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NHS England Evidence Review:

Feminising medicines comprising oestrogen with gonadotrophin releasing hormone (GnRH) analogues for children and young people with gender incongruence who identify as a female gender and wish to undergo a binary physical transition

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NHS England Evidence Review

Feminising medicines comprising oestrogen with gonadotrophin releasing hormone (GnRH) analogues for children and young people with gender incongruence who identify as a female 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

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1. Introduction

This evidence review examines the clinical effectiveness, safety and cost-effectiveness of feminising medicines comprising oestrogen 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 no intervention, for children and young people (CYP) with gender incongruence who identify as female 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. Feminising medicines are used to help make the patient's body more congruent with their gender identity. Treatment includes oestrogen which will result in the patient's body developing a more female physical appearance, and usually a GnRH analogue and/or anti-androgen is needed in addition to oestrogen treatment. These treatments will be used in combination with a number of other interventions. This evidence review focusses on individuals that use oestrogen 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 oestrogen and GnRH analogues

more than the wider population, the criteria used by research studies to define gender incongruence, oestrogen dosing regimens, GnRH analogue dosing regimens, circumstances in which any CYP aged 15 years or younger received oestrogen and GnRH analogues, monitoring arrangements and study exclusion criteria.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost-effectiveness of feminising medicines comprising oestrogen 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 no intervention, for children and young people (CYP) with gender incongruence who identify as female 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 who identify as a female gender and wish 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 study referenced in this review may use historical terms which are no longer considered appropriate (Table 1, Appendix E: Evidence Table, Appendix G: GRADE profiles).

The searches for evidence published since 01 January 2005 were conducted on 12 June 2025 and identified 1,273 references. These were screened using their titles and abstracts, and 26 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 feminising medicines comprising oestrogen with GnRH analogues for CYP with gender incongruence who identify as a female gender and wish 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 liver dysfunction and odds of hypertension associated with treatment with oestrogen and GnRH analogues in transgender and gender diverse CYP (n=125). Patients receiving feminising hormone treatment were compared to transgender and gender diverse youth (TGDY) not receiving gender-affirming hormone treatment (GAHT) (n not clear[1]). All TGDY in the study were treated at paediatric hospitals in the United States (US); duration of treatment was not reported.

[1] Range of assigned male at birth (AMAB) not on feminising treatment, n=666 to n=933. Full details of these calculations can be found in Appendix E.

In terms of clinical effectiveness:

Critical Outcomes

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

Important Outcomes

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

In terms of safety:

- One cross-sectional study (n=125) reported *statistically significantly higher* odds of liver dysfunction and hypertension when comparing CYP with gender incongruence who identify as a female gender and wish a binary physical transition receiving feminising medicines, comprising of oestrogen and GnRH analogues, for an unknown duration to those not receiving GAHT[2], in unadjusted analyses. The odds were *no longer statistically significant* following adjustment for confounders.

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 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[3] concept ID)."* No further details of *"related diagnoses"* were provided.

In terms of the starting criteria, formulation, duration and dose of oestrogen treatment:

- No evidence was identified for oestrogen dosing.

[2] We have assumed that the 'no GAHT' comparator group for individuals with a prescription for oestrogen and GnRH analogues includes individuals who are AMAB only, but this is not explicitly stated in the paper.
[3] 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 analogue treatment:

- No evidence was identified for GnRH analogue dosing.

In terms of CYP aged 15 years and younger that received oestrogen with GnRH analogue treatment:

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

In terms of the monitoring arrangements that were in place for CYP with gender incongruence who identify as female and wish a binary transition receiving feminising medicines, comprising of oestrogen with GnRH analogues:

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

In terms of the exclusion criteria of 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 included 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 (feminising medicines) and outcome (liver dysfunction and hypertension) are measured at the same point in time. The authors noted that it was not possible to determine if the cardiovascular symptomology occurred before or after the use of feminising medicines. Furthermore, the data came from an electronic patient records database of six paediatric research hospitals in the US. The database uses a mixture of codes to identify individuals diagnosed with gender incongruence who were prescribed feminising medicines, and their outcomes. This method has high specificity, but lower sensitivity and it is possible that the population of persons with gender incongruence is underestimated. This may be higher in the population of individuals with gender

incongruence not taking GAHT as they may not be accessing medical care for their gender incongruence and would not be identified in these datasets.

The study likely included individuals that were out-of-scope for this rapid evidence review (RER) as the population was gender diverse and included CYP that identified as both binary female and non-binary; the study was downgraded for indirectness. The PICO for this RER specified oestrogen with GnRH analogue feminising therapy but the authors reported that 24% of the assigned male at birth (AMAB) population received spironolactone and 6.4% of CYP in the study (both AMAB and assigned female at birth (AFAB) populations) received GnRH analogue monotherapy; it is unclear if these individuals were included in the GAHT or control groups. The authors did not report on prior treatments, particularly the use of GnRH analogues in the context of puberty suppression; it is assumed that the included population did not receive GnRH analogues in this context, but it is not certain. The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions was also not reported.

The study included individuals accessing care at paediatric hospitals involved in a research network in the US. 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 needed in generalising results to the NHS.

Conclusion

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

The included study provides very low certainty evidence for safety. No studies were identified for the critical or important outcomes of interest. No studies were identified that reported on cost-effectiveness or subgroups.

The cross-sectional study reported statistically significant increased odds of liver dysfunction and hypertension in CYP with gender incongruence on oestrogen with GnRH analogues compared to individuals not receiving GAHT, in unadjusted analyses. These results were no longer statistically significant after adjusting for confounding factors.

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

3. Methodology

Review questions

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

1. For CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition, what is the clinical effectiveness of treatment with oestrogen 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 female gender and wish to undergo a binary physical transition, what is the short-term and long-term safety of oestrogen 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 female gender and wish to undergo a binary physical transition, what is the cost-effectiveness of oestrogen 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 subgroups of CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition that may benefit more from treatment with oestrogen 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 are the starting criteria, formulation, duration and dose of oestrogen 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 oestrogen 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 female gender and wish to undergo a binary physical transition receiving oestrogen 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 12 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 2024). This cross-sectional study of transgender and gender diverse youth assessed the association of GAHT with cardiometabolic-related diagnoses and reported results separately for a subgroup prescribed oestrogen with GnRH analogues. The study did not report on duration of treatment or the timepoint of outcome measurement relative to the use of GAHT.

No evidence was identified for the critical outcomes of impact on gender incongruence, impact on mental health and impact on quality of life; or the important outcomes of feminising physical changes, psychosocial impact, fertility, feasibility of feminising genital surgery, cognitive outcomes, detransition after receipt of feminising medicines and regret after receipt of feminising 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 female 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 study 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 (six centres)	4,172 transgender and gender-diverse youth (TGDY)[a] 1,407 (33.7%) AMAB n=125 individuals on oestrogen + gonadotropin releasing hormone analogues number of individuals not on GAHT unclear[b] Age (years) at first visit, median (IQR): 10.0 (4.4 to 14.6)[c]	**Intervention** Prescription of oestrogen and GnRH analogues in electronic health record[d] (EHR) Specific formulations and doses were not detailed **Comparators** Not prescribed GAHT The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions were not reported.	Duration of treatment not reported **Safety[e]** • Hypertension • Liver dysfunction

Study	Population	Intervention and comparison	Outcomes reported
	Age (years) at last visit, median (IQR): 16.7 (14.6 to 18.3)[c] No subgroups reported		

Abbreviations

AMAB: assigned male at birth; EHR: electronic health record; GAHT: gender-affirming hormone treatment; GnRH: gonadotrophin releasing hormone; IQR: interquartile range; n: number; TGDY: transgender and gender-diverse youth; USA: United States of America

Footnotes

a. Transgender and gender diverse youth were defined as *"having a diagnosis of gender dysphoria or related diagnosis (by PEDSnet concept ID…which includes codes extracted from the EHR problem list or diagnosis code from any encounter"* 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

b. We have assumed that the 'no GAHT' comparator group for individuals with a prescription for oestrogen and GnRH analogues includes individuals who are AMAB only, but this is not explicitly stated in the paper.

c. Baseline characteristics were only presented for the full TGDY cohort and not reported separately for the AMAB population

d. ATC and RxNorm codes were used to pull prescription information from the PEDSnet database: GnRH analogues (L02AE) and oestrogen (G03C, not including combined oral contraceptive, G03A)

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

5. Results

For CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition, what is the clinical effectiveness, short-term and long-term safety of treatment with oestrogen 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	
Feminising 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 feminising medicines can reduce fertility. Prior to commencing feminising 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.**
Feasibility of feminising genital surgery **Certainty of evidence:** Not applicable	*This outcome is important to patients because feminising medicines can have an impact on surgical outcomes. Treatments may alter the amount of genital tissue available for vaginoplasty, clitoroplasty and/or vulvoplasty.* **No evidence was identified for this outcome.**

Outcome	Evidence statement
Cognitive outcomes **Certainty of evidence:** Not applicable	*This outcome is important to patients because feminising medicines can negatively impact cognitive processes such as concentration, memory, and executive function.* **No evidence was identified for this outcome.**
Detransition after receipt of feminising 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 feminising medicines **Certainty of evidence:** Not applicable	*This outcome is important to patients because some patients who choose to take feminising 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 safety in CYP with gender incongruence who identify as a female gender and wish a binary physical transition taking feminising medicines, comprising of oestrogen and GnRH analogues. Mean duration of treatment and follow-up was unknown. *Oestrogen with GnRH analogues vs no hormones* **Duration on treatment and timepoint of outcome measurement relative to use of treatment not reported** • Dyslipidaemia • One cross-sectional study (Valentine et al 2022) reported that CYP with gender incongruence who identify as a female gender and wish a binary physical transition receiving oestrogen and GnRH analogues had a *statistically significantly increased* odds of hypertension compared to individuals not on gender-affirming hormone treatment[4] in unadjusted analyses (OR 2.1 (95% CI 1.2 to 3.6), p<0.01); this was *not statistically significant* after adjusting for confounders (results not presented). **(VERY LOW)** Liver dysfunction • One cross-sectional study (Valentine et al 2022) reported that CYP with gender incongruence who identify as a female gender and wish a binary physical transition receiving oestrogen and GnRH analogues had a *statistically significantly increased* odds of liver dysfunction compared to individuals not on gender-affirming hormone treatment in unadjusted analyses (OR 2.1 (95% CI 1.3 to 3.4), p<0.01); this was *not statistically*

[4] We have assumed that the 'no GAHT' comparator group for individuals with a prescription for oestrogen and GnRH analogues includes individuals who are AMAB only, but this is not explicitly stated in the paper.

Outcome	Evidence statement
	significant after adjusting for confounders[5] (results not presented). **(VERY LOW)** **One cross-sectional study reported *statistically significantly higher* odds of liver dysfunction and hypertension when comparing CYP with gender incongruence who identify as a female gender and wish a binary physical transition receiving feminising medicines, comprising of oestrogen and GnRH analogues, for an unknown duration to those not receiving gender-affirming hormone treatment, in unadjusted analyses. The odds were no longer statistically significant following adjustment for confounders. This study provided very low certainty evidence.**
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 female gender and wish to undergo a binary physical transition, what is the cost-effectiveness of oestrogen 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?

Outcome	Evidence statement
Cost-effectiveness	**No evidence was identified for cost-effectiveness.**

From the evidence selected, are there particular subgroups of CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition that may benefit more from treatment with oestrogen with GnRH analogues than the wider population?

Subgroup	Evidence statement
	No evidence was identified for subgroups.

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 oestrogen for those aged 16 up to their 18th birthday?**

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

[5] Analyses were adjusted for electronic health record recorded sex / sex assigned at birth, age at last visit, duration in PEDSnet / EHR, overweight / obesity status, depression status and antipsychotic prescription

d) **Did any CYP aged 15 years or younger receive oestrogen 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 female gender and wish to undergo a binary physical transition receiving oestrogen with GnRH analogues?**

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

Outcome	Evidence statement
Definitions of gender incongruence	One cross-sectional study provided a definition of gender incongruence. • One cross-sectional study (Valentine et al 2022) defined transgender and gender diverse youth as *"having a diagnosis of gender dysphoria or related diagnosis (by PEDSnet[6] concept ID)."* No further details *of "related diagnoses"* were provided.
Oestrogen dosing	No evidence was identified for oestrogen dosing.
GnRH analogue dosing	No evidence was identified for GnRH analogue dosing.
Oestrogen and GnRH analogue for those <15 years	No evidence was identified for CYP aged under 15 receiving feminising medicines.
Monitoring arrangements	No evidence was identified regarding monitoring arrangements for CYP receiving feminising medicines.
Study exclusion criteria	One cross-sectional study provided exclusion criteria for their study. • One cross-sectional study (Valentine et al 2022) 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.
Abbreviations CYP: children and young people; GnRH: gonadotropin releasing hormone	

[6] 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

6. Discussion

This evidence review examines the clinical effectiveness, safety, and cost-effectiveness of feminising medicines comprising oestrogen 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 children and young people (CYP) with gender incongruence who identify as a female gender and wish to undergo a binary physical transition.

One study was identified for inclusion in this review (Valentine et al 2022). This is a cross-sectional study of transgender and gender diverse CYP which reports on safety outcomes (liver dysfunction and hypertension) for a subgroup of individuals prescribed oestrogen with GnRH analogues. 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 feminising physical changes, psychosocial impact, fertility, feasibility of feminising genital surgery, cognitive outcomes, detransition after receipt of feminising medicines or regret after receipt of feminising medicines. No cost-effectiveness evidence or evidence about specific subgroups 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 US. 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 125 individuals on oestrogen 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 liver dysfunction and hypertension in this subgroup compared to individuals without a prescription for GAHT. No further information was provided on the comparator group, including the sample size. It is also unclear if the comparator group included CYP with gender incongruence who identify as a male gender or identify as non-binary. The authors did not report on dose or duration of treatment with oestrogen or GnRH analogues.

The study presented odds ratios visually in a forest plot for other safety outcomes, including dysglycaemia and dyslipidaemia. 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 be exercised when interpreting the presented results due to selective reporting of statistically significant results.

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

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 (feminising medicines) and outcome (liver dysfunction and hypertension) are measured at the same point in time. The study noted that it was not possible to determine if the cardiovascular symptomology occurred before or after the use of feminising medicines. Furthermore, the data came from an electronic patient records database of six paediatric research hospitals in the US. The database uses a mixture of codes to identify individuals diagnosed with gender incongruence who were prescribed feminising medicines, and their outcomes. This method has high specificity, but lower sensitivity and it is possible that the population of persons with gender incongruence is underestimated. This may be higher in the population of individuals with gender incongruence not taking GAHT as they may not be accessing medical care for their gender incongruence and would not be identified in these datasets.

The study likely included individuals that were out-of-scope for this rapid evidence review (RER) as the population was gender diverse and included CYP that identified as both binary female and non-binary; the study was downgraded for indirectness. The PICO for this RER specified oestrogen with GnRH analogue feminising therapy but the authors reported that 24% of the assigned male at birth (AMAB) population received spironolactone and 6.4% of CYP in the study (both AMAB and assigned female at birth (AFAB) populations) received GnRH analogue monotherapy; it is unclear if these individuals were included in the GAHT or control groups. The authors did not report on prior treatments, particularly the use of GnRH analogues in the context of puberty suppression; it is assumed that the included population did not receive GnRH analogues in this context, but it is not certain. The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions was also not reported.

The study included individuals accessing care at paediatric hospitals involved in a research network in the US. 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 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 oestrogen with GnRH analogues compared to individuals not on GAHT. No longitudinal studies were identified comparing results before and after intervention.

The included study provides very low certainty evidence for safety. 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 feminising physical changes, psychosocial impact, fertility, feasibility of feminising genital surgery, cognitive outcomes, detransition, or regret after receipt of feminising medicines.

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

The study reported statistically significant increased odds of liver dysfunction and hypertension in CYP with gender incongruence on oestrogen with GnRH analogues compared to individuals not receiving GAHT, in unadjusted analyses. These results were no longer statistically significant after adjusting for confounding factors.

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 feminising 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 female gender and wish to undergo a binary physical transition, it is not possible to draw conclusions on the impact of treatment with oestrogen with GnRH analogues. Published studies which allow conclusions to be drawn about the effectiveness of oestrogen with GnRH analogues for this population are needed.

Appendix A PICO document

The review questions for this evidence review are:

1. For CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition, what is the clinical effectiveness of treatment with oestrogen 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 female gender and wish to undergo a binary physical transition, what is the short-term and long-term safety of oestrogen 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 female gender and wish to undergo a binary physical transition, what is the cost-effectiveness of oestrogen 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 subgroups of CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition that may benefit more from treatment with oestrogen 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 are the starting criteria, formulation, duration and dose of oestrogen 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 oestrogen 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 female gender and wish to undergo a binary physical transition receiving oestrogen 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 female gender and wish to undergo a binary physical transition. [Some terms used to describe this population include, but are not limited to, male to female (MTF; M2F), gender queer, transperson, transfeminine, transfemale, transfem, transwoman, transgender, transgendered, gender non-conforming, transexual, 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 oestrogen with GnRH analogues

	• 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	Feminising medicines comprising oestrogen with gonadotrophin-releasing hormone (GnRH) analogues. Individuals taking feminising medicines may also be receiving psychological or psychosocial support. [Feminising 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. Oestrogen can be given as a patch, gel, spray, injection or a tablet. Examples include: oral oestradiol and its salts including valerate and hemihydrate (Zumenon, Progynova, Elleste Solo, Bedol, Delestrogen); oestrogen gel (Sandrena, Oestrogel); oestradiol patch (Evorel, Estradot, Estraderm, Progynova TS patch, FemSeven patch); oestradiol spray (Lenzetto); injectable oestrogens (Depo-Estradiol, Delestrogen). Oestrogen may also be referred to as estrogen, oestradiol, estradiol, 17beta-estradiol, E2, E3, estriol, oestriol and ethinylestradiol. This list is not exhaustive. 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 feminising medicines. This PICO excludes individuals taking oestrogen 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	**Clinical Effectiveness** *There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected.* *Critical to decision-making:* • **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.] *Important to decision making:* • **Feminising 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.* [Feminising physical changes can include: facial/body/head hair, breast growth, body fat and muscle distribution, erectile dysfunction, testicular size and function and voice change. 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 feminising medicines can reduce fertility. Prior to commencing feminising medicines patients should be counselled on the impact of treatment on their fertility and offered fertility preservation options.* [Examples of fertility outcomes include presence, number and quality of mature spermatozoa. Alternative measures may be used as reported in studies.]

	• **Feasibility of feminising genital surgery** *This outcome is important to patients because feminising medicines can have an impact on surgical outcomes. Treatments may alter the amount of genital tissue available for vaginoplasty, clitoroplasty and/or vulvoplasty.* • **Cognitive outcomes** *This outcome is important to patients because feminising 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 feminising 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 feminising medicines** *This outcome is important to patients because some patients who choose to take feminising 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, reduced bone density, pancytopenia, cardiovascular disease, pre-diabetes (glycosylated haemoglobin (HbA1c) 42mmol/mol – 47mmol/mol,

	6% vs 6.4%) or diabetes (HbA1c ≥48mmol/mol, ≥6.5%), angioedema, QT prolongation on ECG, hypertension. ○ Gallstones, nausea, vomiting, jaundice, haemorrhage, breast cancer, vision disorders, seizures, impaired liver function, hot flushes, night sweats, headaches, muscle pain, reduced libido, inflammation of lungs or lung disease, 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 20 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, case reports, commentaries, letters, editorials, guidelines and pre-prints were excluded.

Search dates: 01 January 2005 to 12 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 or masculini?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.

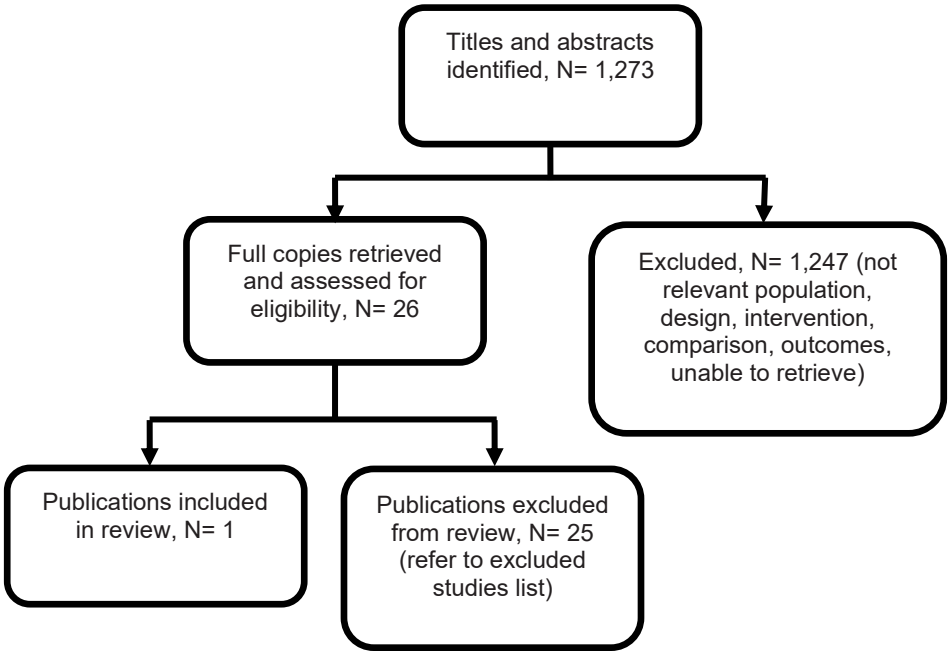
31 27 and 30

32 29 or 31

Appendix C Evidence selection

The literature searches identified 1,273 references. These were screened using their titles and abstracts and 26 references were obtained in full text and assessed for relevance. Of these, one reference is included in the evidence summary. The remaining 25 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
Boogers LS, Wiepjes CM, Klink DT, Hellinga I, van Trotsenburg ASP, den Heijer M, et al. Transgender Girls Grow Tall: Adult Height Is Unaffected by GnRH Analogue and Estradiol Treatment. J Clin Endocrinol Metab. 2022;107(9):e3805-e15.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (GnRH analogues followed by oestrogen).
Brik T, Vrouenraets L, Schagen SEE, Meissner A, de Vries MC, Hannema SE. Use of Fertility Preservation Among a Cohort of Transgirls in the Netherlands. J Adolesc Health. 2019;64(5):589-93.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (GnRH analogue monotherapy).
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.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (GnRH analogue monotherapy).
Chen D, Abrams M, Clark L, Ehrensaft D, Tishelman AC, Chan YM, et al. Psychosocial Characteristics of Transgender Youth Seeking Gender-Affirming Medical Treatment: Baseline Findings From the Trans Youth Care Study. J Adolesc Health. 2021;68(6):1104-11.	GnRH analogues used in the context of puberty suppression. Interventions out-of-scope (GnRH analogue monotherapy and oestrogen monotherapy cohorts).
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.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
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.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Feigerlova E. Prevalence of detransition in persons seeking gender-affirming hormonal treatments: a systematic review. J Sex Med. 2025;22(2):356-68.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. J Pediatr. 2014;164(4):906-11.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (GnRH analogues followed by oestrogen).
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.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (GnRH analogues followed by oestrogen).

Study reference	Reason for exclusion
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.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (GnRH analogues followed by oestrogen).
Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. J Clin Endocrinol Metab. 2015;100(2):E270-5.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (GnRH analogues followed by oestrogen).
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.	Incorrect intervention (intervention not specified, "cross-sex" hormones only; PICO refers to GnRH analogues + oestrogen only)
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.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (GnRH analogues followed by oestrogen).
Millington K, Schulmeister C, Finlayson C, Grabert R, Olson-Kennedy J, Garofalo R, et al. Physiological and Metabolic Characteristics of a Cohort of Transgender and Gender-Diverse Youth in the United States. J Adolesc Health. 2020;67(3):376-83.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (GnRH analogues monotherapy and oestrogen monotherapy only).
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.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (majority had GnRH analogues followed by oestrogen or GnRH analogues only).
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.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
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.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
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.	GnRH analogues used in the context of puberty suppression. Includes both in-scope treatment (people receiving oestrogen + GnRH analogues) and out-of-scope treatment (people receiving oestrogen monotherapy) with no separate reporting of in-scope interventions.

Study reference	Reason for exclusion
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.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (GnRH analogues followed by oestrogen)
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.	None of the patients received an in-scope intervention (oestrogen + GnRH analogues)
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.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
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.	Includes both in-scope treatment (people receiving oestrogen + GnRH analogues) and out-of-scope treatment (people receiving GnRH analogue monotherapy for puberty suppression) with no separate reporting of in-scope interventions. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
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.	No PICO defined outcomes (bone geometry). GnRH analogues used in the context of puberty suppression.
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.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (3/13 people currently on oestrogen, unclear how many on oestrogen + GnRH analogues).
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.	Includes both in-scope treatment (people receiving oestrogen + GnRH analogues - 6/20) and out-of-scope treatment (people receiving oestrogen + anti-androgens 14/20) with no separate reporting of in-scope interventions.
Abbreviations GnRH: gonadotrophin-releasing hormone	

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** US **Study type** Cross-sectional (multi-centre, electronic register-based study) **Study aim**	**Inclusion criteria** Patients entered on the Paediatric Learning Health System network with a diagnosis of gender dysphoria (or related diagnosis) and at least one outpatient visit between 2009 and 2019 TGDY are defined in this study as *"having a diagnosis of gender dysphoria or related diagnosis (by PEDSnet concept ID…which include codes extracted from the EHR problem*	**Intervention** Prescription for oestrogen and GnRH analogues[8] **Comparator** TGDY without a prescription for GAHT	Duration of treatment not reported **Safety** *Odds of liver dysfunction* • OR (95% CI), p value: 2.1 (1.3 to 3.4), p<0.01 • odds were not statistically significant following adjustment for confounders[9] *Odds of hypertension* • OR (95% CI), p value: 2.1 (1.2 to 3.6), p<0.01 • odds were not statistically significant following adjustment for confounders	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 8. Yes **Other comments:** This paper reported a cross-sectional, registry-based analysis

[8] ATC or RxNorm codes were used to pull prescription information from the PEDSnet database: GnRH analogues (L02AE) and oestrogen (G03C, not including combined oral contraceptives, G03A)
[9] Analyses were adjusted for EHR recorded sex (sex assigned at birth), age at last visit, duration in PEDSnet, overweight/obesity status, depression and antipsychotic prescription

Study details	Population	Interventions	Study outcomes	Appraisal and funding
1) to evaluate the risk of diagnoses related to cardiometabolic health among transgender and gender diverse youth (TGDY) compared to matched controls, and 2) evaluate the potential association of various gender-affirming hormone treatments (GAHTs) on cardiometabolic-related diagnoses among TGDY **Study dates** 2009 to November 2019	*list or diagnosis code from any encounter).”* **Exclusion Criteria** • Aged ≤2 years • No outpatient clinical contact **Total sample size** N=1,407 assigned male at birth (AMAB) **No. of participants in each treatment group** Oestrogen + GnRH analogues: n=125 No GAHT: not clear[7] **Baseline characteristics** Baseline characteristics were only presented for the full TGDY cohort and not reported separately for the AMAB population			comparing cardiometabolic health in the US transgender adolescent population. The individuals included in this study were identified from a national paediatric health system database which includes data from a number of institutions[10] and is used for research purposes. Individuals were included if they had a diagnosis code for gender dysphoria from any encounter. Only the data for the participants taking oestrogen + GnRH analogues treatment are presented here. The total number of participants assigned male at birth included in the study was 1,407; 125 participants were prescribed oestrogen with a GnRH analogue. The inclusion criteria included all transgender persons, over the age of two years, thus, it included both binary and non-binary transgender individuals. The number of non-binary individuals was not stated but they would be out-of-scope for this RER therefore the population

[7] We have assumed that the ‘no GAHT’ comparator group for individuals with a prescription for oestrogen and GnRH analogues includes individuals who are AMAB only, but this is not explicitly stated in the paper.
[10] 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. The PEDSnet system includes data from the following institutions: 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

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Male in electronic health record (EHR) / AMAB, n (%): 1,407 (33.7% of total cohort) Age (years) at first visit, median (IQR): 10.0 (4.4 to 14.6) Age (years) at last visit, median (IQR): 16.7 (14.6 to 18.3) Ethnicity, n (%): • White: 3,027 (72.5%) • Black: 257 (6.2%) • Asian: 98 (2.3%) • Unknown: 401 (9.6%) • Other: 390 (9.3%) Total number of outpatient visits, median (IQR): 10 (4 to 26) Authors also reported Hispanic/non-Hispanic ethnicity, duration in PEDSnet, Site number and insurance type			indirectly relates to the population specified for this RER. The number of individuals in the comparator group for these analyses was not stated. The authors state that some TGDY AMAB had a prescription for spironolactone (23.6%); however, they do not indicate if they were included in the analysis of those not on GAHT. Likewise, 267 individuals (unknown assigned sex at birth) had a prescription for GnRH analogues alone; it is unclear if they were included in the control group. Both of these groups are out-of-scope for this RER. No information was provided on any concurrent treatments. No information was provided regarding any psychological support or social transitioning prior to referral to the gender incongruence service. Outcomes were assessed using the electronic health register. Transgender persons not in contact with hospital or outpatient services would be excluded from the study. Persons with severe physical or mental illness who may not be

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				eligible for GAHT will also be excluded from the study. Missing data were not reported, and any attempts made to include missing data were not reported. The study controlled for sex assigned at birth, age at last visit, duration in PEDSnet, overweight/obesity status, depression and antipsychotic prescription in adjusted analyses. Confidence intervals and p values were both reported. No subgroup analysis was reported. Individuals were treated at private paediatric hospitals in the US. It is not clear how generalisable these findings might be to current NHS settings. **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

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				Adolescent Health and Medicine. The funders had no role in the design or conduct of the study.

Abbreviations

AMAB: assigned male at birth; CI: confidence interval; EHR: electronic health record; GAHT: gender-affirming hormone treatment; GnRH: gonadotropin-releasing hormone; IQR: interquartile range; NHS: National Health Service; OR: odds ratio; RER: rapid evidence review; TGDY: transgender and gender diverse youth; US: United States of America

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 table.

Table 2. Oestrogen + gonadotropin-releasing hormone analogues compared to no gender-affirming hormone treatment (GAHT)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Oestrogen + GnRH analogues	No GAHT	Result		
Safety (1 cross-sectional study)									
Odds of hypertension[a], at mean duration of oestrogen + GnRH analogues unknown; OR (95%CI), p value									
1 cross-sectional study Valentine et al 2022	Serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	125	Unclear[b]	• OR (95% CI), p value: 2.1 (1.2 to 3.6), p<0.01 • odds were not statistically significant following adjustment for confounders[c]	Important	Very low
Odds of liver dysfunction[a], at mean duration of oestrogen + GnRH analogues unknown; OR (95%CI), p value									
1 cross-sectional study Valentine et al 2022	Serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	125	Unclear[b]	• OR (95% CI), p value: 2.1 (1.3 to 3.4), p<0.01 • odds were not statistically significant following adjustment for confounders[c]	Important	Very low

Abbreviations

AFAB: assigned female at birth; AMAB: assigned male at birth; CI: confidence interval; EHR: electronic health record; GAHT: gender-affirming hormone treatment; 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 as the population included individuals on the transfeminine spectrum, including feminine non-binary individuals and 24% of the population received the intervention spironolactone and 6.4% (of both AMAB and AFAB) had GnRH analogue prescriptions only, it is unclear if these individuals were in the analyses*

a. *Outcomes were assessed using an electronic health register, collated for research purposes. 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*
b. *We have assumed that the 'no GAHT' comparator group for individuals with a prescription for oestrogen and GnRH analogues includes individuals who are AMAB only, but this is not explicitly stated in the paper.*
c *Analyses were adjusted for EHR recorded sex (sex assigned at birth), age at last visit, duration in PEDSnet, overweight/obesity status, depression and antipsychotic prescription. Numerical results for adjusted analyses were not reported.*

Glossary

Term	Definition[11]
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
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.
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).
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention. The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.
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.

[11] 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[11]
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
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 fluid	An experience of gender that is not fixed, but changes between two or more identities
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”.
Gonadotropin releasing hormone analogues (also known as hormone blockers and puberty blockers) (GnRH)	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.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
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.

Term	Definition[11]
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Paediatrics	The branch of medicine dealing with children and their medical conditions.
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.
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.

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

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