NHS England Evidence Review:

Masculinising medicines comprising testosterone with gonadotrophin-releasing hormone (GnRH) analogues for children and young people with gender incongruence who identify as a male gender and wish to undergo a binary physical transition

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Masculinising medicines comprising testosterone with gonadotrophin-releasing hormone (GnRH) analogues for children and young people with gender incongruence who identify as a male gender and wish to undergo a binary physical transition

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Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety, and cost-effectiveness of masculinising medicines comprising testosterone with gonadotrophin-releasing hormone (GnRH) analogues with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention for children and young people (CYP) with gender incongruence who identify as male and wish binary physical transition.

The International Classification of Diseases (ICD)-11 (WHO, 2025) splits gender incongruence into that identified in childhood and that identified in adolescents and adults. Gender incongruence of childhood is characterised by a marked incongruence between an individual's experienced/expressed gender and the assigned sex in pre-pubertal children. The incongruence must have persisted for about two years. Gender incongruence of adolescence and adulthood is a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender. The diagnosis cannot be assigned prior to the onset of puberty. Gender variant behaviour and preferences alone are not a basis for assigning the diagnosis.

Although the diagnosis of gender incongruence includes both adolescence and adulthood, this evidence review refers specifically to CYP up to their 18th birthday.

Treatment for gender incongruence aims to help people live the way they want to, in their preferred gender identity, whilst aiming to improve mental health and quality of life outcomes. Masculinising medicines are used to help make the patient's body more congruent with their gender identity. Treatment includes testosterone which will result in the patient's body developing a more male physical appearance and can be used alongside a GnRH analogue. These treatments will be used in combination with a number of other interventions. This evidence review focusses on individuals that use testosterone and GnRH analogues in combination.

Studies in which GnRH analogues are used in the context of puberty suppression or used as puberty suppressing hormones are outside of the scope of this evidence review. NHS England and the National Institute of Health and Care Research (NIHR) are working together to set up a study into the potential benefits and harms of puberty suppressing hormones as a treatment option for CYP with gender incongruence.

In addition, the review scope included the identification of possible subgroups of CYP within the included studies who might benefit from treatment with testosterone and GnRH analogues more than the wider population, the criteria used by research studies to define gender incongruence, testosterone dosing regimens, GnRH analogue dosing regimens, circumstances in which any CYP aged 15 years or younger received testosterone and GnRH analogue therapy, monitoring arrangements and study exclusion criteria.

2. Executive summary of the review

This review examines the clinical effectiveness, safety, and cost-effectiveness of masculinising medicines comprising testosterone with GnRH analogues with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention for CYP with gender incongruence who identify as male and wish binary physical transition.

The terminology in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase ‘CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition’ rather than saying natal or biological sex and ‘cross-sex hormones’ are now referred to as ‘masculinising or feminising medicines.’ The data extracted from studies into Table 1, Appendix E: Evidence Table and Appendix G: GRADE profiles may use historical terms which are no longer considered appropriate.

The searches for evidence published since 01 January 2005 were conducted on 13 June 2025 and identified 1,382 references. The titles and abstracts were screened, and 34 full text papers were obtained and assessed for relevance against the criteria defined in the PICO for this review.

No studies assessing the clinical effectiveness or cost-effectiveness of masculinising medicines comprising testosterone with GnRH analogues for CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition were identified for this review.

Safety was reported in one cross-sectional study (Valentine et al 2022), which provided very low certainty evidence for the odds of dyslipidaemia and odds of liver dysfunction for a subgroup of 106 in scope individuals. Patients receiving masculinising hormone treatment were compared to transgender and gender diverse youth (TGDY) not on gender-affirming hormone treatment (GAHT) (n not reported). All TGDY in the study were treated at paediatric hospitals in the United States of America (USA); duration of treatment was not reported.

None of the included studies reported on subgroups of interest.

In terms of clinical effectiveness:

- No evidence was identified for the critical outcomes of impact on gender incongruence, impact on mental health and impact on quality of life.

- No evidence was identified for the important outcomes of masculinising physical changes, psychosocial impact, fertility, feasibility of masculinising genital surgery, cognitive outcomes, detransition after receipt of masculinising medicines and regret after receipt of masculinising medicines.

In terms of safety:

- *Testosterone with GnRH analogues vs no hormones*
  One subgroup (n=106) of individuals on testosterone with GnRH analogues from a cross-sectional study of CYP with gender incongruence reported statistically significant increased adjusted odds of dyslipidaemia (OR 3.7 (95% CI 2.0 to 6.7)) and liver dysfunction (OR 2.5 (95% CI 1.4 to 4.3)) compared to individuals not on hormones[1].

- *Testosterone (no comparator)*
  No evidence was identified for this outcome.

In terms of cost effectiveness:

- No evidence was identified for cost-effectiveness.

In terms of subgroups:

- No evidence was identified for any subgroups of interest.

In terms of the criteria used by the research studies to define gender incongruence:

- The study defined transgender and gender diverse youth as "*having a diagnosis of gender dysphoria or related diagnosis (by PEDSnet[2] concept ID).*" No diagnostic criteria were provided.

In terms of the starting criteria, formulation, duration and dose of testosterone for those aged 16 up to their 18th birthday:

- No evidence was identified for testosterone dosing.

[1] The paper reports the comparator group as TGDY never prescribed GAHT with no further details provided. We have assumed that the 'no GAHT' comparator group for individuals with a prescription for testosterone and GnRH analogues includes individuals who are AFAB only, but this is not explicitly stated in the paper
[2] PEDSnet is a Partner Network Clinical Data Research Network in the National Patient Centered Clinical Research Network, an initiative funded by the Patient Centered Outcomes Research Institute. PEDSnet institutions include the Children's Hospital Colorado, Children's Hospital of Philadelphia, Nemours Children's Health (cities not stated), Nationwide Children's Hospital (Columbus, Ohio), St. Louis Children's Hospital, and Seattle Children's Hospital

In terms of the starting criteria, formulation, duration and dose of GnRH analogues treatment for those aged 16 years up to their 18th birthday:

- No evidence was identified for GnRH analogue dosing.

In terms of CYP aged 15 years or younger receiving testosterone with GnRH analogues for gender transition and if so, in what circumstances:

- No evidence was identified for CYP aged under 15 receiving masculinising medicines.

In terms of monitoring in place for CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition receiving testosterone with GnRH analogues:

- No evidence was identified regarding monitoring arrangements for CYP receiving masculinising medicines.

In terms of the exclusion criteria in the studies:

- The study did not report on exclusion criteria. Inclusion criteria were transgender and gender diverse youth aged >2 years at last visit with at least one outpatient visit from 2009 to 2019 at one of six paediatric hospitals included in a clinical research network in the USA.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

The available evidence was limited to results from a subgroup analysis from one cross-sectional study. This study design is inherently limited in its ability to determine causality, because both exposure (masculinising medicines) and outcome (dyslipidaemia and liver dysfunction) are measured at the same point in time. The study did not report on the time point of outcome measurement relative to the use of masculinising medicines, so it is not possible to determine whether the use of masculinising medicines preceded the development of the outcomes and if so by how long. The study did not report on dose or duration of testosterone and GnRH analogues. A further important issue is it is not possible determine whether some out-of-scope individuals were included. The study included a mixed population of transgender and gender-diverse CYP with no breakdown of binary and non-binary individuals. Furthermore, the study did not report on prior treatments, in particular the use of GnRH analogue monotherapy for puberty suppression prior to the addition of testosterone. Of particular note was the lack of reporting of psychological or psychosocial

support / interventions in both the intervention and control populations; this increases the risk of bias through potential confounding. Additionally, although the cross-sectional study adjusted for some confounding factors, it could not adjust for confounding factors not recorded in electronic health records such as comorbidities or health behaviours (eg smoking or alcohol use) associated with gender minority status. Other quality issues include limited information on the comparator group and selective reporting of statistically significant results.

The study included individuals accessing care at paediatric hospitals involved in a research network in the USA. It is not clear if the individuals and aspects of care in the study reflect those seen in clinical practice in England and care is therefore needed in generalising results to the NHS.

Conclusion

This evidence review includes a cross-sectional study that provides results on a subgroup of CYP with gender incongruence on testosterone with GnRH analogues compared to individuals not on GAHT.

No studies were identified for the critical or important outcomes of interest.

One included study provides very low certainty evidence for safety; reporting statistically significant increased odds of dyslipidaemia and liver dysfunction in CYP with gender incongruence on testosterone with GnRH analogues compared to individuals not on masculinising medicines.

Given the limited evidence available on CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition, it is not possible to draw conclusions on the impact of treatment with testosterone with GnRH analogues. Published studies which allow conclusions to be drawn about the effectiveness of testosterone with GnRH analogues for this population are needed.

No evidence was identified on cost-effectiveness or in relation to subgroups of interest.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. For CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition, what is the clinical effectiveness of treatment with testosterone with GnRH analogues with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention?
2. For CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition, what is the short-term and long-term safety of testosterone with GnRH analogues with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention?
3. For CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition, what is the cost-effectiveness of testosterone with GnRH analogues with or without psychological and psychosocial support compared to one or a combination of psychological support or social transitioning to the desired gender or with no intervention?
4. From the evidence selected, are there particular sub-groups of CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition that may benefit more from treatment with testosterone with GnRH analogues than the wider population?
5. From the evidence selected:
    a) What were the criteria used by the research studies to define gender incongruence?
    b) What were the starting criteria, formulation, duration and dose of testosterone for those aged 16 up to their 18th birthday?
    c) What were the starting criteria, formulation, duration and dose of GnRH analogue treatment for those aged 16 years up to their 18th birthday?
    d) Did any CYP aged 15 years or younger receive testosterone with GnRH analogues for gender transition? If so, in what circumstances?
    e) What monitoring was in place for CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition receiving testosterone with GnRH analogues?

f) What were the exclusion criteria in the studies?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 13 June 2025.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

One study was identified for inclusion (Valentine et al 2022). This cross-sectional study included TGDY and assessed the association of masculinising and feminising medicine on cardiometabolic-related diagnoses. The study reported results separately for a subgroup of in-scope patients prescribed testosterone with GnRH analogues. The study did not report on duration of treatment or the timepoint of outcome measurement relative to the use of treatment.

No studies were identified that reported on critical outcomes of impact on gender incongruence, impact on mental health and impact on quality of life, or the important outcomes of masculinising physical changes, psychosocial impact, fertility, feasibility of masculinising genital surgery, cognitive outcomes, detransition after receipt of masculinising medicines, or regret after receipt of masculinising medicines.

No cost-effectiveness studies were identified.

The terminology in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'children and young people with gender incongruence who identify as a male gender and wish to undergo a binary physical transition' rather than saying natal or biological sex and 'cross-sex hormones' are now referred to as 'masculinising or feminising medicines.' The data extracted from studies into Table 1, Appendix E: Evidence Table and Appendix G: GRADE profiles may use historical terms which are no longer considered appropriate.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Valentine et al 2022 Cross-sectional study USA (6 centres)	4,172 TGDY[a] • n=2,766 (66.3%) AFAB TGDY total sample[b] Age (years), median (IQR): • At first visit: 10.0 (4.4 to 14.6) • At last visit: 16.7 (14.6 to 18.3)	**Intervention** Prescription of testosterone with GnRH analogues[c] • n=106 **Comparison** Never prescribed GAHT[d] • n not reported	Duration of treatment and timepoint of outcome measurement relative to the use of treatment not reported **Safety** • Dyslipidaemia[a] • Liver dysfunction

Study	Population	Intervention and comparison	Outcomes reported
	Race: • White: 3,027 (72.5%) • Unknown: 401 (9.6%) • Other: 390 (9.3%) • Black: 257 (6.2%) • Asian: 98 (2.3%) No subgroups reported	Among AFAB, 112 (4.1%) had a prescription for a progestin (norethindrone, medroxyprogesterone) and 199 (7.2%) for COCP The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions were not reported	

Abbreviations

AFAB: assigned female at birth; ATC: anatomical therapeutic chemical classification; COCP: combined oral contraceptive pill; EHR: electronic health record; GAHT: gender-affirming hormone therapy; GnRH: gonadotrophin-releasing hormone; IQR: interquartile range; PEDSnet: pediatric electronic health record data sharing network; SNOMED: systematised nomenclature of medicine; TGDY: transgender and gender-diverse youth

Footnotes

a. Defined as having a diagnosis of gender dysphoria or related diagnosis by PEDSnet concept ID. PEDSnet is a partner network clinical data research network in the National Patient Centered Clinical Research Network, an initiative funded by the Patient Centered Outcomes Research Institute. PEDSnet institutions include the Children's Hospital Colorado, Children's Hospital of Philadelphia, Nemours Children's Health, Nationwide Children's Hospital, St. Louis Children's Hospital, and Seattle Children's Hospital

b. Baseline characteristics not reported separately for AFAB group

c. Ascertained from electronic health record prescriptions via ATC/RxNorm codes and structured vocabularies to capture and group similar and synonymous medications into categorical classes: GnRH analogues (L02AE) and testosterone (G03B)

d. The paper reports the comparator group as TGDY never prescribed GAHT with no further details provided. We have assumed that the 'no GAHT' comparator group for individuals with a prescription for testosterone and GnRH analogues includes individuals who are AFAB only, but this is not explicitly stated in the paper

e. Outcomes were captured using SNOMED concept codes and were defined as having either a diagnosis (billing code, problem list) or at least 2 abnormal measurements (anthropometric or laboratory value) recorded in the electronic health record

5. Results

In CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition, what is the clinical effectiveness and safety of treatment with testosterone with GnRH analogues with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Impact on gender incongruence **Certainty of evidence:** Not applicable	*This outcome is important to patients because gender incongruence is associated with significant distress and problems functioning.* **No evidence was identified for this outcome.**
Impact on mental health **Certainty of evidence:** Not applicable	*This outcome is important to patients because gender incongruence is associated with psychological distress which can lead to the development of mental health problems.* **No evidence was identified for this outcome.**
Impact on quality of life **Certainty of evidence:** Not applicable	*This outcome is important to patients because gender incongruence may be associated with a significant reduction in health-related quality of life.* **No evidence was identified for this outcome.**
Important outcomes	
Masculinising physical changes **Certainty of evidence:** Not applicable	*This outcome is important because most patients with gender incongruence wish to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their experienced gender.* **No evidence was identified for this outcome.**
Psychosocial impact **Certainty of evidence:** Not applicable	*This outcome is important to patients because gender incongruence is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning.* **No evidence was identified for this outcome.**
Fertility **Certainty of evidence:** Not applicable	*This outcome is important to patients because masculinising medicines can reduce fertility. Prior to commencing masculinising medicines patients should be counselled on the impact of treatment on their fertility and offered fertility preservation options.* **No evidence was identified for this outcome.**

Outcome	Evidence statement
Feasibility of masculinising genital surgery **Certainty of evidence:** Not applicable	*This outcome is important to patients because masculinising medicines can have an impact on surgical outcomes. Treatment may alter the amount of genital tissue available for phalloplasty, metoidioplasty, hysterectomy and bilateral salpingo-oophorectomy.* **No evidence was identified for this outcome.**
Cognitive outcomes **Certainty of evidence:** Not applicable	*This outcome is important to patients because masculinising medicines can negatively impact cognitive processes such as concentration, memory, and executive function.* **No evidence was identified for this outcome.**
Detransition after receipt of masculinising medicines **Certainty of evidence:** Not applicable	*Medical detransition is a complex experience encompassing medical, psychological, social implications and is important to patients because they may choose to discontinue treatment. The decision to detransition may or may not be associated with regret.* **No evidence was identified for this outcome.**
Regret after receipt of masculinising medicines **Certainty of evidence:** Not applicable	*This outcome is important to patients because some patients who choose to take masculinising medicines may regret this decision. Regret may or may not be associated with detransition.* **No evidence was identified for this outcome.**
Safety	
Safety **Certainty of evidence:** Very low	*It is important to assess whether treatment causes acute side effects that may lead to withdrawing the treatment or long-term effects that may impact on decisions for transitioning.* One cross-sectional study provided comparator evidence relating to short and long-term safety of testosterone with GnRH analogues in CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition. *Testosterone with GnRH analogues vs no hormones*[3] **Duration on treatment and timepoint of outcome measurement relative to use of treatment not reported** Dyslipidaemia[4]

[3] The paper reports the comparator group as TGDY never prescribed GAHT with no further details provided. It is not clear whether the comparator group is individuals not prescribed testosterone or individuals not prescribed testosterone with GnRH analogues

[4] Outcomes were captured using SNOMED concept codes and were defined as having either a diagnosis (billing code, problem list) or at least 2 abnormal measurements
(anthropometric or laboratory value) recorded in electronic health records

Outcome	Evidence statement
	• One cross-sectional study (Valentine et al 2022) of CYP with gender incongruence reported that a subgroup of CYP on testosterone with GnRH analogues (n=106) had a *statistically significant* increased odds of dyslipidaemia compared to individuals not on hormones[5] (adjusted[6] OR 3.7 (95% CI 2.0 to 6.7), p<0.0001). **(VERY LOW)** <u>Liver dysfunction</u> • One cross-sectional study (Valentine et al 2022) of CYP with gender incongruence reported that a subgroup of CYP on testosterone with GnRH analogues (n=106) had a *statistically significant* increased odds of liver dysfunction compared to individuals not on hormones[7] (adjusted OR 2.5 (95% CI 1.4 to 4.3), p<0.01). **(VERY LOW)** *Testosterone (no comparator)* No evidence was identified for this outcome. ***Testosterone with GnRH analogues vs no hormones*** **One cross-sectional study of CYP with gender incongruence provided very low certainty evidence on safety. A subgroup (n=106) of individuals on testosterone with GnRH analogues had *statistically significant* increased odds of dyslipidaemia (OR 3.7 (95% CI 2.0 to 6.7)) and liver dysfunction (OR 2.5 (95% CI 1.4 to 4.3)) compared to individuals not on hormones. Duration on treatment and timepoint of outcome measurement relative to use of treatment was not reported.** ***Testosterone (no comparator)*** **No evidence was identified for this outcome.**
Abbreviations CI: confidence interval; CYP: children and young people; GnRH: gonadotrophin-releasing hormone; OR: odds ratio	

In CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition, what is the cost-effectiveness of testosterone with GnRH analogues with or without psychological and psychosocial support compared to one or a combination of psychological support or social transitioning to the desired gender or with no intervention?

[5] The paper reports the comparator group as TGDY never prescribed GAHT with no further details provided. It is not clear therefore whether the comparator group is individuals never prescribed testosterone or individuals never prescribed testosterone with GnRH analogues

[6] Analyses were adjusted for EHR sex, age at last visit, duration in PEDSnet, overweight/obesity, depression, and antipsychotic prescription

[7] The paper reports the comparator group as TGDY never prescribed GAHT with no further details provided. We have assumed that the 'no GAHT' comparator group for individuals with a prescription for testosterone and GnRH analogues includes individuals who are AFAB only, but this is not explicitly stated in the paper

Outcome	Evidence statement
Cost-effectiveness	**No evidence was identified for cost-effectiveness.**
Abbreviations CYP: children and young people; GnRH: gonadotrophin-releasing hormone	

From the evidence selected, are there any subgroups of patients that may benefit from treatment with testosterone with GnRH analogues with or without psychological and psychosocial support more than the wider population of interest?

Subgroup	Evidence statement
Subgroups	**No evidence was identified for any subgroups.**
Abbreviations CYP: children and young people; GnRH: gonadotrophin-releasing hormone	

From the evidence selected:

a) **What were the criteria used by the research studies to define gender incongruence?**

b) **What were the starting criteria, formulation, duration and dose of testosterone for those aged 16 up to their 18th birthday?**

c) **What were the starting criteria, formulation, duration and dose of GnRH analogue treatment for those aged 16 years up to their 18th birthday?**

d) **Did any CYP aged 15 years or younger receive testosterone with GnRH analogues for gender transition? If so, in what circumstances?**

e) **What monitoring was in place for CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition receiving testosterone with GnRH analogues?**

f) **What were the exclusion criteria in the studies?**

Outcome	Evidence statement
Definitions of gender incongruence	The study defined transgender and gender diverse youth as "*having a diagnosis of gender dysphoria or related diagnosis (by PEDSnet[8] concept ID).*" No diagnostic criteria were provided.
Testosterone dosing	No evidence was identified for testosterone dosing.

[8] PEDSnet is a Partner Network Clinical Data Research Network in the National Patient Centered Clinical Research Network, an initiative funded by the Patient Centered Outcomes Research Institute. PEDSnet institutions include the Children's Hospital Colorado, Children's Hospital of Philadelphia, Nemours Children's Health (cities not stated), Nationwide Children's Hospital (Columbus, Ohio), St. Louis Children's Hospital, and Seattle Children's Hospital

Outcome	Evidence statement
GnRH analogue dosing	No evidence was identified for GnRH analogue dosing.
Testosterone and GnRH analogue for those <15 years	No evidence was identified for CYP aged under 15 receiving masculinising medicines.
Monitoring arrangements	No evidence was identified regarding monitoring arrangements for CYP receiving masculinising medicines.
Study exclusion criteria	The included study did not report any exclusion criteria. Inclusion criteria were TGDY[9] (aged >2 years at last visit) with at least one outpatient visit from 2009 to 2019 at a PEDSnet institution.
Abbreviations CYP: children and young people; GnRH: gonadotrophin-releasing hormone; PEDSnet: pediatric electronic health record data sharing network; TGDY: transgender and gender-diverse youth	

[9] Defined as having a diagnosis of gender dysphoria or related diagnosis by PEDSnet concept ID. PEDSnet is a Partner Network Clinical Data Research Network in the National Patient Centered Clinical Research Network, an initiative funded by the Patient Centered Outcomes Research Institute

6. Discussion

This evidence review examines the clinical effectiveness, safety, and cost-effectiveness of masculinising medicines comprising testosterone with GnRH analogues with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention for CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition. The critical outcomes of interest are impact on gender incongruence, impact on mental health and impact on quality of life. The important outcomes of interest are masculinising physical changes, psychosocial impact, fertility, feasibility of masculinising genital surgery, cognitive outcomes, detransition after receipt of masculinising medicines, regret after receipt of masculinising medicines and short and long-term safety.

One study was identified for inclusion in this review (Valentine et al 2022). The study is a cross-sectional study of transgender and gender diverse CYP which provides comparative results for a subgroup of individuals prescribed testosterone with GnRH analogues. The study reports on safety outcomes (dyslipidaemia and liver dysfunction). No studies were identified that reported on the critical outcomes of impact on gender incongruence, impact on mental health or impact on quality of life, or the important outcomes of masculinising physical changes, psychosocial impact, fertility, feasibility of masculinising genital surgery, cognitive outcomes, detransition after receipt of masculinising medicines or regret after receipt of masculinising medicines. No cost-effectiveness evidence was identified.

Valentine et al 2022 included 4,172 transgender and gender diverse CYP accessing care at one of six paediatric hospitals involved in a clinical data research network in the USA. Electronic health records were used to identify CYP with a gender dysphoria diagnosis or related diagnosis and to capture data on prescriptions and cardiometabolic-related diagnoses. The study reported results on a subgroup of 106 individuals on testosterone with GnRH analogues. This subgroup was considered in-scope for this review and outcomes have been extracted for this subgroup only. Odds ratios were reported for dyslipidaemia and liver dysfunction in this subgroup compared to individuals never prescribed GAHT. No further information was provided on the comparator group, including the sample size and whether the individuals were never prescribed testosterone or never prescribed testosterone with GnRH analogues. The study also presented odds ratios visually in a forest plot for the outcomes, overweight/obesity, dysglycaemia, hypertension and polycystic ovary syndrome. These results were statistically non-significant and for this reason the authors did not report the numerical results, meaning that they could not be included in this evidence review. Caution should therefore be exercised when interpreting the dyslipidaemia and liver

dysfunction results included in this evidence review due to selective reporting of statistically significant results.

No minimal clinically important thresholds or differences were reported for the outcomes considered.

The included study did not report on relevant subgroup analyses.

The study was considered to be at high risk of bias and the certainty of the evidence for the safety outcome was very low when assessed using modified GRADE. Of particular note was the lack of reporting of psychological or psychosocial support / interventions in both the intervention and control populations; this increases the risk of bias through potential confounding. The available evidence was limited to results from a subgroup analysis from one cross-sectional study. This study design is inherently limited in its ability to determine causality, because both exposure (masculinising medicines) and outcome (dyslipidaemia and liver dysfunction) are measured at the same point in time. The study did not report on the time point of outcome measurement relative to the use of masculinising medicines, so it is not possible to determine whether the use of masculinising medicines preceded the development of the outcomes and if so by how long. The study did not report on dose or duration of testosterone and GnRH analogues. A further important issue is it is not possible determine whether some out-of-scope individuals were included. The study included a mixed population of transgender and gender-diverse CYP with no breakdown of binary and non-binary individuals. Furthermore, the study did not report on prior treatments, in particular the use of GnRH analogue monotherapy for puberty suppression prior to the addition of testosterone. The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions was also not reported. Additionally, although the cross-sectional study adjusted for some confounding factors, it could not adjust for confounding factors not recorded in electronic health records such as comorbidities or health behaviours (eg smoking or alcohol use) associated with gender minority status. Other quality issues include limited information on the comparator group and selective reporting of statistically significant results.

The study included individuals accessing care at paediatric hospitals involved in a research network in the USA. It is not clear if the individuals and aspects of care in the study reflect those seen in clinical practice in England and care is therefore needed in generalising results to the NHS.

7. Conclusion

This evidence review includes a cross-sectional study that provides results on a subgroup of CYP with gender incongruence on testosterone with GnRH analogues compared to individuals not on masculinising treatment.

No studies were identified for the critical or important outcomes of interest.

One included study provides very low certainty evidence for safety; reporting statistically significant increased odds of dyslipidaemia and liver dysfunction in CYP with gender incongruence on testosterone with GnRH analogues compared to individuals not on masculinising medicines.

Limitations include the cross-sectional design of the study which prevents causal inference; the use of results from a subgroup of individuals some of whom may have been out-of-scope; lack of information on the comparator group, dose and duration of masculinising medicines, and use of other gender-affirming treatments; and selective reporting of results.

Given the limited evidence available on CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition, it is not possible to draw conclusions on the impact of treatment with testosterone with GnRH analogues.

No evidence was identified on cost-effectiveness or in relation to subgroups of interest.

Appendix A PICO document

The review questions for this evidence review are:

1. For CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition, what is the clinical effectiveness of treatment with testosterone with GnRH analogues with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention?
2. For CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition, what is the short-term and long-term safety of testosterone with GnRH analogues with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention?
3. For CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition, what is the cost-effectiveness of testosterone with GnRH analogues with or without psychological and psychosocial support compared to one or a combination of psychological support or social transitioning to the desired gender or with no intervention?
4. From the evidence selected, are there particular sub-groups of CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition that may benefit more from treatment with testosterone with GnRH analogues than the wider population?
5. From the evidence selected:
    a) What were the criteria used by the research studies to define gender incongruence?
    b) What were the starting criteria, formulation, duration and dose of testosterone for those aged 16 up to their 18th birthday?
    c) What were the starting criteria, formulation, duration and dose of GnRH analogue treatment for those aged 16 years up to their 18th birthday?
    d) Did any CYP aged 15 years or younger receive testosterone with GnRH analogues for gender transition? If so, in what circumstances?
    e) What monitoring was in place for CYP with gender incongruence who identify as a male gender and wish to undergo a binary physical transition receiving testosterone with GnRH analogues?
    f) What were the exclusion criteria in the studies?

P –Population and Indication	Children and young people (up to their 18th birthday) who have gender incongruence as defined by the study and identify as a male gender and wish to undergo a binary physical transition. [Some terms used to describe this population include, but are not limited to, female to male (FTM; F2M), gender queer, transperson, transmasculine, transmale, transmasc, transman, transgender, transsexual, trans-sex, trans*, cross gender or cross-sex (alternate spellings may be considered). The term gender incongruence may also be referred to as, but is not limited to, gender dysphoria, gender identity disorder, gender dysfunction, gender diverse, gender questioning or transsexualism. 'Gender incongruence of childhood' is a diagnostic term used by health professionals, found in the WHO International Classification of Diseases ICD-11 characterised by a marked incongruence between an individual's experienced/expressed gender and the assigned sex in pre-pubertal children. It includes a strong desire to be a different gender than the assigned sex; a strong dislike on the child's part of his or her sexual anatomy or anticipated secondary sex characteristics and/or a strong desire for the primary and/or anticipated secondary sex characteristics that match the experienced gender; and make-believe or fantasy play, toys, games, or activities and playmates that are typical of the experienced gender rather than the assigned sex. The incongruence must have persisted for about 2 years (WHO, 2025). Gender variant behaviour and preferences alone are not a basis for assigning the diagnosis. 'Gender incongruence of adolescence or adulthood' is a diagnostic term used by health professionals, found in the WHO International Classification of Diseases ICD-11. Gender incongruence is characterised by "a marked and persistent incongruence between an individual's experienced gender and the assigned sex". It is important to note that it has been moved out of the "Mental and behavioural disorders" chapter and into the "Conditions related to sexual health" chapter so that it is not perceived as a mental health disorder. It does not include references to dysphoria or dysfunction. Gender dysphoria, within the section of gender identity disorders, is the term used in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) (American Psychiatric Association, 2022). In the DSM-5-TR definition, gender dysphoria has to be associated with clinically significant distress or impairment of function. Gender dysphoria is the more commonly used term clinically and among research papers. It is also most likely to be familiar to the lay public since it has been used widely in mainstream and social media. It is a label that is used colloquially to describe feelings, as well as being a formal diagnosis.] The following subgroups of CYP with gender incongruence are of interest: • Peri-pubertal vs post-pubertal • The stated duration of gender incongruence is either less than 6 months, 6-24 months or more than 24 months at time of assessment and/or treatment

	• The age of onset of gender incongruence • The age of onset of puberty • The age/ Tanner stage at which treatment was initiated with masculinising medicines • CYP with gender incongruence who have a preexisting diagnosis of neurodiversity • CYP with gender incongruence who have a preexisting diagnosis of a learning disability • CYP with gender incongruence with a history of severe enduring mental disorder including anxiety, depression (with or without a history of self-harm and suicidality), psychosis, personality disorder, and eating disorders
I – Intervention	Masculinising medicines comprising testosterone with GnRH analogues Individuals taking masculinising medicines may also be receiving psychological or psychosocial support. [Masculinising medicines may be referred to as gender affirming hormones, cross sex hormones, sex reassignment, sex change, sex transformation, sex hormones, gender reassignment, gender change, gender transformation or gender hormones. Testosterone can be given an as intramuscular injection (IM), oral tablet or applied as a gel. Examples include: testosterone gel (Tostran, Testogel, Testim, Testavan), short-acting intramuscular injections such as testosterone propionate, phenypropionate, isocaproate and decanoate (Sustanon), testosterone enantate (Delatestryl) and long-acting injection testosterone undecanoate (Nebido, Roxadin, Aveed), oral testosterone capsules in the form of testosterone undecanoate (Restandol Testocaps, Andriol testocaps, Jatenzo, Kyzatrex, Tlando). GnRH analogues may be referred to as LHRH analogues or LHRH agonists. Examples of GnRH analogues include: goserelin, triptorelin, leuprorelin, nafarelin, buserelin, gonadorelin. Goserelin is given subcutaneously, triptorelin and leuprorelin are given as subcutaneous or intramuscular injections, nafarelin is given as a nasal spray. Buserelin is given as nasal spray or subcutaneous injection. Gonadorelin is given via intravenous or subcutaneous injection. Any reference to GnRH analogues in the context of puberty suppression or used as puberty suppressing hormones must be excluded. In this context, GnRH analogues may also be described as, but are not limited to puberty blockers, puberty inhibitors or hormone blockers. Individuals may also have experienced a period of time or process known as ‘real-life experience’ (RLE), sometimes historically called ‘real-life test’ (RLT) where they have lived full-time in their identified gender role in order to be eligible for masculinsing medicines. This PICO excludes individuals taking testosterone monotherapy.]
C – Comparator(s)	One or a combination of: 1. Psychological and psychosocial support 2. Social transitioning to the gender with which the individual identifies

	OR 3. No intervention [Psychological and psychosocial support include cognitive behavioural therapy (CBT), Psychoanalytic and Psychodynamic therapies, Humanistic and Existential Therapies, Interpersonal and Relational Therapies, Trauma-Focused Therapies, Arts and Expressive Therapies, mindfulness and self-compassion, attachment-based family therapy, attachment therapy, psychoeducation, gender exploratory therapy, exploratory therapy. • Examples of Cognitive and Behavioural Therapies include: Cognitive Behavioural Therapy (CBT), Dialectical Behaviour Therapy (DBT), Acceptance and Commitment Therapy (ACT), Exposure Therapy, Behaviour Therapy Examples of Psychoanalytic and Psychodynamic Therapies include: Psychoanalysis, Psychodynamic Therapy, Intensive short-term dynamic psychotherapy (ISTDP), sensorimotor psychotherapy • Examples of Humanistic and Existential Therapies include: Person-Centered Therapy (Carl Rogers), Gestalt Therapy, Existential Therapy • Examples of Interpersonal, Relational and Systemic Therapies include: Interpersonal Therapy (IPT), Couples Therapy, Family Therapy, Group Therapy, Narrative Therapy, Mentalisation-based Therapy, Dyadic Developmental Psychotherapy (DDP), Narrative exposure therapy • Examples of Trauma-Focused Therapies include: Eye Movement Desensitization and Reprocessing (EMDR), Trauma-Focused CBT (TF-CBT) • Examples of Mindfulness-Based Therapies include: Mindfulness-Based Stress Reduction (MBSR), Mindfulness-Based Cognitive Therapy (MBCT) • Examples of Arts and Expressive Therapies include: Art Therapy, Music Therapy, Drama Therapy, Play-based Therapy, Theraplay • Examples of Integrative and Holistic Therapies include: Integrative Therapy, integrative counselling • Examples of Specialised Therapies include: Compassion-Focused Therapy (CFT), Schema Therapy, Solution-Focused Brief Therapy (SFBT). Psychosocial support also includes: assessment, extended assessment, therapeutic assessment. These longer assessments allow exploration at a deeper level to seek understanding. Interventions can be delivered by psychological practitioners including Clinical and Counselling Psychologists, Psychotherapists, other healthcare professionals with additional training and supervision (e.g., specialist nurse or therapeutic social worker), trained facilitators or counsellors. Interventions can be delivered face to face or online, individually or in groups. Duration of intervention can range from a single session to having no fixed duration or number of sessions.

	No intervention may include individuals who actively choose not to take any interventions.]
O – Outcomes	**<u>Clinical Effectiveness</u>** *There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected.* *<u>Critical to decision-making:</u>* • **Impact on gender incongruence** *This outcome is important to patients because gender incongruence is associated with significant distress and problems functioning.* [This outcome may be measured using the Utrecht Gender Dysphoria Scale (UGDS), Gender Dysphoria Questionnaire, Gender Identity Interview for Adolescents and Adults, Gender Identity Interview for Children, Gender Distress Scale (TYC-GDS), Self-reported satisfaction. Other measures (including self-reported) may be used as an alternative to the stated measures.] • **Impact on mental health** *This outcome is important to patients because gender incongruence is associated with psychological distress which can lead to the development of mental health problems.* [Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, suicide, eating disorders, depression/low mood, anxiety, psychotic symptoms/psychosis, substance abuse, minority stress and trauma. This outcome may be measured using Child Behaviour Checklist (CBCL), Youth Self Report (YSR), Childhood Global Assessment Scale (CGAS), Revised Children's Anxiety and Depression Scale (and Subscales) (RCADS), The Child and Adolescent Psychiatric Assessment (CAPA), ED-15-Y eating disorder measure, Depression Anxiety Stress Scales (DASS-Y), Patient health questionnaire (PHQ-9) Modified for Teens, Beck Depression Inventory for Youth (BDI-Y), Beck Depression Inventory-II (BDI-II), Quick Inventory of Depressive Symptoms [QIDS], Generalised Anxiety Disorder Questionnaire (GAD-7), Hospital Anxiety and Depression Scale (HADS), Screen for Child Anxiety Related Emotional Disorders (SCARED), Ask Suicide Screening Questions (ASQ), Suicide Ideation Questionnaire Junior, Children's Rosenberg Self-Esteem Scale (CRSES), Clinical Outcomes in Routine Evaluation (CORE), Child Revised Impact of Events Scale 8 or 13 (CRIES 8 or 13), Dissociative Experiences Scale (DES), Assessment Checklist for Adolescents (ACA), Assessment Checklist for Children (ACC). Other measures (including self-reported) may be used as an alternative to the stated measures.] • **Impact on Quality of Life** *This outcome is important to patients because gender incongruence may be associated with a significant reduction in health-related quality of life.* [Quality of life can be measured using a recognised quality of life score for example KINDL questionnaire, Kidscreen 10/27/52, Pediatric Quality of Life Inventory (PedsQL), EuroQuality of Life Five

	Dimensions Youth (EQ-5D-Y/EQ-5D-3L/EQ-5D-5L), Satisfaction with Life Scale for Children (SWLS-C), Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF), General Well-Being Scale (GWBS). Other measures (including self-reported) may be used as an alternative to the stated measures.] *<u>Important to decision making:</u>* • **Masculinising physical changes** *This outcome is important because most patients with gender incongruence wish to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their experienced gender.* [Masculinising physical changes can include: menstrual cycling, facial/body/head hair, body shape, voice changes, sexual and genital effects. Measures can include The Children's Body Image Scale (CBIS), Body Image Scale for Children (BISC), Body Dysmorphia scale YBOCS, Yale-Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder (BD D-YBO CS). Other measures (including self-reported) may be used as an alternative to the stated measures.] • **Psychosocial impact** *This outcome is important to patients because gender incongruence is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning.* [Examples of psychosocial impact are coping mechanisms (such as substance misuse) which may impact on family relationships; peer relationships, living arrangements, educational attendance, work participation, romantic involvement, prosocial skills. Measures that may be used are The Work and Social Adjustment Scale – Youth versions (WSAS-Y), Strengths and Difficulties Questionnaire (SDQ), Multidimensional Scale of Perceived Social Support (MSPSS), Inventory of Interpersonal Problems (IIP32), Family Adaptability, Partnership, Growth, Affection and Resolve test. Other measures (including self-reported) may be used as an alternative to the stated measures.] • **Fertility** *This outcome is important to patients because masculinising medicines can reduce fertility. Prior to commencing masculinising medicines patients should be counselled on the impact of treatment on their fertility and offered fertility preservation options.* [Examples of fertility outcomes include, but are not limited to ovulation, pregnancy as well as pregnancy outcomes.] • **Feasibility of masculinising genital surgery** *This outcome is important to patients because masculinising medicines can have an impact on surgical outcomes. Treatment may alter the amount of genital tissue available for phalloplasty, metoidioplasty, hysterectomy and bilateral salpingo-oophorectomy.* • **Cognitive outcomes**

	This outcome is important to patients because masculinising medicines can negatively impact cognitive processes such as concentration, memory, and executive function. [Observations and cognitive testing are performed by a trained professional which may include a key worker, support worker, social care, social worker or through school observations. This might include assessment of visuospatial ability, verbal memory, verbal fluency, verbal reasoning, verbal comprehension, visual memory, working memory, processing speed, computation, motor coordination, executive functioning, timed task completion or cognitive flexibility. Measures can include Wechsler Intelligence Scale for Children (WISC), Wechsler Adult Intelligence Scale (WAIS), Adaptive Behaviours Assessment System (ABAS) or Wechsler Preschool and Primary Scale of Intelligence (WPPSI).] • **Detransition after receipt of masculinising medicines** *Medical detransition is a complex experience encompassing medical, psychological, social implications and is important to patients because they may choose to discontinue treatment. The decision to detransition may or may not be associated with regret.* [Detransitioning is a concept that has evolved over time. Older studies may incorporate terminology relating to retransition. Relevant terms in the literature may include: detransitioner, desistence, discontinuation, cessation, termination, reversion, reversal, disidentification, reidentification.] • **Regret after receipt of masculinising medicines** *This outcome is important to patients because some patients who choose to take masculinising medicines may regret this decision. Regret may or may not be associated with detransition.* [This may be expressed as a proportion of the study population or other measures such as documentation of regret or semi-structured interviews.] **<u>Safety</u>** *It is important to assess whether treatment causes acute side effects that may lead to withdrawing the treatment or long-term effects that may impact on decisions for transitioning.* • Aspects to be reported could include: o Of most importance: Thromboembolic disease, cardiovascular events, pancytopenia, polycythaemia, reduced bone density, pre-diabetes (glycosylated haemoglobin (HbA1c) 42mmol/mol – 47mmol/mol, 6% vs 6.4%) or diabetes (HbA1c ≥48mmol/mol, ≥6.5%), QT prolongation on ECG, hypertension, pulmonary oil microembolism. o Anaemia, breast, ovarian or endometrial cancer, , migraine or seizures, sleep apnoea, sexually transmitted infections, hot flushes, night sweats, headaches, migraines, vision disorder, muscle pain, reduced libido, sleep apnoea, jaundice, impaired liver function, nausea, vomiting, haemorrhage (bleeding), inflammation of lungs or lung disease, gynaecomastia, skin reactions, severe acne and for those with diabetes, worsening control e.g. increase in HbA1c despite treatment or as defined in study.

	Cost effectiveness
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	Up to 18 years
Date limits	2005-2025
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, PsycINFO and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Searches were not limited by hormone type (masculinising / feminising) or final transition goals (binary transition or non-binary transition); this was to ensure that the widest selection of papers were included in the search. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints, guidelines, case reports and resource utilisation studies were excluded.

Search dates: 01 January 2005 and 13 June 2025

1	adolescent/ or young adult/ or child/
2	adolescent health/ or child health/
3	Transition to Adult Care/
4	Pediatrics/
5	Puberty/
6	(child* or school* or p?ediatric* or adolescen* or preadolescen* or teen* or preteen* or young or youth? or girl? or boy? or puberty or pubescen*).ti,ab,kf.
7	or/1-6
8	Gender Dysphoria/
9	gender identity/ or transsexualism/
10	gender-nonconforming persons/ or transgender persons/
11	(gender adj2 (incongruen* or dysphoria* or dysfunction* or identit* or divers* or question*)).ti,ab,kf.
12	(trans or transgender* or transsex* or transperson* or transwom?n or transfem* or transm?n or transmale? or transmasc* or crossgender* or cross gender* or cross sex* or crosssex* or mtf or m2f or ftm or f2m or queer*).ti,ab,kf.
13	or/8-12
14	(femini?ing adj2 (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.
15	((gender* adj2 (affirm* or reassign* or re-assign* or transform* or transition* or chang*)) and (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.
16	(gender adj2 (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.
17	((sex adj2 (affirm* or reassign* or re-assign* or transform* or transition* or chang*)) and (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.
18	Gonadotropin-Releasing Hormone/tu
19	buserelin/ or goserelin/ or leuprolide/ or nafarelin/ or triptorelin pamoate/
20	(gonadotrophin releasing hormone? or gnrh or Luteinising hormone-releasing hormone? or lhrh).ti,ab,kf.

21 (buserelin or goserelin or leuprolide or nafarelin or triptorelin or gonadorelin).ti,ab,kf.

22 (lupron or eligard or zoladex or suprecur or suprefact or synarel or trelstar or decapeptyl or gonapeptyl or salvacyl).ti,ab,kf.

23 or/14-22

24 7 and 13 and 23

25 (animal or rat or rats or mice or mouse or murine or rodent? or cows or heifers or sheep or ewes or goats or pigs or cats or dogs).ti.

26 24 not 25

27 limit 26 to (english language and yr="2005 -Current")

28 (comment or editorial or letter or preprint or review).pt. or case report.ti.

29 27 not 28

30 ("systematic review" or scoping review).pt. or "Systematic Reviews as Topic"/ or ("Cochrane Database of Systematic Reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or (((((comprehensive or comprehensively) adj (analysis or review or reviewed)) or ((literature or scoping) adj (search or searches))).ti,ab,kf,kw. not "narrative review".ti.) and (database or databases or cinahl or cochrane or embase or psycinfo or pubmed or medline or scopus or (web adj1 science) or ((bibliographic or literature) adj (review or reviews)) or (((electronic adj (database or databases)) or (databases adj3 searched)) and (eligibility or excluded or exclusion or included or inclusion))).ti,ab,kf,kw.) or (((comparative adj effectiveness) and (effectiveness adj review)) or ((critical adj interpretive) and ((interpretive adj review) or (interpretive adj synthesis)))).ti,ab,kf,kw. or ((diagnostic adj test) and ((accuracy adj review) or (accuracy adj reviews) or (accuracy adj studies) or (accuracy adj study)) and (meta-analysis or scoping or systematic)).ti,ab,kf,kw. or ((evidence adj assessment) and GRADE).ti,ab,kf,kw. or ((evidence adj2 gap) and (gap adj map)).ti,ab,kf,kw. or ((evidence adj mapping) or (evidence adj review) or (exploratory adj review) or (framework adj synthesis) or (mapping adj review)).ti,ab,kf,kw. or ((meta adj (epidemiological or ethnographic or ethnography or interpretation or narrative or review or study or synthesis or summary or theory)) or metaethnographic or metaethnography or metasynthesis).ti,ab,kf,kw. or ((methodological or methodology) adj1 review).ti,ab,kf,kw. or ((mixed adj methods) and (methods adj1 (review or synthesis))).ti,ab,kf,kw. or ((narrative adj1 synthesis) or (overview adj4 reviews) or ("PRISMA" adj4 (guideline or guidelines or preferred or reporting or requirements)) or (PRISMA adj "P")).ti,ab,kf,kw. or (((prognostic or psychometric) adj1 review) or ((qualitative adj (evidence or research)) and ((evidence or research) adj synthesis))).ti,ab,kf,kw. or (((rapid adj evidence) and (evidence adj assessment)) or (rapid adj realist) or (rapid adj2 (review or reviews)) or (realist adj2 (review or reviews or syntheses or synthesis))).ti,ab,kf,kw. or (((review adj economic) and (economic adj1 (evaluation or evaluations))) or ((scoping or systematic) adj2 (review or reviews or studies or study))).ti,ab,kf,kw. or ((review adj1 reviews) or ((systematic adj evidence) and (evidence adj map)) or (systematic adj2 mapping) or (systematic adj2 literature) or (systematic adj2 (Embase or Medline or PsycInfo or PubMed)) or (systematic adj2 (review or reviews)) or ((systematical or systematically) adj2 (review or reviewed reviews)) or (systematically adj identified) or (systematized adj review) or (umbrella adj (review or reviews))).ti,ab,kf,kw. or "Meta-Analysis".pt. or "meta-analysis as topic"/ or (meta adj2 (analyse or analyser or analyses or analysis

or analytic or analytical or analytics or analyze or analyzed or analyzes)).ti,ab,kf,kw. or (metaanalyse or Metaanalysen or metaanalyser or metaanalyses or metaanalysis* or metaanalytic or metaanalytical or metaanalytics or metaanalyze or metaanalyzed or metaanalyzes).ti,ab,kf,kw. or "network meta-analysis"/ or (network adj1 (meta or metaanalyses or metaanalysis or metaregression)).ti,ab,kf,kw. or (systematic and ((meta adj regression) or metagression)).ti,ab,kf,kw.

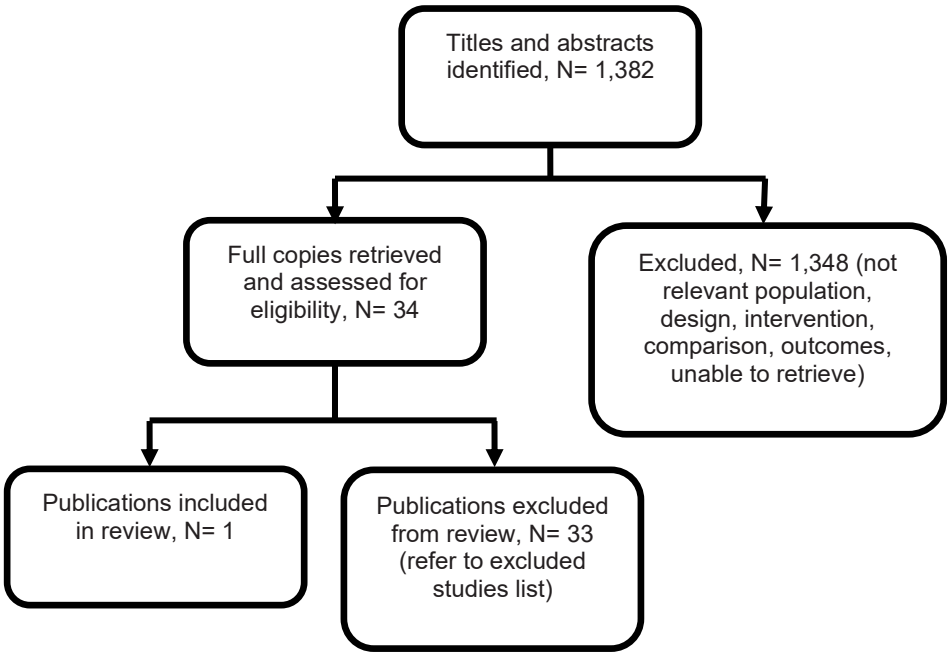
31 27 and 30

32 29 or 31

Appendix C Evidence selection

The literature searches identified 1,382 references. These were screened using their titles and abstracts and 34 references were obtained in full text and assessed for relevance. Of these, one reference is included in the evidence summary. The remaining 33 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Not applicable.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Bauer GR, Pacaud D, Couch R, Metzger DL, Gale L, Gotovac S, et al. Transgender Youth Referred to Clinics for Gender-Affirming Medical Care in Canada. Pediatrics. 2021;148(5):11.	Prospective cohort study (n=174) of a mixed population (youth referred to Canadian medical clinics for hormonal suppression or gender affirming hormone therapy). Only includes 3 patients on GnRH analogues with testosterone. Results not reported separately for this group.
Brik T, Vrouenraets L, de Vries MC, Hannema SE. Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria. Arch Sex Behav. 2020;49(7):2611-8.	Retrospective case series (n=143) of a mixed population (children and adolescents attending a gender clinic in the Netherlands who were started on GnRH analogue monotherapy). 125 (89 transboys) followed with subsequent GAHT. Intervention out of scope – GnRH analogues followed by GAHT.
Butler G, Adu-Gyamfi K, Clarkson K, El Khairi R, Kleczewski S, Roberts A, et al. Discharge outcome analysis of 1089 transgender young people referred to paediatric endocrine clinics in England 2008-2021. Arch Dis Child. 2022;107(11):1018-22.	Discharge outcome analysis (n=1,089) of mixed population (transgender young people referred to paediatric endocrine clinics). No mention of people on testosterone with GnRH analogues.
Cheung AS. Adult Height in Transgender Youth Who Receive GnRH Analogues Followed by Gender-Affirming Hormone Therapy. J Clin Endocrinol Metab. 2025;110(2):e538-e9.	Publication out of scope – commentary.
Chew D, Anderson J, Williams K, May T, Pang K. Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics. 2018;141(4):04.	Narrative SR of mixed population (transgender adolescents on GnRH analogues, GAHT, anti-androgens, and/or progestins). Results not reported separately for in-scope population.
Crabtree L, Connelly KJ, Guerriero JT, Battison EAJ, Tiller-Ormord J, Sutherland SM, et al. A More Nuanced Story: Pediatric Gender-Affirming Healthcare is Associated With Satisfaction and Confidence. J Adolesc Health. 2024;75(5):772-9.	Cross sectional study (n=150) of mixed population (attenders of a paediatric gender clinic). 129 AFAB respondents. 78 were binary transmale. 120 out of 128 AFAB had taken testosterone. Intervention out of scope - testosterone only for in-scope patients.
Feigerlova E. Prevalence of detransition in persons seeking gender-affirming hormonal treatments: a systematic review. J Sex Med. 2025;22(2):356-68.	Narrative SR of a mixed population (transgender persons on GnRH analogues and/or GAHT). Results not reported separately for in-scope population.
Ghelani R, Lim C, Brain C, Fewtrell M, Butler G. Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria. J Pediatr Endocrinol Metab. 2020;33(1):107-12.	Intervention out of scope – GnRH analogue monotherapy given for puberty suppression.
Jensen RK, Jensen JK, Simons LK, Chen D, Rosoklija I, Finlayson CA. Effect of Concurrent Gonadotropin-Releasing Hormone Agonist Treatment on Dose and Side Effects of Gender-Affirming Hormone Therapy in Adolescent Transgender Patients. Transgend Health. 2019;4(1):300-3.	Retrospective case series (n=85) of a mixed population (patients receiving GAHT at a paediatric gender clinic). 17 were on GnRH analogues (11 AFAB) prior to starting GAHT. Intervention out of scope – GnRH analogue monotherapy followed by testosterone.
Kain EJ, Fuqua JS, Eugster EA. A Retrospective Study of the Use of Gonadotropin-Releasing Hormone Analogs and Testosterone in Transgender Boys: Who, What, When, and for How Long? Transgend Health. 2024;9(4):357-60.	Retrospective case series (n=101) of transgender boys. 44% of total sample were on GnRH analogues and 70% of total sample were on testosterone. % on testosterone with GnRH analogues not reported and results not reported separately for this group.
Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. J Pediatr. 2014;164(4):906-11.	Retrospective case series (n=84) of a mixed population (youth with a diagnosis of gender dysphoria at a centre in Canada). Intervention out of

Study reference	Reason for exclusion
	scope – GnRH analogues given for puberty suppression.
Klaver M, De Mutsert R, Van Der Loos MATC, Wiepjes CM, Twisk JWR, Den Heijer M, et al. Hormonal treatment and cardiovascular risk profile in transgender adolescents. Pediatrics. 2020;145(3):e20190741.	Retrospective case series (n=71 transwomen and 121 transmale) of a mixed population (adolescents diagnosed with gender dysphoria at one centre). Intervention out of scope – GnRH analogues given for puberty suppression followed by testosterone.
Klaver M, de Mutsert R, Wiepjes CM, Twisk JWR, den Heijer M, Rotteveel J, et al. Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. J Sex Med. 2018;15(2):251-60.	Retrospective case series (n=71 transwomen and 121 transmen) of mixed population (adolescents diagnosed with gender dysphoria at a centre in the Netherlands). Intervention out of scope – GnRH analogue monotherapy given for puberty suppression followed by GAHT.
Knaus S, Steininger J, Klinger D, Riedl S. Body Mass Index Distributions and Obesity Prevalence in a Transgender Youth Cohort - A Retrospective Analysis. J Adolesc Health. 2024;75(1):127-32.	Retrospective case series (n=269) of mixed population (transgender and gender diverse patients). Of the 203 AFAB, 70% received GAHT (either GnRH analogues, sex steroids, or a combination of both). Number on testosterone with GnRH analogues not reported. Insufficient information to be able to extract results for in-scope population/intervention.
Lavender R, Shaw S, Maninger JK, Butler G, Carruthers P, Carmichael P, et al. Impact of Hormone Treatment on Psychosocial Functioning in Gender-Diverse Young People. LGBT health. 2023;10(5):382-90.	Retrospective case series (n=38) of mixed population (young people from ages 12 to 15 years, at Tanner stage 2+, and accessing GnRH analogues followed by GAHT at an endocrine centre). Intervention out of scope – GnRH analogue monotherapy followed by subsequent GAHT.
Ludvigsson JF, Adolfsson J, Hoistad M, Rydelius PA, Kristrom B, Landen M. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. Acta Paediatr. 2023;112(11):2279-92.	Narrative SR of a mixed population (children with gender dysphoria on GAHT with/without GnRH analogues). Results not reported separately for in-scope population.
Martinez-Martin FJ, Kuzior A, Hernandez-Lazaro A, de Leon-Durango RJ, Rios-Gomez C, Santana-Ojeda B, et al. Incidence of hypertension in young transgender people after a 5-year follow-up: association with gender-affirming hormonal therapy. Hypertens Res. 2023;46(1):219-25.	Retrospective case series (n=302) of mixed population (transgender patients >16 years on GAHT). 153 transgender men all treated with testosterone. Intervention out of scope - in-scope patients treated with testosterone only.
Masic U, Butler G, Carruthers P, Carmichael P. Trajectories of transgender adolescents referred for endocrine intervention in England. Arch Dis Child. 2022;107(11):1012-7.	Retrospective cohort study (n=668) of mixed population (transgender adolescents referred for endocrine intervention). 279 AFAB consented to GnRH analogues and 136 consented to GAHT after GnRH analogues (results not reported separately for this group). Study states that the most common pathway (98%) was for referral to GnRH analogues followed by GAHT if eligible. Intervention out of scope – GnRH analogues monotherapy followed by testosterone for in-scope population.
Nahata L, Tishelman AC, Caltabellotta NM, Quinn GP. Low Fertility Preservation Utilization Among Transgender Youth. J Adolesc Health. 2017;61(1):40-4.	Retrospective case series (n=78) of a mixed population (people with gender dysphoria referred to Paediatric Endocrinology for hormone therapy). Intervention out of scope – GnRH analogues given for puberty suppression.
Nokoff NJ, Scarbro SL, Moreau KL, Zeitler P, Nadeau KJ, Reirden D, et al. Body composition and markers	Intervention out of scope - none of the participants were receiving testosterone.

Study reference	Reason for exclusion
of cardiometabolic health in transgender youth on gonadotropin-releasing hormone agonists. Transgend Health. 2021;6(2):111-9.	
Norup PB, Haahr ME, Christiansen P, Aksglaede L, Cleemann L, Johannsen TH, et al. Growth and Adult Height Attainment in Danish Transgender Adolescents Treated With GnRH Analog and Sex Hormones. J Clin Endocrinol Metab. 2024;109(11):2764-73.	Cohort study (n=219) of mixed population (transgender adolescents). Subgroup of 62 patients were given GnRH analogues and testosterone at the same time. Results not reported separately for in-scope population. Outcomes out of scope.
Nunes-Moreno M, Furniss A, Cortez S, Davis SM, Dowshen N, Kazak AE, et al. Mental Health Diagnoses and Suicidality Among Transgender Youth in Hospital Settings. LGBT health. 2025;12(1):20-8.	Case control study (n=3,414) of mixed population (transgender youth). 13.4% of total sample prescribed GnRH analogues and 20.6% of total sample prescribed testosterone. Results not reported separately for in-scope population.
Nyquist CB, Torgersen L, David LW, Diseth TH, Gulbrandsen K, Waehre A. Treatment trajectories among children and adolescents referred to the Norwegian National Center for Gender Incongruence. Acta Paediatr. 2025;114(5):1006-14.	Retrospective cohort study (n=1,258) of mixed population (CYP referred to the Norwegian National Center for Gender Incongruence). 135 were started on GnRH analogue monotherapy and 96 of these patients continued to GAHT. Results not reported separately for these 96 patients. Intervention out of scope – GnRH analogue monotherapy with subsequent GAHT.
Roy MK, Bothwell S, Kelsey MM, Ma NS, Moreau KL, Nadeau KJ, et al. Bone Density in Transgender Youth on Gender-Affirming Hormone Therapy. J. 2024;8(5):bvae045.	Cross sectional study (n=56) of mixed population (transgender youth on GAHT). 21 AFAB were on testosterone, of whom 5 had prior GnRH analogues (not with testosterone). Intervention out of scope – GnRH analogue monotherapy with subsequent testosterone.
Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE. Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones. J Clin Endocrinol Metab. 2020;105(12):01.	Observational prospective study (n= 51 transgirls and 70 transboys receiving GnRH analogues and 36 transgirls and 42 transboys receiving GnRH analogues and gender-affirming hormones). Intervention out of scope – GnRH analogues given to suppress endogenous sex steroid production. GnRH analogues started as monotherapy and testosterone was added subsequently if given.
Schulmeister C, Millington K, Kaufman M, Finlayson C, Kennedy JO, Garofalo R, et al. Growth in Transgender/Gender-Diverse Youth in the First Year of Treatment With Gonadotropin-Releasing Hormone Agonists. J Adolesc Health. 2022;70(1):108-13.	Prospective observational study (n=55) of TGD youth initiating GnRH analogue treatment for puberty suppression. Intervention out of scope – GnRH analogue treatment for puberty suppression.
Segev-Becker A, Israeli G, Elkon-Tamir E, Perl L, Sekler O, Amir H, et al. Children and Adolescents with Gender Dysphoria in Israel: Increasing Referral and Fertility Preservation Rates. Endocr Pract. 2020;26(4):423-8.	Retrospective case series (n=106) of a mixed population (children and adolescents with gender dysphoria referred to a gender dysphoria clinic in Israel). 59 were AFAB with insufficient information to confirm if they had GnRH analogues/GAHT (with no PSH).
Steininger J, Knaus S, Kaufmann U, Ott J, Riedl S. Treatment trajectories of gender incongruent Austrian youth seeking gender-affirming hormone therapy. Front Endocrinol (Lausanne). 2024;15:1258495.	Retrospective case series (n=310) of mixed population (CYP with gender incongruence seeking gender affirming medical care). GnRH analogues were commenced contemporaneously with sex steroid therapy in 91 patients but number that were on testosterone with GnRH analogues not reported. Results not reported separately for in-scope population.

Study reference	Reason for exclusion
Tollit MA, May T, Maloof T, Telfer MM, Chew D, Engel M, et al. The clinical profile of patients attending a large, Australian pediatric gender service: A 10-year review. Int J Transgend Health. 2023;24(1):59-69.	Retrospective case series (n=359) of a mixed population (attenders of a paediatric gender service). The proportion of patients who received medical intervention for gender dysphoria including GnRH analogues, menses suppression, anti-androgens, and/or GAHT - was determined in a subcohort of 234 patients (112 assigned females, 122 assigned males). GnRH analogues referred to as puberty blockers. No numbers reported for those on testosterone with GnRH analogues. Insufficient information to be able to extract results for in-scope population/ intervention.
Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K. Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care. JAMA netw. 2022;5(2):e220978.	Prospective cohort (n=104) of mixed population (transgender and non-binary youths aged 13 to 20 years in receipt of gender-affirming care including puberty blockers and gender affirming hormones). GnRH analogues referred to as puberty blockers. 14 received GAHT and puberty blockers. Proportion of this group who were on testosterone with GnRH analogues and were binary was not reported. Insufficient information to be able to extract results for in-scope population/ intervention.
van der Loos MA, Hellinga I, Vlot MC, Klink DT, den Heijer M, Wiepjes CM. Development of Hip Bone Geometry During Gender-Affirming Hormone Therapy in Transgender Adolescents Resembles That of the Experienced Gender When Pubertal Suspension Is Started in Early Puberty. J Bone Miner Res. 2021;36(5):931-41.	Retrospective study (n=322) of mixed population (people who visited a gender clinic in Amsterdam). Intervention out of scope – GnRH analogue monotherapy followed by subsequent testosterone.
Van Donge N, Schvey NA, Roberts TA, Klein DA. Transgender Dependent Adolescents in the U.S. Military Health Care System: Demographics, Treatments Sought, and Health Care Service Utilization. Mil Med. 2019;184(5-6):e447-e54.	Retrospective case series (n=53) of a mixed population (transgender Dependent Adolescents in the U.S. Military Health Care System). 12/53 were on an injectable or implantable GnRH analogues for puberty blocking (8/40 AFAB). Intervention out of scope – GnRH analogues given as a puberty blocker.
Vehmas N, Holopainen E, Savolainen-Peltonen H. Metabolic and Anthropometric Changes and Adverse Effects in Finnish Adolescents Using Gender-Affirming Hormonal Treatment. Transgend Health. 2024.	Retrospective study (n=119) of mixed population (transgender adolescents using GAHT). 83% of transgender males on GAHT. 46% of transgender males used GnRH analogues during or before testosterone. Results not reported separately for in-scope population.

Abbreviations

AFAB: assigned female at birth; CYP: children and young people; GAHT: gender-affirming hormone therapy; GnRH: gonadotropin-releasing hormone; PSH: puberty suppressing hormones; SR: systematic review; TGD: transgender and gender diverse

Appendix E Evidence table

The language used in this table is that of the study authors and may not reflect current language used by NHS England or NHS Gender Identity Services.

Data extraction for the studies in this table is limited to the outcomes for the population and interventions in-scope for this evidence review. For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Valentine A, Davis S, Furniss A, Dowshen N, Kazak AE, Lewis C, et al. Multicenter Analysis of Cardiometabolic-related Diagnoses in Transgender and Gender-Diverse Youth: A PEDSnet Study. J Clin Endocrinol Metab. 2022;107(10):e4004-e14. **Study location** USA (multicentre)	**Inclusion criteria** TGDY[10] (aged >2 years at last visit) with at least one outpatient visit from 2009 to 2019 at a PEDSnet institution[11] **Exclusion criteria** None **Total sample size** n=4,172[12]	**Interventions** Prescription for testosterone with GnRH analogues[14] **Comparators** Never prescribed GAHT[15] Among AFAB, 112 (4.1%) had a prescription for a progestin (norethindrone, medroxyprogesterone) and 199 (7.2%) for COCP	**Safety** **Dyslipidaemia[16]** • Adjusted[17] OR (95% CI), p value: 3.7 (2.0 to 6.7), p<0.0001 The authors noted no differences in significance or directionality in unadjusted models **Liver dysfunction** • Adjusted OR (95% CI), p value: 2.5 (1.4 to 4.3), p<0.01	This study was appraised using the JBI checklist for analytical cross-sectional studies. 1. YES 2. NO 3. YES 4. NO 5. YES 6. YES 7. YES

[10] Defined as having a diagnosis of gender dysphoria or related diagnosis by PEDSnet concept ID. PEDSnet is a Partner Network Clinical Data Research Network in the National Patient Centered Clinical Research Network, an initiative funded by the Patient Centered Outcomes Research Institute
[11] PEDSnet institutions include the Children's Hospital Colorado, Children's Hospital of Philadelphia, Nemours Children's Health, Nationwide Children's Hospital, St. Louis Children's Hospital, and Seattle Children's Hospital
[12] 16,648 matched controls were also included in the study to evaluate the risk of diagnoses related to cardiometabolic health among TGYD
[14] Ascertained from electronic health record prescriptions via ATC/RxNorm codes and structured vocabularies to capture and group similar and synonymous medications into categorical classes: GnRHa (L02AE) and testosterone (G03B)
[15] The paper reports the comparator group as TGDY never prescribed GAHT with no further details provided. We have assumed that the 'no GAHT' comparator group for individuals with a prescription for testosterone and GnRH analogues includes individuals who are AFAB only, but this is not explicitly stated in the paper
[16] Outcomes were captured using SNOMED concept codes and were defined as having either a diagnosis (billing code, problem list) or at least 2 abnormal measurements (anthropometric or laboratory value) recorded in electronic health records
[17] Analyses were adjusted for EHR sex, age at last visit, duration in PEDSnet, overweight/obesity, depression, and antipsychotic prescription

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study type Cross-sectional study **Study aim** To evaluate the risk of diagnoses related to cardiometabolic health among TGDY compared to matched controls, and to evaluate the potential association of various GAHTs on cardiometabolic-related diagnoses among TGDY **Study dates** 2009 to 2019	• n=2,766 AFAB **No. of participants in each treatment group** Testosterone with GnRH analogues: n=106 No GAHT: n not reported **Baseline characteristics** Total sample (n=4,172)[13] Age (years), median (IQR): • At first visit: 10.0 (4.4 to 14.6) • At last visit: 16.7 (14.6 to 18.3) Race: • White: 3,027 (72.5%) • Unknown: 401 (9.6%) • Other: 390 (9.3%) • Black: 257 (6.2%) • Asian: 98 (2.3%) Ethnicity: • Non-Hispanic: 3,538 (84.8%) • Hispanic: 354 (8.5%) • Unknown: 281 (2.5%)		The authors noted no differences in significance or directionality in unadjusted models ORs were visually presented in forest plots for the following outcomes: overweight/obesity, dysglycaemia, hypertension and polycystic ovary syndrome. All results were statistically non-significant. Results were not reported numerically and therefore have not been included in this evidence review.	8. YES **Other comments:** This paper reports on a cross-sectional study using electronic health records of 4,172 TGDY from 6 paediatric hospitals in the USA. The study compared the risk of cardiometabolic related diagnoses among TGDY prescribed GAHT with TGDY never prescribed GAHT. The study also included a propensity-matched comparison of TGDY to cisgender controls. These results have not been extracted as they are not applicable to this evidence review. 2,766 (66.3%) AFAB individuals were included in the study, 106 of whom were prescribed testosterone with GnRH analogues. Results were reported separately for this group and only these results have been extracted for this evidence review. Inclusion criteria were clearly defined and sufficiently broad for the population to be representative of TGDY. TGD was defined as having a diagnosis of gender dysphoria or related diagnosis in the electronic health record. No further information was provided on the criteria used to diagnose TGD. The number of non-binary

[13] Baseline characteristics not reported separately for AFAB population

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Insurance: • Private: 2530 (60.6%) • Public: 1287 (30.8%) • Other: 253 (6.1%) • Unknown: 103 (2.5%) Total number of outpatient visits, median (IQR): 10 (4 to 26)			individuals included, if any, were not reported. It has been assumed that the majority were binary individuals. Baseline characteristics were not reported separately for AFAB, only for the total sample size. Insufficient information was provided on the comparator group. We have assumed that the 'no GAHT' comparator group for individuals with a prescription for testosterone and GnRH analogues includes individuals who are AFAB only, but this is not explicitly stated in the paper The sample size of this group was not reported and it was not clear whether this group represented individuals never prescribed testosterone or individuals never prescribed testosterone with GnRH analogues. GAHT exposure was ascertained from electronic health record prescriptions via ATC/RxNorm codes. The dose and duration were not reported. Furthermore, any previous use of GnRH analogue monotherapy for possible puberty suppression prior to the addition of testosterone was not reported. Outcomes were captured using SNOMED concept codes and were defined as having either a diagnosis or at least 2 abnormal measurements (anthropometric or

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				laboratory value) in the electronic health records. Multivariable logistic regression adjusted for sex at birth, age at last visit, duration in PEDSnet, overweight/obesity, depression, and antipsychotic prescription were used. Although the study adjusted for some confounding factors, it could not adjust for confounding factors not recorded in electronic health records. The majority of the population were White and had private insurance. The study was conducted in the USA which may limit the applicability of the results to the UK. **Source of funding:** This work was supported by the National Institutes of Health / National Institute of Child Health and Human Development, the National Institutes of Health / National Heart, Lung and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the Doris Duke Foundation, the Pediatric Endocrine Society and the Society for Adolescent Health and Medicine. The funders had no role in the design or conduct of the study.
Abbreviations				

Study details	Population	Interventions	Study outcomes	Appraisal and funding
AFAB: assigned female at birth; ATC: Anatomical Therapeutic Chemical classification; CI: confidence interval; COCP: combined oral contraceptive pill; EHR: electronic health record; GAHT: gender-affirming hormone therapy; GnRH: gonadotrophin-releasing hormone; IQR: interquartile range; JBI: Joanna Briggs Institute; OR: odds ratio; PCOS: polycystic ovary syndrome; PEDSnet: Pediatric EHR Data Sharing Network; SNOMED-CT: Systematized Nomenclature of Medicine—Clinical Terms; TGDY: transgender and gender-diverse youth				

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

1. Were criteria for inclusion in the samples clearly defined?
2. Were the study subjects and the setting described in detail?
3. Was the exposure measured in a valid and reliable way?
4. Were objective, standard criteria used for measurement of the condition?
5. Were the confounding factors identified?
6. Were strategies to deal with confounding factors stated?
7. Were the outcomes measured in a valid and reliable way?
8. Was appropriate statistical analysis used?

Appendix G GRADE profiles

The language used in this table is that of the study authors and may not reflect current language used by NHS England or NHS Gender Identity Services.

For abbreviations and footnotes see end of tables

Table 2. Testosterone with gonadotropin-releasing (GnRH) analogues compared to no gender-affirming hormone therapy (GAHT)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Testosterone + GnRH analogues	No GAHT[a]	Result		
Safety (1 cross-sectional study)									
Dyslipidaemia[b], adjusted[c] OR (95%CI), p value, duration on treatment and timepoint of outcome measurement relative to use of feminising medicines not reported									
1 cross-sectional study Valentine et al 2022	Serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	106	Not reported	• 3.7 (2.0 to 6.7), p<0.0001	Important	Very low
Liver dysfunction, adjusted OR (95%CI), p value, duration on treatment and timepoint of outcome measurement relative to use of feminising medicines not reported									
1 cross-sectional study Valentine et al 2022	Serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	106	Not reported	• 2.5 (1.4 to 4.3), p<0.01	Important	Very low

Abbreviations

CI: confidence interval; GAHT: gender-affirming hormone therapy; GnRH: gonadotropin-releasing hormone; OR: odds ratio

1.Risk of bias: Serious limitations due to not reporting baseline characteristics of in-scope individuals and not providing details on comparator group sample size and population

2.Indirectness: Very serious indirectness due to no data provided to determine whether out-of-scope individuals were included (non-binary individuals or individuals with prior use of GnRH analogue monotherapy for puberty suppression)

a. The paper reports the comparator group as TGDY never prescribed GAHT with no further details provided. We have assumed that the 'no GAHT' comparator group for individuals with a prescription for testosterone and GnRH analogues includes individuals who are AFAB only, but this is not explicitly stated in the paper

b. Outcomes were captured using SNOMED concept codes and were defined as having either a diagnosis (billing code, problem list) or at least 2 abnormal measurements (anthropometric or laboratory value) recorded in electronic health records

c. Analyses were adjusted for EHR sex, age at last visit, duration in PEDSnet, overweight/obesity, depression, and antipsychotic prescription

Glossary

Term	Definition[18]
Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Child and/or young person	In law, everyone under 18 years of age is a child (Children Act 1989) but we recognise that it may be more appropriate to refer to those approaching the age of 18 as a young person, and that such young people may not recognise themselves as a "child". In places, we have referred only to "young person", or only to "child", for example where treatment in question is only given towards the later stages of childhood, closer to the age of 18, or in reference to the parent/ child relationship, in which they remain the parents' child, regardless of their age. Otherwise, we have used the phrase "child and/or young person" throughout the report for this reason only, and do not intend there to be a material difference between them other than that.
Cisgender	Used to describe a person whose personal identity and gender identity is the same as their birth registered sex.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Comparator	The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care).
Cost effectiveness analysis	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
Cross-sectional study	A 'snapshot' observation of a set of people at 1 time. This type of study (sometimes called a cross-sectional survey) contrasts with a longitudinal study, which follows a set of people over a period of time.
Detransition/ detransitioners	The process of discontinuing or reversing a gender transition, often in connection with a change in how the individual identifies or conceptualises their sex or gender since initiating transition.
Diagnostic and Statistical Manual of Mental Disorders Fifth edition (DSM-5)	The standard classification of mental disorders used by mental health professionals in the UK, and internationally, published by the American Psychiatric Association. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5) is the latest version.

[18] These definitions are taken from the NICE glossary https://www.nice.org.uk/glossary and the glossary from the Cass Review [ARCHIVED CONTENT] Final Report – Cass Review

Term	Definition[18]
Feminising and masculinising hormones (also known as cross-sex hormones, and gender affirming hormones)	Sex hormones given as part of a medical transition for gender dysphoric individuals (testosterone for transgender males and oestrogen for transgender females).
Gender dysphoria	Diagnostic term used by health professionals and found in DSM-5 outlined above. Gender dysphoria describes “a marked incongruence between one’s experienced/ expressed gender and assigned gender of at least six months duration” which must be manifested by a number of criterion.
Gender identity	The developmental experience of a child or young person in seeking to understand their gender identity over time.
Gender incongruence	Diagnostic term used by health professionals, found in the WHO International Classification of Diseases ICD-11. Gender incongruence is characterised by “a marked and persistent incongruence between an individual’s experienced gender and the assigned sex”.
Gender-questioning	A broad term used to describe children and young people who are in a process of exploration about their gender.
Gender-related distress	A way of describing distress that may arise from a broad range of experiences connected to a child or young person’s gender identity development. Often used for young people whereby any formal diagnosis of gender dysphoria has not yet been made.
Gonadotropin releasing hormone analogues (also known as hormone blockers and puberty blockers) (GnRH analogues)	Taking these hormones stops the progress of puberty. The GnRH analogues (puberty blockers) act by competing with the body’s natural gonadotrophin releasing hormone. This competition blocks the release of two gonadotrophin hormones important in puberty called Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
International Classification of Diseases 11th Revision (ICD-11)	The International Classification of Diseases (ICD) is a globally used medical classification of anything that is relevant to health care and is used clinically for medical diagnosis. It is developed and annually updated by the World Health Organization (WHO) and is the mandatory global data standard for recording health information. It is currently in its 11th revision (ICD-11).
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Non-binary	A gender identity that does not fit into the traditional gender binary of male and female.
Odds ratio	Compares the odds of something happening in 1 group with the odds of it happening in another. An odds ratio of 1 shows that the odds of the event happening (for example, a person developing a disease or a treatment working) is the same for both groups. An odds ratio of greater than 1 means that the event is more likely in the first group than the second. An odds ratio of less than 1 means that the event is less likely in the first group than in the second group.
Paediatrics	The branch of medicine dealing with children and their medical conditions.

Term	Definition[18]
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Psychosocial	Describes the psychological and social factors that encompass broader wellbeing.
Puberty blockers	See gonadotropin-releasing hormone analogues above.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.
Subgroup analysis	A way to find out from a study if a treatment is more effective in one group of people (for example, who are a particular age or have particular symptoms) than another. It uses evidence from a defined subgroup within the whole analysis set.
Transgender (trans)	This is an umbrella term that includes a range of people whose gender identity is different from the sex they were registered at birth.
Transition	These are the steps a person may take to live in the gender in which they identify. This may involve different things, such as changing elements of social presentation and role and/or medical intervention for some.

References

Included studies

- Valentine A, Davis S, Furniss A, Dowshen N, Kazak AE, Lewis C, et al. Multicenter Analysis of Cardiometabolic-related Diagnoses in Transgender and Gender-Diverse Youth: A PEDSnet Study. J Clin Endocrinol Metab. 2022;107(10):e4004-e14.

Other references

- American Psychiatric Association, DSM-5 Task Force. (2013). Diagnostic and statistical manual of mental disorders: DSM-5™ (5th ed.). American Psychiatric Publishing, Inc.. https://doi.org/10.1176/appi.books.9780890425596
- American Psychiatric Association (2022). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). https://doi/book/10.1176/appi.books.9780890425787
- American Psychiatric Association (2022). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). https://doi/book/10.1176/appi.books.9780890425787

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