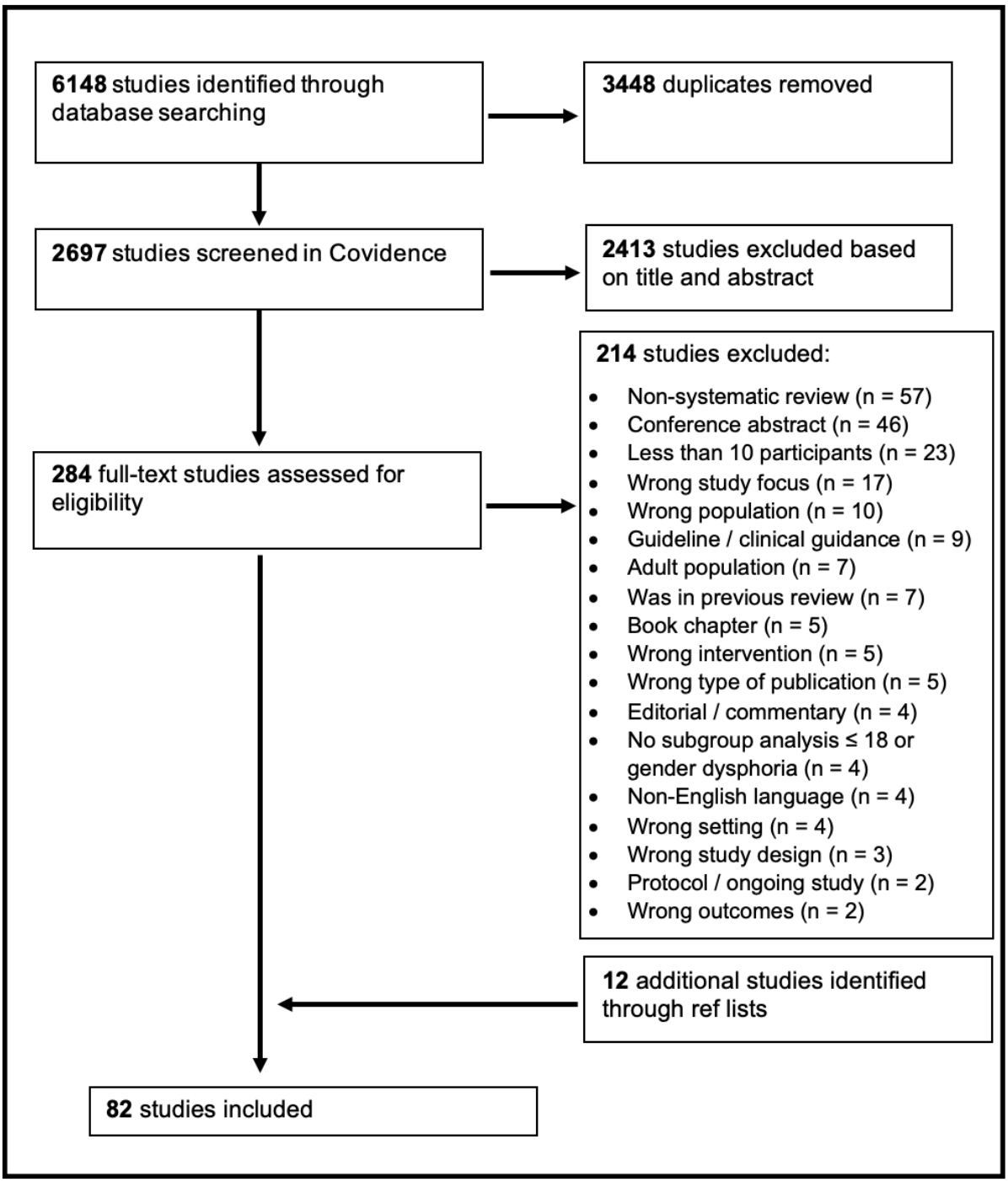
## Included studies

After removal of duplicate citations, we identified 2697 citations in the initial databases search. Using Covidence, we screened the studies by title and abstract and excluded 2413 citations based on study inclusion and exclusion criteria (Table 1). The remaining 284 citations were progressed to full-text review, where a further 214 studies were excluded. We identified an additional 12 citations from the reference lists of studies and clinical practice guidelines. The full texts of these additional citations

were examined and they were subsequently included in this Evidence Check. In total, 82 reports met the criteria for consideration in this Evidence Check update. The flow diagram for the literature search and selection phases is detailed in Figure 1.

**Figure 1—Flow diagram for the literature search and selection process**

The literature was included or excluded in three phases: identification, title and/or abstract screening and full-text screening. The number of records considered at each stage is indicated in brackets.



## Evidence grading and quality appraisal

Consistent with the previous Evidence Check, we assessed the quality of included studies using the National Health and Medical Research Council (NHMRC) levels of evidence and grades for recommendations for guideline developers.[15] We critically appraised all 82 included studies using appropriate appraisal tools for each study design. Appendix 2 details the characteristics of studies by NHMRC level of evidence, study design, appraisal approach and number of identified studies.

## Data analysis and reporting

We categorised studies that examined multiple interventions for gender dysphoria using their stated primary aim. Further details of the review protocol, including search strategies and yields by database, plus results of cross-checking of clinical practice guidelines, are contained in Appendix 2.

As with the previous Evidence Check, meta-analysis was not a valid approach to synthesise the findings because of the heterogeneity of the included studies. The most appropriate approach was a narrative synthesis of findings, which included consideration of the level of evidence of the studies. It should be noted that some review papers among the included studies may have sourced the same primary studies, and this Evidence Check update may have encompassed primary studies included within those systematic reviews. Care has been taken in interpreting the findings of such reviews to ensure results or certain primary sources are not overstated.

To support comparison, we compiled the findings across the five intervention categories covered by the previous Evidence Check:

- **Puberty suppression treatment**
- **Gender-affirming hormone therapy**
- **Gender-affirming chest surgery**
- **Fertility preservation**
- **Psychosocial interventions.**

As in the previous review, the findings for each of these intervention categories reported across eligible studies were compiled under the following headings:

- Context—treatment information (e.g. definition, various medications)
- Benefits—benefits / effectiveness of treatment across key outcomes
- Risks—adverse events and risks of treatment, including side effects
- Variation in the effectiveness and risks—information about how benefits and risks may vary according to age, treatment stage or other relevant domains
- Strengths and limitations of evidence
- Conclusions of Evidence Check update.

We created detailed data extraction tables in order to capture a more detailed summary of the parameters of individual studies relevant to each intervention category. Reflecting the variability in the characteristics of the studies included in this Evidence Check, readers with specific interests are encouraged to access the relevant evidence tables detailing individual study characteristics.

For *systematic reviews,* we extracted the following data:

- Author, date, aims, number of quality criteria met, and number applied
- Groups targeted by the intervention in the included studies
- Intervention
- Age or stage of puberty
- Benefits
- Risks
- Key conclusions reported by study authors (headline findings, headline conclusions on strength of evidence contained in the review).

For *primary studies,* we extracted the following data:

- Author, date, aims, number of quality criteria met and number evaluated
- Country, design, setting
- Intervention (primary intervention of interest as reported by the study authors)
- Sample size, age and gender identity of subjects
- Main outcomes
- Benefits
- Risks
- Key conclusions reported by study authors (headline findings, strengths /limitations of the study).

We ordered the data extraction tables on two levels; first, from highest to lowest level by study design (i.e. Level I to Level IV) and then from highest to lowest based on the number of quality criteria met using the appropriate quality appraisal tool. For example, the findings of systematic reviews are presented first in each intervention category (Level I on the NHMRC level of evidence) and each systematic review is then ordered from highest to lowest according to the number of quality criteria met based on appraisal using the AMSTAR 2[16] critical appraisal tool for systematic reviews, in the data extraction tables.

With respect to interpreting the results of the quality appraisal analyses, it is important note that the denominator for the same quality appraisal tool varies as a count of which items are applicable to an individual study. Additionally, some quality appraisal tools (e.g. the AMSTAR 2) do not recommend creating a summed measure of 'quality criteria', because each individual criterion is not necessarily considered 'equal'. Therefore, the ranking of study designs has taken primacy when interpreting the findings of this Evidence Check, with the ranking by quality criteria used as an indicative guide to relative quality only.

In the years since the previous Evidence Check there has been increased focus on gender detransition, defined as *"the process of reidentifying with one's birth sex after having undergone a gender transition"*.[17(p270)] To this end, a short narrative summary of identified evidence relating to care use has been included in this Evidence Check in Appendix 2. This reflects that **care use was not a primary focus of this review, which focused on intervention effectiveness. Where studies included in this review also reported on care use, that information has been extracted, but it does not represent all the available evidence on this topic.**

Table 2 shows the distribution of the 82 included studies by evidence grade (rows) across the five intervention areas and the additional category of care use (columns).

### Table 2—Included studies by NHMRC evidence grading[15] and intervention

| Level and study design | Puberty suppression treatment (n = 17) | Gender-affirming hormone therapy (n = 39) | Gender-affirming surgery (n = 8) | Fertility preservation (n = 6) | Psychosocial interventions (n = 7) | Care use (n = 5) |
|---|---|---|---|---|---|---|
| **I. A systematic review* (n=16)** | 3 | 7 | 1 | 2 | 3 | |
| **II. A randomised controlled trial (n=1)** | | | | | 1 | |
| **III-1. A pseudo-nonrandomised controlled trial (n=0)** | | | | | | |
| **III-2. A comparative study with concurrent controls (n=12)**<br>• Non-randomised experimental trial<br>• Cohort study<br>• Case-control study<br>• Interrupted time series with a control group | 4 | 5 | 3 | | | |
| **III-3. A comparative study without concurrent controls (n=5)**<br>• Historical control study<br>• Two or more single arm studies<br>• Interrupted time series without a parallel control group | 1 | 2 | | 1 | 1 | |
| **IV. Case series / cross sectional study (n=48)** | 9 | 25 | 4 | 3 | 2 | 5 |

While level I evidence is strictly classified as systematic reviews of RCTs (Level II studies), almost no RCTs have been conducted in this area to date. The systematic reviews enumerated here have used systematic principles, and so provide the best quality evidence in the absence of reviews of RCTs.

# Findings

All included studies were analysed according to their NHMRC level of evidence grading. The appropriate tools for each study design were used to assess the quality of the studies. A summary of this process is presented in Table 3.

### Table 3—Level of evidence grading and critical appraisal tool used by study

NHMRC evidence grading, study design definitions, number and citations of included studies by study design and critical appraisal tools and processes used are summarised below.

| Level | Study design and definition | N | Critical appraisal tool and approach |
|---|---|---|---|
| I | **A systematic review of level II studies**<br><br>*"Systematic location, appraisal and synthesis of evidence from scientific studies".*[14(p20)] NOTE: The NHMRC definition specifies that systematic reviews are focused on Level II studies (randomised controlled trials). The systematic reviews in this Evidence Check did NOT review Level II studies. | 16 studies[3,11,12,18–30] | The AMSTAR 2 tool for evaluating quality of systematic reviews.[16] We appraised all systematic reviews in duplicate, with disagreements resolved through discussion. |

| | | | |
|---|---|---|---|
| **II** | **A randomised controlled trial**<br><br>*"Experimental studies meet three conditions: manipulation, control and random assignment. Specifically, the researchers manipulate the intervention of interest and the control condition and they randomly allocate the participants to the intervention or control group (Shadish et al. 2002). Random allocation refers to an authentically random process such as the toss of a coin or use of a table of random numbers (Shadish et al. 2002)".*[31(p72)] | 1 study[32] | The revised JBI critical appraisal tool for the assessment of risk of bias for randomised controlled trials[33]: appraised in duplicate with disagreements resolved through discussion. |
| **III-1** | **A pseudo-nonrandomised controlled trial (i.e. alternate allocation or some other method)**<br><br>*" … allocation may not use an authentically random process. For example, if investigators use alternate group allocation like even and odd dates, they cannot ensure that each participant has an equal chance of landing in either group. Experimental studies without authentic random allocation but using systematic alternate group allocation methods mentioned above are experimental studies with pseudo randomisation, or pseudo-RCTs".*[31(p72)] | 0 | N/A |
| **III-2** | **A comparative study with concurrent controls** | | |
| | **Non-randomised experimental trial:** "*Quasi-experimental studies are studies where the intervention of interest and the control condition are controlled (manipulated) by the researchers, however, the allocation of participants is not a* | 1 study[34] | JBI checklist for quasi-experimental studies (non-randomised experimental studies)[35]: appraised by one reviewer. |

| | | | |
|---|---|---|---|
| | *random, systematic or pseudo-random allocation. Frequently, participants self-select into groups or the researchers decide which persons should get the intervention and which persons should get the control (Shadish et al 2002)".*[31(p72)] | | |
| | **Cohort study:** *"… outcomes for groups of people observed to be exposed to an intervention, or the factor under study, are compared to outcomes for groups of people not exposed".* Prospective = followed prospectively with further outcomes recorded as they happen; retrospective = defined at a point of time in the past and information collected on subsequent outcomes [NHMRC 2008].[14] | 11 studies[36–46] | JBI checklist for cohort studies[47]: appraised by one reviewer with a second reviewer also undertaking two appraisals as a quality check. |
| | **Case-control study:** *"… people with the outcome or disease (cases) and an appropriate group of controls without the outcome or disease (controls) are selected and information obtained about their previous exposure/non-exposure to the intervention or factor under study"* [NHMRC 2008].[14] | 0 | N/A |
| | **Interrupted time series with a control group:** *"… trends in an outcome or disease are measured over multiple time points before and after the intervention (factor under study) is introduced to a group of people, and then compared to the outcomes at the same time points for a group of people that do not receive the intervention (factor under study)"* [NHMRC 2008].[14] | 0 | N/A |

| | | | |
|---|---|---|---|
| **III-3** | **A comparative study without concurrent controls** | | |
| | **Historical control study:** *"… outcomes for a prospectively collected group of people exposed to the intervention (factor under study) are compared with either (1) the outcomes of people treated at the same institution prior to the introduction of the intervention (i.e. control group/usual care), or (2) the outcomes of a previously published series of people undergoing the alternate or control intervention"* [NHMRC 2008].[14] | 3 studies[48,49,50] | JBI checklist for case control studies[51]: appraised by one reviewer with a second reviewer also undertaking one appraisal as a quality check. |
| | **Two or more single arm studies:** *"… the outcomes of a single series of people receiving an intervention (case series) from two or more studies are compared"* [NHMRC 2008].[14] | 0 | N/A |
| | **Interrupted time series without a parallel control group:** *"… trends in an outcome or disease are measured over multiple time points before and after the intervention (factor under study) is introduced to a group of people, and compared*" [NHMRC 2008].[14] | 2 studies[52,53] | JBI checklist for quasi-experimental studies (non-randomised experimental studies)[35]: appraised in duplicate with disagreements resolved through discussion. |
| **IV** | **Case series** with either post-test or pre-test/post-test outcomes. | 42 studies[5–8, 54–91] | The National Institutes of Health (NIH) quality assessment tool for before-after (pre-post) study with no control group.[92] Appraised by one reviewer with a second reviewer also undertaking four appraisals as a quality check. |

| | | | |
|---|---|---|---|
| | **Cross-sectional study**: *"… a group of people are assessed at a particular point (or cross-section) in time and the data collected on outcomes relate to that point in time"* [NHMRC 2008].[14] | 6 studies[93–98] | JBI checklist for analytical cross-sectional studies.[99] Appraised by one reviewer with a second reviewer also undertaking one appraisal as a quality check. |

# Question 1—Effective clinical medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria

Question 1a—What have been shown to be the most effective medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria ?
Question 1b—What have been shown to be the risks or potential harms from medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria?
Question 1c—Is there variation in the effectiveness and risks associated with medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria?

## Puberty suppression treatments

### *Context*

Puberty suppression treatments, also referred to as puberty blockers, are designed to delay the development of secondary sexual characteristics such as breasts in trans males and deepening voice and laryngeal prominence in trans females. Gonadotrophin releasing hormone analogues (GnRHa) are used to achieve puberty suppression.[24,26,27]

Puberty suppression is intended to relieve distress associated with the onset and development of secondary sexual characteristics in people experiencing gender dysphoria, and to give time to discuss and explore less reversible interventions.

Puberty suppression treatment may be undertaken in conjunction with psychological counselling and may be followed by the use of gender-affirming hormone therapy (GAHT: the use of hormones to induce development of physical sex characteristics consistent with preferred gender identity).[25] Therefore, studies examining the effectiveness of puberty suppression may have recruited participants who received both puberty suppression treatment and GAHT. This is especially the case for retrospective research designs or studies conducted over long time periods of clinical interventions. In this Evidence Check, we have classified studies according to their stated primary focus. This means *participants in the studies listed in this section may have received both puberty suppression treatment and GAHT, but their stated primary focus is the effectiveness of puberty suppression*.

This Evidence Check update identified 17 studies focusing on puberty suppression treatment—three systematic reviews (Level I evidence); four comparative studies with concurrent control (Level III-2); one comparative study without concurrent control (Level III-3); and nine case series and cross-sectional studies (Level IV).

The additional information about the benefits of puberty suppression provided by this Evidence Check is summarised below (Table 4). It covers the overall effectiveness of treatments, reversibility, safety and tolerance, and psychological outcomes.

## Table 4a—Benefits of puberty suppression treatment

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| A gonadotropin-releasing hormone agonist (GnRHa) is the most effective treatment to suppress puberty. | **Overall effectiveness for suppression of puberty**<br>Eight studies reported positive findings regarding effectiveness of GnRHA for puberty suppression. Two Level I studies reported that GnRHa is well tolerated by the target population[26,27] and one of these also reported that GnRHa is preferred for puberty suppression.[27] Two comparative studies with controls (III-2)[42,46], one comparative study without concurrent controls (III-3)[49], and three Level IV studies[64,84,85] reported that GnRHa was effective for puberty suppression. One Level IV study reported eight cases of pubertal escape in a sample of 49 patients using histreline.[84] |
| Puberty suppression treatment for TGD adolescents appears to be **effective, safe, well tolerated and reversible**, thus allowing the adolescent to explore their gender identity before embarking on irreversible, or partially irreversible, treatment (eight references, NHMRC levels III-2 to IV). | **Reversibility**<br>Two systematic reviews (I) reported that puberty suppression treatment is reversible.[26,27]<br><br>**Safety and tolerance**<br>Seven included studies reported that puberty suppression treatment is safe, well tolerated, or has few side effects. These comprised two systematic reviews (I)[26,27], one comparative study with a control group (III-2)[39] and four pre-post cross-sectional studies (IV).[69,84,85,97]<br><br>One Level IV study examined the effects of GnrHa on the heart by measuring the electrocardiographic QTc interval. It found no significant effect for the GnRHa drug leuprolide acetate (noting no other GnRHa drugs were explored in this study).[91]<br><br>One III-2 study reported mixed findings—while puberty suppression reduced breast development and lessened the need for or extent of chest surgery in trans men, the subsequent reduction in penile development in |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | trans women could result in the need for more extensive genital surgery.[46] |
| Puberty suppression treatment reduces emotional and behavioural problems associated with gender dysphoria (one reference). A key psychological benefit associated with puberty suppression treatment is the prevention of future psychological distress that TGD adolescents may experience when they develop the secondary sexual characteristics of the sex they were assigned at birth (one reference). However, it is also possible that puberty suppression treatment may increase social isolation for adolescents, who remain in a prepubertal state and thus out of synchrony with their age-group peers. | **Psychological outcomes**<br>The review undertaken by the National Institute for Health and Care Excellence (NICE) (2020)[24] reported that GnRHa had positive effects on psychosocial functioning and may reduce depression; Rew (2021)[27] reported improvements in affect and social life and decreases in depressive symptoms, emotional and behavioural problems and suicidal ideation. Ramos (2021)[26] reported improved mental health. Additionally, two Level IV studies reported lower odds of lifetime suicidal ideation (Turban 2020)[97]; and reduced emotional and behavioural problems (van der Miesen 2020).[98]<br><br>NICE (2020)[24] also reported that GnRHa had no impact on gender dysphoria, anger, anxiety or body image. Similarly, one Level IV study |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | reported no change in psychological functioning, quality of life or gender dysphoria.[64] |
| To achieve the appearance of the desired sex, the outcomes of gender-affirming hormone therapy (GAHT) and surgery are better among individuals for whom puberty was suppressed compared with those who initiated physical transition after puberty had been completed (one reference, NHMRC level III-2). | No relevant information pertaining to this finding was identified in this update. |

### Table 4b—Costs and risks of puberty suppression treatment

The additional information on the costs and risks of puberty suppression provided by this Evidence Check is summarised below. It covers treatment costs, bone density and other side effects.

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| GnRHa is the most effective treatment for puberty suppression; however, it is also the most expensive. | **Treatment costs**<br>One Level III-2 study reported that two puberty suppression treatment implants (Vantas and SupprelinLA) were equally effective—with Vantas being approximately 10% of the cost of SupprelinLA.[42]<br><br>Similarly, the Level III-2 study by Eitel (2023)[39] found intramuscular Lupron and subcutaneous Eligard were equally effective in suppressing clinical puberty progression, with Eligard approximately 25% of the cost of Lupron. Additionally, Eligard was superior for *biochemical* puberty suppression.<br>Little data about costs was provided in the updated studies, although some compared more and less expensive forms of puberty suppression treatment. |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| For young people with needle phobia, GnRHa may not be acceptable as it is delivered via injection. | No relevant information pertaining to this finding was identified in this update. |
| Some adolescents experience a loss of bone density mineralisation from a lack of oestrogen or testosterone, which is a concern as it increases the future risk of osteoporosis and bone fractures. More research is needed to understand whether the bone density mineralisation changes are fully reversible, and why only some adolescents experience this adverse side effect (four references, NHMRC levels III-2 to IV). Other side effects such as hot flushes, weight gain, acne and mood changes are common but are generally well tolerated. | **Bone density**<br>The Level I study by NICE (2020)[24] reported that while three studies had found GnRHa reduced bone density, the observed reductions were largely within one standard deviation of normal. Another Level I study by Ramos (2021)[26] reported either maintenance or reduction of bone mineral density across three studies, two of which reported that addition of cross-sex hormones tended to re-establish BMD. The Level I study by Rew (2021)[27] reported reduced turnover and bone mineral density with use of GnRHa, particularly in young trans women.<br><br>Three Level IV studies reported mixed findings on bone density:<br>• No significant change over three years, but significant fall in first year; baseline measures were lower in trans boys compared with trans girls[74]<br>• Negative effects on bone mineral density were reported; however the majority of participants were deficient in Vitamin D. Spinal X-rays of four participants with significant decreases in bone mineral density revealed no fractures.[79]<br><br>**Other side effects**<br>A range of side effects was reported across included studies. These are listed below with reference to study design.<br>• Headache (Level I: NICE 2020[24], Level IV: Carmichael 2021[64])<br>• Pain (Level I: NICE 2020[24], Level IV: Schwartz[85])<br>• Changes in body fat (Level I: Ramos 2021, Rew 2021[26,27]) |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | • Mood swings and emotional lability (Level I: Rew 2021[27], Level IV: Schwartz 2023[85])<br>• Reduced height velocity if starting later in puberty / at later Tanner stages (Level III-2: Schulmeister et al. 2022[43])<br>• Histrelin implant can be difficult to remove / replace but this is a rare complication (Level IV: Pine-Twaddle 2023[84])<br>• Hot flush (Level IV: Carmichael 2021[64]).<br><br>Two Level IV studies showed no effects<br>• Withdrawal of sex hormones had no effect on body composition of trans boys; unexpected decrease in height and lean mass in trans girls (Ghelani 2020)[69]<br>• Body fat redistribution (android vs. gynoid) was in keeping with participants' affirmed gender (Navabi 2021).[79] |
| Fertility may be compromised in individuals who start puberty suppression treatment at a young age because the treatment impairs the development of sperm cells (spermatogenesis) and egg formation in the ovary (oocyte maturation) (one reference).<br>Fertility preservation options should be discussed with patients and their caregivers before starting GnRHa. We found no empirical evidence for fertility compromise in adolescents in any empirical studies but recommendations for discussion of fertility preservation prior to medical intervention for TGD children and adolescents were given in guidelines, reviews without meta-analyses and position statements (six references). | No identified studies provided updates to this finding. |
| There is a theoretical potential for increased social isolation for TGD adolescents as they undergo treatment because the timing of puberty may be out of synchrony with their age-group peers (one reference—NHMRC level ungraded: clinical practice guideline). | No identified studies provided updates to this finding. |

### Table 4c—Variation in the benefits and risks of puberty suppression treatment

As summarised below, this Evidence Check produced no additional information on variation in the benefits and costs and risks of puberty suppression.

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| There is no minimum age to start puberty suppression treatment; rather, the pubertal stage is used to determine what is most appropriate for each child or adolescent. The recommendation is for trans males to start at Tanner stage 2 and trans females at Tanner stage 2–3 (three references) depending on individual circumstances (NHMRC level of evidence ungraded: standards of care and clinical practice guidelines). For example, a trans female who has already gained desired height may wish to begin GnRH earlier than a trans girl who has not gained their desired height, as long as they have reached Tanner stage 2. | No identified studies provided updates to this finding (noting that clinical practice guidelines were out of scope for this Evidence Check update). |
| Careful monitoring is required regarding bone density. Where loss of bone density is evident, it is recommended that a shorter use of GnRHa or an earlier start of GAHT be considered (three references—NHMRC level of evidence ungraded: clinical practice guideline and reviews without meta-analyses). | No identified studies provided updates to this finding (noting that clinical practice guidelines were out of scope for this Evidence Check update). |

#### *Strengths and limitations of evidence*

All three systematic reviews commented on limitations in the design of included studies, mitigating against firm conclusions. Additionally, Rew et al.[27] emphasised limitations in diversity of study participants, with the vast majority being Caucasian or white.[27] Limitations of small sample sizes, weak study designs and lack of diversity in participants were also acknowledged across the included primary studies.

#### *Conclusions of Evidence Check update—puberty suppression treatment*

We identified 17 studies pertaining to puberty suppression treatment (PS) in this Evidence Check update. Broadly, the newly identified evidence reinforced the previous finding regarding **benefits and effectiveness.** That is, PS agents (generally referred to as GnRHa) were reported to be safe,

effective and reversible. As a counterpoint, this update identified one study describing differential implications of PS for later surgery, with reduced need for mastectomy in trans men but potential complications for genital surgery in trans women as penile inversion may be compromised. Psychological effects of PS on conditions such as depression and anxiety appear modest in comparison with GAHT, with the primary impact being reduction of distress associated with unwanted secondary sexual characteristics; to this end, two Level IV studies reflected positive impacts on gender dysphoria.

With regard to **risks and potential harms,** reductions in bone density remain the primary concern with PS. Although findings pertaining to bone density were mixed in newly identified studies, monitoring of BMD was recommended. Conversely, studies reported that there appeared to be no indications to monitor liver or renal function in the PS setting. Other reported side effects of PS were also relatively minor. Instances of pubertal escape were reported, but satisfaction with PS treatment was reported as good overall. In summary, this Evidence Check update predominantly reinforces findings of the previous review and adds to the evidence base underpinning these findings; with the qualification that the strength of the evidence remains poor.

Table 5 below summarises the main features of each of the reports on PS included in this Evidence Check.

## Included studies in this Evidence Check update—puberty suppression treatment

**Table 5a—NHMRC Level I. Systematic reviews—puberty suppression treatment (n = 3)**

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions reported by study authors |
|---|---|---|---|---|---|
| **National Institute for Health and Care Excellence (NICE) 2020[24]**<br>Examined clinical effectiveness, safety, cost-effectiveness, subgroups for whom benefits are higher or lower, criteria used to define GD, age when treatment commenced and treatment duration for GnRH analogues. | 9 observational studies:<br>5 retrospective observational; 3 prospective longitudinal; 1 cross-sectional.<br><br>People aged 18 years or less. | **GnRHa**<br>GD defined by DSM criteria (reported in 6/9 studies).<br>Treatment started age 11–18 years.<br>Duration of treatment not reported in 6 studies and ranged from a few months to 5 years. | Reduction in depression, positive psychosocial impact.<br><br>No impact on GD, anger, anxiety, body image. | No difference in bone density<br>Changes in cognitive function not statistically tested.<br>No effect on renal or liver function.<br>Reports of sterile abscess (1), leg pain and headache (1), weight gain (1).<br>One study reported 9/143 stopped treatment—5 no longer wanted therapy, 4 had side effects; one study | Little change with GnRH analogues from baseline to follow-up on mental health (depression, anger and anxiety), body image and psychosocial impact. GnRH analogues may reduce the expected increase in bone density (which occurs during puberty).<br><br>*"A key limitation to identifying the effectiveness and safety of GnRH analogues for children and adolescents with gender dysphoria is the lack of reliable comparative studies … the studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding, and all the results are* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions reported by study authors |
|---|---|---|---|---|---|
| Score on quality criteria = 8.5 / 13. | | | | reported 11/26 stopped treatment. | *of very low certainty using modified GRADE … Many of the studies did not report statistical significance or confidence intervals."* |
| **Ramos 2021**[26]<br>To review treatment of gender incongruity with GnRHa analogues.<br><br>Score on quality criteria = 6 / 13. | 11 studies mostly conducted in centres assisting transgender children and adolescents. | **GnRHa + GAHT (GnRHa focus)**<br>Some study participants also received gender-affirming hormones (testosterone, oestradiol, triptorelin, among others). | Reversible treatment and allowed time for patients to experience social transition first.<br>Seemed to be well tolerated by the target population.<br>Improved mental health reported in three studies. | Individual studies reported on side effects (aseptic abscesses, pain in the lower limbs, headaches, weight gain); and changes in body fat with a decline in lean mass and waist-hip index.<br>Three studies reported BMD maintenance and one showed reduction; two reported that addition of cross-sex hormones tended to re-establish BMD. | *"The use of GnRHa seems to be well tolerated by the studied population. When started … In addition to preventing the irreversible phenotypic changes that occur in cross-hormonal therapy, the use of GnRHa can equally contribute to the mental health of these adolescents."*<br><br>*"Studies found are heterogeneous (different definitions, population and evaluation techniques) and sometimes based on small sample size, restricting statistical power. Even fewer studies accessed long-term consequences of puberty blockage with or without posterior cross hormone therapy."* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions reported by study authors |
|---|---|---|---|---|---|
| | | | | One study reported 9 / 84 cases of discontinuation; another reported 1 / 84 cases of discontinuation. | |
| **Rew 2021**[27]<br>To review literature about the practices of administering gonadotropic-releasing hormone agonists (GnRHa) for children and the outcomes and risks.<br><br>Score on quality criteria = 5.5 / 12. | 9 studies:<br>4 retrospective chart reviews, 2 case reports, 1 cross-sectional and 1 prospective study. | **GnRHa + GAHT (GnRHa focus)**<br>Some study participants also received gender-affirming hormones.<br>Children eligible for puberty suppression treatment if they were diagnosed with gender dysphoria. | Benefits described across studies included anthropometric measurements returning to normal limits in adulthood; positive changes in secondary sexual characteristics along with lack of sustained creatinine or LFT abnormalities; improvement in affective and social life; improvements in general functioning; and | Known risks and adverse outcomes of using GnRHa in children included mood swings and emotional lability. Other adverse risks described included slow growth, decrease in lean body mass, increased fat, decreased height velocity, and decrease in bone turnover markers. | *"The evidence to date supports the finding of few serious adverse outcomes and several potential positive outcomes.*<br><br>*" … large long-term studies with diverse and multicultural populations have not been done … The need for additional well-designed longitudinal and mixed methods studies is critical to support and even improve current practice for this very vulnerable population."* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions reported by study authors |
|---|---|---|---|---|---|
| | | | decreases in depressive symptoms, emotional and behavioural problems and suicidal ideation. | | |

**Table 5b—NHMRC Level III-2. Comparative studies with concurrent control—puberty suppression treatment (n = 4)**

| Author, date, aims, quality criteria score | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions reported by study authors |
|---|---|---|---|---|---|---|
| **Olson-Kennedy 2021**[42]<br>To investigate the effectiveness of histrelin implant | US<br>Case series: retrospective chart review study.<br>Center for Transyouth Health and | **GnRHa only**<br>Histrelin implants<br>N=66<br>M age = 11.3 years, Tanner stage 2–3, 32 | Changes in gonadotropin, sex steroid levels. | Both implants (Vantas and SupprelinLA) were successful in suppressing puberty progression among early | No apparent side effects reported. | *"… both Vantas and SupprelinLA are equally effective at reducing gonadotropin and hormone levels into a pre- or early pubertal range".*<br><br>*"Limitations of this study include a relatively small sample size. Future* |

| Author, date, aims, quality criteria score | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions reported by study authors |
|---|---|---|---|---|---|---|
| for puberty suppression.<br><br>Score on quality criteria = 7 / 9. | Development at Children's Hospital Los Angeles (CHLA). | trans females, 34 trans males. | | and mid-adolescent patients. | | *studies with larger sample sizes will assist in validating these findings."* |
| **Schulmeister 2022[43]**<br>To quantify the growth of TGD youth starting GnRHa therapy.<br><br>Score on quality criteria = 6 / 8. | US<br>Comparative with control.<br>Four multidisciplinary transgender clinics based at academic medical centres. | **GnRHa only**<br>N=55 transgender adolescents.<br>Mean age: 11.5 ± 1.2 years. | Growth and height velocity (HV), | Individuals who initiated GnRH agonist at a later Tanner stage / chronological age had significantly lower height velocity (HV) in the first year. | Those starting treatment in late puberty had a lower HV range compared with prepubertal children (not statistically significant). | *"Overall, TGD youth treated with GnRHa have HV similar to that of prepubertal children, but TGD youth who start GnRHa later in puberty have an HV below the prepubertal range. Ongoing follow-up of this cohort will determine the impact of GnRHa treatment on adult height."*<br><br>*"Limitations of this study include a relative lack of diversity of participants and lack of data on bone age and pretreatment HV."* |
| **van de Grift 2020[46]**<br>To investigate the long-term | Netherlands<br><br>Single-centre retrospective | **GnRHa + GAHT (GnRHa focus)** | Physical sex characteristics (e.g. height, weight, breast | Less breast development among trans men, indicating | Shorter penile length among trans women, increasing | *"PS effectively reduces the physical development of sex characteristics … Transgender girls and women, especially, should be* |

| Author, date, aims, quality criteria score | Country, design, setting | Intervention<br><br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions reported by study authors |
|---|---|---|---|---|---|---|
| effect of PS on development of sex characteristics and gender-affirming surgical implications.<br><br>Score on quality criteria = 6 / 8. | cohort study (comparative with control). | GnRHa, gender-affirming surgeries<br>N=300<br>M age: 23 years ±2.9.<br>Tanner stage 2–5; 184 trans men; 116 trans women. | development, penile length). | less invasive mastectomy (or becoming unnecessary). | possibility of intestinal (rather than penile inversion) vaginoplasty. | *informed that they might require more extensive, centralized surgical care with long-term aftercare."*<br><br>Reported limitations included small subgroup sample size; potential for selection bias (non-enrolled candidates not followed up; missing data due to retrospective design). |
| **Eitel 2023**[39]<br>To compare the effect of Eligard and Lupron in assisting puberty suppression.<br><br>Score on quality criteria = 4 / 8. | US<br>Case series (retrospective chart review).<br>Seattle Children's Gender Clinic 2016–2021. | **GnRHa + GAHT (GnRHa focus)**<br>Intramuscular **Lupron** and subcutaneous **Eligard**<br>N=48<br>Mean age at start: 13.7 years (50% also concurrently | Sex hormone levels (one hour after injection) and clinical PS outcomes (i.e. menarche or breakthrough bleeding in those AFAB). | All patients experienced clinical puberty suppression; biochemical suppression rates were superior with Eligard (90% vs 69%). | No apparent adverse effects reported. | *"Eligard and Lupron were both effective in suppressing clinical puberty progression."*<br><br>Limitations of this study include small sample size, retrospective nature and limited Tanner staging data due to telemedicine visits conducted during the COVID-19 pandemic. In addition, 50% of patients were receiving concurrent GAH. |

| Author, date, aims, quality criteria score | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions reported by study authors |
|---|---|---|---|---|---|---|
| | | receiving GAHT). | | | | |

**Table 5c—NHMRC Level III-3. Comparative studies without concurrent control—puberty suppression treatment (n = 1)**

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions reported by study authors |
|---|---|---|---|---|---|---|
| **Mejia-Otero 2021**[49]<br>To investigate the effectiveness of GnRH for puberty suppression among transgender youths. | US<br>Case series: retrospective chart review<br>GENder, Education and Care Interdisciplinary Support (GENECIS). | **GnRHa only**<br>(leuprolide and histrelin)<br>N=60<br>(n=30 transgender adolescents with mean age (SD) of 13.0 ± 2.1; | Suppression of hypothalamic-pituitary gonadal (HPG) axis. | GnRHa produces a similar effect on transgender and children with CPP. | A higher oestradiol level was observed in transgender group after treatment. | *"GnRHa are effective in suppressing the HPG axis in transgender youth"*<br>"Our study has important limitations … different doses of leuprolide and histrelin", small number of patients to compare the effectiveness of each dose, data from "different laboratories", and |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions reported by study authors |
|---|---|---|---|---|---|---|
| Score on quality criteria = 6 / 10. | | n=30 children with central precocious puberty (CPP) with mean age of 7.7 ± 2.3).<br>50% of the trans group at Tanner stage 4–5. | | | | "significant ethnic and racial differences between groups". |

**Table 5d—NHMRC Level IV. Case series / cross-sectional—puberty suppression treatment (n = 9)**

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| ***Turban 2020[97]**<br>To examine the association between pubertal suppression (PS) access | US<br><br>Cross-sectional survey<br><br>2015 US Transgender | **GnRHa + GAHT (GnRHa focus: GAHT examined as a confounder)**<br>GnRHa | Mental health outcomes (psychological distress, binge drinking, drug use, suicidal | Access to PS treatment associated with a lower odds of lifetime suicidal ideation when compared with | No apparent adverse effect reported. | Transgender adults *"who received treatment with pubertal suppression, when compared with those who wanted pubertal suppression but did not receive it, had lower odds of lifetime suicidal ideation".* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| and mental health outcomes.<br><br>Score on quality criteria = 7 / 8. | Survey (USTS) conducted by National Center for Transgender Equality (NCTE). | N=20,619<br>Mean age = 23.4 years (45.2% assigned male at birth). | ideation and attempts). | those who wanted PS but did not have access to it. | | *"Limitations include the study's cross-sectional design, which does not allow for determination of causation."* |
| **Ghelani 2020[69]**<br>To examine the effect of sudden sex hormone withdrawal on body composition of late pubertal adolescents.<br><br>Score on quality criteria = 8 / 10. | UK<br><br>Pre-post design<br><br>University College London Hospital (UCLH) Gender Identity Development Service. | **GnRHA only**<br>Triptorelin sex hormone, administered for at least one year.<br>N=36 (n=11 trans male, n=25 trans female) aged 15–17 years with GD. | Body composition; height, weight and BMI measured at 0, 6 and 12 months. | Withdrawal of sex hormones does not seem to affect body composition of trans boys, with no significant differences in any variable from baseline to 12 months. | *"There is a significant slowing of height and lean mass in transgirls. This could, however, be potentially detrimental if the patient decides not to go ahead with transition."* | *"GnRH analogues do not appear to have significant harmful effects on body composition when used in healthy postpubertal adolescents … Effects of the treatment on anthropometry and body composition were gender-specific…"*<br><br>*"The main limitation of our study was the relatively small sample size, especially for the transgirls … we were not able to measure bone mass which would also be of relevance in these patients."* |
| **Pine-Twaddell 2023[84]** | US<br><br>Pre-post | **GnRHa + GAHT (GnRHa focus)** | Pubertal suppression outcomes (i.e. | The use of HI over one year has been found | 1 patient did not react well to GnRHa and | *"Extended use of HI (>= 17 months) in TG/NB and CPP youth was efficacious and resulted in* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| To examine the impact of histrelin in a longer time (>12 months).<br><br>Score on quality criteria = 8 / 10. | Two US paediatric centres. | GnRHa, histrelin implant (HI).<br>N=49<br>Mean age = 11.6 years ± 2.4<br>Tanner stage 2–5.<br>Transgender or nonbinary (TG/NB) youth.<br>• Group A (n=25): HI<br>• Group B (n=15): GAHT + HI<br>• Group C (n=2): no treatment + HI<br>• Group D (n=7): central precocious | increase in Tanner stage, hormonal concentration). | to be safe and efficacious for patients.<br>Adoption of HI is associated with few surgical procedures and lower costs. | discontinued suppression at 15 months.<br>8 cases of pubertal suppression escape.<br>Can be difficult to remove or replace the implant. | *sustained biochemical and clinical pubertal suppression in majority of our study subjects."*<br><br>*"Limitations of the study include retrospective design, nonstandardization of assays used, timing of laboratory and clinical examinations, and lack of GnRH stimulation testing."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| | | puberty (CPP). | | | | |
| **van der Loos 2023**[7]<br>To investigate the continuation rate of adolescents starting PS and GAHT.<br><br>Score on quality criteria = 8 / 10 | Netherlands<br><br>Pre-post<br><br>Amsterdam UMC. | **GnRHa + GAHT (GnRHa focus)**<br>GnRHa for a minimum of three months and then GAHT.<br>N=720 (n=220 trans girls, 69%, median age: 14.1 years. n=500 trans boys, median age: 16 years). | Continuation of GAHT (based on prescription of gender-affirming hormones). | High rate of continuation from PS with GnRH to GAHT (98%). | Discontinuation rate appears to increase with older-age trans females. | *"This study confirmed a steep increase of referrals to our gender identity clinic … Novel findings are that detransition was very rare and that the majority of people starting GnRHa continued with subsequent GAH."*<br><br>Study limitations: *"… the results may be different for centers following a different treatment approach … Due to the retrospective design, data might be lacking … calculated proportions in the most recent years are likely an underestimation."* |
| **Joseph 2019**[74]<br>To investigate the impact of GnRHa on bone density in | UK<br><br>Pre-post<br><br>Early Intervention | **GnRHA only**<br>GnRHa for one year or ongoing until they reach 16 years old.<br>N=31: | BMD for lumbar spine and femoral neck (hip), z-scores for birth sex and age. | No significant change in the absolute values of hip or spine BMD or lumbar | Progressive fall in BMD and BMAD z-scores, most rapid in the first year of | *"… although there is an immediate drop in BMD and BMAD Z-scores, we have shown that absolute BMD and BMAD does not change substantially over a 3-year period in* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| adolescents with GD.<br><br>Score on quality criteria = 7 / 9. | program national endocrine clinic. | • Trans girls (n=10), mean (SD) age at first, second and third scan: 13.0 (1.1 ), 14.5 (1.2) and 15.8 (1.3)<br>• Trans boys (n=21), mean (SD) age at first, second and third scan:12.9 (3.0), 14.3 (3.3) and 15.6 (3.5).<br><br>A further 39 had two scans; main analysis on 31. | | spine BMAD over 3 years.<br><br>Lower fall in BMD / BMAD z-scores in the longitudinal analysis group in the second year (i.e. *"31 subjects who had three DXA [dual energy X-ray absorptiometry] scans").* | treatment for both groups. | *transgender adolescents on GnRHa treatment".*<br><br>*"… results have come from a retrospective analysis of clinical scans which were not acquired for the sole purpose of this study … Although 70 is a large sample size for the first-year data, the pure longitudinal data set is smaller (n=31)."* |
| **Schwartz 2023[85]**<br>To compare the effectiveness of | US<br><br>Pre-post | **GnRHa + GAHT (GnRHa focus)** | Method choice, continuation, bleeding patterns, | Overall satisfaction with menstrual | Patients taking norethindrone acetate reported more side | *"Most of our patients achieved amenorrhea, or at least improved menstrual bleeding, as well as improved menstrually related* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| various menstrual management methods.<br><br>Score on quality criteria = 7 / 9. | Nemours Children's Hospital Delaware Gender Wellness Program. | Oral norethindrone acetate or a 52-mg levonorgestrel (LNG) intrauterine device (IUD).<br>N=101<br>Transgender and gender diverse adolescents. | amenorrhea rates, effect on moods and dysphoria, and side effects. | management methods. Almost all patients had improved bleeding and high rates of amenorrhea at the second follow-up. | effects (e.g. pain, mood swing) compared with those using IUD. | *dysphoria, with fairly low rates of side effects."*<br><br>*"The main limitation is its retrospective design, which relies on adequate documentation and resulted in missing data."* Also, it *"may have limited generalizability"* as the *"patients were all seen in a specialized gender clinic, and the majority had a dedicated visit with a pediatric gynecologist, which introduces selection bias and may overestimate the degree of gender dysphoria in general".* |
| **Navabi 2021**[79]<br>To examine evidence on effects of GnRHa on bone health and body composition among adolescents. | Canada<br><br>Pre-post<br><br>Children's Hospital of Eastern Ontario (CHEO). | **GnRHa focus (scan within 90 days of starting treatment)**<br>GnRHa, starting with 3 doses of 7.5 mg every 4 weeks, followed by 11.25 mg | (1) Bone mass—measured with dual energy radiograph absorptiometry (DXA); (2) body composition. | No change in BMI and is below obesity risk (85% cutoff).<br>No bone fracture detected. | GnRHa negatively affects bone mineral density. However, the majority of transgender youth had vitamin D | *"GnRHa monotherapy negatively affected bone mineral density of youth with GD without evidence of fractures or changes in BMI z score."*<br><br>Study limitations: *"Lack of consistent records of physical activity at baseline and follow-up visits limited analysis of physical* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| Score on quality criteria = 6 / 8. | | every 12 weeks after confirmation of puberty suppression. N=172 (< 18 years old):<br>• 119 (69.2%) transgender males: M age 15.2 ± 1.8 [SD] years; 90.7% Tanner 4–5)<br>• 51 (29.7%) transgender females (M age 15.4 ± 2.0 years; 80.3% Tanner 4–5)<br>• 2 (1.1%) youth as nonbinary. | | | insufficiency or deficiency. Transgender youth body fat redistribution (android vs. gynoid) was in keeping with patients' affirmed gender. | *activity's role as a potential contributing factor to bone health and body composition. The small sample size of youth in early puberty prevented comparison of GnRHa effects in early versus late puberty."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Carmichael 2021**[64]<br>To examine the short-term outcomes of pubertal suppression on adolescents with GD.<br><br>Score on quality criteria = 8 / 11. | UK<br><br>Pre-post<br><br>Gender Identity Development Service (GIDS), London. | **GnRHa only**<br>GnRHa with psychological support and therapy.<br>N=44<br>Age: 12–15 years<br>Persistent GD. | Bone mineral content (BMC) and bone mineral density (BMD); Child Behaviour CheckList (CBCL) total t-score; Youth Self-Report (YSR) total t-score; CBCL and YSR self-harm indices. | All patients achieved PS by 6 months.<br>No change identified in psychological functioning, quality of life or degree of GD. | Expected adverse events were prevalent during the initial two years, notably mild headaches or hot flushes, with reported incidences of 25% at 0–6 months, 23% at 7–12 months, and 22% at 13–24 months.<br>One patient ceased PS and did not start gender-affirming hormones. | *"Treatment of young people with persistent and severe GD aged 12–15 years with GnRHa was efficacious in suppressing pubertal progression. Anticipated effects of withdrawal of sex hormones on symptoms were common and there were no unexpected adverse events."*<br><br>*"The study size and uncontrolled design were key limitations. The small sample size limited our ability to identify small changes in outcomes. This was an uncontrolled observational study and thus cannot infer causality."* |
| **Waldner 2023**[91]<br>To examine the rate of gender-diverse adolescents | Canada<br><br>Pre-post | **GnRHa + GAHT (GnRHa focus)** | The rate-corrected QT interval (QTc) prolongation. | None of the patients experienced clinically | QTc prolongation appears to be more prevalent in trans girls; | *"This retrospective review of ECGs in gender-diverse youth on leuprolide acetate demonstrated that none of 33 subjects had clinically significant QTc* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| with QTc prolongation on leuprolide acetate therapy.<br><br>Score on quality criteria = 7 / 10. | Stollery Children's Hospital Pediatric Endocrinology Gender Clinic. | N=33 (10 trans girls, 23 trans boys).<br>Mean age (SD): 13.7 (SD 2.1) years.<br>Range 9–18 years. | | significant QTc prolongation. | however, the study was unable to conduct a subgroup analysis due to the limited sample size in this group. | *prolongation, using a conservative cutoff value of 460 ms."*<br><br>*"The limitations of this investigation include the small sample size and retrospective nature."* |
| **van der Miesen 2020[98]**<br>To examine the effect of receiving gender-affirming care (GAC) on transgender adolescents' psychological wellbeing.<br><br>Score on quality criteria = 6 / 10. | Netherlands<br><br>Pre-post<br><br>Center of Expertise on Gender Dysphoria of the VU University Medical Center (VUmc) in Amsterdam. | **GnRHa only**<br>N=1101<br>• n=651 cisgender adolescents, mean age 15.39 (1.36) years.<br>• n=272 transgender at referral, mean age 14.47 (2.18) years.<br>• n=178 transgender | Internalising, externalising, suicidality and peer relations. | Emotional and behavioural problems of transgender reduced when receiving GAC at a similar level to their cisgender peers. | No apparent adverse events or effect reported. | *"Our study also showed that transgender adolescents receiving gender-affirmative care involving puberty suppressing treatment not only have less emotional and behaviour problems than transgender adolescents who have just been referred to gender-affirmative care but also reported similar rates of mental health problems as their nonclinical cisgender peers on internalizing problems (with a lower clinical range percentage) and self-harm/suicidality but not on peer relation problems."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| | | using PS, mean age at 16.75 (1.24) years. | | | | Limitations: *"… this study did not make use of a random nonclinical national probability sample … the cross-sectional design of this study with different participants in the groups before and after puberty suppression may potentially limit the results with participants being different on characteristics not measured and controlled for."* |

*This article was subject to an Erratum—"The following disclosure was omitted: Dr JM Carswell has received an advisory board stipend from Endo Pharmaceuticals."

## Gender-affirming hormone therapy

### *Context*

Gender-affirming hormone therapy (GAHT, also referred to as cross-sex hormone treatment) aims to induce development of the physical sex characteristics congruent with an individual's gender expression.[25] For transgender men testosterone is used; for transgender women oestrogen is used in conjunction with anti-androgen agents, as oestrogen is insufficient to suppress testosterone to female levels.[18,28] In addition to its effect on physical sex characteristics, GAHT aims to improve mental health and quality of life.[21,25]

Because GAHT may follow puberty suppression treatment, studies examining its effectiveness may contain participants who have also received puberty suppression. In this Evidence Check, we have classified studies according to their stated primary focus. This means that *studies contained in this section may contain participants who have received both puberty suppression treatment and GAHT, but their stated primary focus is the effectiveness of GAHT*.

This Evidence Check update identified 39 studies focusing on GAHT, comprising seven systematic reviews (Level I); five comparative studies with concurrent controls (III-2); two comparative studies without concurrent controls (III-3); and 25 case series or cross-sectional studies (IV).

The additional information about the benefits of GAHT provided by this Evidence Check is summarised below (Table 6). It covers the overall effectiveness of treatment for changes in body composition, BMI, growth and bone maturation, amenorrhoea (menstrual suppression), body image, gender dysphoria, overall effects on psychological health, depression, anxiety, suicide risk, behavioural problems, quality of life and wellbeing, mental health care use, cognitive and brain function and bone density.

### Table 6a—Benefits of gender-affirming hormone therapy

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| GAHT promotes changes in body composition in ways that align with the desired gender. | **Overall effectiveness of changes in body composition**<br>One Level I study concluded that *"the body of available data on GAHT in trans people is steadily increasing, and short-to-midterm outcomes are quite reassuring in relation to effectiveness and safety"*.[20(p587)]<br><br>**Body mass index (BMI)**<br>One Level III-2 study of 124 transgender males reported that GAHT increased BMI; however, this study noted possible confounding due to |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | racial differences between groups.[45] A further Level III-2 study of 85 adolescents reported increases in BMI after initiation of GAHT.[41]<br>One Level IV study of 46 trans male adolescents reported that although testosterone increased BMI within 6 months of initiation, no significant change in BMI was recorded between baseline and 12 months.[86]<br><br>**Growth and bone maturation**<br>One Level III-2 study reported that bone maturation and growth rate reduced during GnRHa and increased during GAHT in 161 trans females, with an adult height lower than predicted prior to GnRHa but not to a statistically significant degree.[37]<br>One Level IV study of 154 transgender masculine youth reported that early treatment with oxandrolone was associated with increased adult height.[71]<br><br>**Amenorrhea or menstrual suppression**<br>Overall evidence about amenorrhea was mixed across four Level IV studies. These encompassed several different agents including the contraceptive pill. One Level IV study reported a menstrual cessation rate of 54% with a dose of 140mg subcutaneous testosterone, rising to 97% with a 200mg dosage[76]; another reported high effectiveness (94%) with menstrual suppression in a cohort of more than 500 patients receiving oral contraceptive pills (47% of cohort), norethindrone (30%) or intramuscular medroxyprogesterone (15%).[6]<br><br>However, one Level IV study of 220 patients on GnRHa and GAHT reported less than 50% achieved amenorrhoea within six months[54]; and Grimstad (2021b)[70] reported breakthrough bleeding in 58 out of 232 patients after 12 months of testosterone therapy. Longer duration of time receiving testosterone and endometriosis |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | were associated with breakthrough bleeding in this study. |
| GAHT is associated with improved body image, decreased body dissatisfaction, reduced gender dysphoria and improved psychological wellbeing (five studies referenced, levels III-2–IV). | **Body image**<br>One Level I study reported unclear evidence about body image.[25]<br>One Level III-3 study of 38 transgender young people reported improved satisfaction with body image following GAHT.[52]<br>One Level IV study of 42 transgender adolescent boys reported improved body satisfaction following testosterone treatment.[93]<br><br>**Gender dysphoria**<br>One Level I study[25] and one Level III-3 study of 38 transgender young people[52] reported that GAHT reduced gender dysphoria. A further Level IV study of 315 transgender participants reported that GAHT improved appearance congruence.[65] However, one Level IV study of 530 patients reported menstrual suppression therapy (including GAHT) was not associated with a change in gender dysphoria.[6]<br><br>**Overall effects on psychological health**<br>Findings across two Level I studies regarding overall effects of GAHT on psychological health were inconclusive or neutral, with Ludvigsson (2023)[22] unable to reach conclusions owing to bias and small participant numbers in included studies and Baker (2021)[19] reporting there was no evidence of harm to mental health from GAHT.<br><br>**Depression**<br>Findings pertaining to depression were generally positive for higher-ranked study designs, with two Level IV studies reporting no change in depressive symptoms. |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | Two Level I studies reported GAHT reduced depression.[25,28] Five Level IV studies reported GAHT reduced depression.[65,75,82,89,94]<br>One Level IV study of 80 transgender youth reported no improvement in depression at 4-month follow up after GAHT.[63] A further Level IV study of 530 patients reported that menstrual suppression therapy (including GAHT) was not associated with a change in depression symptoms.[6]<br><br>**Anxiety**<br>Two Level I studies (NICE 2020b, Rowniak 2019)[25,28] and three Level IV studies[65,75,82] reported GAHT reduced anxiety. A further Level IV study of 42 transgender adolescent boys reported reductions in social anxiety.[94]<br>In contrast, three Level IV studies reported no change in anxiety following GAHT[6,63,89] and one Level IV study reported that two participants out of 315 experienced severe anxiety during clinic visits.[65]<br><br>**Suicide risk**<br>One Level I study[25], one Level III-3 study[52] and six Level IV studies[55,75,89,80,93,94] reported reductions in suicidality following GAHT.<br>However, one Level IV study[63] reported no change in suicidality and a further Level IV study[65] reported that 11 of 315 participants had suicidal ideation and a further 2 died by suicide.<br><br>**Behavioural problems**<br>One Level I study reported reductions in behavioural problems following GAHT treatment.[25]<br><br>**Quality of life / wellbeing**<br>Two Level I studies[25,28] reported increased quality of life following GAHT, and a further Level I study[19] reported no evidence that GAHT harms quality of life. |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | Two Level IV studies reported positive affect and life satisfaction[65] and enhanced wellbeing[55] following GAHT.<br>One Level IV study reported no change in adolescent development (i.e. relationships, living situation, peer contacts) following GAHT.[75]<br><br>**Mental health care use**<br>One Level IV study reported that mental health care visits overall did not significantly change following gender-affirming pharmaceutical care. However, TGD participants were more likely to have a mental health diagnosis at baseline compared with controls (siblings).[73] A further Level IV study reported no change in psychiatric treatment needs for any reason (i.e. overall), but reductions in need for treatment for depression, anxiety and suicidality.[75]<br><br>**Disordered eating**<br>One Level IV study reported no significant improvement in disordered eating following gender-affirming care including GAHT.[83]<br><br>**Cognitive and brain function**<br>One Level IV study reported no impact on IQ scores / educational achievement compared with the general population in a sample of 72 adolescents.[56]<br>One Level IV study of transgender youth reported better executive function in patients undergoing GAHT but poorer executive function with long-term puberty suppression treatment (however these patients had ASD and anxiety symptoms).[87]<br>One Level IV study demonstrated stronger functional connectivity between the right amygdala (involved in processing emotional content) and the ventromedial prefrontal cortex (involved in cognitive control of emotion processing) in 36 transgender youth receiving GAHT compared with 46 transgender youth not |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | receiving GAHT. The amygdala–ventromedial prefrontal cortex can be disrupted in multiple psychiatric disorders, including anxiety and depression.[94] |
| GAHT appears to increase bone density following the negative impact of puberty suppression treatment on bone density (three studies, levels III-2–III-3). | **Bone density**<br>One Level I study[22] reported that children with gender dysphoria have lower group mean values for bone mineral density (BMD) prior to puberty suppression (GnRHa) treatment; that puberty suppression treatment delays puberty-induced BMD gain; and that this is almost fully compensated by subsequent GAHT. A further Level I study[25] reported mixed evidence on bone mineral density, with two studies reporting that GAHT may increase bone density (measured in lumbar spine and femoral neck) and one reported no significant difference following GAHT treatment.<br>One Level III-3 study of 121 transgender youth[53] reported decreases in bone mineral apparent density (BMAD) during GnRHa therapy followed by increases with GAHT. While trans boys had normal z-scores at baseline and study end, trans girls had relatively low z-scores at baseline and after three years of oestrogen treatment. Implications for adverse outcomes such as increased fracture risk for trans girls as they grow older were reported as uncertain.<br>One Level IV study of 87 adolescents[60] reported that 6 mg oestradiol or 100–200 µg ethinyl oestradiol resulted in greater increases in bone mineral density compared with 2 mg oestradiol. |
| Where GnRH has not been used for puberty suppression in trans girls, anti-androgen medications such as cyproterone acetate or spironolactone may be used in addition to GAHT to also relieve gender dysphoria (one study, NHMRC Level III-2). | No identified studies examined cyproterone use independent of puberty suppression:<br>• One Level I study reported that **cyproterone acetate**, leuprolide and medroxyprogesterone acetate may be more effective than **spironolactone** or oestradiol alone for suppression of serum total testosterone concentration.[18] |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | • A further Level I study reported that although **cyproterone acetate** (commonly used alongside oestrogen therapy) may cause increases in depression, there was no evidence for overall harms to mental health or quality of life.[19]<br>• One Level IV study[93] included patients receiving spironolactone as monotherapy, although no subgroup analysis of this cohort was conducted.<br>• A further Level IV study[77] examined the effect of spironolactone on hyperkalaemia; however, participants were also receiving GnRHa and / or oestrogen and no subgroup analysis was conducted. |

The additional information on the risks of GAHT provided by this Evidence Check is summarised below. It covers overall safety, cardiometabolic effects and thrombosis, risk of meningioma and prolactinoma, kidney diseases, physiological and mixed effects, physical side effects and fertility.

### Table 6b—Risks of gender-affirming hormone therapy

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| Rarely, other serious adverse outcomes, including breast and ovarian cancer among trans boys receiving androgen therapy, have been reported in the literature. However, there are too few cases to suggest a causative link between GAHT and gynaecological malignancy (one reference to committee opinion). | **Overall safety**<br>One Level I study[28] reported that the limited GAHT research identified few long-term risks. A further Level I study[20] reported short-to-medium outcomes as 'reassuring' in relation to effectiveness and safety.<br><br>**Cardiometabolic effects and thrombosis** |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | Rowniak (2019)[28] also quoted a previous review reporting low-quality evidence that GAHT increased triglyceride levels in both trans men and trans women, could have a minor effect on high density lipoprotein (HDL) and systolic BP in trans men; however, this evidence was from before 2010).<br>A further Level I study reviewing more than 80 studies on cardiometabolic risk and thrombosis[21] concluded that *"although the currently available literature lacks power and is at moderate risk for bias, most of the studies reported no increase in cardiovascular morbidity for transgender people taking HT in short-to-medium (10 years) follow-up periods"*.[21(p131)]<br>One Level III-2 study reported that GAHT reduced HDL; however, this study noted possible confounding due to racial differences between groups.[45]<br>A larger Level III-2 study (4172 transgender youths vs. 16,648 controls) reported that oestradiol and GnRHa alone did not appear to relate to cardiometabolic diagnoses.[44] The same study found higher odds of overweight / obesity vs. controls in the overall group; higher odds of dyslipidaemia and liver dysfunction in those taking testosterone with or without GnRHa; and higher odds of overweight / obesity and hypertension if taking testosterone alone[44]; however, the time of diagnosis in relation to the initiation of GAHT could not be determined.<br>One Level IV study of 611 transgender adolescents[78] reported no incidental occurrence of arterial or venous thrombosis associated with GAHT.<br><br>**Meningioma / prolactinoma risk**<br>One Level I study[18] reported that use of cyproterone acetate in transgender women has been associated with a four times higher incidence rate of meningioma when compared with a female reference population, with this risk |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | associated with cumulative dose exposures greater than 3g. Additionally, this review reported that hyperprolactinaemia was associated with cyproterone acetate, which is reversible following discontinuation. Although a fourfold increase in prolactinomas in transgender women has been observed, the review conclusion was unclear regarding the significance of this result as it may reflect increased prolactin monitoring; the incidence of *symptomatic* prolactinomas was not elevated.<br><br>**Kidney**<br>One Level III-2 study[41] reported changes in serum creatinine among a cohort of 286 transgender patients within 6 months of treatment. In transgender males the increase was to levels similar to baseline measurements for those designated male at birth. In transgender females, the increase brought levels above baseline measurements for those designated female at birth. When compared with a reference group of adolescents, serum creatinine was more similar when compared by gender than when compared by designated sex. These changes are likely related to changes in body size and composition. Although there were no changes in mean serum creatinine for the entire cohort beyond 12 months of GAH, two transgender males out of 194 had estimated glomerular filtration rate (eGFR) rises between 12 and 24 months that were potentially indicative of chronic kidney disease using accepted thresholds; however these rates were below these thresholds when the male formula for eGFR rather than the female formula was used.<br><br>**Physiological / mixed**<br>One Level I study[25] reported small increases in blood pressure and body mass index (BMI) as well as non-significant changes in creatinine and alkaline phosphatase (ALP). A further three cases of erythrocytosis on testosterone were |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | reported (one due to incorrectly high testosterone dosage). Four patients had elevations in alanine aminotransferase (ALT) on oxandrolone and two had elevations in aspartate aminotransferase (AST) on oxandrolone. These elevations resolved either spontaneously or after switching to testosterone.<br>One Level IV study of 85 adolescents[77] reported hyperkalaemia (defined as serum potassium concentration above 5.0 mmol/L) in 5 participants. None of the subjects had symptoms of hyperkalaemia, and all elevated measurements were normal when repeated. |
| Side effects such as acne, weight gain, mood swings and hot flushes are common with GAHT but rarely lead to cessation of therapy. Scalp hair loss may also occur in trans boys (three references NHMRC level III-2). | **Physical side effects**<br>One Level III-2 study reported nausea and vomiting associated with GAHT.[37]<br>One Level III-2 study reported higher odds of headache in trans feminine and trans masculine youth receiving GAHT vs. those who had not received GAHT[40]; another Level III-2 study also reported headaches as a side effect of GAHT.[37]<br>One Level IV study[5] reported almost 25% of 158 of patients with GAHT (testosterone) reported pelvic pain, with higher rates if using additional agents for menstrual suppression. |
| GAHT is only partially reversible. Voice deepening, facial hair growth and reduction in scalp hair growth may be irreversible for trans boys. Reversing the effects of breast development in trans girls may require surgery (two references, clinical guideline and committee opinion). | No relevant updated information identified. |
| Because GAHT may affect future fertility, recommendations to discuss fertility preservation before medical intervention for TGD children and adolescents were given in guidelines, reviews without meta-analyses and position statements (six references). | **Fertility**<br>One Level IV study of 214 transgender women reported that commencing GAHT early in puberty (Tanner stage 2–3) reduces mature spermatozoa production, resulting in reduced ability to collect mature spermatozoa for assisted reproduction later in life. However, more than 85% of the |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | cohort had the option of harvesting spermatogonial stem cells. Furthermore, fertility preservation options were not influenced by cessation of GAHT prior to genital gender-affirming surgery or duration of GAHT prior to surgery.[66] |

This Evidence Check found no additional information on variation in the benefits and risks of GAHT.

### Table 6c—Variation in the benefits and risks of gender-affirming hormone therapy

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| Historically, GAHT has rarely been started before 16 years of age. However, recent studies and expert consensus suggest the most appropriate stage at which to begin treatment should not be decided on age alone. Comorbidities such as mental health issues and medical conditions should be taken into account when considering medical interventions, as well as psychosocial factors such as parental support and the readiness of the adolescent for informed consent (one reference—NHMRC level of evidence: ungraded; clinical practice guideline). | No identified studies provided updates to this finding (noting that clinical practice guidelines were out of scope for this Evidence Check update). |
| A multidisciplinary team may include a paediatrician, adolescent physician, endocrinologist, general practitioner, fertility counsellors, nurse, counsellors, speech pathologists, family workers, psychiatrists and psychologists (five references—NHMRC level of evidence ungraded: reviews without meta-analyses and clinical practice guidelines). | No identified studies provided updates to this finding (noting that clinical practice guidelines were out of scope for this Evidence Check update). |

#### *Strengths and limitations of the evidence*

The seven Level I studies (systematic reviews) ranged in quality, with four of moderate-to-high relative quality[19,22,25,28] and three of lower relative quality.[18,20,21]

The Level I studies collectively highlighted a range of limitations in the literature that they discussed in their conclusions. Two Level I studies[22,25] noted numerous limitations in study design that meant firm conclusions about reported effects could not be made. More specific observations across the Level I studies encompassed:

- Treatment: variations in hormone dosage, route of administration and length of time using hormones[28]
- Bias and confounding: uncontrolled confounding factors[19,25,28]; recruitment bias (clinics)[19,20]; lack of RCTs[22]; small sample sizes[18,19]; failure to enumerate drop-outs[22]
- Outcome measurements: validity of quality-of-life measures questioned[28]; validity of psychological outcome scales[19]; group-level analysis where intra-individual change was more appropriate[22]; many different scoring tools with conflicting results[25]; lack of distinction between statistical and clinical significance[25]; serum testosterone level not a suitable surrogate marker of therapy as the mechanism of many GAHTs is through androgen receptor antagonism[18]
- Lack of long-term studies.[21,22]

A number of these issues were acknowledged as limitations in the included primary studies. Most frequently these were small sample sizes, retrospective study designs, lack of diversity in participant cohorts and use of a single-centre cohort.

Additionally, 25 of the 39 included studies were Level IV, which is the weakest study design in the NHMRC hierarchy.

### *Conclusions of Evidence Check update—GAHT*

We identified a considerable volume of evidence pertaining to GAHT in this Evidence Check update, reflecting an overall rise in the research into interventions for gender dysphoria since 2019–2020. Although the newly identified studies support the conclusions of the previous review, which reported that GAHT was effective for changes in body composition, evidence was mixed for changes to body mass index (BMI) and growth and bone maturation. Additionally, mixed results were reported for menstrual suppression, albeit in Level IV studies. The largest volume of new evidence pertains to the psychological benefits of GAHT. The identified studies reported positive results across the domains of body image, gender dysphoria, depression, anxiety, suicide risk, quality of life and cognitive function. However, neutral and some negative findings were also reported in these domains. Additionally, two Level IV studies reported no changes in mental health care use following gender-affirming pharmaceutical care. Although studies reporting positive mental health outcomes following GAHT outnumber those with neutral or negative findings, considerable flaws remain in the evidence because of generally low participation rates of target groups, inadequate representation of adolescents and / or poor study designs and conduct. The relevant systematic reviews identified underline this observation. Several studies support the finding of the previous review, which reported that GAHT appears to increase bone density following the negative impact of puberty suppression treatment on bone density.

Similar increases in research volume were observed in studies reporting on the risks and potential harms of GAHT. Findings on overall safety, cardiometabolic risk, kidney and physiological parameters support the previous review's findings that serious adverse outcomes associated with GAHT are rare. One Level I study flagged the risk of meningioma associated with cumulative dose exposures of cyproterone acetate greater than 3g, as well as prolactinoma risk, which may reflect increased monitoring, with symptomatic prolactinoma risk not elevated. Minor changes in physiological

parameters were reported. For example, blood pressure and elevated potassium—in the case of potassium, none of the subjects had symptoms of hyperkalaemia and all elevated measurements were normal when repeated. Newly identified primary studies reported a range of less serious side effects (for example, headaches, nausea and vomiting), consistent with the previous review. Some evidence was identified regarding the fertility impacts of GAHT, although only from two Level IV studies. Overall, despite increases in research volume, the conclusions of the previous review with respect to GAHT are largely unchanged as the increased number of studies is offset by generally poor study designs. Table 7 summarises the main features of each of the reports about GAHT included in this Evidence Check.

## Included studies in this Evidence Check update—gender-affirming hormone therapy

**Table 7a—NHMRC Level I. Systematic reviews—gender-affirming hormone therapy (n = 7)**

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| **Rowniak 2019**[28]<br>Evaluate effectiveness of use of gender-affirming hormones in improving quality of life, depression and anxiety in transgender individuals.<br><br>Score on quality criteria = 12.5 / 13. | N = 7 studies<br>(all observational: 1 case-control, 2 cross-sectional, 4 case series). | **GAHT**<br>Hormones not specified. All patients in hospital setting seeking gender transition.<br>Predominantly adult cohorts but no age restrictions at level of search.<br>Studies that included participants who had gender-affirming surgery were excluded. | Studies reported significant improvement in scores on validated scales for quality of life, anxiety and depression compared with transgender participants not yet on cross-sex hormones.<br>Three studies reported significantly higher QOL in hormone vs. no hormone transgender patients. | *"The review found low-quality evidence suggesting that the hormones could increase triglyceride levels in both trans men and trans women, and could have a minor effect on high-density lipoprotein cholesterol levels and systolic blood pressure in trans men."* | *"The included studies found improvement in the scores for the outcomes and concluded that the hormones were responsible for this improvement. However, the certainty of these conclusions is low at best, and the reason for this improvement is not completely understood, nor is it explored in any of the included studies."*<br><br>Limitations of included studies: *"The greatest risk of bias was related to the lack of clarity concerning differences in the* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | | | *intervention as related to hormone dosage, route of administration and length of time using hormones prior to assessment … The other risk of bias was regarding confounding factors. Although all of the studies reported possible confounders, only two stated that they used linear regressions to control for the confounding variables …[O]ne question that arose while conducting this review was the validity of the quality-of-life measures with regard to the actual lived experience of the transgender population being surveyed."* |
| **Baker 2021**[19]<br>To review the effects of gender- | N=20 studies<br>(1 RCT, 2 pre-post trials, 12 | **GnRHa: 3 studies**<br>**GAHT: 17 studies** | Improved quality of life and decreases | No reported adverse effects of hormone therapy on patients' mental health. | *"… our review indicates that gender-affirming hormone therapy is likely associated* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| affirming hormone therapy on psychological outcomes of transgender people.<br><br>Score on quality criteria = 8.5 / 13. | prospective cohorts, 1 retrospective cohort and 4 cross-sectional studies. | Three studies focused on adolescents; mean age was over 25 in most studies. | in depression and anxiety symptoms.<br>Associations were similar across gender identity and age. | *"… some evidence indicates that cyproterone acetate, a common anti-androgen assessed in many studies alongside estrogen therapy, may increase depression".* | *with improvements in QOL, depression, and anxiety. No studies showed that hormone therapy harms mental health or quality of life among transgender people."*<br><br>Limitations of included studies: *"Certainty in this conclusion is limited by high risk of bias in study designs, small sample sizes, and confounding with other interventions … Uncontrolled confounding was a major limitation in this literature. Many studies simultaneously assessed different types of gender-affirming care and did not control for gender-affirming surgery status, making it difficult to isolate the effects of hormone therapy ...* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | | | *Another source of potential bias was recruitment of participants from specialized clinics that impose strict diagnostic criteria as a prerequisite for gender-affirming care. Most studies used well-known scales for measuring psychological outcomes. None of these scales, however, have been specifically validated for use in transgender populations."* |
| **Ludvigsson 2023[22]**<br>To evaluate the impact of hormone treatment on psychosocial and physical outcomes in children diagnosed with gender dysphoria. | N=24 studies<br>(All observational). | **GnRHa: 8 studies**<br>**GnRHa + GAHT: 13 studies**<br>**GAHT: 3 studies**<br>Age range: 11–15 years; treatment usually continued for approximately two years. | Some studies reported improved global function and quality of life; however, the long-term effects of hormone treatment on psychosocial health (i.e. global function, suicide ideation, gender | *"… lower group mean values for BMD already prior to GnRHa treatment, and that GnRHa treatment delays the physiologically occurring BMD gain during pubertal sex hormone stimulation. However, this GnRHa-induced delay in BMD gain is almost fully compensated for by later* | *"… the long-term effects of hormone therapy on psychosocial health could not be evaluated. Concerning bone health, "GnRHa treatment delays bone maturation and bone mineral density gain, which, however, was found to partially recover during* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| Score on quality criteria = 8.5 / 13. | | | dysphoria, depression, anxiety, cognition, quality of life) could not be evaluated. | *ensuing (cross-sex hormone treatment) CSHT. Although study participants were followed up to 22 years of age, the observed remaining deficit may depend on the limited study group size or on too short an observation time."* | *CSHT when studied at age 22 years."*<br>*"Our review highlights several specific knowledge gaps … randomised controlled trials are lacking in gender dysphoria research …*<br>*… observational data have frequently been analysed at a group level where intra-individual changes would have been more appropriate …*<br>*… many studies only present data on chronological age but fail to account for puberty stage and biological age …*<br>*… long-term studies are lacking …*<br>*… individuals who stop GnRHa treatment before the start of CSHT need to be* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | | | *described and followed up …*<br>*… some of the findings underlying this review are old …*<br>*… we could not evaluate the frequency of individuals who drop out from GnRHa treatment and no longer wish to continue with gender transition."* |
| **National Institute for Health and Care Excellence (NICE) 2020[25]**<br><br>Examined clinical effectiveness, safety, cost-effectiveness, subgroups for whom benefits are higher or lower, criteria used to | 10 observational studies<br>7 retrospective observational; 3 prospective longitudinal.<br>People aged 18 years or less. | **GAHT was the primary focus; included studies had participants who had also received GnRHa**<br>GD defined by DSM criteria (reported in 5/10 studies).<br>GAHT treatment started aged 16–17 | Reduction in GD, depression, anxiety, suicide risk, behavioural problems.<br>Increase in quality of life.<br>Unclear effect on body image.<br>Mixed evidence on family function unchanged vs. | Reduction in people with normative peer contacts between baseline assessment and 1 year after starting GAHT.<br>No evidence of de-transition, defined as ceasing treatment.<br>Glucose, insulin, insulin resistance, cholesterol unchanged; HbA1c, AST, ALT, GCT unchanged; ALP increased at some time | *"Results from 5 uncontrolled observational studies suggest that in children and adolescents with gender dysphoria, gender-affirming hormones are likely to improve symptoms of gender dysphoria, and may also improve depression, anxiety, quality of life, suicidality, and psychosocial functioning. The impact of* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| define GD, age when treatment commenced and treatment duration for gender-affirming hormones.<br><br>Score on quality criteria = 8.5 / 13. | | years old (range 14–19).<br>Duration of treatment was between 1 and 5.8 years. | reductions in participants living with parents / guardians.<br>May increase bone density (mixed evidence). | points but not sig. at 24 months; creatinine increased but within UK reference range.<br>BP increased (absolute increases small).<br>BMI increased (most participants in healthy weight range).<br>Minor complications were severe acne (n=7), androgenic alopecia (n=1), mild dyslipidaemia (n=3) and significant mood swings (n=1). | *treatment on body image is unclear."*<br><br>*"The key limitation … is the lack of reliable comparative studies. All the studies included in the evidence review are uncontrolled observational studies, which are subject to bias and confounding and were of very low certainty using modified GRADE ...*<br>*… many different scoring tools and methods were used to assess the same outcome, often with conflicting results."*<br>*"… most outcomes reported across the included studies do not have an accepted minimal clinically important difference (MCID), making it difficult the determine* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | | | *whether any statistically significant changes seen are clinically meaningful."* |
| **Angus 2021**[18]<br>Review effectiveness of 'antiandrogens' in feminisation.<br><br>Score on quality criteria = 6.5 / 12. | N=4 studies, (all retrospective)<br>Women aged 16+ were eligible, but all included studies had adult women. | **GnRHa + GAH**<br><br>'Antiandrogens' (GnRHa, progestogens, 5α-reductase inhibitors, androgen receptor antagonists). | CPA, GnRH analogues and MPA are more effective than spironolactone at suppressing testosterone. | Use of CPA in transgender women has been associated with a four times higher incidence rate of meningioma when compared with a female reference population.<br>While meningiomas are rare, both the European Medicines Agency and the United Kingdom Medicines and Healthcare Products Regulatory Agency advise against use of CPA at doses of ⩾ 10 mg daily unless there are no other treatment options.<br>CPA use has been associated with hyperprolactinaemia of | *"[T]here are inadequate data to support enhanced feminization with any particular antiandrogen … The comparative effects on breast development, body fat redistribution and reduction in facial and body hair are unclear."*<br><br>*"Existing studies are mostly retrospective analyses of clinic data, with a small number of study participants, lacking clinically relevant endpoints and without adequate comparison to different treatment groups. Instead, the serum total testosterone concentration is typically* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | | uncertain clinical significance—reversible.<br>Fourfold increase in prolactinomas was also observed in transgender women—this may reflect increased prolactin monitoring in this population. | *reported as a surrogate marker of therapy, a significant flaw given some commonly prescribed antiandrogens work predominantly via androgen receptor antagonism rather than decreasing testosterone levels."* |
| **Defreyne 2019**[21]<br>Review effects of gender-affirming hormone therapy on cardiometabolic risk and thrombosis.<br><br>Score on quality criteria = 6.5 / 13. | 77 included studies, including 11 reviews.<br>4 studies on cardiovascular mortality; 12 on cardiovascular morbidity; 12 on blood pressure; 25 on lipids; 24 on body composition; 19 on markers of increased thrombosis. | **GAHT**<br>Transgender people without age limitation. | N/A—focus of review was on risks. | CV mortality: Several reviews inconclusive, with no long-term prospective follow-up studies.<br>CV morbidity: Meta-analysis reported no increased risk of myocardial infarction, stroke or venous thromboembolism (VTE) but may be due to lack of reported outcomes. Conflicting findings in primary studies.<br>Conflicting findings on diabetes possibly | *"Although the currently available literature lacks power and is at moderate risk for bias, most of the studies reported no increase in cardiovascular morbidity for transgender people taking HT in short-to-medium (10 years) follow-up periods. Known biochemical markers of CVD show conflicting results for transgender people prescribed HT."* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | | confounded by screening prior to hormone therapy. | *"We must acknowledge the fact that our data* [i.e. the included studies in the review] *are limited by a relatively short follow-up duration, without data on older transgender people."* |
| **D'hoore 2022**[20]<br>The focus of this paper is to give an update on hormone treatments from recent data in larger cohorts, when available.<br><br>Score on quality criteria = 5.5 / 12. | 91 studies from 2015–2021<br>Adults n=69<br>Adolescents n=21<br>Both adults and adolescents n=1. | **Studies examined GnRHa and GAHT** (oestrogens, antiandrogens, testosterone, progestational agents). | GAHT reduces mental health problems in trans people and helps obtain the desired physical features.<br>In trans men, BMD was found to increase during GAHT; in trans women, it was less conclusive.<br>Blood pressure is not significantly changed by GAHT. | In trans women there is a significantly increased risk of VTE (1 study in comparison to cis controls; 1 study compared with both reference cis women and cis men; 1 study associated with recent progestin prescriptions). The use of oestrogens in transgender women is associated with an elevated risk of myocardial infarction and stroke.<br>Trans men have an increased risk of elevated hematocrit levels, but this is manageable. | *"The body of available data on GAHT in trans people is steadily increasing, and short-to-midterm outcomes are quite reassuring in relation to effectiveness and safety."*<br>*"For this review we relied on published data from a limited group of clinical research teams that are active in this field. Per definition, this is biased literature, with participants having access to well-organized research centers."* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| | | | In general, lipid profile is favourably changed in trans women in contrast to trans men. But in trans women treated with CPA, a negative effect is seen in HDL levels.<br>There is no evidence of elevated cancer risk of breast, endometrium or prostate. | There is a small but higher risk of prolactinoma occurrence in trans women and a small increased risk of meningioma in trans women on CPA. | |

**Table 7b—NHMRC Level III-2. Comparative studies with concurrent control—gender-affirming hormone therapy (n = 5)**

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Valentine 2021**[45]<br>To examine changes in BMI and lipids in adolescent transgender males undergoing testosterone treatment.<br><br>Score on quality criteria = 5 / 7. | US<br>Retrospective chart review study.<br>A large Midwestern paediatric academic centre. | **GAHT only**<br>Testosterone<br>N=124<br>Transgender male adolescents (n=42), M age: 16.6 years (14–19).<br>Cisgender males (n=82): 15.5 years (14–21). | Body mass index (BMI) and lipid profile changes. | | Significant increase in BMI in transgender males over time.<br>A reduction in high-density lipoprotein in the transgender males. | *"… exogenous testosterone administration in adolescents who were assigned female at birth may lead to increased body mass over time."*<br><br>Study limitations: *"… racial discrepancy and limitations related to retrospective study design, small sample size, single site data collection, and variable length of follow-up."* |
| **Valentine 2022**[44]<br>To determine the probability of cardiometabolic-related | US<br>Retrospective, cross-sectional study.<br>Five children's hospital / health | **GnRHa + GAHT**<br>GAHT (oestradiol, testosterone), GnRHa. | Odds of having cardiometabolic-related diagnoses. | Oestradiol and GnRHa alone not associated with cardiometabolic- | Treatment group w/ testosterone and/or GnRHa had higher odds of overweight / obesity, | *"TGDY have increased odds of overweight / obesity compared to matched controls. Screening and tailored weight management, sensitive to the needs of TGDY, are needed."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| diagnoses in transgender and gender diverse youth (TGDY).<br><br>Score on quality criteria = 5 / 7. | services in the US. | TGDY (n=4172)<br>Controls (n=16 648). | | related diagnoses. | dyslipidemia and liver dysfunction.<br>Testosterone group had higher rate of overweight / obesity and hypertension. | *"We were not able to determine if cardiometabolic-related diagnoses occurred before or after receiving a prescription for GAHT given limitations of the data set."* |
| **Boogers 2022**[37]<br>To investigate the effect of GnRH and GAHT on growth of height.<br><br>Score on quality criteria = 5 / 8. | Netherlands<br>Retrospective cohort study<br>Center of Expertise on Gender Dysphoria in Amsterdam. | **GnRHa + GAHT**<br>N=161<br>(transgender girls). | Height, weight, bone age. | Bone maturation and growth rate reduced during GnRHa (but increased with GAHT).<br>All patients had lower than predicted adult height (PAH), with the group treated with EE having the | Side effects of high-dose oestradiol and EE were not examined; nausea, vomiting and headache are commonly reported side effects. | *"Growth decelerated during GnRHa and accelerated during GAHT. After regular-dose treatment, adult height was slightly lower than predicted at start of GnRHa, likely due to systematic overestimation of PAH as described in boys from the general population, but not significantly different from target height."*<br><br>Study limitations: *"A limitation is the retrospective character of* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| | | | | largest difference (3cm). | | *the study with some missing data. Another limitation is the delayed introduction of the growth-reductive treatment in some individuals and the difference in baseline characteristics between the 3 treatment groups."* |
| **Millington 2022**[41]<br>To investigate the effect of GAHT on serum creatinine in transgender and gender diverse youth.<br><br>Score on quality criteria = 5 / 9. | US<br>Prospective longitudinal observational study<br>Boston Children's Hospital, Benioff Children's Hospital, Lurie Children's Hospital and Children's | **GAHT only** (oestradiol, testosterone)<br>N=286 TGD individuals aged between 12 and 22 years.<br>92 trans girls; 194 trans boys. | Serum creatinine level. | Serum creatinine level of trans boys treated with GAHT increased to a similar level to cis boys.<br>Serum creatinine levels in TGD youth closely resembling those of the reference population when matched by gender identity. | After 12 months of treatment, mean serum creatinine in trans girls decreased but still remained above that of participants designated female at birth at baseline. | *"We observed significant changes in serum creatinine and corresponding eGFR within 6 months of GAH treatment in TGD youth."*<br>Study limitations: *"Direct measurement of GFR and analysis of body composition were not performed as part of this study, presenting significant limitations to the study. Additionally, information regarding the method and precision of serum creatinine measurements was not* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| | Hospital Los Angeles. | | | | | *collected. Lack of racial diversity in the cohort is an additional limitation."* |
| **Hranilovich 2023**[40]<br>To investigate the potential side effect of GAHT causing headache among transgender and gender diverse youth (TGD).<br><br>Score on quality criteria = 4 / 7. | US<br>Retrospective case-control study<br>Boston Children's Hospital Gender Multispecialty Service (GeMS). | **GAHT only**<br>N=763 TGD adolescents<br>• Trans feminine (n=273)<br>• Trans masculine (n=490)<br>10–20 years old. | Headache prevalence. | N/A | Higher rate of headache in patients receiving GAHT. Of those with headache, 28 received testosterone and 13 did not; 9 received oestrogen and 2 did not. | *"Among transfeminine and transmasculine youth, those who received gender-affirming hormone therapy had higher odds of headache compared to those not taking gender-affirming hormone therapy."*<br><br>Study limitations: *"… reliance on incidental reports of headache in medical record"* and *"a risk of both transfeminine and transmasculine adolescents who received GAHT having more documentation of headache".* |

**Table 7c—NHMRC Level III-3. Comparative studies without concurrent control—gender-affirming hormone therapy (n = 2)**

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Lavender 2023[52]**<br>To investigate the impact of hormonal treatment on gender diverse young people's psychological functioning and behaviours.<br><br>Score on quality criteria = 6 / 8. | UK<br>Retrospective observational study<br>An endocrine clinic. | **GnRHa + GAHT**<br>N=38 gender diverse young people<br>n=28 assigned female at birth and n=10 assigned male at birth.<br>Aged 12–15 years, at >= Tanner stage 2, and treated with GnRHa followed by GAHT. | Sexual characteristics, social motivation, behaviours, gender dysphoria (GD) experience. | Improved satisfaction with body image, GD and social motivation.<br>Reduced self-harm and suicidality concerns and internalising behavioural problems. | No information on side effects. | *"Improvements over time were noted in GD, primary sexual characteristic satisfaction, and social motivation. Caregiver reports of improvements in internalizing and externalizing behaviors were most evident with GnRHa, while young person reporting indicated improvements in externalizing behaviors with GnRHa, which increased with GAH."*<br><br>*"Due to the uneven distribution of young people assigned male and assigned female at birth, although consistent with UK and international referral trends, we were unable to compare groups statistically … In addition, data were available from a small number of individuals, and thus, generalizability should not be assumed."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| **Schagen 2020**[53]<br>To investigate the impact of hormonal treatment on bone development in transgender adolescents.<br><br>Score on quality criteria = 6 / 8. | Netherlands<br>Observational prospective study<br>Setting: not mentioned. | **GnRHa + GAHT** (Sustanon, 17beta-oestradiol, testosterone-esters)<br>n=51 trans girls and 70 trans boys receiving GnRHa; of this cohort, n=36 trans girls and 42 trans boys subsequently received GAHT.<br>GnRHa initiation at 12.6 (12.1–12.8) years old for trans girls and 12.7 (11.9–14.0) for trans boys. | Bone mineral apparent density (BMAD), age- and sex-specific BMAD z-scores, and serum bone markers. | BMAD z-scores increased during GAHT treatment. | BMAD z-scores decreased during GnRHa treatment.<br>Bone markers reduced in trans girls and early pubertal trans boys while on GnRHa.<br>"The consequences of lower BMD for long-term bone health in these individuals remains unclear." | *"Gender-affirming hormone treatment increases bone accretion and normalizes the age- and sex-specific BMAD z-scores in transboys."*<br><br>*"An important limitation of this study is the lack of an untreated control group."* |

**Table 7d—NHMRC Level IV. Case series / cross-sectional—gender-affirming hormone therapy (n = 25)**

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Grannis 2021**[93]<br>To assess the effect of GAHT on internalising symptoms, body image satisfaction.<br><br>Score on quality criteria = 7 / 8. | US<br>Cross-sectional<br>A large children's hospital. | **GnRHa + GAHT**<br>N=42<br>Transgender adolescent boys<br>• n=19 receiving testosterone cypionate (T)<br>• n=23 not receiving GAH (UT)<br>Aged 9–21 years. | Anxiety, social anxiety, depression, suicidality, body image dissatisfaction and brain activation. | Lower level of mental health issues and less suicidal ideation in the past year and a higher body satisfaction level. | No apparent side effects reported. | *"A primary finding of this study is that symptoms of anxiety, depression, and suicidality were lower in testosterone-treated transgender adolescents than in a comparable group of transgender adolescents not receiving GAH."*<br><br>*"The present study's most important limitation was our modest sample size … Notably, our sample size precluded the analysis of other potential factors related to internalizing symptoms, such as duration of T treatment or dose-dependent responses … Second is the cross-sectional design and lack of randomization."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| **Grannis 2023**[94]<br>To explore the applicability of GAHT benefits to both transgender and nonbinary populations, and examine the associations among body image satisfaction, neural circuitry, and internalising problems.<br><br>Score on quality criteria = 7 / 8. | US<br>Cross-sectional<br>A large children's hospital. | **GnRHa + GAHT**<br>GAHT (i.e. testosterone or oestrogen)<br>N=82 transgender and nonbinary youth.<br>AFAB:<br>• Receiving GAHT (treatment): mean age 17.04 (1.18)<br>• No GAHT: mean age 15.24 (1.72).<br>AMAB:<br>• Receiving GAHT+: M age 17.64 (0.86) | Mental health (anxiety, depression and suicidal ideation in the past year).<br>Brain activation (i.e. amygdala response and amygdala-vmPFC co-activation). | GAHT treatment associated with lower levels of social anxiety, depression and suicidality among trans boys.<br>Enhanced functional connectivity observed between the amygdala and vmPFC. | No apparent side effects reported. | *"Exploratory analyses revealed that GAHT duration was associated with internalizing symptoms, such that longer duration of GAHT was negatively associated with body image dissatisfaction and symptoms of depression and suicidality."*<br><br>*"… the study is limited by its cross-sectional design, small sample size, and omission of mental health related considerations, such as length of mental health interventions and information regarding psychiatric cooccurrences (e.g. autism). … [A] further limitation is the decision to include youth receiving puberty blockers or Spironolactone as monotherapy in the GAHT group."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| | | • No GAHT: M age 16.27 (1.49). | | | | |
| **Boogers 2023**[60]<br>To investigate the dose-dependent impact of oestrogen on bone mineral density.<br><br>Score on quality criteria = 8 / 10. | Netherlands<br>Pre-post<br>Centre of Expertise on Gender Dysphoria in Amsterdam. | **GnRHa + GAHT**<br>GnRHa, followed by GAHT and then gradually increased doses of oestradiol.<br>N=87 adolescents<br>Mean age 13.5 ± 1.2. | Bone mineral density (BMD) z-scores. | Higher doses of oestrogen associated with increased in lumber spine BMD z-scores. | High dose group had slightly lower vitamin D concentrations compared with the regular group.<br>No evaluation of side effects. | *"In conclusion, individuals treated with 6 mg estradiol, and with 100-200 µg EE especially, had a greater increase in BMD compared to trans girls treated with the regular dosage of 2 mg estradiol that resulted in low serum estradiol concentrations. This indicates a dose-dependent effect of estrogen on BMD."*<br><br>*"However, the number of individuals in the growth reductive treatment groups was relatively small. Due to the retrospective character of the study, missing data were inevitable … Since the type of treatment schedule was based on participants' characteristics, the three* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| | | | | | | *treatment groups were not similar at baseline."* |
| **Hisle-Gorman 2021**[73]<br>To examine the use of mental health services in transgender youth who received gender dysphoria care, including pharma-ceuticals.<br><br>Score on quality criteria = 8 / 10. | US<br>Pre-post<br>Data extracted from the Military Healthcare Data Repository (MDR). | **GnRHa + GAHT**<br>N=10,357, mean age at 8.5 years:<br>• Transgender and gender diverse adolescents (n=3754), median age 10 [8–13]<br>• Control cisgender siblings (n=6603), median age 9 [4–14]. | Number of mental health diagnoses and appointments, psychotropic medication prescriptions. | N/A | Those receiving gender-affirming care, including pharma-ceuticals, continue to need mental health support. There was an increase in psychotropic medication prescriptions in transgender patients. | *"Results strongly support clinical recommendations for screening of mental health conditions in TGD youth and availability of healthcare for those in need."*<br><br>Study limitations: *"… limited by the use of healthcare data in the form of ICD-9/10 codes which cannot indicate the severity of diagnoses or the full breadth of complex TGD identities"* … *"the short duration of care following gender-affirming pharmaceutical treatment, which may be insufficient to observe any clinically significant change"*, and *"unable to control for differing, regional, family level, and care provider acceptance"*. |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| **Laurenzano 2021**[76]<br>To describe the impact of subcutaneous testosterone (SC-T) on menstrual cessation rate and other health outcomes in trans masculine and gender diverse (TM/GD) youth.<br><br>Score on quality criteria = 8 / 10. | US<br>Pre-post<br>Rady Children's Hospital San Diego (RCHSD). | **GnRHa + GAHT (GAHT focus)**<br>GAHT (testosterone), started at 25–50mg biweekly and increased at provider's prescription.<br>N=119 TM/GD) youth<br>Mean age 16 years (10.1–19.8). | Menstrual cessation. | High successful rate of menstrual cessation at 54% at 140 mg monthly and 97% at 200 mg monthly. Testosterone was found to be an effective and safe choice providing gender-affirming care for (TM/GD) youth. | Reduction in high-density lipoprotein and an increase in hematocrit detected from baseline to follow-up.<br>Other side effects can include mild acne (common), injection site reaction, hypertension, transaminitis, and dyslipidaemia (less common). | *"This study, to date the largest pediatric study of SC-T, adds to the currently limited literature supporting the efficacy and safety of SC-T as an alternative to IM testosterone injections for GAHT in TM/GD youth."*<br><br>*"The primary limitations of the study are its retrospective nature and single-center cohort. Detailed information on exact timing of blood draws was not always possible to ascertain retrospectively, so separation of the cohort into mid-injection or trough T levels based on treating providers may not have been accurate in all cases."* |
| **Moussaoui 2022**[5] | Australia<br>Pre-post | **GnRHa + GAHT (GAHT focus)** | Prevalence rate of pelvic pain. | Not discussed as this study evaluated pelvic | Almost a quarter of patients | *"In conclusion, we report here—in what is to our knowledge the first time—the prevalence rate of* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| To examine the prevalence of pelvic pain in trans adolescents treated with testosterone.<br><br>Score on quality criteria = 8 / 10. | Royal Children's Hospital Gender Service (RCHGS). | GAHT with testosterone.<br>N=158 trans masculine adolescents<br>(n=121 no pelvic pain, n=37 with pelvic pain)<br>Median age: 16.6 years. | | pain prevalence rate. | reported pelvic pain.<br>The risk of having pelvic pain increased >5 times for those treated with additional agents for menstrual suppression (26.3%) compared with those who were not (4.8%, p = 0.028). | *pelvic pain in trans adolescents on gender-affirming testosterone treatment, and observe that a quarter of them described pelvic pain."*<br><br>*"Limitations of our study include its retrospective nature, which is likely to be associated with under-reporting of pelvic pain, and the limited documentation of the nature and likely causes of this pain within the medical records."* |
| **Allen 2019[55]**<br>To evaluate the effectiveness of gender-affirming hormones for enhancing | US<br>Pre-post<br>Children's Mercy Hospital Gender | **GnRHa (8 patients) + GAHT**<br>N=47 adolescents and young adults | Wellbeing, suicidality. | Enhanced wellbeing and reduced level of suicidality. | No information on side effects. | *"To our knowledge, this is the first study to demonstrate that levels of suicidality decrease, and general well-being increases, among adolescents diagnosed with GD after receiving GAH."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| mental health in transgender adolescents.<br><br>Score on quality criteria = 7 / 9. | Pathway Services (GPS) clinic. | (mean age 16.59, SD 1.19). | | | | *"Confounding variables of this study may include level of familial support, whether a patient is actively receiving psychotherapy, or differences in the specifics of gender-affirming medications (e.g. dosage)."* |
| **Grimstad 2021a**[71]<br>To examine the effect of oxandrolone on trans male adolescents.<br><br>Score on quality criteria = 7 / 9. | US<br>Pre-post<br>A paediatric academic medical centre. | **GnRHa + GAHT** (oxandrolone + testosterone)<br>N=154 (transgender masculine youth) including 34 receiving oxandrolone with M age 14.5 (1.7).<br>+ Other groups (n = 120): M age | Height | Greater heights for patients treated with oxandrolone. | Transient elevations in aspartate amino-transferase (AST) or alanine amino-transferase (ALT) detected in 2 participants and erythrocytosis in 3 participants while on testosterone. | *"Our retrospective review of height in TM youth suggests that early therapy with oxandrolone with or without GnRHa is associated with increased adult height … Our findings highlight the importance of early individualization of therapy and the need to include height in transition-related care discussions."*<br><br>Study limitations: *"The cohort is predominantly White, so* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| | | at 120 16.8 (1.6). | | | | *generalizability to those of other races or ethnicities may be limited. In addition, multiple possible selection biases may have influenced our findings. Treating physicians may have been more likely to be proactive with height-preserving therapies if the patient showed evidence of continued growth potential."* |
| **Pham 2023[83]**<br>To explore disordered eating in transgender and nonbinary adolescents after receiving gender-affirming care, including pharma-ceuticals. | US<br>Pre-post<br>Seattle Children's Gender Clinic (SCGC). | **GnRHa + GAHT**<br>N=91 transgender and nonbinary adolescents:<br>61% trans boys, 30% trans girls, and 7% nonbinary / gender-fluid<br>Mean age (SD): 15.2 years (2.1). | Disordered eating thoughts and behaviours. | N/A | There was no significant improvement in disordered eating after receiving GAC. | *"There were no significant changes in disordered eating after initiating gender-affirming medical care, possibly due to the limited study time frame of 12 months. Given the high prevalence of disordered eating behaviors, clinicians should consider screening all TGNB adolescents for disordered eating thoughts / behaviors throughout gender affirming care."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| Score on quality criteria = 7 / 9. | | | | | | *"Main study limitations include that generalizability is difficult given the homogenous sample size of mostly white and gender binary adolescents … Although analyses included age, we did not gather information on participants' pubertal stages; this is likely a confounding variable … Additionally, the shortened version of the EDE-Q we used in this study has not been validated."* |
| **Sequeira 2019[86]**<br>Effect of GAHT on body mass index (BMI) in trans masculine adolescents.<br><br>Score on quality criteria = 7 / 9. | US<br>Pre-post<br>An adolescent medicine clinic at a large urban children's hospital for gender-affirming hormone therapy. | **GAHT only**<br>Testosterone<br>BMI of patients measured at 6 and 12 months.<br>N=46 trans masculine adolescents aged 13–19 years. | (BMI) z-score. | Increased BMI measured at 6 months after GAHT initiation. | No significant change in BMI between baseline and 12 months, which conflicts with prior literature; further research needed to explore the cause. | *"Additional study is needed to understand the full short- and long-term impact of testosterone use on BMI z-score in transmasculine adolescents to provide appropriate informed consent and develop interventions to improve health outcomes."*<br><br>*"This study is limited by its small sample from a single academic* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| | | | | | | *institution and use of retrospective electronic health record data."* |
| **Grimstad 2021b[70]**<br>To examine the breakthrough bleeding patterns of transgender and gender diverse adolescent and young adults (TGD AYA) on GAHT > 1 year.<br><br>Score on quality criteria = 6 / 8. | US<br>Pre-post<br>Tertiary-care children's hospital. | **GnRHa + GAHT** (testosterone) > one year<br>N=232 TGD AYAs:<br>Without breakthrough bleeding (BTB), mean age at 16.3 ± 1.8<br>With BTB: n=58, mean age at 16.3 ± 2.2. | Prevalence of breakthrough bleeding. | N/A | Patients experiencing breakthrough bleeding were receiving GAHT longer (25%), potentially worsening GD experience.<br>They were also more likely to have endometriosis. | *"Breakthrough bleeding is relatively common (25%) on T-GAHT despite early amenorrhea. Most cases do not have an identifiable cause. Our data did not show superiority of any 1 method for managing breakthrough bleeding on T-GAHT."*<br><br>*"The limitations of this study include its retrospective nature, limited statistical power, and the inability to control which medications were used, as much of the choice of whether to initiate, change, or stop medications was due to patients' goals and provider preferences. In addition, many patients initiated menstrual suppression therapies in advance* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| | | | | | | *of T-GAHT and continued them through testosterone initiation."* |
| **Nos 2022**[81]<br>To evaluate whether GnRHa use increased the likelihood of using GAHT among transgender and gender diverse adolescents.<br><br>Score on quality criteria = 6 / 8. | US<br>Pre-post<br>US Military Health System (MHS). | **GnRHa + GAHT**<br>GnRHa, GAHT<br>N= 434, mean (SD) of 15.4 (1.6) years at the time of their first TGD-related encounter<br>• n=312 (71.9%) trans girls<br>• n=122 (28.1%) trans boys. | Initiation of GAHT | GnRHa use was not found to be associated with increased subsequent GAH use. | N/A | *"In this cohort study of TGD adolescents, GnRHa use was not associated with increased subsequent GAH use. These findings suggest that clinicians can offer the benefits of GnRHa treatment without concern for increasing rates of future GAH use."*<br><br>Study limitations: *"It is a retrospective cohort analysis of administrative data from patients enrolled in the US military health plan program, TRICARE. The children of active duty or retired service members identified in our study are different from the general population in several ways (e.g. higher socioeconomic standing, higher parental* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| | | | | | | *education, better healthcare coverage, higher geographic mobility)… We also did not capture information on individual patient, parent, and clinician factors that may influence decisions about starting or stopping gender-affirming medical treatments, or to seek out these treatments at all."* |
| **Olsavsky 2023**[82]<br>To examine the interaction between GAHT and social support and its effect on psychological wellbeing. | US<br>Pre-post<br>A gender-affirming multidisciplinary clinic. | **GnRHa + GAHT**<br>GAHT, transgender and nonbinary (TNB) adolescents.<br>N=75 TNBs<br>Mean age: 16.39 years. | Anxiety and depressive symptoms, non-suicidal self-injury (NSSI) and suicidality in the past year, and social support. | GAHT associated with better mental health outcomes (i.e. anxiety and depression). | Information on side effects not reported. | *"TNB adolescents had better mental health outcomes in the context of receiving gender-affirming hormonal interventions and having greater support from family and friends. Findings highlight the important role of quality family and friend support for TNB mental health."*<br><br>Study limitations: *"… all adolescents in this study were receiving care through a gender-* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
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| Score on quality criteria = 5 / 7. | | | | | | *affirming multidisciplinary clinic where they had access to counselors and therapists, and therefore, likely represent a more supported population than a community sample … Finally, this study was cross-sectional, which means we could not investigate causality, and our sample was primarily White with a greater proportion of transmasculine participants."* |
| **de Nie 2022**[66]<br>To assess the impact of puberty suppression treatment on exocrine testicular function by determining the most advanced | Netherlands<br>Pre-post<br>Center of Expertise on Gender Dysphoria of Amsterdam UMC between 2006 and 2019. | **GnRHa + GAHT (GAHT focus)**<br>GAHT, gGAS<br>N = 214 transgender women<br>(6 subgroups at Tanner stage 2–3, Tanner stage 4–5, adult). | Fertility preservation possibility: preservation of spermatozoa, preservation of spermatogonial stem cells or absence of germ cells. | The options for fertility preservation appear independent of whether GAHT is ceased before surgery and the duration of GAHT prior to gender-affirming | Commencing GAHT in early pubertal adolescence (Tanner stage 2–3) restricts the ability to collect mature spermatozoa suitable for direct use in | *"The results of this study show that there may still be options for fertility preservation using orchiectomy specimens obtained during gGAS. … In addition, the vast majority (>85%) of transgender women in our cohort could still opt for cryopreservation of testicular tissue harboring spermatogonial stem cells. A complete absence of germ cells* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| germ cell type orchiectomy specimens obtained during genital gender-affirming surgery (gGAS).<br><br>Score on quality criteria = 7 / 10. | | | | genital surgery (gGAS). | assisted reproductive techniques. | *was only observed in a small number (7%) of transgender women in our cohort, who all commenced GAHT as adults."*<br><br>*"A limitation of this study is the lack of data on serum hormone levels on the day of gGAS. We were therefore unable to verify if the transgender women who were asked to temporarily stop hormonal treatment four weeks prior to surgery actually did so, and if people with complete spermatogenesis were compliant to treatment … We were therefore unable to assess if different estrogen formulations have different effects on testicular histology and spermatogenesis."* |
| **Cantu 2020[63]** | US<br>Pre-post | **GnRHa + GAHT**<br>N=80 | Not stated | No changes in depression, anxiety or | No improvement in acute distress | *"Neither distance from medical center nor initiation of hormone therapy was associated with* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| To examine changes in anxiety, depression and suicidality from initial appointment to first follow-up.<br><br>Score on quality criteria = 6 / 9. | An academic medical centre. | Young adults, mean age 15.1 (1.8)<br>Trans female (n=15), trans males (n=58), nonbinary (n=7). | | suicidality were identified within the average 4-month time frame from initial visit to first follow-up. | level at 4-month follow-up.<br>Hormone initiation not related to the mental health outcome. | *symptom changes. While research shows decreased distress with initiation of hormones, study findings suggest changes may actually take longer to occur."*<br><br>Study limitations: *"Data collected were limited to one clinic, with a relatively small sample size and only two time points examined. Power analyses revealed that the current sample would have been well powered to detect large effects, but not small-to-moderate effects, which are more likely when looking at shorter time frames. Due to sample size, we could not examine how age, affirmed gender, or initiation of hormone blockers were associated with changes in symptoms of distress. Sample size also limits the ability to* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| | | | | | | *examine differences among those with genderqueer and nonbinary identities."* |
| **Millington 2019[77]**<br>To investigate the likelihood of having hyperkalaemia when taking spironolactone for gender transition.<br><br>Score on quality criteria = 6 / 9. | US<br>Pre-post<br>A specialty gender clinic at a tertiary care paediatric hospital. | **GnRHa + GAHT (GnRHa focus)**<br>spironolactone<br>N=85 adolescents<br>16.6 ±1.7 years. | Incidence of hyperkalaemia. | Low rate of hyperkalaemia, detected in 5 participants (2.2%). | One subject discontinued spironolactone after an elevated potassium measurement. | *"Hyperkalaemia in patients taking spironolactone for gender transition is rare and when present is transient and asymptomatic. In the absence of other medical comorbidities, routine electrolyte monitoring in this population may be unnecessary."*<br><br>*"The generalizability of this study is limited by the relatively small sample size and the use of only one study site. Its retrospective nature introduces potential selection bias; for example, clinicians may have avoided spironolactone use in patients* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| | | | | | | *with premorbid conditions or prior hyperkalemia."* |
| **Chen 2023[65]**<br>To examine the effect of GAHT on psychological functioning in transgender youths at two-year follow-up.<br><br>Score on quality criteria = 7 / 11. | US<br>Pre-post<br>Ann and Robert H. Lurie Children's Hospital. | **GnRHa + GAHT (GAHT focus)**<br><br>N=315 transgender and nonbinary participants:<br>190 participants (60.3%) trans males<br>Mean [±SD] age at 16±1.9 years. | Psychological outcomes (anxiety, depression, gender congruence, life satisfaction). | Improved mental outcomes, including enhanced gender congruence, positive affect, and life satisfaction, and reduced anxiety and depression. | Adverse events:<br>11 participants (3.5%) had suicidal ideation, 2 severe anxiety when visiting clinics, and 2 deaths by suicide.<br>Elevated anxiety and depression and low life satisfaction persisted in some patients. | *"In this 2-year study involving transgender and nonbinary youth, GAH improved appearance congruence and psychosocial functioning."*<br><br>*"Because participants were recruited from four urban pediatric gender centers, the findings may not be generalizable to youth without access to comprehensive interdisciplinary services or to transgender and nonbinary youth who are self-medicating with GAH … Finally, our study lacked a comparison group, which limits our ability to establish causality."* |
| **Kaltiala 2020[75]** | Finland<br>Pre-post | **GAHT 1+ years** | Adolescent development, | Proportion requiring | No change pre-post in | *"Medical gender reassignment is not enough to improve functioning* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| Assess how adolescent development progresses and psychiatric symptoms develop among transsexual adolescents after starting cross-sex hormone treatment.<br><br>Score on quality criteria = 5 / 8. | Two gender identity service facilities for minors in Finland. | Transsexual adolescents presenting for treatment prior to age 18.<br>N=52. | psychiatric symptoms. | specialist level psychiatric treatment *"during the so-called real-life phase of living in the desired role*" was similar.<br>Treatment needs due to depression, anxiety and suicidality / self-harm had diminished. | proportion progressing age-appropriately in school / work; dealing with matters outside of home; being involved in dating / steady relationships.<br>Proportion of those functioning age-appropriately in peer relationships decreased. | *and relieve psychiatric comorbidities among adolescents with gender dysphoria. Appropriate interventions are warranted for psychiatric comorbidities and problems in adolescent development."*<br><br>Study limitations: *"Collected from medical files, the data is as accurate as clinical documentation can be …The follow-up period was approximately only a year, which inhibits drawing conclusions on long-term outcomes."* |
| **Moussaoui 2023**[6]<br>To investigate the | Australia<br><br>Pre-post | **GnRHA and GAHT**<br>Oral contraceptive | Effectiveness of menstrual suppression, satisfaction, | High rate of effectiveness (93.8% of | No apparent adverse effect reported. | *"Effectiveness of and satisfaction with menstrual suppression were high in TGD adolescents receiving this treatment ...* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| effectiveness of menstrual suppression in transgender and gender diverse (TGS) adolescents.<br><br>Score on quality criteria = 5 / 8. | A paediatric tertiary referral clinic for TGD children and adolescents younger than 18 years. | pill, norethindrone, intramuscular medroxy-progesterone.<br><br>N=530 (GD patients assigned female at birth)<br>M age: 15.2±1.3 years. | distress related to menstrual bleeding. | participants) and satisfaction.<br>No difference in risks of GD, depression and anxiety between those receiving menstrual suppression or not. | | *However, menstrual suppression was not associated with any difference in gender dysphoria, depression, or anxiety symptoms in this cross-sectional study, and longitudinal studies are required to better investigate this."*<br><br>Study limitations: *"Firstly, information on menstrual suppression was retrospectively retrieved … and was limited by missing data. Secondly, the findings of this study may not be generalizable to all TGD adolescents, because participation was restricted to adolescents presenting to a specialized gender service in a tertiary pediatric hospital … Thirdly, the cross-sectional design does not provide information on longitudinal follow-up and does* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| | | | | | | *not allow any conclusions about potential causality."* |
| **Arnoldussen 2022[56]**<br>To examine the potential effect of gender-affirming care treatment (GAHT) on cognitive development and educational achievement.<br><br>Score on quality criteria = 6/10. | Netherlands<br>Case series pre-post<br>Center of Expertise on Gender Dysphoria (CEGD) of Amsterdam University Medical Center. | **GnRHa + GAHT (GAHT focus)**<br>Puberty suppression, GAHT, affirming surgeries.<br>N=72 adolescents;<br>trans boys = 45<br>trans girls = 27<br>Mean age: 12.78 years. | IQ, educational achievement. | IQ scores and educational achievements pre and post GAC were not significantly different. Cognitive development of adolescents receiving GAC is similar to the general population. | Not reported in this study. | *"… gender-affirming medical treatment including puberty suppression does not negatively affect the association between IQ and educational achievement."*<br><br>*"Limitations in this study were the lack of a control group, the small sample size (N=72) and the heterogeneous study population (e.g. age, treatment duration). In addition, since the demographic characteristics of our sample and the methods used to examine IQ and educational achievement were not similar to the studies that have examined this association in the general population, the comparison of the results of these* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| | | | | | | *studies should be interpreted with caution."* |
| **Strang 2022**[87]<br>To investigate whether executive function (EF) is overrepresented in transgender youth and those under GD medical treatment.<br><br>Score on quality criteria = 6 / 10. | US<br>Pre-post<br>A multi-component study of cognitive, mental health, and neurological development. | **GnRHa + GAHT (GAHT focus)**<br>N = 124 transgender youth<br>Mean age (SD): 16.67 (2.03), aged 11–21 years:<br>• Female (n=41)<br>• Male (n=81)<br>• Nonbinary (n=2). | Global executive functioning (EF). | Patients undergoing GAHT reported better EF. | Poorer EF detected in patients on long-term puberty suppression treatment. | *"Regarding gender-affirming medical interventions, gender-affirming hormonal intervention status was associated with EF, where youth receiving GAH had fewer parent-reported EF problems when accounting for age, gender, assigned sex, mental health and ASD diagnostic status."*<br><br>*"Although our sample was intentionally recruited from both clinical and community sources, it was not representative in terms of race or ethnicity. Further, we did not assess socioeconomics, which is itself a predictor of EF.. The study includes treatment durations, but the cross-sectional assessments preclude* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| | | | | | | *interpretations of causal influences on EF."* |
| ***Turban 2022[90]**<br>To examine the relationship between access to gender-affirming care and mental health outcomes.<br><br>Score on quality criteria = 5 / 9. | US<br>Case series: cross-sectional online survey<br>Community organisations. | **GnRHa + GAHT (GAHT focus)**<br>N=21,598 transgender adults, who had access to GAC:<br>• During early adolescence (n=119, 0.6%), aged 13–15 years<br>• During late adolescence (n=1.7%), aged 16–17 years<br>• In adulthood (n=12,257, 56.8%) | Psychological distress, binge drinking, illicit drug use, suicidal ideation. | Access to GAC associated with improved mental health outcomes (i.e. lower odds of past-year suicidal ideation). | The study mentioned (but did not evaluate as an outcome) the potential delayed bone development due to long-term use of pubertal suppression. | *"Access to GAH during adolescence and adulthood is associated with favorable mental health outcomes compared to desiring but not accessing GAH."*<br><br>*"Limitations include its non-probability cross-sectional design, which reduces generalizability and limits determination of causality."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| | | • Never had access (8860, 41.0%). | | | | |
| **Mullins 2021**[78]<br>To assess the risk of thrombosis among trans adolescents.<br><br>Score on quality criteria = 4 / 8. | US<br>Pre-post<br>Cincinnati Children's Hospital Medical Center (CCHMC) Transgender Health Clinic. | **GnRHa + GAHT (GAHT focus)**<br>GAHT (oestrogen, testosterone)<br>N=611<br>Trans adolescents<br>Median age 17 years (15–19). | Thrombosis risk. | No arterial or venous thrombosis associated with GAHT detected in the study cohort. | More studies needed to explore thrombosis risk when exposed longer to GAHT. | *"GAHT in youth, titrated within physiologic range, does not carry a significant risk of thrombosis in the short term, even with the presence of preexisting thrombosis risk factors."*<br><br>*"Our study has several limitations. First, the study was conducted at a single institution; however, the study included all youth who were started on GAHT since the inception of the Transgender Health Clinic. Second, as a retrospective study, the data were limited to that available through extraction of existing records in the electronic medical record (EMR). On the basis of the EMR, it was sometimes not possible to* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| | | | | | | *determine if a subject had discontinued GAHT or was lost to follow-up."* |
| **Tordoff 2022**[89]<br>To examine impact of gender-affirming care on mental health of transgender and nonbinary youths.<br><br>Score on quality criteria = 5 / 10. | US<br>Pre-post<br>Seattle Children's Gender Clinic. | **GnRHa + GAHT**<br>N=104 transgender and nonbinary (TNB) youths<br>Mean [SD] age at 15.8 [1.6] years:<br>n=63 trans males,<br>n=27 trans females,<br>n=10 nonbinary / gender fluid,<br>n=4 opted for 'I don't know'. | Mental health outcomes: depression, anxiety and suicidal ideation. | Improved depressive symptoms and reduced suicidal ideation over 12 months. | No association between GAC and anxiety.<br>No data on long-term outcomes. | *"This study found that gender-affirming medical interventions were associated with lower odds of depression and suicidality over 12 months."*<br><br>Study limitations: *"This was a clinical sample of TNB youths, and there was likely selection bias toward youths with supportive caregivers who had resources to access a gender-affirming care clinic … Our sample also primarily included White and trans masculine youths, limiting the generalizability of our findings."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Alaniz 2023**[54]<br>To examine the time to cessation of menses in adolescent and young adult transgender males.<br><br>Score on quality criteria = 3 / 7. | US<br>Pre-post<br>Tertiary children's hospital. | **GnRHa + GAHT**<br>Testosterone, norethindrone acetate, depot medroxy-progesterone acetate, progestin).<br>N=220<br>(n=211 trans males, n=6 gender fluid / nonbinary, n=2 'something else', n=1 'male'<br>Median age 15.8 years. | Time needed to reach menstrual cessation under the treatment conditions. | Shortest time to cessation of menses observed in group treated with testosterone and norethindrone acetate (NETA). | Less than 50% patients were able to achieve amenorrhea within a 6-month period. | *"Patients used a variety of different hormonal regimens for menstrual suppression. Less than half achieved cessation of menses within 6 months. NETA and depot leuprolide users reported the most rapid cessation of menses."*<br><br>*"The study is limited by a relatively small sample size of predominantly white patients and is further limited by the retrospective study design, which might have overestimated time to menstrual cessation."* |

*This article was subject to an Erratum—"Concerns were raised, post-publication, regarding common publications of the handling Academic Editor and some of the authors. A second and independent member of the *PLOS ONE* Editorial Board has reevaluated the manuscript and reviews, and has confirmed that the article is scientifically sound and meets *PLOS ONE*'s Publication Criteria. They also confirmed that there are no concerns with the original reviews. The authors discovered an error in the original manuscript. Specifically, throughout the article, the "early adolescence" group was mislabelled and inadvertently included all participants who accessed GAH prior to age 16, including some respondents who accessed GAH at ages younger than that recommended in the most recent Endocrine Society

Guidelines. Analyses for this “early adolescence” group have been updated to include only those who accessed GAH during the younger adolescent age group outlined by the most recent Endocrine Society guidelines (i.e. ages 13–15) [2]. The following specific errors have been corrected:

- The early adolescence group age (14–16) appears incorrectly throughout the article. The correct group age is (13–15). The Endocrine Society Guidelines note an age of 13.5, and the authors chose age 13 as a lower cutoff to include individuals who would have accessed GAH at this age.
- The number and percentage of the early adolescent group reporting access to GAH appears incorrectly through the article. The correct values are 99 (0.5%).
- The sample of individuals ever desiring GAH appears incorrectly throughout the article as 21,598. The correct value is 21,578, now that those reporting access to GAH younger than age 13 have been excluded.

The following sentence has been added to the first paragraph of the Methods section: We additionally excluded any participants who reported accessing GAH prior to age 13, as this would represent an age lower than the current threshold mentioned in the most recent Endocrine Society Guidelines.

## Gender-affirming chest surgery ('top surgery')

***Context***

Gender-affirming surgery is undertaken to affirm preferred gender identity by altering physical characteristics. In the case of transgender men this can involve breast reduction (mammoplasty) or other types of chest reconstruction such as alterations to the chest wall, and genital surgery to create a penis (metoidioplasty) and scrotum, and removal of the vagina, uterus and ovaries. Transgender women may undergo breast augmentation and genital surgery to create a vagina, clitoris and labia. Additionally, both transgender men and women may have facial masculinisation or feminisation surgery as well as surgery to alter their vocal cords and related organs.[3]

Given the focus of this Evidence Check update on children and young people, genital surgery was considered out of scope. **Therefore, only studies pertaining to chest and other 'top' surgery were eligible for inclusion in this update.** Studies pertaining to chest surgery are summarised in Tables 8a–8c and outlined in Tables 9a–9c. Tables 9a–9c also contain some additional information about facial surgery, Adam's apple surgery and vocal cord surgery from the included systematic review.

This Evidence Check update identified eight studies focusing on gender-affirming surgery, comprising one systematic review (Level I); three comparative studies with concurrent control (Level III-2); and two case series / cross-sectional studies (Level IV).

The additional information about the benefits of chest surgery provided by this Evidence Check is summarised below (Table 8). It covers psychosocial outcomes, sexual function, quality of life and gender incongruence.

### Table 8a—Benefits of gender-affirming chest surgery (top surgery)

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| Few studies have examined gender-affirming surgery in children and adolescents, and clinical guidelines rely heavily on expert opinion. We identified only three studies, all focusing on chest surgery in trans boys. The paucity of studies is to be expected given the age restrictions on gender-affirming surgery and the inclusion criteria of this Evidence Check for studies of young people, where treatment was undertaken under the age of 18 years. The evidence for the effectiveness of this chest surgery is very weak (NHMRC Level IV) and should be considered preliminary. | **Psychosocial outcomes**<br>One Level I study[3] reported positive findings for psychosocial wellbeing in transgender women and no difference pre- and post-surgery in transgender men.<br>One Level IV study of 75 adolescents[58] included 10 who received surgery. The surgery group reported emotional and behavioural problems similar to the population-based German norm mean.<br>One Level IV cross-sectional study of 288 transgender adults[95] reported positive outcomes of gender-affirming care, including surgery, on |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | suicidal ideation, anxiety, depression and stress symptoms. However, as the mean age in this survey-based study was 32.8 years (SD 13), it has limited relevance to adolescent population.<br><br>**Sexual function**<br>One Level I study[3] reported positive findings for sexual wellbeing in transgender women and no difference pre- and post-surgery in transgender men.<br>One Level III-2 study[38] of 113 transgender people aged 18–25 receiving a combination of PS, GAHT and various surgical procedures (vaginoplasty = 38; breast augmentation = 9; mastectomy = 63; metoidioplasty = 6) reported a significant increase in sexual activity one year post-surgery (noting transgender people were also less experienced in all types of sexual activities compared with the general population).<br><br>**Quality of life**<br>One Level IV study of 75 adolescents[58] included 10 who received surgery. The surgery group reported physical quality of life scores similar to the German norm mean. |
| Keeping in mind the preliminary nature of the evidence, existing studies suggest trans boys have a high level of satisfaction with chest surgery and that chest surgery is associated with a reduction in gender dysphoria. | **Gender incongruence**<br>One Level III-2 study[36] of gender-affirming mastectomy in 36 adolescents and young people compared with 34 controls reported that top surgery was associated with improved chest dysphoria, gender congruence and body image satisfaction. However, 11 patients were lost to follow-up. |
| It has been suggested that clinical protocols for gender-affirming treatments need adjustment to meet the specific needs of nonbinary adolescents (NHMRC ungraded: qualitative). | No evidence pertaining to this finding was identified in this update. |

The additional information on the risks of gender-affirming chest surgery provided by this Evidence Check is summarised below. It covers satisfaction and safety.

### Table 8b—Risks of gender-affirming chest surgery (top surgery)

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| Top surgery (mastectomy for trans boys and breast contouring for trans girls) is considered to be irreversible (4 references—NHMRC ungraded: position statement, standard of care and guidelines). | No evidence pertaining to this finding was identified in this update; however, the irreversibility of surgery is generally self-evident. |
| While the majority of young people who had top surgery experienced high levels of satisfaction, varying degrees of satisfaction with the outcome have been reported (2 references—NHMRC level of evidence IV). | **Satisfaction / regret**<br>One Level I study[3] reported long-term satisfaction with chest surgery in both transgender men and women. Regret / dissatisfaction was reported as rare, with two cases of regret out of 182 transgender men in one study and dissatisfaction in transgender women rare (usually relating to breasts perceived as being too small). |
| | **Safety**<br>One Level III-2 study[38] of 113 transgender people aged 18–25 receiving a combination of PS, GAHT and various surgical procedures reported no adverse events.<br>One Level III-2 study[36] of gender-affirming mastectomy in 36 adolescents reported low complication rates (1 haematoma, 2 seromas, 1 instance of nipple loss). However, 11 patients were lost to follow-up. |

### Table 8c—Variation in the benefits and risks of gender-affirming chest surgery (top surgery)

This Evidence Check found several Level IV studies reporting on variation in the benefits and risks of gender-affirming chest surgery, these are reported in the table below.

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| Top surgery is not generally performed before 18 years of age because of the irreversibility of these procedures (5 references—NHMRC level of evidence ungraded: clinical practice guidelines, standards of care and position statements). | The Level IV study of Tang (2022)[88] recruited 209 adolescents undergoing gender-affirming mastectomy. The median age at referral was 16 (range 12–17). This study reported that two patients expressed regret; prevalence of any complication was 7.3% and revision rate was 10.9% for those with at least a one-year follow-up. This study also observed a 13-fold increase in this surgery over a seven-year period (2013–2020).<br>One Level III-2 study[34] of 10 patients undergoing reinnervation of the nipple-areolar complex recruited patients with a mean age of 17.5 (range 16–19). This study reported significant improvement in sensation compared with a control group (mean age 36.6, range 18–59).<br>One Level IV study[61] of chest reconstruction enrolled 153 patients including 59 adolescents with a mean age of 16.7 (SD 0.8) at initial assessment. This study reported improved gender and appearance congruence and decreased chest dysphoria in both nonbinary and binary patients for both the total sample and the adolescent subgroup.<br>The remaining studies did not report exclusively on patients aged under 18. The Level III-2 study of Bungener (2020)[38] recruited 113 participants with a mean age of 20.8 and a mean time since surgery of 1.6 years; Ascha's Level III-2 study of mastectomy (2022)[36] had participants with a mean age of 18.6 (SD 2.7); Becker-Hebly's study[58] containing 75 adolescents had only 11 who had received surgery, with a mean age of 16 at baseline and 19 at follow-up. No conclusions specific to this group were made. The mean age in Hughto's study (2020)[95] was 32.8. |

***Strengths and limitations of the evidence—gender-affirming chest surgery (top surgery)***

The Level I review[3] identified limitations in the evidence consistent with research into puberty suppression treatment and GAHT—retrospective study designs, small sample sizes, lack of diversity in participants and limitations in validity of quality of life measures. These limitations—especially small

sample sizes and retrospective designs—were acknowledged in the primary studies, with further limitations of single-centre recruitment, loss to follow-up and potentially inadequate length of follow-up also described.

It is also important to note that the *volume* of evidence pertaining to chest surgery is relatively low; most studies (49 / 79) in the Level I review pertained to genital surgery, which was out of scope of this Evidence Check update.

### *Conclusions of Evidence Check update—gender-affirming chest surgery (top surgery)*

This update identified eight studies evaluating surgery including one review, thus expanding the evidence base from the previous Evidence Check. With regards to **benefits / effectiveness,** the updated evidence reports generally positive findings for gender dysphoria, psychosocial outcomes and sexual function and quality of life. However, neutral findings on psychosocial outcomes in transgender men were reported as well as mixed positive / negative findings on quality of life. The irreversible nature of surgery remains a key **risk / potential harm**; however, regret rates were low where reported. Complication rates for chest surgery were also reported to be low. In contrast with the previous Evidence Check, several studies reported on outcomes in adolescents referred for chest surgery at 16–17 years of age. Findings were generally positive across these studies on sexual function, gender incongruence and chest dysphoria, with relatively few reported rates of regret or complications. Although the evidence base is expanded and generally supportive of top surgery, confidence in findings is low because of a lack of studies and / or poor study quality, use of mixed surgery populations and the confounding effect of hormone and other therapies, which almost always preceded surgery. Offsetting these limitations are three high-quality comparative studies with positive findings specific to adolescents. In summary, this update provides some additional evidence supporting top surgery; however, further studies focusing on the specific effect of surgery in adolescents are required.

Table 9 summarises the main features of each of the reports on gender-affirming surgery included in this Evidence Check.

## Included studies in this Evidence Check update—gender-affirming surgery

**Table 9a—NHMRC Level I. Systematic reviews—gender-affirming surgery (n = 1)**

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| **Javier 2022**[3]<br>To conduct a systematic literature review into the longer-term (i.e. ⩾ 1 year) surgical satisfaction and quality of outcomes following various forms of gender-affirming surgery in transgender populations.<br><br>Score on quality criteria = 8.5 / 13. | 79 studies, most retrospective:<br>9 studies on chest surgery; 49 studies on genital surgery; 6 facial surgery; 8 vocal cord surgery. | Chest, genital, facial, vocal cord, and Adam's apple removal surgeries.<br>No age restrictions.<br>Note: genital surgery information not extracted. | Chest surgery, transgender men (4 studies)—positive for satisfaction, no difference pre-post for psychosocial function.<br>Chest surgery in transgender women (5)—positive for satisfaction and psychosocial function.<br>Facial feminisation surgery (6)—positive for | Chest surgery in transgender men: 2 cases of regret out of 182 patients across two studies.<br>Chest surgery in transgender women: dissatisfaction was rare and generally was that breasts were too small. | *"Overall, the findings in this literature review suggest both transgender men and women who undergo gender-affirming surgery report being satisfied with their surgery in the longer term, with very few reporting regret."*<br><br>Limitations of included studies:<br>*"… most of the studies examined in this review were retrospective (i.e. involving participants reflecting upon outcomes of their surgeries; see Appendix for more detail) …*<br>*… employed very small sample sizes, with findings for several quality of life outcome constructs being classified as having low strength of evidence due to its studies sampling fewer than 100 participants in total …* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage of puberty | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | satisfaction and health-related QoL, reduced gender incongruence.<br>Vocal cord surgery in transgender women (8 studies)—satisfaction with surgery but mixed findings on quality of life. | | *… employed non-validated self-report measures when measuring transgender men and women's quality of life …*<br>*… findings generally come from countries that are Westernized, and generally accepting of transgender people."* |

**Table 9b—NHMRC Level III-2. Comparative studies with concurrent control—gender-affirming surgery (n = 3)**

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Bungener 2020[38]**<br>To describe the sexual and romantic development during and after receiving GAC.<br><br>Score on quality criteria = 8 / 9. | Netherlands<br>Retrospective study<br>Centre of Expertise on Gender Dysphoria at the Amsterdam University Centres. | **PS, GAHT and GAS**<br>N=113 transgender adolescents<br>• 38 trans women<br>• 75 trans men.<br>Mean age 20.79 years, SD 1.36). | Sexual experiences. | One-year post surgery, young transgender adults reported a significant increase in experiences with all types of sexual activities. | No apparent adverse events or effect reported. | *"This study on the sexual and romantic experiences of young transgender adults during and after early GAT reveals an increase in sexual activity after gender-affirmative surgeries."*<br><br>Study limitations: *"… the data on sexuality during GAT (before surgery) were collected retrospectively."* |
| **Rochlin 2020[34]**<br>To explore the effect of a new technique to reinnervate the nipple–areolar complex (NAC) | US<br>Prospective study<br>Setting not stated. | Gender-affirming top surgery:<br>• Treatment / surgery group undergoing | NAC sensory restoration. | Significant improvement in the NAC sensation areas, including nipple, areola | Adverse events or effect not stated. | *"This proof of concept study suggests that immediate reinnervation of the NAC after mastectomy enhances recovery of NAC sensation in patients undergoing female-to-male mastectomy."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| after mastectomy.<br><br>Score on quality criteria = 8 / 9. | | NAC reinnervation (n=10); Mean age at 17.5 years (range: 16–19 years)<br>• Control group (n=10): Mean age at 36.6 years (range: 18–59 years). | | and peripheral breast skin, for treated patients. | | *"The limitations of our study include the small study size … In addition, the placebo effect is a potential bias, as knowledge of neurotization may have impacted the treated group's perception of sensation."* |
| **Ascha 2022**[36]<br>To determine whether top surgery enhances chest dysphoria, gender congruence, | US<br>A nonrandomised prospective cohort study<br>3 institutions in a large | Gender-affirming top surgery (mastectomy).<br>81 transgender and nonbinary (TGNB) adolescents and young | Chest dysphoria, gender congruence, and body image satisfaction. | GAC top surgery is related to enhanced chest dysphoria, gender congruence, and body | 1 haematoma (3%), 2 seromas (6%), and 1 instance of nipple loss (3%). | *"Top surgery is associated with low complication rates. Top surgery is associated with improved chest dysphoria, gender congruence, and body image satisfaction in this age group."*<br><br>Study limitations: *"Analyses omit 11 patients whose outcomes were not measured due to attrition … patients in* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| and body image.<br><br>Score on quality criteria = 7 / 9. | metropolitan location. | adults (AYA) designated female at birth (DFAB).<br><br>Mean [SD] age, 18.6 [2.7] years.<br><br>Surgical patients n=36; Control: n=34; 11 lost to follow-up. | | image satisfaction. | | *the treatment group who were able to access surgery may have greater socioeconomic status and parental support, possibly introducing sampling bias … We were unable to achieve a high degree of balance on baseline measures between surgery and control groups, even after propensity score adjustments."* |

**Table 9c—NHMRC Level IV. Case series / cross-sectional—gender-affirming surgery (n = 4)**

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Hughto 2020**[95]<br>To investigate prevalence of self-reported suicidal ideation, suicide attempts, and nonsuicidal self-injury (NSSI) before and after initiating the gender affirmation process.<br><br>Score on quality criteria = 8 / 9. | US<br>Cross-sectional<br>Survey data from the Transgender Stress and Health Study. | **GAHT + GAS**<br>N=288 transgender adults (234 trans males and 54 trans females)<br>Mean (SD) age 32.8 (13) years. | Depressive, anxiety and stress symptoms. | Social and medical GAC associated with lower risk of suicidal ideation and improved mental health outcomes (including improved anxiety, depression and stress symptoms). | Not stated. | *"Overall, in the present study, we provide evidence in support of the significant association between social and medical gender affirmation experiences and the mental health of U.S. transgender adults …[O]ur findings add to the collective body of evidence suggesting that multiple sources of gender affirmation may help to curb self-harm and poor mental health symptoms in transgender people."*<br><br>Study limitations: *"Given our study's cross-sectional design, it is not possible to make causal inferences. Given that our measures were self-reported, it is possible that biases in recollection or reporting influenced the results."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Boskey 2023**[61]<br>To examine the effect of chest reconstruction surgery (CRS) on gender congruence and chest dysphoria.<br><br>Score on quality criteria = 6 / 9. | US<br>Pre-post<br>Centre for Gender Surgery at Boston Children's Hospital. | Chest reconstruction surgery.<br>N=153, trans masculine and nonbinary adolescents and young adults:<br>• Subgroup of adolescents (n=59, mean age 16.7 (0.8). | Chest dysphoria and gender congruence. | Significant differences in gender congruence, appearance congruence, and chest dysphoria between at least two assessment points for the total sample and each subgroup (binary / nonbinary and adult / minor). | Medical, social and behavioural assessment undertaken to reduce potential regret given changes are irreversible. | *"The results of our longitudinal cohort study of TMNB adolescents and young adults demonstrate that, in the context of a gender center where a multidisciplinary team is available to provide wrap around assessment and support, gender-affirming chest reconstruction is an effective way to improve gender and appearance congruence and reduce chest dysphoria in both nonbinary and binary populations across this age range."*<br><br>*"Limitations include the fact that all individuals accessed gender-affirming surgery at a single center, by a single surgeon, the lack of racial diversity, the relatively low number of nonbinary individuals in our analytical sample, and the fact that it was not possible to have a control group as well as it would be unethical to withhold medically necessary care."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Becker-Hebly 2021**[58]<br>To describe mental health needs of adolescents diagnosed with GD prior to treatment.<br><br>Score on quality criteria = 5 / 10. | Germany<br>Pre-post<br>University Medical Center Hamburg-Eppendorf. | **Psychosocial only (n=21); GnRHa (11) + GAHT (32) + GAS (11)**<br>n=75 adolescents and young adults with GD.<br>• PS: 8 trans males (72.7%), 3 trans females<br>• PS+GAHT: 28 trans males, 4 trans females<br>Surgery: 10 trans males, 1 trans female. | Emotional and behavioural problems, quality of life. | Adolescents in the gender-affirming hormone (GAH) and surgery (GAS) group reported emotional and behavioural problems and physical quality of life scores similar to the German norm mean.<br>Improved mental health outcomes, cognitive functioning and quality of life observed in GAC group. | No evaluation of physical side effects due to the ethical research protocol. | *"Adolescents who underwent puberty suppression or GA (hormonal and surgical) interventions showed better scores in some of the psychosocial health dimensions, although we did not test whether this difference was statistically significant."*<br><br>Study limitations: *"Due to the descriptive nature of the present analyses, the findings cannot be generalized to other samples. Because of the small sample size caused by the high drop-out rates during data collection, this study does not provide sufficient power for hypothesis testing … This study did not focus on the physical side effects of interventions because the ethical research protocol did not allow direct comparison with medical charts from the endocrinological department."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Tang 2022**[88]<br>To evaluate the prevalence of gender-affirming mastectomy and surgical results.<br><br>Score on quality criteria = 4 / 9. | US<br>Pre-post<br>Integrated healthcare system (Kaiser Permanente Northern California). | Mastectomy<br>N=209 adolescents<br>Median age 16 years (range 12–17). | Incidence of gender-affirming mastectomy, prevalence of entailed complications. | Generally low prevalence of surgical complications. | 10 patients (7.3%) had at least one surgical complication: haematoma (3.6%), infection (2.9%), hypertrophic scars requiring steroid injection (2.9%), seroma (0.7%), and suture granuloma (0.7%); 15 patients (10.9 %) underwent revision. | *"Between 2013–2020, we observed a marked increase in gender-affirming mastectomies in adolescents. The prevalence of surgical complications was low and of over 200 adolescents who underwent surgery, only two expressed regret, neither of which underwent a reversal operation."*<br><br>Study limitations: *"First, its retrospective design meant we were unable to measure patient satisfaction and quality-of-life outcomes … Next, our study was conducted at KPNC in an insured cohort of individuals with access to gender-affirming medical and surgical care. Therefore, our outcomes may not be representative of the general population, many of whom lack similar access to care. Finally, the time to develop postoperative regret and/or dissatisfaction remains unknown and* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| | | | | | Two expressed regret. | *may be difficult to discern given that regret is quite rare."* |

## Fertility preservation

***Context***

Puberty suppression treatment and GAHT have a range of impacts on fertility. In transgender women, puberty suppression and GAHT can inhibit or prevent spermatogenesis. When puberty suppression and GAHT are ceased, spermatogenesis may return but the time course is uncertain. For transgender males, testosterone can inhibit the maturation of oocytes and follicle-stimulating hormone. They are not completely inhibited, however, and therefore ovulations and pregnancies can still occur in the setting of testosterone treatment. The effect of puberty suppression has also been shown to be reversible based on data from testosterone treatment given to people experiencing precocious puberty.[29] However, gender-affirming genital surgery to remove the testicles (orchiectomy / orchidectomy) or ovaries (oophorectomy) causes permanent fertility loss.[30]

For these reasons, transgender people who want children can require access to assisted reproductive technology. To facilitate this, consideration needs to be given to fertility preservation options prior to beginning pharmaceutical and / or surgical gender-affirming care, so that transgender people can access assisted reproduction later in life.[29,30] Preservation generally involves harvesting and cryopreservation (freezing) of semen (for transgender women) or oocytes (for transgender men).[29] Less frequently, testicular sperm extraction (TESE, also referred to as testicular sperm aspiration, TESA) may be used. This involves a small surgical procedure to harvest viable sperm from testicular tissue, and is used for transgender females unable to ejaculate for biological reasons or because of gender dysphoria.[29,30]

This Evidence Check update identified six studies focusing on fertility preservation, comprising two systematic reviews (Level I); one comparative study without concurrent control (Level III-2); and three case series / cross-sectional studies (Level IV).

The additional information on the benefits of fertility preservation provided by this update is summarised below (Table 10). It covers the effectiveness of semen and oocyte cryopreservation, pregnancy in transgender males, and the effectiveness of TESE.

### Table 10a—Benefits of fertility preservation

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| Compromised fertility is a likely consequence of GAHT and fertility discussion is recommended with transgender adolescents before commencing GAHT.<br>Expert statements warn testosterone therapy for trans boys may lead to sterility (two references) although it does not necessarily protect against unwanted pregnancy (one | **Effectiveness of semen cryopreservation**<br>One Level I study[30] reported that semen cryopreservation was simple and reliable, with lower semen parameters offset by multiple sample collection.<br>Two Level I studies[29,30] reported that banked sperm is of a lower quality compared with cis male samples. Stolk (2023)[29] reported |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| reference). Ovarian reserve and fertility preservation should be discussed with trans boys starting GAHT (one reference).<br>Fertility may be compromised if GnRHa is started early and followed by GAHT. The only feasible option for fertility preservation among prepubertal trans girls is testicular tissue cryopreservation, or harvesting of oocytes for trans boys, both of which are still experimental and invasive. Clinical guidelines are unanimous in recommending that fertility preservation counselling is conducted with the young person and their family before initiating puberty suppression. | lowered sperm quality even prior to gender-affirming hormone treatment, with uncertain recovery of spermatogenesis after discontinuing treatment.<br>One Level IV study[62] of 35 trans girls, included in both Level I reviews and identified in this Evidence Check update, reported that one third of patients were unable to produce a semen sample due to early stage of puberty and an additional 17% were uncomfortable with masturbation.<br>A Level IV study by Dilday (2022)[67] compared semen quality in trans girls with adolescents with cancer (n = 45, mean age 15.8) finding semen parameters within the normal range for healthy adults. None were undergoing PS or GAHT.<br>**Effectiveness of oocyte cryopreservation**<br>One Level I study[29] reported that oocyte vitrification showed successful outcomes across 17 studies, even after testosterone cessation, with similar outcomes to both cisgender individuals and TGD individuals who have not yet initiated GAHT. The Stolk review[29] included a Level IV study by Barrett (2022)[57], also identified in this Evidence Check update. This study reported successful oocyte cryopreservation in 19 out of 20 patients with no significant adverse events.<br>**Pregnancy in transgender males**<br>One Level I study[29] reported 169 live births (39%), 142 miscarriages (33%) and 92 abortions (21%) in a cohort of 203 transgender males reporting ever being pregnant. Evidence from a smaller cohort of 41 reported that pregnancy, delivery and birth outcomes did not differ in relation to prior testosterone use. |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | Note that sections on GnRHa and GAHT also update relevant findings pertaining to the fertility implications of these interventions. |
| For prepubertal transgender youth, the only feasible option of fertility preservation is testicular tissue cryopreservation, which is still experimental and not yet proven successful in humans (one reference, Level B–C). | **Effectiveness of testicular sperm extraction (TESE)**<br>One Level I study[29] reported that there is evidence from a small number of primary studies in the setting of gender dysphoria that TESE can be successful. One of the studies in this review was a Level III-3 study by Peri (2021)[50], also identified in this Evidence Check update. This study examined cryopreservation outcomes in 25 transgender females with a median age of 13.4 (Tanner stage 2–5). Outcomes were successful in 17 patients; no sperm was detected in patients with testicular volume under 10ml and this was therefore advised as a threshold. |

### Table 10b—Risks of fertility preservation

The additional information on the risks of fertility preservation provided by this Evidence Check is summarised below. It covers adverse effects.

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| No specific information on risk and harms reported. | **Adverse effects**<br>Two Level I studies[29,30] reported that oocyte cryopreservation procedures were invasive and psychologically challenging and could worsen gender dysphoria.<br>Other risk descriptions focused on risks associated with hormone therapy and lower semen quality. |

### Table 10c—Variation in the effectiveness and risks of fertility preservation

The information on variation in the effectiveness, risks and costs of fertility preservation are summarised in the table below. It covers desire for biological children and uptake of fertility preservation treatment.

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| Fertility preservation is an issue for adolescents undergoing GAHT (one reference). A recent Australian study reported that no trans boys opted for fertility preservation and suggested this population were electing to delay this procedure until they were older. However, 62% of trans girls underwent fertility preservation. The rate of trans girls undergoing fertility preservation was higher than that reported in studies from the US (one reference) or the Netherlands (one reference). Pang et al. (see Pang et al.[69] in Watson et al. 2020[2]) suggested timely fertility preservation that did not substantially delay gender-affirming treatment explained the higher uptake. These authors suggested that being co-located with an onco-fertility centre and being publicly funded might explain the uptake rates. It is strongly recommended by expert consensus that fertility counselling be provided for all adolescents embarking on GAHT. | **Desire for biological children**<br>One Level I study[29] reported that while more than 50% of adolescents reported a desire to have children, biological offspring was not the preferred option for most.<br>**Uptake of fertility preservation treatment**<br>One Level I study[30] reported fertility preservation is underused, potentially due to cost barriers, late referral and low awareness. A further Level I study[29] reinforced this finding, especially in countries with no insurance and in transgender men.<br>One Level IV study[62] of 35 trans girls with a mean age of 14.8 reported a 38% uptake of fertility preservation in those counselled. This study was included in both Level I reviews and identified in this Evidence Check update. |

#### *Strengths and limitations of the evidence—fertility preservation*

Consistent with previous interventions, the Level I study of Stolk et al. (2023)[29] identified limitations in study design (cross-sectional, case series, no control groups), small sample sizes and limited follow-up time. The Level I study of Yan et al. (2021)[30] also identified lack of information about dosages of hormone therapy or sperm / ovarian stimulation medication.

Acknowledged limitations in the primary studies included small sample sizes, single institution recruitment, retrospective design and lack of information on desire to have children.

It is also important to note that three of the four primary studies identified in this Evidence Check update were also included in at least one of the two Level I reviews. This has been taken into account in the conclusions for this intervention.

### *Conclusions of Evidence Check update—fertility preservation*

This update has added two systematic reviews and a further four primary studies to the evidence base pertaining to cryopreservation (noting that three of the four primary studies were included in the two Level I reviews). Desire to have children among transgender adolescents is relatively high. Uptake of fertility preservation treatment remains low, however, owing to cost barriers, late referral and low awareness. Another factor contributing to low uptake of fertility preservation is evidence from one Level I review that having biological offspring was not the preferred option for most people who expressed an interest in having children. Although the newly identified evidence generally reports favourable **benefits and effectiveness** outcomes for both semen and oocyte cryopreservation, some **risks or potential harms** warrant mention**.** Studies consistently reported that semen was of lower quality if patients had received puberty suppression and / or GAHT. Furthermore, harvesting semen can be challenging in early puberty and / or due to discomfort with masturbation. There is emerging evidence that testicular sperm extraction can mitigate these limitations; however, this research is in its infancy and semen cryopreservation remains the dominant approach. Oocyte preservation was reported as generally effective with no adverse events; however, cryopreservation procedures are invasive and psychologically challenging and can worsen gender dysphoria.

In summary, while we identified additional evidence supporting fertility preservation, both reviews and primary studies remain limited by small sample sizes, single centre recruitment, study design limitations and variation in use of hormones in participant cohorts. Notwithstanding this, outcomes reported are predominantly positive and very few adverse effects were described in identified studies.

Table 11 below summarises the main features of each of the reports on fertility preservation included in this Evidence Check.

## Included studies in this Evidence Check update—fertility preservation

**Table 11a—NHMRC Level I. Systematic reviews—fertility preservation (n = 2)**

| Author, date, aims, quality criteria | Target population / included studies | Intervention Age or stage | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| **Stolk 2023**[29]<br>To examine the literature that discusses the desire for children and parenthood, available options for fertility preservation (FP), and the resulting outcomes for transgender and gender diverse (TGD) people.<br><br>Score on quality criteria = 7.5 / 13. | 76 studies:<br>19 studies on the desire for children and parenthood; 22 on fertility counselling and use; and 36 on options and outcomes. | AFAB (assigned female at birth): Oocyte and embryo cryopreservation, ovarian tissue cryopreservation and in vitro maturation.<br>AMAP (assigned male at birth): Semen cryopreservation, testicular sperm extraction and testicular tissue cryopreservation. | > 50% of adolescents and adults expressed a desire for (future) parenthood; biological offspring was not the preferred option for most.<br>Overall low FP use rate, with the lowest rate in countries with no insurance and in people AFAB.<br>Oocyte vitrification in TGD individuals | TGD people AMAB prior to GAHT showed lower semen parameters compared with cisgender controls.<br>High financial costs associated with FP. | *"This review showed that the majority of TGD adults and adolescents have a desire for children, but biological relatedness is less important."*<br><br>*"Even though we included many studies, most were cross-sectional questionnaires, case series, or small sample size cohort studies with limited follow-up time and lack of control groups. Furthermore, the quality assessment of the included studies was low to moderate. Interpretation of this evidence requires caution."* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention Age or stage | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | AFAB, whether conducted during or after testosterone cessation, demonstrated similar outcomes to both cisgender individuals and TGD individuals who have not yet initiated GAHT. | | |
| **Yan 2021**[30]<br>To review evidence for the outcomes of FP options in transgender people.<br><br>Score on quality criteria = 6.5 / 13. | 15 articles.<br>8 articles describing FP options for transgender men, 7 for transgender women and one for both. | GAHT, gender-affirming surgery. | Semen cryopreservation is simple and reliable. If the sperm quality is low, multiple samples can be collected; additional methods such as intrauterine insemination (IUI) | Semen parameters are lower in transgender women in comparison with cisgender men.<br>For transgender men, FP can involve invasive procedures, which | *"Several fertility preservation methods have shown to be effective in the transgender population. Our review shows that fertility preservation should be discussed early during gender transition and if possible, before any exogenous hormonal therapy is started, as the timeline for these interventions is important in order to preserve their reproductive potential as much as possible."* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention Age or stage | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | and in vitro fertilisation (IVF) can also be used.<br>Testicular sperm extraction is an option for patients who are unable to ejaculate or for those with severe oligospermia or obstructive azoospermia.<br>The most common method for fertility preservation in transgender men is oocyte cryopreservation. | can be a physically and psychologically challenging experience and may worsen gender dysphoria.<br>Early oocyte retrieval could prevent patients having to temporarily stop their hormonal therapy. Discontinuing testosterone could worsen gender dysphoria.<br>In patients undergoing hormonal therapy where spermatogenesis can be affected | Study limitations: *"… several studies did not provide the dose of the hormone therapy or sperm/ ovarian stimulation medication."* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention Age or stage | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | | testicular sperm harvesting at the time of GAS can be contemplated. Immature testicular tissue cryopreservation is another experimental method. | |

**Table 11b—NHMRC Level III-3. Comparative studies without concurrent control—fertility preservation (n = 1)**

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Peri 2021**[50]<br>To identify factors that contribute to the success rate of sperm retrieval for cryo-preservation via testicular biopsy.<br><br>Score on quality criteria = 7 / 10. | Australia<br><br>Retrospective cohort study<br>The Royal Children's Hospital Gender Service (RCHGS). | Testicular biopsy.<br>N=25 transgender feminine adolescents.<br>Median age 13.4, Tanner stage 2–5. | Successful sperm retrieval and potential predictors (i.e. age, testicular volume and serum testosterone, serum LH and FSH levels). | 17/25 patients had successful sperm retrieval, with one case undergoing puberty suppression for more than 2 years. | No sperm was detected in anyone with less than 10 mL testicular volume.<br>Adolescent patients should wait until their testicular volumes are ⩾ 10 mL before attempting FP via testicular biopsy. | *"… testicular volume was significantly higher in those with successful sperm retrieval …[and] is most useful in predicting successful sperm retrieval following testicular biopsy in transgender adolescents."*<br><br>Study limitations: small number of participants; *"… our threshold might overpredict the likelihood of sperm being present … [and we were] missing data on testicular volume, Tanner stage, and serum hormone levels for a small number of patients, and we are unsure how these might have affected our results."* |

**Table 11c—NHMRC Level IV. Case series / cross-sectional—fertility preservation (n = 3)**

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Barrett 2022**[57]<br>To review authors' oocyte cryopreservation outcomes and best practices to guide treatment.<br><br>Score on quality criteria = 8 / 9. | US<br>Pre-post<br>New York University Langone Fertility Center (NYULFC). | Transvaginal oocyte aspiration.<br>N=44 adolescent and young adult trans men.<br>Median age: 16 (12–23) at consultation. | Oocyte cryopreservation outcomes. | 95% per cent (19/20) underwent successful transvaginal oocyte aspiration. | No significant adverse events. | *"Oocyte cryopreservation is a safe fertility preservation option in AYA trans men and is an important aspect of providing comprehensive transgender care."*<br><br>Study limitations: *"… limited in its generalizability as it was completed at a single institution"*, and *"retrospective design and reliance on chart documentation"*. |
| **Dilday 2022**[67]<br>To describe outcomes of sperm cryopreservation in trans girls and | US<br>Pre-post<br>The Fertility and Advanced Reproductive Medicine clinic | Sperm cryopreservation<br>N=45<br>Trans girls (n=18) at Tanner stages | Successful rate of sperm cryo-preservation. | Semen parameters on GAHT were within normal range for healthy adults. | Information about side effects not reported. | *"This study supports the feasibility of sperm cryopreservation in the adolescent population, and assures that sperm cryopreservation does not* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| compare their semen parameters with adolescents with cancer.<br><br>Score on quality criteria = 5 / 7. | of the University of Texas (UT). | of IV or V; mean (SD) age: 15.8 (1.6). | | Sperm cryopreservation for transgender youth is feasible and cost-effective, with the added benefit of not causing significant treatment delays. | | *significantly delay initiation of GAHT."*<br><br>*"The limitations of this retrospective analysis include its small study population ... Given the retrospective design, demographic factors that could be confounders also impacting semen parameters were not available for evaluation."* |
| **Brik 2019**[62]<br>To examine the prevalence of fertility preservation (FP) attempts among transgender girls. | Netherlands<br>Pre-post<br>Curium-Leiden University Medical Centre. | GnRHa<br>N=35 trans girls<br>Mean age (SD): 14.8 ±1.9. | Rate of FP attempts. | Out of those counselled about FP, 38% actually attempted it, which is higher than reported in prior studies in the US. | 32% were unable to produce a semen sample due to early puberty, and an additional 17% felt uncomfortable | *"In conclusion, one third of the trans girls attempted FP, and most were able to store sperm suitable for future intrauterine insemination or ICSI."*<br><br>*"Limitations of this study are its retrospective design and the small study population. Information on* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| Score on quality criteria = 4 / 6. | | | | | with masturbation. | *sexual orientation or desire to have children was not documented for all individuals. The influence of these factors could be further explored in a prospective study using standardized questionnaires or interviews about reasons for declining FP."* |

# Question 2—Effective psychosocial interventions for trans and gender diverse young people under 18 years old with gender dysphoria

## Psychosocial interventions

### *Context*

Review-level evidence has demonstrated that transgender individuals experience an elevated prevalence of mental health problems, which negatively impact wellbeing and quality of life.[11] For example, suicidal ideation and suicide rates in the transgender population are higher than in the general population.[12] Based on gender-minority theory, this is driven in part by a combination of external stressors, for example events of prejudice such as rejection, discrimination and victimisation combined with internalised reactions such as anticipated stigma and gender-identity concealment. These influences are mediated by individual-level cognitive and emotional characteristics.[11]

In addition to whole-of-population statistics, elevated levels of mental illness have been demonstrated in adolescents, who experience gender-minority stressors in settings such as schools and through other peer interactions, for example teen dating violence.[12]

Gender-affirming psychological interventions are designed to support individuals experiencing gender dysphoria by providing respectful, aware and supportive interventions such as psychotherapy, family therapy and crisis support for those experiencing extreme distress such as suicidal ideation.[11,12,23] Psychosocial therapies are provided in parallel with the pharmaceutical, surgical and fertility preservation interventions described in previous sections of this Evidence Check update. This section focuses on studies that have a stated primary aim of evaluating the effectiveness of psychosocial interventions for transgender individuals.

This Evidence Check update identified seven studies focusing on psychosocial interventions, comprising three systematic reviews (Level I); one randomised controlled trial (II); one comparative study without concurrent control (III-3); and two case series / cross-sectional studies (IV).

The additional information about the benefits of psychosocial interventions provided by this Evidence Check is summarised below (Table 12). It covers suicidal ideation or attempt, psychological distress, depression, anxiety, social support, gender minority stress, belief in coping abilities and coping skills and access to care.

## Table 12a—Benefits of psychosocial interventions

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| There is a lack of evidence from which to draw any conclusions regarding the effectiveness of psychosocial interventions for treating children and young people with gender dysphoria.<br>Only one paper empirically examined the effect of psychological support for a cohort of transgender adolescents (Level D). This study compared the effect of psychological support and GnRHa with psychological support alone. It found all participants reported an improvement in psychological functioning at six months. However, only participants who received both GnRHa and psychological support continued to improve over the next 12 months. Another paper described a pilot program of group work for parents and carers of transgender adolescents (Level C–D) and one paper reported a single subject case study in which a trans girl in a youth justice facility received intensive voice feminisation therapy (Level D). | **Suicidal ideation or attempt**<br>One Level I study[12] focused on transgender and gender diverse youth reported that gender-affirming crisis hotlines, gender-affirming medical care such as GnRHa and GAH, online media-based outreach, safety and connectedness, and family system-based interventions may influence suicide-related thoughts and behaviours. The importance of safety and connectedness was emphasised, with acceptance of gender identity in family, school and other settings reported as protective—for example by promoting help-seeking behaviours when having suicidal thoughts.<br><br>**Psychological distress**<br>One Level I study[11] reported that Transgender Affirmative Psychotherapy + Building Awareness of Minority-Related Stressors [TA + BAMS], group transgender affirmative cognitive-behavioural therapy [AFFIRM], and Transgender Empowerment by Text [TExT] showed significant improvements in psychological distress.<br><br>**Depression**<br>One Level I study[11] reported that Transgender Affirmative Psychotherapy + Building Awareness of Minority-Related Stressors [TA + BAMS], group transgender affirmative cognitive-behavioural therapy [AFFIRM], and Transgender Empowerment by Text [TExT] showed significant improvements in depression.<br>One Level III-3 study of 142 transgender youth compared with a historical control group[48] reported that a First Assessment Single-Session Triage (FASST) clinic decreased depression. |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | One Level IV study of 41 transgender and gender diverse adolescents[59] reported that an online self-compassion intervention had positive effects on depression.<br><br>**Anxiety**<br>One Level I study[11] reported that Transgender Affirmative Psychotherapy + Building Awareness of Minority-Related Stressors [TA + BAMS], group transgender affirmative cognitive-behavioural therapy [AFFIRM], and Transgender Empowerment by Text [TExT] showed significant improvements in anxiety.<br>One Level III-3 study of 142 transgender youth compared with a historical control group[48] reported that a First Assessment Single-Session Triage (FASST) clinic decreased anxiety.<br>One Level IV study of 41 transgender and gender diverse adolescents[59] reported that an online self-compassion intervention had positive effects on anxiety.<br><br>**Social support**<br>One Level I study[11] reported that Transgender Affirmative Psychotherapy + Building Awareness of Minority-Related Stressors [TA + BAMS], group transgender affirmative cognitive-behavioural therapy [AFFIRM], and Transgender Empowerment by Text [TExT] showed significant improvements in social support.<br>One Level IV study of 41 transgender and gender diverse adolescents[59] reported that an online self-compassion intervention had no effect on sense of belongingness.<br><br>**Gender minority stress**<br>One Level I study[11] reported that Transgender Affirmative Psychotherapy + |

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| | Building Awareness of Minority-Related Stressors [TA + BAMS], group transgender affirmative cognitive-behavioural therapy [AFFIRM], and Transgender Empowerment by Text [TExT] showed significant improvements in some aspects of gender minority stress.<br>One Level IV study of 684 participants aged 13–24[96] examining chest binding practices reported that people who undertook binding reported less 'misgendering'.<br><br>**Belief in coping abilities and coping skills**<br>One Level I study comparing 135 sexual and gender minority youth with 134 controls[32] reported that a web-based application designed to facilitate LGBTQ+ identity affirmation, promote a feeling of connectedness to the LGBTQ+ community and encourage cognitive and behavioural coping skill practice had significant positive effects on belief in coping abilities and coping skills.<br><br>**Access to care**<br>One Level IV study of 684 participants aged 13–24[96] examining chest binding practices reported that most people sought advice on binding online rather through gender care clinics. |

## Table 12b—Risks of psychosocial interventions

The additional information on the risks of psychosocial interventions provided by this Evidence Check is summarised below. It covers safety.

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| There was no evidence of risk or potential harms from the psychosocial interventions identified in this Evidence Check. Of note, we did not identify any studies that met inclusion criteria whose aim was to change an individual's gender identity. | **Safety**<br>One Level I study comparing 135 sexual and gender-minority youth with 134 controls[32] reported that a web-based application designed to facilitate LGBTQ+ identity affirmation promoted a feeling of connectedness to the LGBTQ+ community and encouraged cognitive and behavioural coping skills. The practice reported no adverse events.<br>One Level IV study of 684 participants aged 13–24[96] examining chest binding practices found more than 95% of participants reported physical side effects such as back pain and overheating. |

***Table 12c—Variation in the effectiveness and risks of psychosocial interventions***

The information on variation in the effectiveness and risks of psychological interventions is summarised in the table below. It covers acceptability.

| Conclusions from previous Evidence Check (studies from 2000–2019) | What this Evidence Check update adds (studies from 2019–2023) |
|---|---|
| There was no evidence of effectiveness or risks associated with psychosocial interventions identified in this Evidence Check. | Most newly identified studies reported that there was good acceptability and / or no adverse impacts of the therapies studied. |

***Strengths and limitations of the evidence of psychosocial interventions***

In addition to reinforcing previous conclusions pertaining to other gender dysphoria interventions, the confounding influence of factors such as family support, concomitant pharmaceutical and other gender-affirming interventions and the influence of puberty on mental health independent of gender identity were described in Level I studies.

Additionally, a broad array of psychosocial interventions was explored in review-level studies including psycho-education, transgender affirmative psychotherapy, cognitive behavioural therapy and family therapy. Furthermore, delivery modes varied from in-person to online. The differential effect of these therapy approaches and how they are delivered is therefore difficult to discern given the relatively low volume and quality of identified studies.

It is also important to note that not all review studies focused exclusively on transgender *adolescents* or transgender *individuals*. For example, in the review of Expósito-Campos (2023)[11], nine of the 22

studies explicitly referenced that some participants were aged under 18; of these, five had cohorts entirely aged 20 or under. The authors also noted that only eight of the 22 studies had exclusively transgender / nonbinary participants; two had mixed populations with subgroup transgender / nonbinary analysis; the remaining studies had mixed populations with no subgroup analysis. This review reported that studies focusing on this population were first conducted in 2014, *"while the most methodologically rigorous date from 2018 onwards"*.[11(p16)] Furthermore, the review of family-based therapies by Malpas et al. (2022)[23] encompassed *"transgender and gender expansive (TGE) youth"*.

Further limitations described in Level I studies included inadequate description of interventions, attrition, and lack of sustainment of outcomes at follow-up and lack of representation of participants of colour.[23]

Acknowledged limitations in primary studies included small sample sizes, use of historical controls, short follow-up periods, lack of validated outcome measures specific to adolescent populations, lack of control group and dependence on supportive parents / guardians to facilitate participation of adolescents in research.

### *Conclusions of Evidence Check update—psychosocial therapies*

This Evidence Check update has added considerably to the volume of evidence evaluating psychosocial interventions such as such as psychotherapy, family therapy and mental health / crisis support. The previous Evidence Check identified only three studies, with one a single case study; this Evidence Check has identified three systematic reviews and four primary studies including a randomised controlled trial. The newly identified studies report **benefits and effectiveness** across numerous outcome domains including suicidal ideation, psychological distress, depression, anxiety and gender minority stress. Furthermore, most studies report that interventions are both acceptable and safe, with no **risks or potential harms** reported.

Although the existence of an RCT is unique to this intervention category, it should be noted that this was of a mixed population of sexual and gender-minority youth—the number of people experiencing gender dysphoria is not reported and there is no subgroup analysis of this group. Furthermore, considerable limitations in this body of literature were identified. In addition to the previously observed limitations of small sample sizes and lack of diversity in participant cohorts, these include a large number of psychological interventions with additional variability in delivery mode; and studies of mixed populations with no subgroup analysis of adolescents and / or transgender participants. Therefore, although study designs are stronger relative to other intervention areas in this Evidence Check update, a number of limitations that are applicable to studies of psychological therapies should be borne in mind when interpreting findings of studies of psychological interventions.

Table 13 below summarises the main features of each of the reports on psychosocial interventions included in this Evidence Check.

## Included studies in this Evidence Check update—psychosocial interventions

**Table 13a—NHMRC Level I. Systematic reviews—psychosocial interventions (n = 3)**

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| **Expósito-Campos 2023**[11]<br>To investigate the effect of psychological interventions on transgender and nonbinary (TGNB) individuals.<br><br>Score on quality criteria = 8 / 12. | N=22 articles<br>8 with TGNB only; 2 mixed samples with separate outcome data for TGNB [3 RCTs, 7 pre-post no control].<br>12 mixed samples without disaggregated data [4 RCTs, 2 quasi-experimental, 6 pre-post no control]. | Psycho-education, transgender affirmative psychotherapy, online programs for stigma combating and stress management, online cognitive behavioural therapy (CBT), school-based counselling programs.<br>The studies did not specify whether | Participants in Transgender Affirmative Psychotherapy + Building Awareness of Minority-Related Stressors [TA + BAMS], group transgender affirmative cognitive-behavioural therapy [AFFIRM], and Transgender Empowerment by Text [TExT] showed significant | Interventions for TGNB individuals were heterogeneous and not very well described.<br>Further experimental testing is due, given that the improvements were not generally sustained at follow-up and only TA + BAMS was an RCT. | TA + BAMS, AFFIRM and TExT *"seem to be the most promising interventions"* for TGNB individuals … conclusions *"are limited by moderate-to-high risk of bias". "… the results of the psychological interventions analyzed are encouraging but also limited and, at times, difficult to interpret".*<br><br>Limitations of included studies: *"… various studies presented very high attrition rates and did not analyze whether dropouts differed from completers, which poses a threat to the validity of their results ... only 40.9% of the 22 studies included in the review had a follow-up measurement, making it* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | 2 dissertations. | their participants experienced gender dysphoria (GD) nor the type of gender transition (social, medical, or both) they were embarked on.<br><br>9 studies contained participants under 18. | improvements in psychological distress, depression, anxiety, social support, and some aspects of gender-minority stress.<br>Results overall also suggest improvements in suicidality, substance-related risk behaviours, coping skills / emotion regulation, stress appraisal, self-esteem, self-acceptance, social support, resilience, hope, positive identity and | | *difficult to ascertain if the interventions had long-lasting effects."* |

| Author, date, aims, quality criteria | Target population / included studies<br>Age or stage | Intervention | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | identity acceptance. | | |
| **Christensen 2023**[12]<br>To review interventions for preventing suicide among transgender children and adolescents.<br><br>Score on quality criteria = 7 / 13. | 17 articles<br>Case-control or cohort studies published 2017–2023, mainly in the US.<br>Participants aged 24 years and under. | Crisis interventions; gender-affirming crisis hotline, medical care via interdisciplinary gender clinics, online media-based outreach, safety and connectedness in schools, and family system-based. | Acceptance of gender identity in multiple domains—from family system, school, peers, and in legal documentation—has been found to be protective; for instance, perceived school safety and acceptance promote help-seeking behaviours when having suicidal thoughts.<br>Evidence that gender-affirming | No clear perceivable risks reported for participating in ***psychological*** interventions in the review. | *"Interventions that may influence suicide-related thoughts and behaviours include gender-affirming crisis hotlines; gender-affirming medical care such as GnRHa and GAH; online media-based outreach, safety and connectedness, and family system-based interventions."*<br><br>Limitations of the included studies: *"… the overall quality of evidence was low and the risk of bias high …*<br>*… Common flaws that created high risk of bias included self-reporting, lack of controls for comparability, small sample sizes, and lack of generalizability."*<br>Studies inconsistently used validated rating scales for depression, anxiety, gender dysphoria and suicide, making it |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | care reduced suicidal thoughts or behaviours compared with those not receiving treatment. | | difficult to compare efficacy of intervention methods. |
| **Malpas 2022**[23]<br>To review research literature that provide outcomes for family-based interventions with transgender and gender expansive (TGE) youth.<br><br>Score on quality criteria = 5 / 12. | 34 studies<br>32 studies examining family-based interventions with TGE youth and their families; 2 examining family-based interventions with sexual minority youth. | Family-based interventions and family therapy (e.g. family guidance sessions, offering parents TGE resources, collaborating with schools). | One study found Attachment-Based Family Therapy (ABFT) leads to a significant decrease in suicidal ideation and depressive symptoms in lesbian, gay and bisexual youth and a moderate (but nonsignificant) decrease in attachment-related | Principles of family-based therapy were articulated including provision of psycho-education; enabling caregivers their own supportive spaces; and framing family acceptance and engagement as a protective factor. | *"This systematic review of English-speaking peer-reviewed articles confirms the absence of youth and family outcome data as well as empirical research on the specific mechanisms of effectiveness of family therapy and family-based services for TGE youth."*<br><br>Limitations of the included studies: *"… there are no quantitative outcome studies on family therapy or family-based interventions with TGE youth, [but] there are: (1) a small number of qualitative studies (n= 6) based on small samples of caregivers, (2) case studies (n= 9) arguing for the effectiveness of* |

| Author, date, aims, quality criteria | Target population / included studies | Intervention<br>Age or stage | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | anxiety and avoidance. | | *family-based interventions for TGE youth and their families … there is a glaring absence of quantitative outcome data on family therapy and family-based interventions with LGBT youth in general and with TGE youth in particular … this review yielded no published quantitative outcome studies demonstrating the efficacy of family therapy interventions with TGE youth."* |

**Table 13b—NHMRC Level II. Randomised controlled trial—psychosocial interventions (n = 1)**

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Bauermeister 2022**[32]<br>To examine the effect of a web-based application on supporting mental health of sexual and gender minority youth.<br><br>Score on quality criteria = 9 / 13. | US<br><br>RCT<br><br>Participants were recruited on Instagram. | Web-based application with materials, resources and peer stories.<br>N=270 sexual and gender minority youth (SGM).<br>Mean age 16.5, SD 1.5)<br>• Treatment group (n=135): 29 AMAB and 106 AFAB<br>• Control group (n=134): 32 AMAB and 103 AFAB. | Stress, mental health symptoms, coping skills | Significantly greater improvement in challenge appraisals (i.e. belief in one's coping abilities) compared with control; no differences for threat or resource appraisals.<br>Greater increases in coping skills vs. control.<br>Mental health symptoms improved across both the | No adverse events were reported during the intervention. | *"This study demonstrated that a brief web-based intervention can provide self-guided, asynchronous and confidential support that improves the ability of SGM youth to cope with minority stress."*<br><br>Study limitations: *"… our ability to detect these effects with statistical precision was limited by our small sample size and short follow-up period … Second, some of the indicators used to measure our outcomes (e.g. authenticity and LGBTQ+ community connectedness) were originally developed with adult populations. Given the unique needs of SGM youth, it is possible that the measures used in our study were not optimal for use with SGM youth populations."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| | | | | treatment and control arms; however, there were no differences between arms. | | |

**Table 13c—NHMRC Level III-3. Comparative studies without concurrent control—psychosocial interventions (n = 1)**

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Allen 2021**[48] To examine the clinical impact of an innovative mental health support clinic. | Australia<br><br>A convergent, parallel mixed methods study<br><br>Royal Children's | 90-minute single session consultation provided in the First Assessment Single-Session | Anxiety, depression, quality of life. | Decreased anxiety and depression with enhanced family functioning and sense of agency. | Information on adverse effects or events not reported. | *"The results of this study are nonetheless encouraging and suggest that FASST may help to improve the lives of children and adolescents who are TGD awaiting care."*<br>*"There are several limitations to this study. For the quantitative analysis,* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| Score on quality criteria = 8 / 10. | Hospital Gender Service (RCHGS). | Triage (FASST) clinic.<br>• Transgender youth in treatment group (n=142), median age was 15.0 years<br>• Control group (n=120), median age was 15.0 years. | | | | *only limited outcome measures (CBCL [Parent-rated Child Behavior Checklist] and YSR [Youth Self-Report]) were available from the historical control group. Additionally, our use of historical controls may have introduced confounders that contributed to the observed differences in mental health between those who did and did not attend FASST."* |

**Table 13d—NHMRC Level IV. Case series / cross-sectional—psychosocial interventions (n = 2)**

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| **Julian 2021[96]**<br>To understand binding trends in adolescents and young adults.<br><br>Score on quality criteria = 7 / 8. | US<br><br>Cross-sectional<br><br>Online survey distributed through social networks, social media, and community agencies. | Chest binding<br>N=684 transgender adolescents and young adults (AYA):<br>• Binding group (n=608): 16.49 ±2.69<br>• Non-binding (n=76): 15.89 ± 2.89. | Chest dysphoria, life satisfaction. | More gender congruence reported in the group practising chest binding, which is associated with an enhanced life satisfaction. | 95.6% reported to have experienced physical side effect from chest binding, ranging from back pain to overheating.<br>Both commercial binders and convenient items such as tape, bandages, plastic wrap, tarps, pantyhose and girdles were reportedly used | *"Most youth in this study reported binding every day more than 8 hours to provide protection against being misgendered and achieve psychological comfort, underscoring the importance of this practice. When young people are not given appropriate information about binding practices, they are left to find resources that may not be safe and inhibit help seeking behaviors."*<br><br>*"To maintain institutional review board waiver of parental consent, all questions related to the mental health implications of chest binding were omitted … Another limitation to the study was that participants needed to have access to the Internet and be connected to some* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention Sample N = age, gender identity | Main outcomes | Benefits | Risks | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|---|
| | | | | | for chest binding. | *form of social media or agency to receive the link."* |
| **Bluth 2023[59]**<br>To investigate the impact of an online self-compassion intervention for transgender adolescents.<br><br>Score on quality criteria = 7 / 10. | US & Canada<br><br>Pre-post<br>Online program delivered via Zoom platform. | A self-compassion program, delivered in eight 1.5h sessions.<br>N=41 transgender and gender diverse adolescents, mean age (SD) 14.5 (1.49) years. | Feasibility of the program (attendance and retention), mental health outcomes. | Increased self-compassion and improved anxiety, depression, resilience and life satisfaction.<br>The program demonstrated its feasibility, with 100% of participants attending more than 6 out of 8 classes. | No significant improvement in sense of belongingness. | *"Results suggest that self-compassion interventions can be incorporated into therapy programs to support and improve mental health for transgender adolescents."*<br><br>Study limitations: *"First, the sample was relatively small. Second, there was no control group, which makes it impossible to conclude causality. Third, parents or guardians were required to consent to have their adolescent participate in the study, which meant that only those adolescents with parents or guardians who supported their gender transition could be involved."* |

# Discussion

This Evidence Check update identified a comparatively large volume of new research pertaining to interventions for children and young people with gender dysphoria. This is encouraging, especially considering the smaller span of years (four) covered by the update (2019–2023) compared with the time span (19 years) covered by the original review (2000–2019). The identified papers were published across a broad array of journals. While this was challenging with respect to defining key words to identify papers for the purpose of this Evidence Check, as they were not used consistently (e.g. in abstract indexing), the tailoring to different audiences does suggest a range of disciplines are involved in trans and gender diverse research. This may have positive implications for future work by NSW Health in deciding which groups and representatives can or should be consulted to develop holistic and inclusive models of care.

As shown in Table 13, the distribution of research study designs also showed some shifts relative to the original Evidence Check. There were comparatively more Level IV studies (57% of total research volume in this Evidence Check vs. 30% in the previous review), as well as review papers (20% vs. 13%) and fewer comparative studies. It is likely these differences in part reflect dedicated efforts to report outcomes or 'snapshots' of clinical interest for cohorts over time as they progress through management at specialist gender dysphoria clinics. Examples include the programs led by the Royal Children's Hospital in Melbourne[5,6] and in Amsterdam.[7,8] These studies have followed relatively large patient cohorts—the Melbourne-based studies had cohorts of 158 (2022)[5] and 131 (2023)[6] and the Amsterdam cohorts were 720 (2022)[8] and 1766 (2023).[7] While there has not been a rapid growth in the conventionally accepted gold standard designs of RCTs, this Evidence Check offers important insights into the effectiveness and risks associated with gender dysphoria interventions. The combined total of 128 studies (of varying quality, see below) provides a platform for engaging patients and carers in dialogue on key issues, including defining directions for future research investment.

**Table 14—Comparison of volume and type of evidence in the original Evidence Check and this update**

| Level and study design | n (original review) (% of total) | n (this update) (% of total) |
|---|---|---|
| I. A systematic review (of level II studies*) | 6 (13%) | 16 (20%) |
| II. A randomised controlled trial | 0 | 1 (1%) |
| III-1. A pseudo-nonrandomised controlled trial | 0 | 0 |

| Level and study design | n (original review) (% of total) | n (this update) (% of total) |
|---|---|---|
| III-2. A comparative study with concurrent controls | 14 (30%) | 12 (15%) |
| III-3. A comparative study without concurrent controls | 7 (15%) | 6 (7%) |
| IV. Case series or cross-sectional study | 14 (30%) | 47 (57%) |
| Other (committee opinion/recommendations, qualitative) | 5 (11%) | Not in scope |
| **TOTAL** | **46** | **82** |

* While level I evidence is strictly classified as systematic reviews of RCTs, almost no RCTs have been conducted in this area to date.

Confidence in research findings is highest when research studies compare those receiving treatment with a well-matched control group or a group receiving usual care so that the effect of the treatment can be ascertained. Research using control groups can be challenging in the field of research into interventions for gender dysphoria for several reasons. Ethical concerns arise regarding potential withholding of treatment to people experiencing gender dysphoria, which can cause distress to individuals. This was highlighted in the original Evidence Check of this topic, which forecast that RCTs were unlikely to increase in volume for this reason—a prediction borne out by this update, which identified only one RCT examining an online intervention to support mental health of sexual and gender minority youth.[32]

In addition, the nature of some gender dysphoria treatments themselves can make the selection of appropriate control groups difficult. For example, the one Level III-3 study examining puberty suppression treatment compared outcomes in transgender adolescents with those receiving therapy for central precocious puberty (CPP) who are, by definition, a younger cohort.[49] Another comparative study (Level III-2) of puberty suppression treatment examined the effect of later vs. earlier treatment, again creating inherently different groups with respect to age.[43]

Another key inherent limitation of research into interventions for gender dysphoria, independent of study design, is that gender dysphoria management is undertaken over a long period in which various interventions overlap. This makes it difficult to isolate the differential effect of individual interventions, even where a control group may be present. In this sense, gender dysphoria management can therefore be considered a complex intervention, defined as an intervention comprising numerous interacting components; a corresponding number and variability of outcomes; and flexibility and tailoring in delivery of the intervention.[4]

For example, puberty suppression treatment and gender-affirming hormone therapy, two interventions representing the majority (70%) of all included studies in this Evidence Check update, often overlap. Of the 57 primary studies examining these therapies, 40 contained cohorts that had received both therapies during the period of the study, including 21 of the 23 Level IV studies examining GAHT. The complex nature of gender dysphoria treatment, in addition to the above factors, should be considered when interpreting the findings of this

Evidence Check. Although RCTs are rarely ethically possible in the field of research into interventions for gender dysphoria, it is important to note that RCTs are not considered an optimal approach to evaluating complex interventions, independent of ethical considerations.[100]

Furthermore, other confounding effects, for example the influence of smoking and lifestyle factors on cardiovascular risk, socioeconomic status, geography and race, are generally not controlled for in the studies identified in this Evidence Check update.

Notwithstanding the above considerations, the consistency of findings across included studies are worthy of mention. Several newly identified studies in this update, including reviews and controlled empirical studies, supported the conclusion from the previous Evidence Check that gonadotropin-releasing hormone agonists are the most effective treatment for puberty suppression. Similarly, a relatively large number of studies reported positive impacts of gender-affirming hormone therapy on a range of psychosocial outcomes including gender dysphoria, depression, anxiety and suicide risk. Reviews and primary evidence identified in this update also reported that both semen and oocyte cryopreservation were successful approaches to fertility preservation.

This update had several strengths and limitations. Strengths were the use of a comprehensive search strategy across seven databases; independent screening of citations and full text studies by two researchers; quality appraisal of all included studies and mapping of the updated review outputs and findings against the original review of this topic. Although this update identified a high volume of relevant studies published since the original Evidence Check, some relevant studies may not have been identified for a range of reasons. First, the short time frame of the update mitigated against use of some techniques to ensure comprehensiveness, for example contacting authors of relevant studies to clarify understanding or identify additional papers. Second, given the increase in the volume of research in the period since the original Evidence Check, more relevant studies may have been published since the search was undertaken. Regular updates of the searches are therefore recommended as well as ongoing monitoring of research underway in large gender dysphoria clinics.

Finally, it is important to emphasise that this Evidence Check provides a synthesis of reported findings of eligible studies, the strength of the study design and how each study has been conducted. This Evidence Check is not designed to guide policy or clinical practice. Although knowledge of the state of the research evidence is an important input into policy and clinical practice guideline development, these activities involve considerable additional processes, consultations and inputs. Therefore, this update should not be used in isolation to guide policy or practice.

## Gaps in evidence

Table 15 provides an overview of key gaps in the evidence identified in the previous Evidence Check and the extent to which these gaps have been addressed by newly identified studies in this update.

**Table 15—Update on key gaps in the evidence identified in the previous Evidence Check**

| Identified gap in evidence from previous Evidence Check | Newly identified evidence pertaining to gap | Conclusion |
|---|---|---|
| Understanding the characteristics of trans and gender diverse (TGD) youth in Australia. | As in the previous Evidence Check, examination of the characteristics of trans and gender diverse (TGD) youth in Australia outside the context of interventions was out of scope.<br><br>Notwithstanding this, we identified several Australian studies that provided some description of Australian cohorts. The two Melbourne-based studies of Moussaoui (2022, 2023)[5,6] focused on pelvic pain in a cohort of 158 patients (2022) and menstrual suppression in a cohort of 131 patients compared with 399 controls (2023). Both studies therefore provided descriptive information or relatively large cohorts. Another Melbourne-based study[48] evaluating the effectiveness of a single-session triage and support service also described a large cohort of 142 participants. A smaller Melbourne study examined fertility preservation in 25 participants.[50]<br><br>The NSW study by Elkadi (2023)[68] examined treatment pathways in 79 people with less focus on describing the cohort. | Although not a focus of this Evidence Check, large cohort studies provide description of Melbourne-based cohorts of youth seeking gender-affirming care. Knowledge of characteristics of cohorts in other Australian jurisdictions remains poor. |

| Identified gap in evidence from previous Evidence Check | Newly identified evidence pertaining to gap | Conclusion |
|---|---|---|
| Timing of gender-affirming medical interventions / long-term evaluations of medical intervention. | The previous Evidence Check reported a lack of studies examining short- and long-term effects of initiating GAHT.<br><br>This update identified several longer-term follow-up studies including from large centres such as those in the Netherlands[7,8] and Melbourne[5,6] (as described earlier). Other examples of longer-term follow-up included a large systematic review examining cardiovascular outcomes over 10 years[21] and studies of chest surgery, which generally had follow-up periods of years.[3]<br><br>However, many reviews and primary studies were limited in the extent and length of follow-up with resultant impacts on interpretation.[21,22,63] Those with longer follow-up periods were limited in other ways, for example lack of a control group.[65] One review of 22 studies noted lack of sustainment of outcomes in psychological interventions at follow-up.[11] | Newly identified studies in this Evidence Check update include those that follow up cohorts over longer time periods, including studies of the Dutch cohort focusing on GAHT.[7,8] There are also examples of longer-term follow-up studies examining cardiovascular risk and surgical outcomes.<br><br>However, gaps remain with regards to long-term follow-up studies, as noted across several reviews. Additionally, some longer-term studies have methodological limitations. |
| Social isolation during puberty suppression. | We found no newly identified evidence pertaining to social isolation. | This gap in the evidence remains unchanged. |

| Identified gap in evidence from previous Evidence Check | Newly identified evidence pertaining to gap | Conclusion |
|---|---|---|
| The role of pubertal suppression and GAHT on the outcomes of surgery. | This Evidence Check identified one study exploring the relationship between pubertal suppression, GAHT and surgical outcomes. The findings of this study were mixed. The study found that while puberty suppression treatment reduces the need for mastectomy in trans men, it can create complications for trans women as penile inversion may not be possible (noting that genital surgery was out of scope of this Evidence Check).[46] | This gap in the evidence remains largely unchanged, with only one study explicitly examining the relationship between pubertal suppression and surgical outcomes. |
| The effect of exercise and diet on bone density. | We found no newly identified evidence pertaining to the influence of exercise and diet on bone density. | This gap in the evidence remains unchanged. The confounding effect of these influences on bone density is also inadequately controlled for in studies examining bone density outcomes. |
| A wide range of outcomes measured using validated instruments. | Although a wide range of outcomes have been encompassed by the included studies, use of validated instruments remains sparse (Rowniak 2019[28], Bauermeister 2022[32]—validated in adults but not youth). Lack of validated instruments is noted as a shortcoming across included studies.[12,83] | Despite increases in the volume of studies and breadth of outcomes measured, used of validated instruments remains low. |

| Identified gap in evidence from previous Evidence Check | Newly identified evidence pertaining to gap | Conclusion |
|---|---|---|
| The independent effect of medical interventions on psychological outcomes. | Lack of a control group remains a key limitation, with 46 of the 82 newly identified studies not having a control group and a further five having no concurrent control group. This is compounded by the complex nature of gender-affirming interventions, which makes evaluation of the isolated effects of individual therapies challenging. | Despite increases in the volume of evidence identified, research remains limited by lack of control groups and the multifaceted nature of gender-affirming interventions. |
| Type and effect of psychosocial interventions. | Newly identified evidence in this update has added to the evidence base for psychosocial interventions. Three reviews and four primary studies were identified, compared with three studies including one single case study in the previous Evidence Check. Studies report generally positive findings across multiple domains and few risks or potential harms. However, confidence in findings remains low despite one RCT being identified. | This gap in the evidence has been partially addressed by newly identified studies; however; further research is required to explore specific effects of therapies at different ages and build confidence in reported findings. |

## Recommendations for research

Based on these findings and the volume and nature of the evidence identified in this Evidence Check update, we make the following research recommendations:

1. **Existing identified cohorts from longitudinal studies should continue to be followed up periodically to continue filling persistent gaps in understanding of longer-term outcomes.** This harnesses the considerable research effort already expended in the studies described above on an ongoing basis. In the Australian context, this involves exploring research plans for the study conducted in Melbourne and other jurisdictions. For international studies, periodic searches should be undertaken regularly (e.g. every six months) with a particular focus on the Dutch cohort and other studies conducted in large centres. Longitudinal studies can provide detailed information about patient experiences and outcomes over the life course. While this information may not result in cause and effect information, in the absence of a comparison group descriptive studies remain important as a source of data, particularly if linked to sources of administrative data.

2. **Newly established research studies in Australia should collaborate as much as practicable to build multicentre cohorts.** Research strategies for relatively small clinical populations such as spinal cord injury emphasise the need to conduct multicentre studies.[101,102,103] Similar recommendations have flowed from the experience of COVID-19 research, which was characterised by research waste owing to numerous small and underpowered studies examining the same intervention rather than large multicentre trials.[104] Multicentre cohorts boost statistical power and enable variations in outcome across different contexts to be explored. Likewise, collaborative data sets might potentially harness the power of data linkage, to explore other topics such as service use, including care-seeking for services outside the specialised clinics.

3. **More controlled studies are needed where feasible and ethically acceptable.** In addition to larger cohorts, research should use control groups to better understand the effect of treatment compared with non-treated groups. This is especially important given that the adolescent years, within and outside the context of gender dysphoria, are characterised by significant hormonal, physical and emotional disruptions. Despite the acknowledged limitation of undertaking RCTs in people with gender dysphoria, several studies used innovative approaches to generating control cohorts. For example, the high-quality retrospective cohort (case-control) study by Hisle-Gorman et al. (2021)[73] examined mental health care use in a cohort of 3754 TGD adolescents with 6603 sibling controls. All participants were in military-connected families with equal access to healthcare. While this is a distinctive setting, 18 other studies included in this Evidence Check update used some form of control group, including one RCT and 12 studies with concurrent controls. These included use of cisgender controls[45]; a population-wide cross-sectional study that examined cardiovascular risk in large numbers of participants with gender dysphoria (4172) compared with controls (16,648)[44]; use of population datasets as reference controls[41]; and use of historical control groups.[48] While all these

approaches have limitations, study designs that have a control group of any type are inherently more robust than those that do not, as reflected by the NHMRC hierarchy of evidence.[14]

# Conclusion

This Evidence Check aimed to update a 2020 review of evidence pertaining to the effectiveness of interventions for children and young people with gender dysphoria. A comprehensive search strategy identified 82 studies published since the previous review comprising 16 systematic reviews (Level I—however, reviews did not contain RCTs), one randomised controlled trial (Level II), 12 comparative studies with concurrent controls (III-2), six comparative studies without a concurrent control (III-3) and 47 Level IV case series / cross-sectional studies. The most frequently studied interventions were gender-affirming hormone therapy (38 studies, including 23 Level IV) and puberty suppression treatment (18, including 11 Level IV). We identified fewer than 10 studies for other intervention areas of gender-affirming surgery (eight), psychosocial interventions (seven) and fertility preservation (six). Key conclusions by intervention were:

- *Puberty suppression treatment:* This Evidence Check update predominantly reinforces findings of the previous review, with research reporting that puberty suppression treatment is safe, effective and reversible. However, the strength of this evidence remains low.
- *Gender-affirming hormone therapy:* Conclusions from included studies are consistent with the previous review that GAHT is associated with more positive than neutral / negative psychosocial outcomes and carries few cardiovascular side effects, although meningioma risk associated with cumulative dose exposures of cyproterone acetate greater than 3g was noted in one Level I study. Some physiological parameters such as creatinine were altered, with no serious clinical implications. The large research volume in this area was offset by generally poor study designs.
- *Gender-affirming chest surgery:* Updated evidence reported generally positive findings for chest surgery across satisfaction, dysphoria and psychosocial domains. Although this update provides some additional evidence that supports chest surgery, methodological flaws, particularly the confounding effect of concurrent gender dysphoria interventions, were reported.
- *Fertility preservation:* This update added two systematic reviews and four primary studies. These reported that both semen and oocyte cryopreservation remain the mainstays of treatment and have favourable outcomes and very few adverse effects.
- *Psychosocial therapies:* This Evidence Check added considerably to the evidence base from the original review. Newly identified studies reported a range of benefits across suicidal ideation, depression and anxiety. Furthermore, most studies reported that interventions are both acceptable and safe, with no risks or potential harms reported. Although we identified one RCT, it was not specific to gender dysphoria. Furthermore, the considerable variation in the psychological therapies and delivery modes evaluated should be borne in mind when interpreting findings of studies of psychological interventions.

Analysis of gaps in research when compared against the previous Evidence Check resulted in three research recommendations:

1. Existing identified cohorts from longitudinal studies should continue to be followed up periodically to continue filling persistent gaps in understanding of longer-term outcomes.
2. Newly established research studies in Australia should collaborate as much as practicable with established research teams to build multicentre cohorts.
3. More controlled studies are needed where feasible and ethically acceptable.

# Appendix 1—Care use

**NOTE: Care use was not a primary focus of this Evidence Check, which focused on intervention effectiveness. Where studies included in this update also reported on care use, that information has been extracted, but it does not represent all the available evidence on this topic.**

Few intervention studies included in this Evidence Check reported on the proportion of participants who discontinued gender-affirming medical treatment. One moderate-quality Level I study (NICE 2020a) systematic review of nine observational studies of people aged ⩽ 18 reported rates of people ceasing GnRHa treatment were 9/143 (6.2%) in one study (five no longer wanted therapy, four had side effects) and 11/26 (42%) in another study. However, there was low confidence in the overall findings of this review owing to methodological limitations in the identified studies.

Five Level IV studies focused on care use.

- Elkadi et al. (2023)[68] reported that 9% of patients in a case series of 66 people with confirmed gender dysphoria had desisted, where desistance was defined as *"resolution/disappearance of the gender-related distress that was the foundation for the young person to present to the service"*.[68(p2)]
- A study by Gupta et al. (2023)[72] of 385 mixed age (paediatric 121; adult 264) transgender individuals attending specialised academic centres reported that six participants (1.6%) had discontinued GAHT, with the predominant reasons being external (e.g. insurance, pregnancy, complications) rather than due to change in gender identity. Only two participants discontinued GAHT permanently.[72]
- A study by Nieder et al. (2021)[80] focused on satisfaction with gender-affirming care in 75 trans adolescents and young adults with gender dysphoria attending the Hamburg Gender Identity Service (mean age 17.4). Overall high satisfaction was reported. Nine people suspended or terminated treatment prior to receiving medical interventions; three people receiving GAHT and one person receiving surgical care suspended or terminated treatment. Reasons for terminating or suspending treatment were mental health issues; long distance to service; and other ('did not feel understood'). No adolescents regretted undergoing treatment at follow-up.[80]
- A large longitudinal study by van der Loos (2023)[7] of 1766 children and adolescents in the Amsterdam Cohort of Gender Dysphoria reported that the majority of adolescents (93%) using GnRHa went on to start GAH and only a few individuals (1.6%) discontinued GnRHa, mainly due to remission of GD.[7]
- Another study by van der Loos (2022)[8] examined treatment continuation rates for 715 people who started medical treatment in adolescence with a gonadotropin-releasing hormone agonist (GnRHa) to suppress puberty before the age of 18 years and used GnRHa for a minimum duration of three months before addition of gender-affirming

hormones. The rate of identified prescriptions for gender-affirming hormones, identified through a nationwide prescription registry, was 98%. Twelve of the 16 people for whom no prescription was found had undergone gonadectomy. For these individuals, no prescriptions were found for sex hormones of the sex assigned at birth either (this was suggested to indicate regret by the authors). Reasons postulated for discontinuation included medication side effects and lack of knowledge of the need to continue hormone therapy following gonadectomy.[8]

A key limitation in the identified studies is that because the concept of gender transition is still evolving, comparison of findings between studies is hampered by variability in outcome definition. A 2021 overview of gender detransition by Expósito-Campos (2023)[11] concluded that:

> *"Gender detransition is an emerging yet poorly understood phenomenon in our society, which poses significant professional and bioethical challenges for clinicians working in the field of GD. The absence of systematic research around detransition has given rise to inconsistencies in its conceptual use and application, adding to the unclarity and confusion. A typology of gender detransition based on the cessation or the continuation of a transgender identity could address these issues, while offering clinicians a framework to reflect on their therapeutic endeavour when treating patients with GD".*[11(276–77)]

In addition to this lack of conceptual clarity, there is variability between studies in treatment setting and specifics of care; a range of reasons for discontinuing treatment are reported; and the data identified is from Level IV studies with cohorts ranging in size (66–1766) and age.

For these reasons, no conclusions about care use can be made from the identified evidence.

Table 16 below summarises the main features of each of the reports on care use included in this Evidence Check.

## Table 16—Included studies in this Evidence Check update—care use

***NHMRC Level IV—Case series / cross-sectional—care use (n = 5)***

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Key outcomes | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| **Gupta 2023**[72]<br>To investigate the discontinuation rate after 4 years receiving GAHT and reasons.<br><br>Score on quality criteria = 7 / 10. | US<br>Pre-post<br>Academic centres providing care to TGD adolescents and adults. | **GnRHa + GAHT (GAHT focus)**<br>Transgender and gender diverse (TGD)<br>N=385<br>Paediatric cohorts (n=121): 67 trans male, 54 trans female; **mean age** 15 years.<br>Adults (n=264): 87 trans male, 177 trans female. | Discontinuation rate, reasons. | GAHT discontinuation is uncommon (1.6%), with reasons being external rather than change in gender identity (i.e. insurance issue, pregnancy and medical complications). | *"Our study indicates that the majority of TGD individuals who start GAHT adhere to prescribed therapy."*<br><br>Study limitations: *"An important limitation of our study is the relatively limited success of contacting all study subjects, especially those who disenrolled prior to the end of follow-up. The sensitivity analyses demonstrated the results may change if all participants were followed for the entire study period."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Key outcomes | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| **Nieder 2021**[80]<br>To investigate satisfaction with TRC, regret, and reasons for (dis) satisfaction with transition-related medical interventions.<br><br>Score on quality criteria = 7 / 10. | Germany<br>Pre-post<br>Hamburg Gender Identity Service for children and adolescents (Hamburg GIS). | **Diagnostic / psychosocial only (21), GnRHa (11), GAH (32), GAH + surgery (11)**<br>N=75 trans adolescents and young adults (n=64 AFAB & n=11 AMAB).<br><br>Mean age at 17.4 years. | GAC satisfaction, desistance rate, reasons. | Overall high satisfaction with GAC services and no regret recorded.<br>*"In total, 13 participants (of which 4 were AMAB) indicated at follow-up that they had either suspended or terminated their TRC [transition-related care] at the Hamburg GIS. Nine participants did so while in the no-TRMI group, while three individuals did so* | *"Overall, satisfaction with TRC was high in this population of trans youth, and no participants regretted treatment, reflecting high quality of care at the Hamburg GIS. Participants' focus on physical results of treatment as reason for (dis) satisfaction with TRMI adds to the literature supporting the use of TRMI on adolescent populations."*<br><br>*"In sum, sampling limitations imply that the results cannot be transferable to all other trans populations, particularly non-Western countries or people of color, or youth identifying with nonbinary genders, but also to AMAB youth or those undergoing other types of TRMI, such as genital surgeries."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Key outcomes | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| | | | | *at the GAH stage."* | |
| **van der Loos 2023**[7]<br>To explore the trends in diagnostic and treatment trajectories of children and adolescents referred for GD evaluation.<br><br>Score on quality criteria = 7 / 10. | Netherlands<br>Pre-post<br>Center of Expertise on Gender Dysphoria of the Amsterdam UMC. | **GnRHa + GAHT**<br>N = 1766 children and adolescents.<br>GnRHa initiation: trans girls at a median age of 14 years, and trans boys at 15.5 years.<br>GAHT: trans girls at a median age of 16 years, and trans boys at 16.7 years. | Admission rate, age at admission and initiating GnRHa and GAHT, proportion of individuals assigned a specific sex at birth, puberty stages, reasons for not using GnRHa and rate of individuals undergoing | The majority of adolescents (93%) using GnRHa go on to start with GAH.<br>Only a few individuals (1.6%) discontinued GnRHa. The main reason for discontinuing GnRHa was remission of GD. | *"Risk for retransitioning was very low, providing ongoing support for medical interventions in comprehensively assessed gender diverse adolescents."*<br><br>Study limitations: *"… the results may be different for centers following a different treatment approach … Due to the retrospective design, data might be lacking … calculated proportions in the most recent years are likely an underestimation".* |
| **van der Loos 2022**[8]<br>To investigate the continuation rate of adolescents | Netherlands<br>Pre-post<br>Amsterdam UMC. | **GnRHa + GAHT**<br><br>GnRHa for a minimum of three | Continuation of GAHT (based on prescription of | High rate of continuation from PS with GnRH to GAHT (98%). | *"Overall, 98% of people who had started gender-affirming medical treatment with puberty suppression in adolescence in this study continued gender-affirming hormones."* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Key outcomes | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| starting PS and GAHT.<br><br>Score on quality criteria = 8 / 10. | | months and then GAHT.<br><br>N = 720 (n=220 trans girls, n=500 trans boys).<br>Median age GnRHa started in trans females 14.1 years, trans males 16 years. | gender-affirming hormones). | | *"A limitation of our study is that gender-affirming hormones being prescribed does not necessarily mean that people are using the medication, possibly overestimating the number of people still using gender-affirming hormones."* |
| **Elkadi 2023[68]**<br>To explore the developmental pathway choices of youth presenting to a tertiary Gender Service. | Australia<br>Pre-post<br>Tertiary care hospital. | **Social transition only (1) + GnRHa (49) + GAHT (51) + Surgery (6)**<br>N=68 with GD (of 79 referrals; 2 lost to follow-up). | Persistence and desistance rate—where persistence was defined as *"continuation of the journey to transition to the other gender"* and desistance was defined as *"resolution / disappearance of* | Within the GD subgroup (n=68) (with two lost to follow-up), six had desisted (desistance rate of 9.1%; 6/66), and 60 had persisted on a GD (transgender) | *"The data from this study show that when young people with gender distress present to health services seeking medical interventions, they end up following a diverse range of developmental pathways …*<br>*… the evidence-base pertaining to the gender-affirming medical pathway is sparse and, for the young people who may regret their choice of pathway at a future point in time, the risks for potential harm are significant".* |

| Author, date, aims, quality criteria | Country, design, setting | Intervention<br>Sample N = age, gender identity | Main outcomes | Key outcomes | Key conclusions and limitations reported by study authors |
|---|---|---|---|---|---|
| Score on quality criteria = 6 / 9. | | Young people (13.25–23.75 years old). | *the gender-related distress that was the foundation for the young person to present to the service".* | pathway (persistence rate of 90.9%; 60/66). | Study limitations: *"It did not have a control group …*<br>*the current study does not provide information about possible side effects experienced in relation to cross-sex hormones …*<br>*It is possible that therapists' own perspectives affected the patients' decisions to choose to persist or desist …*<br>*… a substantial percentage of young people who had exited the service could not be contacted at this final follow-up time point … our data pertaining to current mental health concerns are limited …*<br>*… this study is unable to examine issues pertaining to any placebo effects that accompany medication use".* |

# Appendix 2—Evidence Check protocol

## Evidence Check questions

***Question 1—Effective clinical medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria***

- Question 1a—What have been shown to be the most effective medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria?
- Question 1b—What have been shown to be the risks or potential harms from medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria?
- Question 1c—Is there variation in the effectiveness and risks associated with medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria?

***Question 2—Effective psychosocial interventions for trans and gender diverse young people under 18 years old with gender dysphoria***

- Question 2a—What have been shown to be the most effective psychosocial interventions for treating trans and gender diverse young people under 18 years old with gender dysphoria?
- Question 2b—What have been shown to be the risks or potential harms from psychosocial interventions for treating trans and gender diverse young people under 18 years old with gender dysphoria?
- Question 2c—Is there variation in the effectiveness or risks associated with psychosocial interventions for treating trans and gender diverse young people under 18 years old with gender dysphoria?

The agreed final search strategies and yields are contained overleaf:

- Figures in brackets are the yields from the previous Evidence Check
- TOTAL YIELD for screening after deduplication = 2766.

**Database:** Embase Classic+Embase <1947 – 2023 August 25>

**Search date:** 19 Sep 2023

**Yield:** 1923

| # | Query | Results |
|---|---|---|
| 1 | (Transgender or gender dysphoria or trans or gender diverse or "trans or gender diverse" or TGD or gender incongruent or gender incongruence or gender identity or gender identity disorders or non-binary or nonbinary).ti,ab. | 202,123<br>[200,946] |
| 2 | (Treatment* or management or intervention* or hormone blocker* or hormone therap* or puberty suppress* or puberty blocker* or pubertal suppress* or anti-androgen or antiandrogen* or androgen antagonist* or oestradiol or estradiol or gender-affirming hormone or gonadotropin releasing hormone agonist or gender reassignment or clinical psychology or counselling or psychotherapy or gender-affirming or gender-affirming or oestrogen or estrogen or testosterone or fertility preservation or social transitioning or voice training).ti,ab. | 10,637,013<br>[10,390,339] |
| 3 | (Adolescen* or youth* or young person* or young people* or teen* or young adult* or pediatric* or paediatric* or child*).ti,ab. | 2,998,133<br>[2,987,776] |
| 4 | (Safety or benefit* or Side-effect* or risk* or harm* or significant adverse drug reaction* or ADRs or effect* or impact* or outcome*).ti,ab. | 17,068,501<br>[6,417,445] |
| 5 | 1 and 2 and 3 and 4 | 3762<br>[1979] |
| 6 | limit 5 to yr="2019 - 2023" | 1946<br>[1008] |
| **7** | **limit 6 to english language** | **1923**<br>**[991]** |

**Database:** Ovid MEDLINE(R) <1946 – September 15, 2023>

**Search date:** 19 Sep 2023

**Yield:** 830

| # | Query | Results |
|---|---|---|
| 1 | (Transgender or gender dysphoria or trans or gender diverse or "trans or gender diverse" or TGD or gender incongruent or gender identity or gender identity disorders or gender incongruence or non binary or non-binary).ti,ab. | **128,751** [128,172] |
| 2 | (Treatment* or management or intervention* or hormone blocker* or hormone therap* or puberty suppress* or puberty blocker* or pubertal suppress* or anti-androgen or antiandrogen* or androgen antagonist* or oestradiol or estradiol or gender-affirming hormone or gonadotropin releasing hormone agonist or gender reassignment or clinical psychology or counselling or psychotherapy or gender-affirming or gender-affirming or oestrogen or estrogen or testosterone or fertility preservation or social transitioning or voice training).ti,ab. | **6,399,657** [6,241,959] |
| 3 | (Adolescen* or youth* or young person* or young people* or teen* or young adult* or pediatric* or paediatric* or child*).ti,ab. | **1,905,666** [1,900,880] |
| 4 | (Safety or benefit* or Side-effect* or risk* or harm* or significant adverse drug reaction* or ADRs or effect* or impact* or outcome*).ti,ab. | **10,758,706** [3,758,912] |
| 5 | 1 and 2 and 3 and 4 | **1602** [780] |
| 6 | limit 5 to yr="2019 - 2023" | **847** [403] |
| **7** | **limit 6 to english language** | **830 [393]** |

**Database:** SCOPUS

**Search date:** 19 Sep 2023

**Yield:** 1433

( TITLE-ABS ( transgender OR "gender dysphoria" OR trans OR "gender diverse" OR "trans or gender diverse" OR tgd OR "gender incongruent" OR "gender identity" OR "gender identity disorders" OR “gender incongruence” OR “non-binary” OR “non binary”) ) AND ( TITLE-ABS ( treatment* OR management OR intervention* OR "hormone blocker*" OR "hormone therap*" OR "puberty suppress*" OR "puberty blocker*" OR "pubertal suppress*" OR anti-androgen OR antiandrogen* OR "androgen antagonist*" OR oestradiol OR estradiol OR "gender-affirming hormone" OR "gonadotropin releasing hormone agonist" OR "gender reassignment" OR “clinical psychology” OR counselling OR psychotherapy OR “gender affirming” OR “gender-affirming” OR oestrogen OR estrogen OR testosterone OR “fertility preservation” OR “social transitioning” OR “voice training” ) ) AND ( TITLE-ABS ( adolescen* OR youth* OR "young person*" OR "young people*" OR teen* OR "young adult*" OR pediatric* OR paediatric* OR child* ) ) AND ( TITLE-ABS ( safety OR benefit* OR side-effect* OR risk* OR harm* OR "significant adverse drug reaction*" OR adrs OR effect* OR impact* OR outcome* ) ) AND PUBYEAR > 2018 AND ( LIMIT-TO ( LANGUAGE , "English" ) )

**Database:** APA PsycInfo <1806 – September Week 1 2023>

**Search Date:** 19 Sep 2023

**Yield: 582**

| # | Query | Results |
|---|---|---|
| 1 | (Transgender or gender dysphoria or trans or gender diverse or "trans or gender diverse" or TGD or gender incongruent or gender identity or gender identity disorders or gender incongruence or non-binary or non binary).ti,ab. | **23,090** [22,735] |
| 2 | (Treatment* or management or intervention* or hormone blocker* or hormone therap* or puberty suppress* or puberty blocker* or pubertal suppress* or anti-androgen or antiandrogen* or androgen antagonist* or oestradiol or estradiol or gender-affirming hormone or gonadotropin releasing hormone agonist or gender reassignment or clinical psychology or counselling or psychotherapy or gender-affirming or gender-affirming or oestrogen or estrogen or testosterone or fertility preservation or social transitioning or voice training).ti,ab. | **1,275,707** [1,200,881] |
| 3 | (Adolescen* or youth* or young person* or young people* or teen* or young adult* or pediatric* or paediatric* or child*).ti,ab. | **1,044,595** [1,042,962] |
| 4 | (Safety or benefit* or Side-effect* or risk* or harm* or significant adverse drug reaction* or ADRs or effect* or impact* or outcome*).ti,ab. | **2,459,235** [794,681] |
| 5 | 1 and 2 and 3 and 4 | **1220** [605] |
| 6 | limit 5 to yr="2019 - 2023" | **674** [335] |
| **7** | **limit 6 to english language** | **582 [289]** |

**Database:** Joanna Briggs Institute: JBI EBP Database <Current to August 23, 2023>
**Search Date:** 19 Sep 2023
**Yield:** 0

| # | Query | Results |
|---|---|---|
| 1 | (Transgender or gender dysphoria or trans or gender diverse or "trans or gender diverse" or TGD or gender incongruent or gender identity or gender identity disorders or gender incongruence or non-binary or non binary).ti,ab. | **11** [10] |
| 2 | (Treatment* or management or intervention* or hormone blocker* or hormone therap* or puberty suppress* or puberty blocker* or pubertal suppress* or anti-androgen or antiandrogen* or androgen antagonist* or oestradiol or estradiol or gender-affirming hormone dose or gonadotropin releasing hormone agonist or gender reassignment or clinical psychology or counselling or psychotherapy or gender-affirming or gender-affirming or oestrogen or estrogen or testosterone or fertility preservation or social transitioning or voice training).ti,ab. | **1389** [1378] |
| 3 | (Adolescen* or youth* or young person* or young people* or teen* or young adult* or pediatric* or paediatric* or child*).ti,ab. | **451** [454] |
| 4 | (Safety or benefit* or Side-effect* or risk* or harm* or significant adverse drug reaction* or ADRs or effect* or impact* or outcome*).ti,ab. | **801** [426] |
| 5 | 1 and 2 and 3 and 4 | 0 [0] |
| 6 | limit 5 to yr="2019 - 2023" | 0 [0] |
| **7** | **limit 6 to english language [Limit not valid; records were retained]** | **0 [0]** |

**Database:** Cochrane
**Search Date:** 19 Sep 2023
**Yield:** 295

| Query | Results |
|---|---|
| (Transgender:ti,ab OR "gender dysphoria":ti,ab OR trans:ti,ab OR "gender diverse":ti,ab OR "trans or gender diverse":ti,ab OR TGD:ti,ab OR "gender incongruent":ti,ab OR "gender identity":ti,ab OR "gender identity disorders":ti,ab OR “gender incongruence”:ti,ab OR “non-binary”:ti,ab OR “non binary”:ti,ab) | **5749** [5699] |
| (Treatment*:ti,ab OR management:ti,ab OR intervention*:ti,ab OR ("hormone" NEXT blocker*):ti,ab OR ("hormone" NEXT therap*):ti,ab OR ("puberty" NEXT suppress*):ti,ab OR ("puberty" NEXT blocker*):ti,ab OR ("pubertal" NEXT suppress*):ti,ab OR anti-androgen:ti,ab OR antiandrogen*:ti,ab OR ("androgen" NEXT antagonist*):ti,ab OR oestradiol:ti,ab OR estradiol:ti,ab OR "gender-affirming hormone":ti,ab OR "gonadotropin releasing hormone agonist":ti,ab OR "gender reassignment":ti,ab OR “clinical psychology”:ti,ab OR counselling:ti,ab OR psychotherapy:ti,ab OR “gender affirming”:ti,ab OR “gender-affirming”:ti,ab OR oestrogen:ti,ab OR estrogen:ti,ab OR testosterone:ti,ab OR “fertility preservation”:ti,ab OR “social transitioning”:ti,ab OR “voice training”:ti,ab) | **1,215,913** [1,201,199] |
| (Adolescen*:ti,ab OR youth*:ti,ab OR ("young" NEXT person*):ti,ab OR ("young" NEXT people*):ti,ab OR teen*:ti,ab OR ("young" NEXT adult*):ti,ab OR pediatric*:ti,ab OR paediatric*:ti,ab OR child*:ti,ab) | **203,311** [202,361] |
| (Safety:ti,ab OR benefit*:ti,ab OR Side-effect*:ti,ab OR risk*:ti,ab OR harm*:ti,ab OR ("significant adverse drug" NEXT reaction*):ti,ab OR ADRs:ti,ab OR effect*:ti,ab OR impact*:ti,ab OR outcome*:ti,ab) | **1,532,955** [649,385] |
| #1 AND #2 AND #3 AND #4 | **399** |
| **Limit to Jan 2019 to Dec 2023** | **295 [164]** |

**Database:** CINAHL

**Search Date:** 19 Sep 2023

**Yield:** 504

| Query | Results |
|---|---|
| ((TI Transgender OR AB Transgender) OR (TI "gender dysphoria" OR AB "gender dysphoria") OR (TI trans OR AB trans) OR (TI "gender  diverse" OR AB "gender diverse") OR (TI "trans or gender diverse" OR AB "trans or gender diverse") OR (TI TGD OR AB TGD) OR (TI "gender incongruent" OR AB "gender incongruent") OR (TI "gender identity" OR AB "gender identity")OR (TI "gender identity disorders" OR AB "gender identity disorders") OR (TI "gender incongruence" OR AB "gender incongruence") OR (TI "non-binary" OR AB "non-binary") OR (TI "non binary" OR AB "non binary")) | **19,872** [19,619] |
| ((TI Treatment* OR AB Treatment*) OR (TI management OR AB management) OR (TI intervention* OR AB intervention*) OR (TI "hormone blocker*" OR AB "hormone blocker*") OR (TI "hormone therap*" OR AB "hormone therap*") OR (TI "puberty suppress*" OR AB "puberty suppress*") OR (TI "puberty blocker*" OR AB "puberty blocker*") OR (TI "pubertal suppress*" OR AB "pubertal suppress*") OR (TI anti-androgen OR AB anti-androgen) OR (TI antiandrogen* OR AB antiandrogen*) OR (TI "androgen antagonist*" OR AB "androgen antagonist*") OR (TI oestradiol OR AB oestradiol) OR (TI estradiol OR AB estradiol) OR (TI "gender-affirming hormone dose" OR AB "gender-affirming hormone") OR (TI "gonadotropin releasing hormone agonist" OR AB "gonadotropin releasing hormone agonist") OR (TI "gender reassignment" OR AB "gender reassignment") OR (TI "clinical psychology" OR AB "clinical psychology") OR (TI counselling OR AB counselling) OR (TI psychotherapy OR AB psychotherapy) OR (TI "gender affirming" OR AB "gender affirming") OR (TI "gender-affirming" OR AB "gender-affirming") OR (TI oestrogen OR AB oestrogen) OR (TI estrogen OR AB estrogen) OR (TI testosterone OR AB testosterone) OR (TI "fertility preservation" OR AB "fertility preservation") OR (TI "social transitioning" OR AB “social transitioning”) OR TI "voice training" OR AB “voice training”)) | **1,842,601** [1,802,740] |
| ((TI adolescen* OR AB adolescen*) OR (TI youth* OR AB youth*) OR (TI "young person*" OR AB "young person*") OR (TI "young people*" OR AB "young people*") OR (TI teen* OR AB teen*) OR (TI "young adult*" OR AB "young adult*") OR (TI pediatric* OR AB pediatric*) OR (TI paediatric* OR AB paediatric*) OR (TI child* OR AB child*)) | **854,420** |
| ((TI Safety OR AB Safety) OR (TI benefit* OR AB benefit*) OR (TI Side-effect* OR AB Side-effect*) OR (TI risk* OR AB risk*) OR (TI harm* OR AB harm*) OR (TI "significant adverse drug reaction*" OR AB "significant adverse drug reaction*") OR (TI ADRs OR AB ADRs) OR (TI effect* OR AB effect*) OR (TI impact* OR AB impact*) OR (TI outcome* OR AB outcome*)) | **2,919,809** [1,802,740] |

| | |
|---|---|
| 1 and 2 and 3 and 4 | 936 |
| Limit to 2019 – 2023 | **582** |
| **Limit to English** | **581** |

**Reference list checking of supplied guidelines**

Telfer MM, Tollit MA, Pace CC Pang KC. (2020) Australian Standards of Care and Treatment Guidelines for Trans and Gender Diverse Children and Adolescents. Melbourne: The Royal Children's Hospital: **No citations from 2019 were identified.**

AusPATH (2022) Australian Informed Consent Standards of Care for Gender-affirming Hormone Therapy. Australia: Australian Professional Association for Trans Health:

- **One relevant citation was identified, which was already included in the Evidence Check (**Turban JL, King D, Kobe J, Reisner SL, Keuroghlian AS. Access to Gender-Affirming Hormones during Adolescence and Mental Health Outcomes among Transgender Adults. PLOS ONE. 2022;17(1): e0261039. https://doi.org/10.1371/journal.pone.0261039).
- **One relevant additional study was added:** Scheim AI, Perez-Brumer AG, Bauer GR. Gender-Concordant Identity Documents and Mental Health among Transgender Adults in the USA: A Cross-Sectional Study. Lancet Pub Health. 2020;5(4): e196–203. https://doi.org/10.1016/S2468-2667(20)30032-3.

Cheung AS, Wynne K, Erasmus J, Murray S, Zajac JD. Position statement on the hormonal management of adult transgender and gender diverse individuals. Med J Aust. 2019;211(3): 127–33. https://doi.org/10.5694/mja2.50259: **No relevant citations were identified.**

Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema, SE, Meyer WJ, Murad MH et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017;102(11): 3869–3903. https://doi.org/10.1210/jc.2017-01658. **The reference list was not scanned as this guideline was written in 2017.**

Coleman E, Radix AE, Bouman WP, Brown GR, de Vries ALC, Deutsch MB et al. Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, Int J Transgend Health. 2022;23(sup1): S1–S259. https://doi.org/10.1080/26895269.2022.2100644.

We reviewed 29 potentially relevant citations in full text and added an additional nine relevant studies.

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