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Testosterone monotherapy for children and young people with gender incongruence who identify as non-binary and wish partial physical masculinisation

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NHS England Evidence Review

Testosterone monotherapy for children and young people with gender incongruence who identify as non-binary and wish partial physical masculinisation

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

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost-effectiveness of testosterone monotherapy with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired non-binary gender or no intervention, for children and young people (CYP) with gender incongruence who identify as non-binary and wish partial physical masculinisation.

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. People seeking change consistent with non-binary expression of identity often have unique treatment goals that will require a flexible, individually-tailored approach. When deciding what medicines are appropriate for a non-binary trans masculine person it is important that the degree of fluidity of the person's current gender expression is assessed and a clear formulation of the mix of male, female, and neutral physical features is made.

Masculinising medicines are used to help treat gender incongruence and make the patient's body more congruent with their gender identity This may include testosterone which will result in the patient's body developing a more masculine physical appearance. These treatments will be used in combination with a number of other interventions. This evidence review focusses on individuals that use testosterone monotherapy.

Studies in which GnRH analogues are used in the context of puberty suppression or used as puberty suppressing hormones are outside of the scope of this evidence review. NHS England and the National Institute of Health and Care Research (NIHR) are working together

to set up a study into the potential benefits and harms of puberty suppressing hormones as a treatment option for CYP with gender incongruence.

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

2. Executive summary of the review

This review examined the clinical effectiveness, safety and cost-effectiveness of testosterone monotherapy compared with one or a combination of psychological support or social transitioning to the desired non-binary gender or no intervention, for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation. The searches for evidence published since 01 January 2005 were conducted on 13 June 2025 (with an updated Medline search on 29 July 2025) and identified 1,306 references. These were screened using their titles and abstracts, and 122 full text papers were obtained and assessed for relevance against the criteria defined in the PICO for this review.

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 non-binary and wish partial physical masculinisation' rather than using the terms natal or biological sex; and 'cross-sex hormones' are now referred to as 'masculinising or feminising medicines.' The studies referenced in this review may use historical terms which are no longer considered appropriate.

No studies assessing the clinical effectiveness, safety or cost-effectiveness of testosterone monotherapy for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation were identified for this review.

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 masculinising physical changes, psychosocial impact, fertility, feasibility of masculinising genital surgery, cognitive outcomes, detransition after receipt of masculinising medicines and regret after receipt of masculinising medicines.

In terms of safety:

- No evidence was identified for safety.

In terms of cost-effectiveness:

- No evidence was identified for cost-effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation that may benefit more from treatment with testosterone monotherapy than the wider population.
- As no relevant evidence was identified, it was not possible to answer the sub-questions about the criteria used by research studies to define gender incongruence, testosterone dosing, whether any children aged 15 years or younger received testosterone monotherapy, monitoring arrangements and study exclusion criteria.

Limitations

No evidence on the clinical effectiveness, safety or cost-effectiveness of testosterone monotherapy for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation was identified.

Conclusion

No evidence was identified that allowed any conclusions to be drawn about the clinical effectiveness, safety or cost-effectiveness of testosterone monotherapy compared with one or a combination of psychological support or social transitioning to the desired non-binary gender or no intervention, for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation. Published studies which allow conclusions to be drawn about the effectiveness of testosterone monotherapy for this population are needed.

3. Methodology

Review questions

The review questions for this evidence review are:

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

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020). The searches for evidence were informed by the PICO document and were conducted on 13 June 2025.[1]

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.

As no relevant studies were identified, the appendices for data extraction tables, critical appraisal checklists and GRADE profiles were not completed.

[1] The Medline search was updated on 29 July 2025 with no additional relevant papers identified.

4. Summary of included studies

No studies assessing the clinical effectiveness, safety or cost-effectiveness of testosterone monotherapy for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation were identified for this review.

5. Results

For CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation, what is the clinical effectiveness and short-term and long-term safety of treatment with testosterone monotherapy with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired non-binary gender, or no intervention?

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

Outcome	Evidence statement
Not applicable	**No evidence was identified for this outcome.**
Cognitive outcomes **Certainty of evidence:** Not applicable	*This outcome is important to patients because masculinising medicines can negatively impact cognitive processes such as concentration, memory, and executive function.* **No evidence was identified for this outcome.**
Detransition after receipt of masculinising medicines **Certainty of evidence:** Not applicable	*Medical detransition is a complex experience encompassing medical, psychological, and social implications and is important to patients because they may choose to discontinue treatment. The decision to detransition may or may not be associated with regret.* **No evidence was identified for this outcome.**
Regret after receipt of masculinising medicines **Certainty of evidence:** Not applicable	*This outcome is important to patients because some patients who choose to take masculinising medicines may regret this decision. Regret may or may not be associated with detransition.* **No evidence was identified for this outcome.**
Safety	
Safety **Certainty of evidence:** Not applicable	*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.* **No evidence was identified for this outcome.**

For CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation, what is the cost-effectiveness of testosterone monotherapy with or without psychological and psychosocial support compared to one or a combination of psychological support or social transitioning to the desired non-binary 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 non-binary and wish partial physical masculinisation that may benefit more from treatment with testosterone monotherapy than the wider population?

Subgroup	Evidence statement
	No evidence was identified regarding any subgroups of CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation that may benefit more from treatment with testosterone monotherapy than the wider population.

From the evidence selected:

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

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

c) **Did any children aged 15 years or younger receive testosterone monotherapy for gender transition? If so, in what circumstances?**

d) **What monitoring was in place for CYPs with gender incongruence who identify as non-binary and wish partial physical masculinisation receiving testosterone monotherapy?**

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

Outcome	Evidence statement
Definitions of gender incongruence	No evidence was identified to address the sub-questions about the criteria used by research studies to define gender incongruence, testosterone monotherapy dosing, monitoring arrangements and study exclusion criteria.
Testosterone dosing	
Testosterone for those <15 years	
Monitoring arrangements	
Study exclusion criteria	

6. Discussion

No evidence on the clinical effectiveness, safety or cost-effectiveness of testosterone monotherapy for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation was identified.

Searches were conducted on five databases for studies published between 01 January 2005 and 13 June 2025. Study designs considered for inclusion included systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies and case series. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints, guidelines, case reports and resource utilisation studies were not eligible for inclusion.

7. Conclusion

No evidence was identified that allowed any conclusions to be drawn about the clinical effectiveness, safety or cost-effectiveness of testosterone monotherapy compared with one or a combination of psychological support or social transitioning to the desired non-binary gender or no intervention, for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation. Published studies which allow conclusions to be drawn about the effectiveness of testosterone monotherapy 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 non-binary and wish partial physical masculinisation, what is the clinical effectiveness of treatment with testosterone monotherapy with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired non-binary gender or with no intervention?
2. For CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation, what is the short-term and long-term safety of testosterone monotherapy with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired non-binary gender or with no intervention?
3. For CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation, what is the cost-effectiveness of testosterone monotherapy with or without psychological and psychosocial support compared to one or a combination of psychological support or social transitioning to the desired non-binary gender or with no intervention?
4. From the evidence selected, are there particular sub-groups of CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation that may benefit more from treatment with testosterone monotherapy than the wider population?
5. From the evidence selected:
    a) What were the criteria used by the research studies to define gender incongruence?
    b) What were the starting criteria, formulation, duration and dose of testosterone monotherapy for those aged 16 years up to their 18th birthday?
    c) Did any children aged 15 years or younger receive testosterone monotherapy for gender transition? If so, in what circumstances?
    d) What monitoring was in place for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation receiving testosterone monotherapy?
    e) 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 non-binary and wish partial physical masculinisation. [Some terms used to describe this population include, but are not limited to, agender, gender fluid, non-binary transmasculine, transmasc, genderqueer, gender diverse, polygender, gender non-conforming, non-gender, transperson, transgender, transgendered, transexual, trans-sex, trans*, cross-gender, gender non-conforming non-binary (GNNB), trans-sex or cross-sex (alternate spellings may be considered). The term gender incongruence may also be referred to as, but is not limited to, gender dysphoria, gender identity disorder, gender dysfunction, gender diverse, gender questioning or transsexualism. 'Gender incongruence of childhood' is a diagnostic term used by health professionals, found in the WHO International Classification of Diseases ICD-11 characterised by a marked incongruence between an individual's experienced/expressed gender and the assigned sex in pre-pubertal children. It includes a strong desire to be a different gender than the assigned sex; a strong dislike on the child's part of his or her sexual anatomy or anticipated secondary sex characteristics and/or a strong desire for the primary and/or anticipated secondary sex characteristics that match the experienced gender; and make-believe or fantasy play, toys, games, or activities and playmates that are typical of the experienced gender rather than the assigned sex. The incongruence must have persisted for about 2 years (WHO, 2025). Gender variant behaviour and preferences alone are not a basis for assigning the diagnosis. 'Gender incongruence of adolescence or adulthood' is a diagnostic term used by health professionals, found in the WHO International Classification of Diseases ICD-11. Gender incongruence is characterised by "a marked and persistent incongruence between an individual's experienced gender and the assigned sex". It is important to note that it has been moved out of the "Mental and behavioural disorders" chapter and into the "Conditions related to sexual health" chapter so that it is not perceived as a mental health disorder. It does not include references to dysphoria or dysfunction. Gender dysphoria, within the section of gender identity disorders, is the term used in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) (American Psychiatric Association, 2022). In the DSM-5-TR definition, gender dysphoria has to be associated with clinically significant distress or impairment of function. Gender dysphoria is the more commonly used term clinically and among research papers. It is also most likely to be familiar to the lay public since it has been used widely in mainstream and social media. It is a label that is used colloquially to describe feelings, as well as being a formal diagnosis.] The following subgroups of CYP with gender incongruence are of interest: • Peri-pubertal vs post-pubertal • The stated duration of gender incongruence is either less than 6 months, 6-24 months or more than 24 months at time of assessment and/or treatment • The age of onset of gender incongruence • The age of onset of puberty • The age/ Tanner stage at which treatment was initiated with masculinising medicines

	• CYP with gender incongruence who have a preexisting diagnosis of neurodiversity • CYP with gender incongruence who have a preexisting diagnosis of a learning disability • CYP with gender incongruence with a history of severe enduring mental disorder including anxiety, depression (with or without a history of self-harm and suicidality), psychosis, personality disorder, and eating disorders.
I – Intervention	Masculinising medicines comprising testosterone monotherapy. Individuals taking masculinising medicines may also be receiving psychological or psychosocial support. [Masculinising medicines may be referred to as gender affirming hormones, cross sex hormones, sex reassignment, sex change, sex transformation, sex hormones, gender reassignment, gender change, gender transformation or gender hormones. Testosterone can be given an as intramuscular injection (IM), oral tablet or applied as a gel. Examples include: testosterone gel (Tostran, Testogel, Testim, Testavan), short-acting intramuscular injections such as testosterone propionate, phenypropionate, isocaproate and decanoate (Sustanon), testosterone enantate (Delatestryl) and long-acting injection testosterone undecanoate (Nebido, Roxadin, Aveed), oral testosterone capsules in the form of testosterone undecanoate (Restandol Testocaps, Andriol testocaps, Jatenzo, Kyzatrex, Tlando). 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 masculinising medicines. This PICO excludes individuals who are receiving or have received GnRH analogues for the indication of puberty suppression or gender affirmation.]
C – Comparator(s)	One or a combination of: 1. Psychological and psychosocial support 2. Social transitioning to the gender with which the individual identifies **OR** 3. No intervention [Psychological and psychosocial support include cognitive behavioural therapy (CBT), Psychoanalytic and Psychodynamic therapies, Humanistic and Existential Therapies, Interpersonal and Relational Therapies, Trauma-Focused Therapies, Arts and Expressive Therapies, mindfulness and self-compassion, attachment-based family therapy, attachment therapy, psychoeducation, gender exploratory therapy, exploratory therapy. • Examples of Cognitive and Behavioural Therapies include: Cognitive Behavioural Therapy (CBT), Dialectical Behaviour Therapy (DBT), Acceptance and Commitment Therapy (ACT), Exposure Therapy, Behaviour Therapy Examples of Psychoanalytic and Psychodynamic Therapies include: Psychoanalysis, Psychodynamic Therapy, Intensive short-

	term dynamic psychotherapy (ISTDP), sensorimotor psychotherapy • Examples of Humanistic and Existential Therapies include: Person-Centered Therapy (Carl Rogers), Gestalt Therapy, Existential Therapy • Examples of Interpersonal, Relational and Systemic Therapies include: Interpersonal Therapy (IPT), Couples Therapy, Family Therapy, Group Therapy, Narrative Therapy, Mentalisation-based Therapy, Dyadic Developmental Psychotherapy (DDP), Narrative exposure therapy • Examples of Trauma-Focused Therapies include: Eye Movement Desensitization and Reprocessing (EMDR), Trauma-Focused CBT (TF-CBT) • Examples of Mindfulness-Based Therapies include: Mindfulness-Based Stress Reduction (MBSR), Mindfulness-Based Cognitive Therapy (MBCT) • Examples of Arts and Expressive Therapies include: Art Therapy, Music Therapy, Drama Therapy, Play-based Therapy, Theraplay • Examples of Integrative and Holistic Therapies include: Integrative Therapy, integrative counselling • Examples of Specialised Therapies include: Compassion-Focused Therapy (CFT), Schema Therapy, Solution-Focused Brief Therapy (SFBT). Psychosocial support also includes: assessment, extended assessment, therapeutic assessment. These longer assessments allow exploration at a deeper level to seek understanding. Interventions can be delivered by psychological practitioners including Clinical and Counselling Psychologists, Psychotherapists, other healthcare professionals with additional training and supervision (e.g., specialist nurse or therapeutic social worker), trained facilitators or counsellors. Interventions can be delivered face to face or online, individually or in groups. Duration of intervention can range from a single session to having no fixed duration or number of sessions. No intervention may include individuals who actively choose not to take any interventions.]
O – Outcomes	**<u>Clinical Effectiveness</u>** *There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected.* *<u>Critical to decision-making:</u>* • **Impact on gender incongruence** *This outcome is important to patients because gender incongruence is associated with significant distress and problems functioning.* [This outcome may be measured using the Utrecht Gender Dysphoria Scale (UGDS), Gender Dysphoria Questionnaire, Gender Identity Interview for Adolescents and Adults, Gender Identity Interview for Children, Gender Distress Scale (TYC-GDS),

	Self-reported satisfaction. Other measures (including self-reported) may be used as an alternative to the stated measures.] • **Impact on mental health** *This outcome is important to patients because gender incongruence is associated with psychological distress which can lead to the development of mental health problems.* [Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, suicide, eating disorders, depression/low mood, anxiety, psychotic symptoms/psychosis, substance abuse, minority stress and trauma. This outcome may be measured using Child Behaviour Checklist (CBCL), Youth Self Report (YSR), Childhood Global Assessment Scale (CGAS), Revised Children's Anxiety and Depression Scale (and Subscales) (RCADS), The Child and Adolescent Psychiatric Assessment (CAPA), ED-15-Y eating disorder measure, Depression Anxiety Stress Scales (DASS-Y), Patient health questionnaire (PHQ-9) Modified for Teens, Beck Depression Inventory for Youth (BDI-Y), Beck Depression Inventory-II (BDI-II), Quick Inventory of Depressive Symptoms [QIDS], Generalised Anxiety Disorder Questionnaire (GAD-7), Hospital Anxiety and Depression Scale (HADS), Screen for Child Anxiety Related Emotional Disorders (SCARED), Ask Suicide Screening Questions (ASQ), Suicide Ideation Questionnaire Junior, Children's Rosenberg Self-Esteem Scale (CRSES), Clinical Outcomes in Routine Evaluation (CORE), Child Revised Impact of Events Scale 8 or 13 (CRIES 8 or 13), Dissociative Experiences Scale (DES), Assessment Checklist for Adolescents (ACA), Assessment Checklist for Children (ACC). Other measures (including self-reported) may be used as an alternative to the stated measures.] • **Impact on Quality of Life** *This outcome is important to patients because gender incongruence may be associated with a significant reduction in health-related quality of life.* [Quality of life can be measured using a recognised quality of life score for example KINDL questionnaire, Kidscreen 10/27/52, Pediatric Quality of Life Inventory (PedsQL), EuroQuality of Life Five Dimensions Youth (EQ-5D-Y/EQ-5D-3L/EQ-5D-5L), Satisfaction with Life Scale for Children (SWLS-C), Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF), General Well-Being Scale (GWBS). Other measures (including self-reported) may be used as an alternative to the stated measures.] *<u>Important to decision-making:</u>*

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

	• **Cognitive outcomes** *This outcome is important to patients because masculinising medicines can negatively impact cognitive processes such as concentration, memory, and executive function.* [Observations and cognitive testing are performed by a trained professional which may include a key worker, support worker, social care, social worker or through school observations. This might include assessment of visuospatial ability, verbal memory, verbal fluency, verbal reasoning, verbal comprehension, visual memory, working memory, processing speed, computation, motor coordination, executive functioning, timed task completion or cognitive flexibility. Measures can include Wechsler Intelligence Scale for Children (WISC), Wechsler Adult Intelligence Scale (WAIS), Adaptive Behaviours Assessment System (ABAS) or Wechsler Preschool and Primary Scale of Intelligence (WPPSI).] • **Detransition after receipt of masculinising medicines** *Medical detransition is a complex experience encompassing medical, psychological, social implications and is important to patients because they may choose to discontinue treatment. The decision to detransition may or may not be associated with regret.* [Detransitioning is a concept that has evolved over time. Older studies may incorporate terminology relating to retransition. Relevant terms in the literature may include: detransitioner, desistence, discontinuation, cessation, termination, reversion, reversal, disidentification, reidentification.] • **Regret after receipt of masculinising medicines** *This outcome is important to patients because some patients who choose to take masculinising medicines may regret this decision. Regret may or may not be associated with detransition.* [This may be expressed as a proportion of the study population or other measures such as documentation of regret or semi-structured interviews.] **<u>Safety</u>** *It is important to assess whether treatment causes acute side effects that may lead to withdrawing the treatment or long-term effects that may impact on decisions for transitioning.* • Aspects to be reported could include: ○ Of most importance: Thromboembolic disease, cardiovascular events, polycythaemia, pulmonary oil microembolism.

	○ Pre-diabetes (glycosylated haemoglobin (HbA1c) 42mmol/mol – 47mmol/mol, 6% vs 6.4%) or diabetes (HbA1c ≥48mmol/mol, ≥6.5%) and for those with diabetes, worsening control e.g. increase in HbA1c despite treatment or as defined in study, anaemia, breast, ovarian or endometrial cancer, migraine, seizures, impaired liver function, sleep apnoea, sexually transmitted infections, gynaecomastia, skin reactions, severe acne. **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, the Cochrane Library and the TRIPdatabase were searched limiting the search to papers published in the English language in the last 20 years. Searches were not limited by hormone type (masculinising / feminising); 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 13 June 2025 with an updated Medline search on 29 July 2025.

Medline search strategy (updated 29 July 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	1 or 2 or 3 or 4 or 5 or 6
8	Gender-Nonconforming Persons/
9	((gender* adj3 (incongruen* or non-binary or nonbinary or non-conform* or nonconform* or divers* or ambig* or fluid* or fluctuat* or queer*)) or genderqueer or polygender* or poly-gender* or agender* or androgyne? or enby or gnnb or masculine wom?n or masculine female? or transfem* or feminine m?n or feminine male? or transmasc* or third gender or 3rd gender).ti,ab,kf. or transgender*.ti,kf.
10	(gender identity and (incongruen* or non-binary or nonbinary or non-conform* or nonconform* or divers* or ambig* or fluid* or fluctuat* or queer*)).ti,ab,kf.
11	8 or 9 or 10
12	((masculini?ing or femini?ing) adj2 (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.
13	((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.
14	(gender adj2 (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.
15	((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.
16	((cross-sex adj hormon*) or (hormon* adj (therap* or treatment? or "use" or usage or supplement*))).ti,ab,kf.
17	Hormone Replacement Therapy/ or Estrogen Replacement Therapy/
18	Estrogens/tu

19 estradiol/tu

20 Ethinyl Estradiol/

21 (oestrogens or estrogens).ti,kf.

22 ((oestrogen? or estrogen?) adj3 (drug? or medicine? or medication? or agent? or therap* or treatment? or "use" or usage or supplement*)).ti,ab,kf.

23 ((oestrogen? or estrogen?) adj3 (oral* or buccal* or sublingual* or sub-lingual* or pellet? or implant* or patch* or spray* or gel? or cream? or dermal* or transdermal or subcutaneous or sub-cutaneous or inject* or intramuscular or intra-muscular)).ti,ab,kf.

24 (oestradiols or estradiols or ethinylestradiols or oestriols or estriols).ti,kf.

25 ((oestradiol or estradiol or ethinylestradiol or oestriol or estriol) adj3 (drug? or medicine? or medication? or agent? or therap* or treatment? or "use" or supplement*)).ti,ab,kf.

26 ((oestradiol or estradiol or ethinylestradiol or oestriol or estriol) adj3 (oral* or buccal* or sublingual* or sub-lingual* or pellet? or implant* or patch* or spray* or gel? or cream? or dermal* or transdermal or subcutaneous or sub-cutaneous or inject* or intramuscular or intra-muscular)).ti,ab,kf.

27 (zumenon or delestrogen* or sandrena or oestrogel or evorel or estradot or oestraderm or estraderm or progynova or ts patch* or femseven or fem seven or lenzetto or estraor or Elleste Solo or Bedol).ti,ab,kf.

28 Hormone Replacement Therapy/

29 exp Testosterone/tu

30 (testosterone adj3 (drug? or medicine? or medication? or agent? or therap* or treatment? or "use" or usage or supplement*)).ti,ab,kf.

31 (testosterone adj3 (capsule? or tablet? or oral* or buccal* or sublingual* or sub-lingual* or pellet? or implant* or patch* or spray* or gel? or cream? or dermal* or transdermal or subcutaneous or sub-cutaneous or inject* or intramuscular or intra-muscular)).ti,ab,kf.

32 (testosterone adj (isocaproate or undecanoate or enantate)).ti,ab,kf.

33 (tostran or testogel or testavan or sustanon or Testim or Delatestryl or Nebido or Roxadin or Aveed or Restandol Testocaps or Andriol testocaps or Jatenzo or Kyzatrex or Tlando).ti,ab,kf.

34 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35 7 and 11 and 34

36 (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.

37 35 not 36

38 limit 37 to (english language and yr="2005 -Current")

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

40 38 not 39

41 ("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.

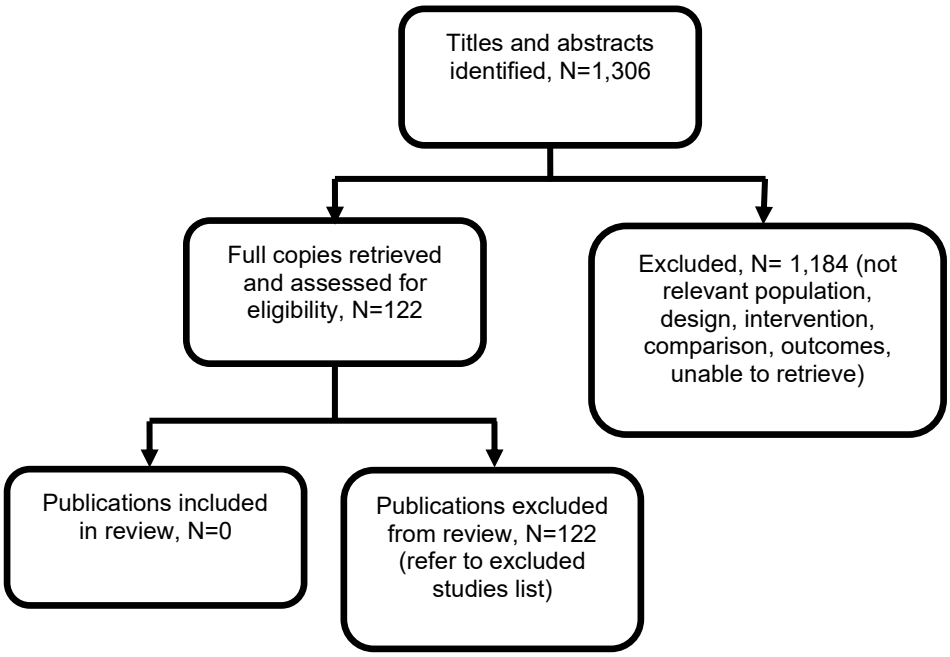
42 38 and 41

43 40 or 42

Appendix C Evidence selection

The literature searches identified 1,306 references. These were screened using their titles and abstracts and 123 references were obtained in full text and assessed for relevance. Of these, 0 papers are included in the evidence summary. The remaining 123 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
Achille C, Taggart T, Eaton NR, Osipoff J, Tafuri K, Lane A, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. Int J Pediatr Endocrinol. 2020;2020:8.	No mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary
Alaniz VI, Sheeder JL, Whitmore GT, Wilde MD, Hutchens KJ, Nokoff NJ, et al. Menstrual Suppression in Adolescent and Young Adult Transgender Males. J Pediatr Adolesc Gynecol. 2023;36(2):116-21.	Only 8 of 220 participants identified as non-binary. No results reported specifically for the non-binary group.
Allen LR, Watson LB, Egan AM, Moser CN. Well-being and suicidality among transgender youth after gender-affirming hormones. Special Issue: Advancing the Practice of Pediatric Psychology With Transgender Youth. 2019;7(3):302-11.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary. The authors state that "Unfortunately, our study did not make any distinction among participants for non-binary gender identities and classified participants based upon sex assigned at birth."
Andrzejewski J, Dunville R, Johns MM, Michaels S, Reisner SL. Medical Gender Affirmation and HIV and Sexually Transmitted Disease Prevention in Transgender Youth: Results from the Survey of Today's Adolescent Relationships and Transitions, 2018. LGBT health. 2021;8(3):181-9.	No information about which gender affirmation treatment (eg testosterone, GnRH analogues, surgery, etc) patients received, just whether they accessed gender affirmation services or not. Also, 25.6% were non-binary but not clear if AFAB or AMAB and results were reported for the full non-binary cohort, not separately for the cohort that were non-binary and AFAB. Also, average age of participants was 19.1 years for the whole study cohort – average age was not reported separately for the non-binary group or for the group that received treatment with testosterone.
Arcelus J, Claes L, Witcomb GL, Marshall E, Bouman WP. Risk Factors for Non-Suicidal Self-Injury Among Trans Youth. J Sex Med. 2016;13(3):402-12.	No mention of non-binary or suggestion that patients might identified as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary. Also, mean age of participants was 19.9 years, so the majority of the population was out of scope (>18 years of age). Insufficient detail was provided to be able to extract results for the population and intervention in-scope.
Arnoldussen M, Hooijman EC, Kreukels BP, de Vries AL. Association between pre-treatment IQ and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents. Clinical Child Psychology and Psychiatry. 2022;27(4):1069-76.	The authors state that "During data collection, people were not specifically asked if they identified outside the gender binary." Therefore no results were reported specifically for the non-binary population. Also, wording suggests that an unknown % had received puberty suppression.

Study Reference	Reason for exclusion
Ascha M, Sasson DC, Sood R, Cornelius JW, Schauer JM, Runge A, et al. Top Surgery and Chest Dysphoria Among Transmasculine and Nonbinary Adolescents and Young Adults. Jama, Pediatr. 2022;176(11):1115-22.	16% of the population were non-binary or "other" gender identity. The paper reports that subgroup analysis for the non-binary group was not possible due to small sample size. Also, the average age of the total cohort was 18.6 years. Results were presented for <18s separately but not separately for the non-binary group which was a minority of the total cohort.
Avila JT, Golden NH, Aye T. Eating Disorder Screening in Transgender Youth. J Adolesc Health. 2019;65(6):815-7.	12 participants were non-binary and results were reported separately for them, but of the 12 participants, 2 were AFAB treated with testosterone and 10 were AMAB of whom 0 were treated with oestrogen. Results were reported only for the full non-binary group of 12 patients, and the majority of the non-binary population was out of scope. No separate results were reported for the 2 AFAB non-binary individuals treated with testosterone.
Baines HK, Connelly KJ. A prospective comparison study of subcutaneous and intramuscular testosterone injections in transgender male adolescents. J Pediatr Endocrinol Metab. 2023;36(11):1028-36.	Only mention of non-binary is "To our knowledge, this study is the first to publish serum testosterone levels based on this lower dosing plan and contributes to data that may benefit non-binary and gender fluid youth." There was no indication that any of, or the majority of, the population in the study identified as non-binary, hence exclude.
Baram S, Myers SA, Yee S, Librach CL. Fertility preservation for transgender adolescents and young adults: a systematic review. Hum Reprod Update. 2019;25(6):694-716.	The only specific result reported for a non-binary person was a case report from a study of adults. Hence the study population is not in-scope. Also, for the studies where sufficient data were reported, patients on average started testosterone treatment at >18 years of age.
Baskaran C, Roberts SA, Barrera E, Pilcher S, Kumar R. Venous thromboembolism in transgender and gender non-binary youth is rare and occurs in the setting of secondary risk factors: A retrospective cohort study. Pediatr Blood Cancer. 2024;71(11):e31284.	2 of 8 who were AFAB and had congenital thrombophilia were reported to identify as non-binary. Both were treated with northethindrone (a progestin) and there was no mention of them being treated with testosterone ie intervention was out of scope.
Bechard M, VanderLaan DP, Wood H, Wasserman L, Zucker KJ. Psychosocial and Psychological Vulnerability in Adolescents with Gender Dysphoria: A "Proof of Principle" Study. J Sex Marital Ther. 2017;43(7):678-88.	Describes the characteristics of adolescents at baseline when none had had either GnRH analogues or GAHT - none of the patients had had the in-scope intervention. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population were non-binary and because no in-scope intervention was received.
Becker I, Auer M, Barkmann C, Fuss J, Moller B, Nieder TO, et al. A Cross-Sectional Multicenter Study of Multidimensional Body Image in Adolescents and Adults with Gender Dysphoria Before and After Transition-Related Medical Interventions. Arch Sex Behav. 2018;47(8):2335-47.	62 AFAB adolescents of whom only 6 had had treatment with testosterone monotherapy. The rest had had no treatment or surgery or GnRH analogues with or without testosterone - hence the intervention for the majority of patients was out of scope. Results were not reported separately for the in-scope group.

Study Reference	Reason for exclusion
	Also, results were presented combined for AFAB and AMAB, adolescents and adults, and the majority of the population were out of scope. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population were non-binary. The authors stated that *"Gender grouping assumed a binary understanding of the division of gender into male (FtM) and female (MtF individuals) without considering possible non-binary identification."*
Becker-Hebly I, Fahrenkrug S, Campion F, Richter-Appelt H, Schulte-Markwort M, Barkmann C. Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: a descriptive study from the Hamburg Gender Identity Service. Eur Child Adolesc Psychiatry. 2021;30(11):1755-67.	The authors report that "the present study represents only two gender groups of adolescents reporting body-related dysphoria and treatment wishes who fulfilled diagnostic criteria for GD. However, future longitudinal studies should address transgender experiences that involve more diverse responses and reactions to the body as well as other gender identifications, e.g., non-binary". Exclude as nothing to suggest that any of the population identified as non-binary. Also, reports results combined for 28 transmasculine plus 4 transfeminine individuals who had had GnRH analogues and GAHT. It is not clear if any patients had been treated with testosterone monotherapy as per the PICO specification for this review - it is not clear that the intervention is in-scope.
Biedermann SV, Asmuth J, Schroder J, Briken P, Auer MK, Fuss J. Childhood adversities are common among trans people and associated with adult depression and suicidality. J Psychiatr Res. 2021;141:318-24.	No information was reported about which hormones were used (eg testosterone, oestrogen, GnRH analogues) and includes AFAB and AMAB populations (94 transfeminine and 93 transmasculine). Results were not reported separately for the AFAB population treated with testosterone monotherapy. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Boogers LS, Wiepjes CM, Staphorsius AS, Klink DT, Ciancia S, Romani A, et al. A European Network for the Investigation of Gender Incongruence in adolescents. J Sex Med. 2024;21(4):350-6.	Only 3 of 121 were AFAB and non-binary. No outcome data have been reported yet - the paper is about the study design and protocol.
Borger O, Perl L, Yackobovitch-Gavan M, Sides R, Brener A, Segev-Becker A, et al. Body Composition and Metabolic Syndrome Components in Transgender/Gender Diverse Adolescents and Young Adults. LGBT health. 2024;11(5):359-69.	No mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest how many of the population identified as non-binary - assume the majority were binary.
Boskey ER, Jolly D, Tabaac AR, Ganor O. Behavioral health concerns and eligibility factors among adolescents and young adults seeking	25 of 158 patients were non-binary Mental health and psychosocial outcomes (nicotine and marijuana use) were reported for the whole

Study Reference	Reason for exclusion
gender-affirming masculinizing top surgery. LGBT health. 2020;7(4):182-9.	group (158). The odds ratio of having each condition for the non-binary group compared to transmen was also reported. However, no absolute results were reported for the non-binary group and the comparison with the binary group is out of scope (in-scope comparison is with non-binary patients who were not treated with testosterone). Also, the non-binary group were less likely to have been treated with testosterone compared to the whole binary/non-binary population (odds ratio 6.7; adjusted odds ratio 9.2). The number on testosterone in the non-binary group was not reported but likely to be <50% given that 82% of the whole cohort were treated with testosterone. Hence exclude as the majority are likely not to have had the in-scope intervention.
Boskey ER, Scheffey KL, Pilcher S, Barerra EP, McGregor K, Carswell JM, et al. A Retrospective Cohort Study of Transgender Adolescents' Gender-Affirming Hormone Discontinuation. J Adolesc Health. 2025;76(4):584-91.	Results were presented for the non-binary group but were not reported separately for those that were AFAB vs AMAB, and treatment was reported as GAHT rather than testosterone. Exclude because there were no results reported specifically for the population of interest who were treated with testosterone monotherapy.
Burke SM, Kreukels BP, Cohen-Kettenis PT, Veltman DJ, Klink DT, Bakker J. Male-typical visuospatial functioning in gynephilic girls with gender dysphoria - organizational and activational effects of testosterone. J Psychiatry Neurosci. 2016;41(6):395-404.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary. Also, wording suggests that all patients had had puberty suppression prior to testosterone treatment. "Methods: Girls with GD underwent fMRI while performing the MRT twice: when receiving medication to suppress their endogenous sex hormones before onset of testosterone treatment, and 10 months later during testosterone treatment." Hence exclude because intervention was not in-scope.
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.	Provides discontinuation numbers for each age group for AFAB but no mention of how many patients were treated with testosterone vs GnRH analogues. Also, no mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest how many of the population identified as non-binary - assume the majority were binary.
Cantu AL, Moyer DN, Connelly KJ, Holley AL. Changes in Anxiety and Depression from Intake to First Follow-Up Among Transgender Youth in a Pediatric Endocrinology Clinic. Transgend Health. 2020;5(3):196-200.	7 of 80 were non-binary but not clear if AFAB or AMAB. 25 of the 80 had GAHT without GnRH analogues but not clear how many of these were AFAB and non-binary. No results reported specifically for non-binary AFAB group, and this group did not make up the majority of the total cohort

Study Reference	Reason for exclusion
	Exclude because no results reported for population of interest.
Carrillo N, McGurran M, Melton BL, Moeller KE. Comparison of inpatient psychiatric medication management in gender diverse youth with cisgender peers. Ment. 2023;13(4):169-75.	No mention of the number that were non-binary. Subgroup analysis on use of GAHT was specifically reported to have excluded non-binary patients.
Carroll R, Sepulveda B, McLeod L, Stephenson C, Carroll RW. Characteristics and gender affirming healthcare needs of transgender and non-binary students starting hormone therapy in a student health service in Aotearoa New Zealand. J Prim Health Care. 2023;15(2):106-11.	No patients were <18 years at time of study and the majority (76%) were between 18 and 22 years when GAHT started - hence out of scope. No separate results for those that started GAHT at <18 years of age, if any. Also, the paper reports pathways and interventions used but not outcomes.
Catlow C, Goffin S, Cunningham V, Abraham A, Grant C. The Health Needs and Management of Young People Accessing Paediatric Hauora Tahine (Transgender Health) Services in Te Tai Tokerau. J Paediatr Child Health. 2025;23:23.	13 of 45 patients had gender reported as "other" which may have meant non-binary. Of these, given the numbers that were transmale and transfemale and assigned female vs assigned male at birth, it is likely that 12 were assigned female at birth and identified as possibly non-binary. 11 of the total 45 patients received GAHT, either testosterone or oestrogen. No information was reported as to how many were treated with testosterone or how many of the non-binary group were treated with testosterone - exclude because population in-scope not known and could have been 0.
Cavve BS, Bickendorf X, Ball J, Saunders LA, Thomas CS, Strauss P, et al. Reidentification With Birth-Registered Sex in a Western Australian Pediatric Gender Clinic Cohort. Jama, Pediatr. 2024;178(5):446-53.	Majority (163 of 196) of the whole study population had had treatment with GnRH analogues (not clear what this % was for the AFAB population). Hence the intervention was not in-scope. Also, no results were reported specifically for the non-binary group, and the majority of the total cohort was not reported to be non-binary - hence exclude.
Chelliah P, Lau M, Kuper LE. Changes in Gender Dysphoria, Interpersonal Minority Stress, and Mental Health Among Transgender Youth After One Year of Hormone Therapy. J Adolesc Health. 2024;74(6):1106-11.	62.6% identified as male/boy/guy, and only a minority were reported to be non-binary. No results were reported specifically for the non-binary group.
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.	Only 6% of total of 316 patients were non-binary and it is not clear if they were AFAB or AMAB. No results were reported specifically for the non-binary group (or non-binary AFAB group).
Chen D, Berona J, Chan YM, Ehrensaft D, Garofalo R, Hidalgo MA, et al. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. N Engl J Med. 2023;388(3):240-50.	Numbers indicate that 14 of 315 were non-binary AFAB. Results were reported only for the whole study cohort and no results were reported specifically for the non-binary group.

Study Reference	Reason for exclusion
Chen D, Simons L, Johnson EK, Lockart BA, Finlayson C. Fertility Preservation for Transgender Adolescents. J Adolesc Health. 2017;61(1):120-3.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary. Also, not enough information to know how many were AFAB and on testosterone treatment without GnRH analogues. Also, none of the reported outcomes were in-scope (reports use of fertility preservation procedures, not fertility outcomes).
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):1-18.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Chu L, Gold S, Harris C, Lawley L, Gupta P, Tangpricha V, et al. Incidence and Factors Associated With Acne in Transgender Adolescents on Testosterone: A Retrospective Cohort Study. Endocr Pract. 2023;29(5):353-5.	No mention of non-binary or suggestion that any of the patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Cipres DT, Shim JY, Grimstad FW. Postoperative Vaginal Bleeding Concerns after Gender-Affirming Hysterectomy in Transgender Adolescents and Young Adults on Testosterone. J Pediatr Adolesc Gynecol. 2023;36(1):33-8.	All patients were >18 years of age. Not clear at what age testosterone treatment was started. All had had hysterectomy as well as testosterone, hence intervention out of scope. No mention of non-binary or suggestion that any of the patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
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.	49 of 129 AFAB individuals were reported to identify as non-binary. Average age of the full cohort of 150 indiduals (AFAB plus AMAB) was 18.6 years. The average age of starting testosterone treatment / for the AFAB group was not reported separately. Reports a single person with regret re starting testosterone but that person started testosterone as an adult. (It was not reported whether that person was non-binary). Exclude because average age of the whole cohort was >18 years and no data to suggest that the non-binary AFAB cohort were <18 years when they started testosterone treatment.
Dopp AR, Peipert A, Buss J, De Jesus-Romero R, Palmer K, Lorenzo-Luaces L. Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. Rand health q. 2025;12(2):2.	No results reported specifically for the non-binary population. In addition, the authors reported that "samples tended to be mostly youth with binary transgender male or female identities, but some non-binary and other gender-expansive youth were included" and "Across outcomes, serious concerns with

Study Reference	Reason for exclusion
	indirectness include … a focus on patients with binary gender identities …" and "Regarding gender identity, non-binary youth were often not included or represented only a small subset of study participants ... and only a few studies reported the proportion of other gender-expansive identities in the sample. Within the diversity of gender identities, studies of transitions beyond binary male or female identities are lacking". Hence exclude because there was no indication that the majority of included patients were non-binary.
Elkadi J, Chudleigh C, Maguire AM, Ambler GR, Scher S, Kozlowska K. Developmental Pathway Choices of Young People Presenting to a Gender Service with Gender Distress: A Prospective Follow-Up Study. Children (Basel). 2023;10(2):07.	One 17 year old who had had GAHT was reported as non-binary but they had had prior GnRH analogue treatment so were not in-scope. Whether any individuals had had only GAHT without GnRH analogue treatment and were non-binary was not reported.
Feigerlova E. Prevalence of detransition in persons seeking gender-affirming hormonal treatments: a systematic review. J Sex Med. 2025;22(2):356-68.	No results were reported specifically for the non-binary population. The authors reported that "The studies varied in how authors defined detransition, and it was not clear whether individuals identified as non-binary were excluded."
Gavidia R, Whitney DG, Hershner S, Selkie EM, Tauman R, Dunietz GL. Gender identity and transition: relationships with sleep disorders in US youth. J Clin Sleep Med. 2022;18(11):2553-9.	82.3% were over 18 years of age and no results were reported specifically for those aged <18 years. Exclude because population out of scope in terms of age. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Gawlik A, Antosz A, Kasparek K, Nowak Z, Grabski B. Gender confirmation hormonal treatment use in young Polish transgender binary and non-binary persons. Endokrynol Pol. 2022;73(6):922-7.	31 patients were non-binary AFAB. In the whole AFAB group (binary and non-binary), 7% started testosterone before age 18 years ie the majority started testosterone treatment at over 18 years of age. Hence population out of scope in terms of age. Not clear that any of the 31 non-binary AFAB participants started using testosterone before 18 years of age (possible that 1 patient may have done so but case reports of n=1 are not in-scope).
Glintborg D, Moller JK, Rubin KH, Lidegaard O, T'Sjoen G, Larsen MJO, et al. Gender-affirming treatment and mental health diagnoses in Danish transgender persons: a nationwide register-based cohort study. Eur. 2023;189(3):336-45.	No mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest how many of the population identified as non-binary - assume majority were binary. Also, average age at index date (date of transgender diagnosis) of AFAB group was 19 years and average duration of follow-up before starting GAHTs was 1.8 years for AFAB group. Hence exclude because on average patients commenced treatment at over 18 years of age.

Study Reference	Reason for exclusion
Grannis C, Mattson WI, Leibowitz SF, Nahata L, Chen D, Strang JF, et al. Expanding upon the relationship between gender-affirming hormone therapy, neural connectivity, mental health, and body image dissatisfaction. Psychoneuroendocrinology. 2023;156:106319.	No results specifically for non-binary group, and the majority of the total cohort was not reported to be non-binary. Only one of the patients who were AFAB and treated with testosterone was non-binary (described as "binary and non-binary". Supplementary information concurs that there was only one non-binary "gender nonconforming" individual among the AFAB group treated with GAHT and no results were reported specifically for that person. In addition, the PICO specification for this review excludes studies with n=1 (case reports).
Green AE, DeChants JP, Price MN, Davis CK. Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. J Adolesc Health. 2022;70(4):643-9.	For the <18 year age group who were on GAHT, 42 of 274 (15.3%) were non-binary but there was no indication about whether they were AFAB or AMAB or what the hormone treatment was eg testosterone vs oestrogen, hence not enough information to know that the population / intervention were in-scope.
Grimstad F, Kremen J, Shim J, Charlton BM, Boskey ER. Breakthrough Bleeding in Transgender and Gender Diverse Adolescents and Young Adults on Long-Term Testosterone. J Pediatr Adolesc Gynecol. 2021;34(5):706-16.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Gupta P, Patterson BC, Chu L, Gold S, Amos S, Yeung H, et al. Adherence to Gender Affirming Hormone Therapy in Transgender Adolescents and Adults: A Retrospective Cohort Study. J Clin Endocrinol Metab. 2023;108(11):e1236-e44.	Results reported separately for the paediatric cohort who were AFAB but the authors reported that "As the number of non-binary individuals was extremely small, we did not present the results for binary vs non-binary gender identities". It was not possible to glean any results specifically for the non-binary <18 years of age cohort of interest from the text.
Harrison DJ, Prada F, Nokoff NJ, Iwamoto SJ, Pastor T, Jacobsen RM, et al. Considerations for Gender-Affirming Hormonal and Surgical Care Among Transgender and Gender Diverse Adolescents and Adults With Congenital Heart Disease. J Am Heart Assoc. 2024;13(3):e031004.	Of the 21 who had had some gender affirming treatment (hormones or surgery), only 4 were reported to be non-binary, gender fluid, etc and it was not clear if these individuals were AFAB or AMAB or if they had had testosterone treatment. No results were reported specifically for the non-binary group.
Hewitt JK, Paul C, Kasiannan P, Grover SR, Newman LK, Warne GL. Hormone treatment of gender identity disorder in a cohort of children and adolescents. Med J Aust. 2012;196(9):578-81.	21 patients of whom 8 were AFAB and 4 of those received hormone treatment (GAHT and/or GnRH analogues). Only 2 patients of all AFAB and AMAB patients received only GAHT (without GnRH analogues). The number of patients that were AFAB and received testosterone monotherapy was not reported and could have been 0, 1 or 2. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Hisle-Gorman E, Schvey NA, Adirim TA, Rayne AK, Susi A, Roberts TA, et al. Mental Healthcare	Average age of starting GAHT or puberty suppression was 18.1 years - not <18 years as per

Study Reference	Reason for exclusion
Utilization of Transgender Youth Before and After Affirming Treatment. J Sex Med. 2021;18(8):1444-54.	the PICO specification for this review (average age not reported separately for the group that were treated with testosterone without puberty suppression). Results presented for all TGD patients together, not separately for the AFAB group (though adjusted for sex assigned at birth). No mention of non-binary or suggestion that any patients might identify as non-binary. Exclude as nothing to suggest that any of the population were non-binary
Hranilovich JA, Millington K. Headache prevalence in transgender and gender diverse youth: A single-center case-control study. Headache. 2023;63(4):517-22.	No mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest that any of the population were non-binary
Hughes LD, Charlton BM, Berzansky I, Corman JD. Gender-Affirming Medications Among Transgender Adolescents in the US, 2018-2022. JAMA Pediatr. 2025;179(3):342-4.	The paper is marked as a letter. Letters are not in-scope. No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population were non-binary. Outcomes reported are numbers of people who identified as transgender and gender diverse between 8 and 17 years old receiving pubertal suppression and GAHT per 100,000 adolescents - no outcome of interest reported.
Jensen RK, Jensen JK, Simons LK, Chen D, Rosoklija I, Finlayson CA. Effect of Concurrent Gonadotropin-Releasing Hormone Agonist Treatment on Dose and Side Effects of Gender-Affirming Hormone Therapy in Adolescent Transgender Patients. Transgend Health. 2019;4(1):300-3.	Excluded one patient who was non-binary due to a different dose of testosterone used and there was no suggestion that any other patients identified as non-binary. Exclude as nothing to suggest that any of the population were non-binary.
Kain EJ, Fuqua JS, Eugster EA. A Retrospective Study of the Use of Gonadotropin-Releasing Hormone Analogs and Testosterone in Transgender Boys: Who, What, When, and for How Long? Transgend Health. 2024;9(4):357-60.	No mention of non-binary or suggestion that patients might be non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Kaltiala R, Heino E, Tyolajarvi M, Suomalainen L. Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. Nord J Psychiatry. 2020;74(3):213-9.	11 transfeminine and 41 transmasculine individuals referred at <18 years of age. No information reported about age of starting hormones or how many had been treated with GnRH analogues. For transmasculine and transfeminine individuals together, average age "at diagnosis" was 18.1 years (age for transmasculine individuals was not reported separately) so likely to have been on average >18 years old when starting testosterone, ie not in-scope. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population were non-binary.

Study Reference	Reason for exclusion
Kanj RV, Conard LAE, Corathers SD, Trotman GE. Hormonal contraceptive choices in a clinic-based series of transgender adolescents and young adults. Int J Transgend. 2019;20(4):413-20.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Karakilic Ozturan E, Ozturk AP, Bas F, Erdogdu AB, Kaptan S, Kardelen AI AD, et al. Endocrinological Approach to Adolescents with Gender Dysphoria: Experience of a Pediatric Endocrinology Department in a Tertiary Center in Turkey. J Clin Res Pediatr Endocrinol. 2023;15(3):276-84.	No mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest that any of the population were non-binary Also, of 15 AFAB patients, 13 had GnRH analogues and 9 had GAHT. Exclude because majority had GnRH analogue treatment.
Karalexi MA, Georgakis MK, Dimitriou NG, Vichos T, Katsimpris A, Petridou ET, et al. Gender-affirming hormone treatment and cognitive function in transgender young adults: a systematic review and meta-analysis. Psychoneuroendocrinology. 2020;119:104721.	No mention of non-binary or suggestion that patients might be non-binary. Exclude as nothing to suggest that any of the population identified as non-binary. The authors state that "gender non-binary or gender non-conforming individuals who do not identify as transgender were absent from to-date published literature" and "further gender-affirming research should focus on the effects on younger transgender individuals, as well as on the full spectrum of diversity in gender identity and gender expression beyond the binary to allow assessment of the potential health-related issues along the entire gender spectrum."
Katz-Wise SL, Williams DN, Keo-Meier CL, Budge SL, Pardo S, Sharp C. Longitudinal associations of sexual fluidity and health in transgender men and cisgender women and men. Psychology of Sexual Orientation and Gender Diversity. 2017;4(4):460-71.	Mean age 25.5 years and no separate results reported for those <18 years of age. Hence exclude because population out of scope in terms of age. Also, the paper is about fluidity in sexual attractions and orientation which is not an in-scope outcome
Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. J Pediatr. 2014;164(4):906-11.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
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.	No mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest how many of the population were non-binary - assume majority binary. Also, number receiving testosterone was a minority and was not clear and no separate results were reported for those treated with testosterone (results reported were combined for testosterone and oestrogen treatment).
Kramer R, Aarnio-Peterson CM, Conard LA, Lenz KR, Matthews A. Eating disorder symptoms among transgender and gender diverse youth. Clin. 2024;29(1):30-44.	The 3 individuals who were non-binary were excluded from the analysis because of "low sample size". No separate results were reported for the 3 non-binary patients.
Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. Pediatrics. 2020;145(4):04.	148 patients of whom 81 identified as male and 9 as "male spectrum" and 3 as "something else". So possibly 12 non-binary AFAB individuals out of 148. Results only reported for the whole group of 148 patients combined and not separately for the non-binary group.

Study Reference	Reason for exclusion
	93 of 148 had GAHT only but it was not clear how many were AFAB and treated with testosterone. ie information on intervention was not clear.
Kyinn M, Banks K, Leemaqz SY, Sarkodie E, Goldstein D, Irwig MS. Weight gain and obesity rates in transgender and gender-diverse adults before and during hormone therapy. Int J Obes (Lond). 2021;45(12):2562-9.	Non-binary individuals treated with testosterone were grouped with other transmasculine patients. No results were reported specifically for the non-binary group and there was no indication of the % of the transmasculine group that were non-binary so assume non-binary were a minority. Also, average age of transmasculine patients was 26.1 years with longest duration of testosterone treatment <5 years. So average age of starting testosterone would have been >18 years, not <18 years as specified in the PICO specification for this review.
Lagrange C, Brunelle J, Poirier F, Pellerin H, Mendes N, Mamou G, et al. Clinical profiles and care of transgender children and adolescents in a specialized consultation in Ile-de-France. Neuropsychiatrie de l'Enfance et de l'Adolescence. 2023;71(5):270-80.	68% of patients (162 of 239) were AFAB. Of the total AFAB and AMAB, 19 were non-binary and 14 "questioned their gender", suggesting that the majority of AFAB were binary. No results reported specifically for the non-binary group. Also, 46.9% of AFAB patients had GAHT and results were not reported separately for the treated group.
Laurenzano SE, Newfield RS, Lee E, Marinkovic M. Subcutaneous Testosterone Is Effective and Safe as Gender-Affirming Hormone Therapy in Transmasculine and Gender-Diverse Adolescents and Young Adults: A Single Center's 8-Year Experience. Transgend Health. 2021;6(6):343-52.	Only 2.5% of participants were non-binary and no separate results were reported for the non-binary group.
Lee MK, Yih Y, Willis DR, Fogel JM, Fortenberry JD. The impact of gender affirming medical care during adolescence on adult health outcomes among transgender and gender diverse individuals in the United States: The role of state-level policy stigma. LGBT health. 2024;11(2):111-21.	Average age of patients was >18 years. Also, no indication in the results that patients were non-binary or the proportion that identified as non-binary. Exclude as nothing to suggest that the majority of the population identified as non-binary.
Lopez de Lara D, Perez Rodriguez O, Cuellar Flores I, Pedreira Masa JL, Campos-Munoz L, Cuesta Hernandez M, et al. Psychosocial assessment in transgender adolescents. An Pediatr (Engl Ed). 2020;93(1):41-8.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary. Also, not clear if patients were treated with testosterone monotherapy and there was a suggestion in the text that patients received GnRH analogues prior to testosterone treatment.
Ma J, Ackley D, III, Reback CJ, Rusow JA, Skeen SJ, Miller-Perusse M, et al. Psychosocial correlates of gender-affirming hormone and medically necessary surgical intervention use among transgender and gender diverse youth and young adults. Psychology of Sexual Orientation and Gender Diversity. 2025:No Pagination Specified.	Outcomes (eg depression and gender congruence) were reported by treatment (hormones, surgery, both or neither). But only one hormone treated patient was <18 years of age and case reports are excluded in the PICO specification for this review. Also, not clear if that one patient identified as non-binary AFAB (37 of 75 hormone treated patients were reported to be "genderqueer", "other" or

Study Reference	Reason for exclusion
	"agender" and it is not clear what age or biological gender those patients were).
MacKinnon KR, Jeyabalan T, Strang JF, Delgado-Ron JA, Lam JS, Gould WA, et al. Discontinuation of gender-affirming medical treatments: Prevalence and associated features in a nonprobabilistic sample of transgender and gender-diverse adolescents and young adults in Canada and the United States. J Adolesc Health. 2024;75(4):569-77.	Unable to confirm that the population (or the majority of the population) is in-scope: between 24% and 100% of non-binary patients were AFAB and did not receive puberty suppression. Also, insufficient information to confirm that patients started testosterone treatment before 18 years of age (average age at survey was 21.1 years and no information reported on duration of GAHT).
Martinez-Martin FJ, Kuzior A, Hernandez-Lazaro A, de Leon-Durango RJ, Rios-Gomez C, Santana-Ojeda B, et al. Incidence of hypertension in young transgender people after a 5-year follow-up: association with gender-affirming hormonal therapy. Hypertens Res. 2023;46(1):219-25.	Average age was 20.2 years, not <18 years, and not clear how long patients had had testosterone treatment for. Also, no mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest that any of the population were non-binary
Marwa A, Misra M, Lopez X. Determinants of Bone Mineral Density in Transgender Youth. Transgend Health. 2022;7(3):213-8.	Reports bone mineral density measures for people who had had GnRH analogues and/or GAHT. No results separately for those only treated with GAHT. Also, no mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest how many of the population were non-binary – assume the majority were binary.
Masic U, Butler G, Carruthers P, Carmichael P. Trajectories of transgender adolescents referred for endocrine intervention in England. Arch Dis Child. 2022;107(11):1012-7.	>90% of patients had treatment with GnRH analogues. 8 had GAHT only. No separate results about stopping treatment were reported for those who were AFAB and had had GAHT without GnRH analogues. Also, no mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest how many of the population were non-binary - assume the majority were binary.
McCallion S, Smith S, Kyle H, Shaikh MG, Wilkinson G, Kyriakou A. An appraisal of current service delivery and future models of care for young people with gender dysphoria. Eur J Pediatr. 2021;180(9):2969-76.	87% had treatment with GnRH analogues. No separate results reported for those treated only with testosterone. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population were non-binary.
McFarlane T, Zajac JD, Cheung AS. Gender-affirming hormone therapy and the risk of sex hormone-dependent tumours in transgender individuals-A systematic review. Clin Endocrinol (Oxf). 2018;89(6):700-11.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary. Also, for those for whom the age of starting testosterone was reported, all started testosterone treatment at >18 years of age.
Millington K, Barrera E, Daga A, Mann N, Olson-Kennedy J, Garofalo R, et al. The effect of gender-	Of those who were AFAB (n=194), 2 were gender fluid, 1 gender queer, 10 non-binary. No separate

Study Reference	Reason for exclusion
affirming hormone treatment on serum creatinine in transgender and gender-diverse youth: implications for estimating GFR. Pediatr Nephrol. 2022;37(9):2141-50.	results were reported for the gender fluid/gender queer/non-binary group.
Millington K, Chan YM. Lipoprotein subtypes after testosterone therapy in transmasculine adolescents. J. 2021;15(6):840-4.	Median age 18.4 years hence population not in-scope in terms of average age. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Millington K, Lee JY, Olson-Kennedy J, Garofalo R, Rosenthal SM, Chan YM. Laboratory Changes During Gender-Affirming Hormone Therapy in Transgender Adolescents. Pediatrics. 2024;153(5):01.	200 AFAB patients treated with testosterone, of whom 5% were non-binary. No separate results reported specifically for the non-binary group.
Moussaoui D, Elder CV, O'Connell MA, McLean A, Grover SR, Pang KC. Pelvic pain in transmasculine adolescents receiving testosterone therapy. Int J Transgend Health. 2024;25(1):10-8.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Nahata L, Tishelman AC, Caltabellotta NM, Quinn GP. Low Fertility Preservation Utilization Among Transgender Youth. J Adolesc Health. 2017;61(1):40-4.	Reports mental health outcomes and use of fertility preservation in 50 transmasculine and 23 transfeminine individuals, some of whom had started testosterone treatment at an average age of 16 years and some had had GnRH analogues. However, no information was reported on how many of the patients had had testosterone monotherapy. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population were non-binary and not enough information on numbers that had the in-scope intervention.
Nieder TO, Mayer TK, Hinz S, Fahrenkrug S, Herrmann L, Becker-Hebly I. Individual Treatment Progress Predicts Satisfaction With Transition-Related Care for Youth With Gender Dysphoria: A Prospective Clinical Cohort Study. J Sex Med. 2021;18(3):632-45.	The authors reported that "Low identification rates with non-binary identities prevented comparisons between non-binary and binary genders." No results were reported specifically for the non-binary group and only 5 of 64 AFAB patients were non-binary. Also, 28 of 64 AFAB patients had had GAHT (average age 17.5 years) whereas others had had GnRH analogues, surgery or no treatment. ie minority of patients had had the intervention of interest (testosterone monotherapy). Exclude due to no results specifically for the small % who were non-binary AFAB and only a minority of AFAB had been treated with the intervention of interest.
Nokoff NJ, Bothwell S, Rice JD, Cree MG, Kelsey MM, Moreau KL, et al. Insulin sensitivity, body	Only 1 of 11 patients identified as agender and no results were reported specifically for this patient. 10

Study Reference	Reason for exclusion
composition and bone mineral density after testosterone treatment in transgender youth with and without prior GnRH agonist therapy. J Clin Transl Endocrinol. 2024;36:100356.	patients identified as male or transgender male (although their gender expression varied): Gender identity: Male or transgender male 10 (91%) Agender 1 (9%) Gender expression (allowed multiple choices): Mostly masculine 9 (82) Sometimes masculine 1 (9) Androgynous/neither 3 (27) Sometimes feminine 1 (9) Mostly feminine 0 (0) The PICO specification for this review talks about identified gender, not gender expression. The paper only described one person with a non-binary gender identity ("agender") and results were not reported separately for this person – hence exclude.
Nokoff NJ, DuBose L, Bothwell S, Cree MG, Kelsey MM, Nadeau KJ, et al. Impact of Testosterone on Endothelial Function Varies by GnRH Agonist Treatment. J. 2025;9(7):bvaf086.	1 of 19 patients was described as "agender" and had not had GnRH analogue treatment. No results were reported specifically for this person and n=1 is also out of scope of the PICO specification for this review.
Nokoff NJ, Nemkov T, Bothwell S, Cree MG, Fuller KNZ, Keller AC, et al. Differences in cardiorespiratory fitness by gonadotropin-releasing hormone agonist treatment before and after testosterone in transgender adolescents. J Appl Physiol. 2024;137(5):1470-83.	Of 19 AFAB patients, 11 were treated with testosterone without GnRH analogues. Of these 19 patients "One participant identified as agender and transgender male (multiple pick), and the rest (n = 18) identified as male or transgender male". Exclude because a minority were non-binary and no separate results were reported for the non-binary population.
Nokoff NJ, Scarbro SL, Moreau KL, Zeitler P, Nadeau KJ, Juarez-Colunga E, et al. Body Composition and Markers of Cardiometabolic Health in Transgender Youth Compared With Cisgender Youth. J Clin Endocrinol Metab. 2020;105(3):01.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary
Nos AL, Klein DA, Adirim TA, Schvey NA, Hisle-Gorman E, Susi A, et al. Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming Hormones Among Transgender Adolescents. JAMA netw. 2022;5(11):e2239758.	Population described as AMAB and AFAB. No mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest that any of the population were non-binary
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.	No mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest how many of the population were non-binary - assume majority were binary.
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.	Mean age of starting GAHT was 18.1 years, median 18 years, range 13-31; 469/783 (59.9%) started at 18 years of age or more. Exclude because average age of starting testosterone treatment was not <18 years. 20 patients identified as non-binary but it is not clear that any of them received GAHT. Exclude as

Study Reference	Reason for exclusion
	nothing to suggest how many of the population who received GAHT were non-binary - assume majority binary.
Oliphant J, Barnett D, Veale J, Denny S, Farrant B. The wellbeing and health needs of a cohort of transgender young people accessing specialist medical gender-affirming healthcare in Auckland. N Z Med J. 2021;134(1541):33-44.	4 patients were non-binary - results and demographics were reported separately for them, but the average age was 18 years, 1 was on puberty blockers and none were on testosterone treatment – ie the non-binary patients were not treated with the in-scope intervention. Exclude because none of the non-binary patients received the in-scope intervention.
Olsavsky AL, Grannis C, Bricker J, Chelvakumar G, Indyk JA, Leibowitz SF, et al. Associations Among Gender-Affirming Hormonal Interventions, Social Support, and Transgender Adolescents' Mental Health. J Adolesc Health. 2023;72(6):860-8.	Of 6 patients who were non-binary, 5 were AMAB according to the text. Elsewhere it says that 43 patients were AFAB and 41 identified as male so it is possible that 2 were AFAB non-binary. But this is still the minority of the non-binary group. No results were reported specifically for the non-binary group. Correlations between binary/non-binary and outcomes were reported but the majority of the non-binary group were AMAB so exclude.
Olson KR, Raber GF, Gallagher NM. Levels of Satisfaction and Regret With Gender-Affirming Medical Care in Adolescence. Jama, Pediatr. 2024;178(12):1354-61.	All but one of the 279 patients had been treated with puberty blockers. Exclude because intervention was not in-scope. Also, 25 patients were non-binary but it was not clear what % of these were AFAB. Exclude because no results reported specifically for the non-binary group who were AFAB and this group was a minority of the whole cohort.
Olson-Kennedy J, Okonta V, Clark LF, Belzer M. Physiologic Response to Gender-Affirming Hormones Among Transgender Youth. J Adolesc Health. 2018;62(4):397-401.	6% of the population were "gender queer" and 3% "bigender". The remaining patients identified as male and results were not presented separately for the non-binary group.
Olson-Kennedy J, Wang L, Wong CF, Chen D, Ehrensaft D, Hidalgo MA, et al. Emotional Health of Transgender Youth 24 Months After Initiating Gender-Affirming Hormone Therapy. J Adolesc Health. 2025;16:16.	No mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest how many of the population were non-binary - assume the majority were binary.
Perl L, Brener A, Borger O, Segev-Becker A, Israeli G, Lebenthal Y, et al. The Role of Body Composition Assessment in Tailoring Gender-Affirming Treatment for Transgender/Gender Diverse Youth. Transgender Health. 2024.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Persky RW, Apple D, Dowshen N, Pine E, Whitehead J, Barrera E, et al. Pubertal Suppression in Early Puberty Followed by Testosterone Mildly Increases Final Height in Transmasculine Youth. J. 2024;8(6):bvae089.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Pham AH, Eadeh HM, Garrison MM, Ahrens KR. A Longitudinal Study on Disordered Eating in Transgender and Nonbinary Adolescents. Acad Pediatr. 2023;23(6):1247-51.	7.1% were non-binary / gender fluid, but not clear if AFAB or AMAB. No results reported specifically for the non-binary group.

Study Reference	Reason for exclusion
	The authors report that the "Main study limitations include that generalizability is difficult given the homogenous sample size of mostly white and gender binary adolescents. With a small number of non-binary / gender fluid adolescents and greater representation of transmasculine participants, we had insufficient power to determine true effect differences between gender identities."
Reisner SL, Jadwin-Cakmak L, Sava L, Liu S, Harper GW. Situated Vulnerabilities, Sexual Risk, and Sexually Transmitted Infections' Diagnoses in a Sample of Transgender Youth in the United States. AIDS Patient Care STDS. 2019;33(3):120-30.	14 of 41 transmasculine individuals were non-binary (34%). Average age was 20.2 years - not clear what the average age at GAHT initiation was and no evidence that it was <18 years as required by the PICO specification for this review. 27 of 41 had hormone treatment or surgery - not clear how many had GAHT vs GnRH analogues or surgery. No results were reported specifically for the transmasculine non-binary group nor specifically for those who were treated with testosterone monotherapy starting from <18 years of age.
Reisner SL, Pletta DR, Mayer KH, Deutsch MB, Poteat T, Potter J, et al. HIV seropositivity and viral non-suppression in transgender, non-binary, and gender-diverse people in primary care receiving gender-affirming hormone therapy in the USA between 2013 and 2019 (LEGACY): an observational, longitudinal, cohort study. Lancet HIV. 2025;12(4):e283-e92.	All patients were >18 years of age; the average age was 29 years. No information was reported on the average duration of GAHT but average "years retained in care" was 6 years for 1 cohort and 3 years for the other cohort. ie there was no indication that any patients started treatment at <18 years of age. Hence population out of scope. Reports HIV seropositivity and viral load reported for the gender affirming hormone treated patients who were AFAB and identified as non-binary but the study is not in-scope because there is no indication that patients were <18 years of age at initiation of testosterone treatment and the average age at the time of the study was 29 years.
Roberts CM, Klein DA, Adirim TA, Schvey NA, Hisle-Gorman E. Continuation of Gender-affirming Hormones Among Transgender Adolescents and Adults. J Clin Endocrinol Metab. 2022;107(9):e3937-e43.	39% of total transmasculine and transfeminine were <18 years at start of GAHT. Majority were >18 years. No mention of non-binary or suggestion that any patients might identify as non-binary. Exclude as nothing to suggest that any of the population were non-binary
Rogers C, Webberley M, Mateescu R, El Rakhawy Y, Daly-Gourdialsing A, Webberley H. A retrospective study of positive and negative determinants of gamete storage in transgender and gender-diverse patients. Int J Transgend Health. 2021;22(1-2):167-78.	The outcomes reported - whether gametes were stored and the reasons for not wanting to store gametes - are not outcomes listed in the PICO specification for this review. They are not fertility outcomes such as ovulation and pregnancy. Also, no mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest that any of the population were non-binary.

Study Reference	Reason for exclusion
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.	No mention of non-binary or suggestion that some patients identified as non-binary. Exclude as nothing to suggest how many of the population were non-binary - assume the majority were binary
Sanchez-Toscano E, Dominguez-Riscart J, Larran-Escandon L, Mateo-Gavira I, Aguilar-Diosdado M. Cardiovascular Risk Factors in Transgender People after Gender-Affirming Hormone Therapy. J. 2023;12(19) (no pagination).	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Schwartz BI, Effron A, Bear B, Short VL, Eisenberg J, Felleman S, et al. Experiences with Menses in Transgender and Gender Nonbinary Adolescents. J Pediatr Adolesc Gynecol. 2022;35(4):450-6.	10% were non-binary. Only mention of testosterone treatment was that only 5% of the group had been treated with testosterone. No results were reported separately/specifically for the testosterone-treated group (ie for the intervention of interest). Also, results were about interest in menstrual suppression, not about outcomes of testosterone treatment. Hence the outcome reported was not in-scope.
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.	77 of 106 transmasculine plus transfeminine patients had received treatment with GnRH analogues. Results were not reported separately for those that did not receive GnRH analogues. Hence intervention not in-scope. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population were non-binary.
Sequeira GM, Kidd K, El Nokali NE, Rothenberger SD, Levine MD, Montano GT, et al. Early Effects of Testosterone Initiation on Body Mass Index in Transmasculine Adolescents. J Adolesc Health. 2019;65(6):818-20.	No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary
Shim JY, Laufer MR, Grimstad FW. Dysmenorrhea and Endometriosis in Transgender Adolescents. J Pediatr Adolesc Gynecol. 2020;33(5):524-8.	No mention that any of the patients identified as non-binary (though non-binary patients were not excluded). Exclude as nothing to suggest that the majority of the population treated with testosterone identified as non-binary.
Spack NP, Edwards-Leeper L, Feldman HA, Leibowitz S, Mandel F, Diamond DA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. Pediatrics. 2012;129(3):418-25.	97 patients of whom 54 were biological females. 12 were described as "queer" or "questioning" but it was not clear if they were AFAB or AMAB. Hence exclude because the number of patients who were AFAB and identified as non-binary was not clear. Also, of the 97 total, 39 were treated with GAHT and 11 with GnRH analogues. Psychiatric / mental health outcomes were reported for the whole cohort of 97, not separately for the 12 non-binary patients of whom an unknown % may have been AFAB. No outcomes were reported specifically for the population of interest.

Study Reference	Reason for exclusion
Steininger J, Knaus S, Kaufmann U, Ott J, Riedl S. Treatment trajectories of gender incongruent Austrian youth seeking gender-affirming hormone therapy. Front Endocrinol (Lausanne). 2024;15:1258495.	7 of 230 AFAB patients were reported to identify as non-binary. Information reported on testosterone treatment, discontinuation, regret, use of fertility preservation and legal gender change was for the whole group of those AFAB and not separately for the non-binary group.
Stoffers IE, de Vries MC, Hannema SE. Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. J Sex Med. 2019;16(9):1459-68.	All patients received GnRH analogues for puberty suppression prior to testosterone. Exclude because intervention not in-scope. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Strang JF, Chen D, Nelson E, Leibowitz SF, Nahata L, Anthony LG, et al. Transgender Youth Executive Functioning: Relationships with Anxiety Symptoms, Autism Spectrum Disorder, and Gender-Affirming Medical Treatment Status. Child Psychiatry Hum Dev. 2022;53(6):1252-65.	Only 2 (2%) patients were non-binary. Results were presented with and without this group as these 2 patients made a difference to the results for depression. However, data on sex assigned at birth suggests that only one of these two non-binary patients was AFAB - the other was AMAB. Single patients / case reports are not in-scope of the PICO specification for this review. Also, results were not reported specifically for the one AFAB non-binary patient, only for the larger/full cohort with and without the 2 non-binary patients, so it is not possible to infer the results for the one non-binary AFAB patient.
Strauss P, Cook A, Watson V, Winter S, Whitehouse A, Albrecht N, et al. Mental health difficulties among trans and gender diverse young people with an autism spectrum disorder (ASD): Findings from Trans Pathways. J Psychiatr Res. 2021;137:360-7.	52% of the total 859 patients were non-binary but the majority had not had any hormone treatment (ie not had testosterone) - only 185 of 859 had had some hormone treatment (not clear if GnRH analogues or testosterone) - and no separate results were reported for those who had received testosterone monotherapy.
Taillefer V, Kelley J, Marsolais S, Chiniara L, Chadi N. Expected vs. perceived effects of gender-affirming hormone therapy among transmasculine adolescents. J Pediatr Endocrinol Metab. 2023;36(11):1072-8.	Only 39% of the population had not used GnRH analogues, 18% not known and 42% had used GnRH analogues. No mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Tan KKH, Byrne JL, Treharne GJ, Veale JF. Unmet need for gender-affirming care as a social determinant of mental health inequities for transgender youth in Aotearoa/New Zealand. J Public Health (Oxf). 2023;45(2):e225-e33.	Mean age 20.52 years. Results were not reported separately for <18 year olds who were also non-binary and AFAB. Results reported for <18 year olds were reported for the whole group for which the subgroup of interest (non-binary and AFAB) could be a minority. No clear results were reported for the intervention of interest (testosterone monotherapy) for the

Study Reference	Reason for exclusion
	population in-scope (non-binary, AFAB and <18 years of age).
Taylor J, Hall R, Langton T, Fraser L, Hewitt CE. Care pathways of children and adolescents referred to specialist gender services: a systematic review. Arch Dis Child. 2024;109(Suppl 2):s57-s64.	Only mention of non-binary was in relation to a single study which was assessed separately (Tollit et al 2023, see below). No other mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Taylor J, Mitchell A, Hall R, Langton T, Fraser L, Hewitt CE. Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: a systematic review. Arch Dis Child. 2024;109(Suppl 2):s48-s56.	Small proportion of the included studies included any non-binary patients and they were always a minority. No results were reported specifically for non-binary patients.
Thoreson N, Grasso C, Potter J, King DS, Peebles JK, Dommasch ED. Incidence and Factors Associated With Androgenetic Alopecia Among Transgender and Gender-Diverse Patients Treated With Masculinizing Hormone Therapy. JAMA Dermatol. 2021;157(3):348-9.	Letter. Letters are excluded in the PICO specification for this review. Also, 29.6% of patients were described as genderqueer / not exclusively male or female. Results were not reported separately for this group.
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.	12 of 193 AFAB patients were non-binary (6.2%) plus 5 more patients (2.6%) were unsure. Results were not reported separately for this group eg the authors state that 3 of 8 non-binary individuals changed to cisgender over time but it is not clear if those 3 were AFAB or had had testosterone treatment.
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.	Results were presented separately for non-binary patients who were <18 years of age but the number of patients in this group who were AFAB vs AMAB was not clear. No information was reported on whether the GAHT that patients received was testosterone or oestrogen. Hence unclear population and unclear intervention - exclude.
Turban JL, King D, Kobe J, Reisner SL, Keuroghlian AS. Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. PLoS ONE. 2022;17(1):e0261039.	For those who initiated GAHT at 14-15 years and at 16-17 years, results were only reported for the whole groups, not separately for non-binary patients who were AFAB. In these 2 age groups, there were 10.92% (13) and 9.67% (35) respectively who were non-binary and AFAB. No results were reported specifically for the non-binary group, and the majority of the total cohort was not reported to identify as non-binary, hence exclude.
Valentine A, Davis S, Furniss A, Dowshen N, Kazak AE, Lewis C, et al. Multicenter Analysis of Cardiometabolic-related Diagnoses in Transgender	All patients were listed as either male or female. There was no mention of non-binary or suggestion that some patients identified as non-binary. Exclude

Study Reference	Reason for exclusion
and Gender-Diverse Youth: A PEDSnet Study. J Clin Endocrinol Metab. 2022;107(10):e4004-e14.	as nothing to suggest that any of the population were non-binary.
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.	40 transmasculine adolescents of whom 6 were non-binary or undecided, 13 were on GAHT and 8 were on puberty suppression. No results were reported specifically for the non-binary group, nor specifically for those treated only with testosterone and these groups were a minority of the total 40 AFAB patients.
Vestering A, van Vugt WLJ, Berner AM, Snijders MLH, Heijer MD, Groenman FA, et al. Incidence of gynaecological (pre-)malignancies and endometrial activity in transmasculine and gender diverse individuals using testosterone: a retrospective, single-centre cohort study. eClinicalMedicine. 2025;(no pagination).	Mean age at start of testosterone treatment was 21 years. Exclude because, on average, population out of scope in terms of age. Results were not reported separately for patients who were <18 years of age. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Walton E, Abhari S, Tangpricha V, Futral C, Mehta A. Family Planning and Fertility Counseling Perspectives of Gender Diverse Adults and Youth Pursuing or Receiving Gender Affirming Hormone Therapy. Urology. 2023;171:244-50.	Exclude because the number who were <18 years of age, AFAB, non-binary and on testosterone treatment was not clear and was clearly only a minority of the youth group. Results were only reported for the whole youth group of 11 patients and not separately for non-binary AFAB patients who were on testosterone treatment. Also, the outcome reported was uptake of fertility preservation interventions, not fertility outcomes such as those listed in the PICO specification for this review eg ovulation and pregnancy.
Willemsen LA, Boogers LS, Wiepjes CM, Klink DT, van Trotsenburg ASP, den Heijer M, et al. Just as Tall on Testosterone; a Neutral to Positive Effect on Adult Height of GnRHa and Testosterone in Trans Boys. J Clin Endocrinol Metab. 2023;108(2):414-21.	All patients received GnRH analogues for puberty suppression prior to testosterone treatment. Exclude because intervention out of scope. Also, no mention of non-binary or suggestion that patients might identify as non-binary. Exclude as nothing to suggest that any of the population identified as non-binary.
Zwickl S, Burchill L, Wong AFQ, Leemaqz SY, Cook T, Angus LM, et al. Pelvic pain in transgender people using testosterone therapy. LGBT health. 2023;10(3):179-90.	Mean age of patients was 27 years. Hence not in scope of PICO specification for this review in terms of average age of population. 23.3% were AFAB and identified as non-binary but results were not reported separately for this group nor for the group who were <18 years and identified as non-binary.

Abbreviations:

AFAB: assigned female at birth; AMAB: assigned male at birth; GAHT: gender affirming hormone treatment; GnRH: gonadotrophin releasing hormone; PICO: population, intervention, comparator, outcomes

Appendix E Evidence table

No studies assessing the clinical effectiveness, safety or cost-effectiveness of treatment with testosterone monotherapy with or without psychological and psychosocial support for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation were identified for this review.

Appendix F Quality appraisal checklists

No checklists were used in this review.

Appendix G GRADE profiles

No studies assessing the clinical effectiveness, safety or cost-effectiveness of treatment with testosterone monotherapy with or without psychological and psychosocial support for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation were identified for this review.

Glossary

Term	Definition[2]
Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether the event is suspected to be related to or caused by the drug, treatment or intervention.
Cognitive	Relating to, or involving, the process of thinking and reasoning.
Comparator	The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care).
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 (2013). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) was released in 2022.
Feminising and masculinising medicines (also known as feminising and masculinising hormones, 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 (American Psychiatric Association 2013). Gender dysphoria describes *"a marked incongruence between one's experienced / expressed gender and assigned gender of at least 6 months duration*" which must be manifested by a number of criteria.
Gender fluid	An experience of gender that is not fixed, but changes between two or more identities.
Gender identity	This term is used to describe an individual's internal sense of being male or female or something else.
Gender incongruence	Diagnostic term used by health professionals, found in the WHO International Classification of Diseases ICD-11 (see below). Gender incongruence is characterised by "*a marked and persistent incongruence between an individual's experienced gender and the assigned sex*".
Gender-questioning	A broad term used to describe CYP who are in a process of exploration about their gender.
Gender-related distress	A way of describing distress that may arise from a broad range of experiences connected to a child or young person's gender identity development. Often used for young people whereby any formal diagnosis of gender dysphoria has not yet been made.
Gonadotropin releasing hormone analogues (also known as hormone	Taking these hormones stops the progress of puberty. The GnRH analogues (puberty blockers) act by competing with the body's natural gonadotrophin releasing hormones. This competition blocks the release of

[2] 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[2]
blockers and puberty blockers)	two gonadotropin 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	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. (https://icd.who.int/en). It is developed and annually updated by the World Health Organisation (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.
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).
Psychosocial	Describes the psychological and social factors that encompass broader wellbeing.
Subgroup analysis	A way to find out from a study if a treatment is more effective in one group of people (for example, who are a particular age or have particular symptoms) than another. It uses evidence from a defined subgroup within the whole analysis set.
Transgender (trans)	This is an umbrella term that includes a range of people whose gender identity is different from the sex they were registered at birth.
Transition	These are the steps a person may take to live in the gender in which they identify. This may involve different things, such as changing elements of social presentation and role and/or medical intervention for some.

References

Included studies

- No studies were included.

Other references

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

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