



Impact of Puberty Blockers in Gender-Dysphoric Adolescents

An evidence brief

This brief is not government policy or a clinical guideline. The information contained within this document is considered correct up to September 2023.

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Glossary

Assigned female at birth (AFAB): a person whose sex was assigned as female at birth; sometimes referred to in the literature as natal female, female sex, girl, woman or female.

Assigned male at birth (AMAB): a person whose sex was assigned as male at birth; sometimes referred to as natal male, male sex, boy, man or male.

Cisgender: describes a person whose identified gender is the same as the sex recorded at their birth.

Gender: a person's social and personal identity as male, female or another gender or genders that may be non-binary.

Gender-affirming health care: treatment to affirm a person's gender identity, including gender-affirming hormone treatment, gender-affirming medical treatment, gender-affirming surgical treatment and gender-affirming psychosocial care/treatment.

Gender dysphoria (GD): the distress experienced by a person due to the incongruence between their gender identity and their sex assigned at birth.

Gender diversity: an umbrella term for gender identification that falls outside of the male/female gender binary.

Gender identity: a person's internal and individual experience of gender.¹

Gender identity service (GIS): a specialist service designed to manage individuals with GD or gender incongruence; also, sometimes referred to as a gender identity clinic, gender clinic or gender identity development service.

Non-binary: someone who does not identify exclusively as either a man or a woman.²

Off-label: describes an approved medicine that is prescribed outside of the approved indications, dose range or route of administration. See further details at Medsafe (2020).³

Puberty blockers: a class of drugs such as gonadotrophin-releasing hormone analogues (GnRHa),⁴ which suppress the development of puberty.

Puberty suppression: treatment which suppresses pubertal development.

¹ Including how others perceive an individual with regards to their gender.

² There are many ways in which people may identify as non-binary. Gender cannot be inferred from the term without additional information.

³ <https://www.medsafe.govt.nz/profs/riss/unapp.asp>

⁴ Some examples of GnRHa are goserelin, leuprorelin and triptorelin.

Sex assigned at birth: the sex recorded at a person's birth (for example, as recorded on their birth certificate).

Transgender: describes a person whose gender is different from the sex recorded at their birth.

Transboy/man: a person who was assigned female at birth who identifies as a boy/man; also referred to as transman, transmale or AFAB.

Transgirl/woman: a person who was assigned male at birth who identifies as a girl/woman; also referred to as transwoman, transfemale or AMAB.

Tanner stages: a clinical description entailing five stages of physical development occurring during puberty.

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Executive summary

Gender dysphoria (GD) is a condition characterised by a discrepancy between an individual's sex assigned at birth and their personal gender identity. Internationally, the population prevalence of GD in adolescents is approximately 1–2%. Puberty is a time of significant sexual maturation and development and may exacerbate the dysphoria some individuals experience. Where an individual seeks to halt puberty progression, a clinician may prescribe gonadotrophin-releasing hormone analogues (GnRHa).

Scope

This evidence brief is limited to:

1. clinical and mental health and wellbeing outcomes in gender-dysphoric adolescents prescribed GnRHa
2. a stocktake of legislative or governance arrangements relating to the prescription of GnRHa for gender-dysphoric adolescents.

Use of cross-sex hormones, gender-affirming hormone treatment such as estrogen or testosterone, gender-affirming surgical treatment and progression from puberty blockers to any of these are outside the scope of this brief.

Methods

This evidence brief is a systematic literature review. All studies published in peer-reviewed journals up to 30 September 2023 were screened for inclusion.

Relevant quality assessment tools were used to assess the quality of quantitative and qualitative evidence.

Key findings

Impact of puberty blockers on clinical outcomes

Three major outcomes the review focused on were bone health, anthropometric measurements and cardiometabolic outcomes⁵. Chronological age, bone age and Tanner stage at the time of GnRHa initiation were found to be contributing variables to height in gender-dysphoric adolescents. Bone mineral density appeared to increase due to GnRHa therapy, although the increase was significantly lower than in matched controls. Cardiometabolic outcomes were reported varying with some studies reporting a change in blood pressure, lipids, and body composition. There was no

⁵ 'Cardiometabolic outcomes' refers to obesity, hypertension, type 2 diabetes mellitus and cardiovascular disease.

evidence of any effect on renal function, liver function, onset of diabetes, or executive function.

Impact of puberty blockers on mental health and wellbeing outcomes

Six outcomes the review focused on were GD, depression, anxiety, self-harm, suicidality and quality of life. Current evidence indicates a significant improvement in depression, anxiety and suicidal ideation for individuals treated with puberty blockers. However, the quality of this evidence is low with a high risk of bias.

Targeted mental health and wellbeing interventions for gender-dysphoric adolescents

Six studies reported on a range of targeted interventions, such as online and in-person adolescent support groups, parent/guardian educational or psychological groups, a multi-disciplinary family and adolescent centre, and a residential camp for adolescents. All studies reported the wider socio-cultural context as well as the necessity of parent/whānau, individual and societal components in an intervention, if it was to have a meaningful impact. However, the quality of these studies varies, and the studies generally involved small samples and one-off or short-course interventions.

Legislation and Governance

Prescription of puberty blockers is a complex issue. A range of governance and legal arrangements to monitor access to puberty blockers and provide greater regulatory oversight are emerging in some countries to support and clarify the legal positions of parents/guardians and adolescents themselves. The World Health Organization (WHO) is in the process of developing a guideline on the health of transgender and gender-diverse people. This will include guidelines related to health policies and the legal recognition of self-determined gender identity WHO (1). Currently, New Zealand does not have specific legislation related to puberty blockers. People can access puberty blockers only through an 'off-label' prescription and only through a medical practitioner. Pharmaceutical and medical regulatory authorities impose legally binding processes that prescribers must adhere to, which also controls access to medications.

Limitations

There were significant limitations in the studies included in this brief. First, no New Zealand-based studies met the inclusion criteria for this review. Second, all evidence was primarily from longitudinal cohort or cross-sectional studies using population-based reference standards. Third, the included studies involved individuals with a wide age range and who were at different stages of pubertal development. Fourth, there was a lack of diversity in the cohorts; most adolescent participants predominantly identified as Caucasian. These individuals had parental/guardian support and lived in middle to high-income socioeconomic areas. There is very little evidence on indigenous adolescents, adolescents living in low socioeconomic conditions or those who do not have parental/guardian support. Finally, the quality of both quantitative and qualitative studies was poor, with the studies presenting a high risk of bias.

Conclusion

Evidence about the impact of GnRHa on clinical and mental health and wellbeing outcomes is scarce, with available evidence largely of poor quality. While there are studies on non-medical interventions that show improvements in the mental health and wellbeing of gender-dysphoric adolescents, these generally rely on small, localised cohorts, making it difficult to extrapolate to other, larger cohorts. In terms of clinical outcomes, bone health and metabolic parameters in particular need ongoing monitoring in gender-dysphoric adolescents prescribed GnRHa.

Legislation and governance mechanisms relating to GnRHa prescription in adolescents has increasingly come under scrutiny internationally. This has resulted in some jurisdictions making substantive changes to prescribing practices. In New Zealand currently, there is no specific legislation related to puberty blockers, only good practice guidelines to enable clinicians to support and manage individuals on GnRHa (2).

Given the dearth and poor quality of evidence, and New Zealand-specific evidence, there is an urgent need for high-quality, longitudinal data and research to help us understand the specific needs of gender-dysphoric adolescents in New Zealand.

Background and context

What is gender dysphoria?

The term 'gender dysphoria' (GD) describes the emotional discomfort or distress (dysphoria) experienced by people with gender incongruence (3). Psychological distress related to GD can emerge prior to puberty, and the development of male or female secondary sexual characteristics may exacerbate the experience of GD. To mitigate GD resulting from changes occurring at puberty, transgender or gender-diverse adolescents may pursue multiple mechanisms of gender affirmation, including social, legal, medical and surgical interventions. (4).

The classification and diagnosis of GD has evolved considerably over the last few decades. The most recent edition (2022) of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (5) no longer considers GD a psychological illness, but still includes the term as a diagnosis with the following clinical criteria.

- There is a marked incongruence between one's experienced/expressed gender and natal gender of at least six months in duration, as manifested by at least two of the following:
 - a marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or, in young adolescents, the anticipated secondary sex characteristics)
 - a strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or, in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
 - a strong desire for the primary and/or secondary sex characteristics of the other gender
 - a strong desire to be of the other gender (or some alternative gender different from one's sex)
 - a strong desire to be treated as the other gender (or some alternative gender different from one's sex)
 - a strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's sex).
- The condition is associated with clinically significant distress or impairment in social, occupational or other important areas of functioning.

The most recent World Health Organization (WHO) International Classification of Diseases (ICD-11) (6) has also updated the way it considers gender identity-related health. It has moved gender incongruence out of the 'Mental and behavioural disorders' chapter and into the new 'Conditions related to sexual health' chapter, to support a change of approach to health care provision for gender-diverse people. In contrast to the DSM-5 criteria, the latest ICD-11 codes place less emphasis on the degree of clinical distress and the resulting functional impairment to the individual.

Gender incongruence may lead to a desire to ‘transition’ to live and be accepted as a person of the preferred gender. This may be pursued through accessing hormonal treatment, surgery or other health care services to make the individual’s body align, to the extent desired and the extent possible, with the experienced gender. However, gender variant behaviour and preferences alone are not a basis for assigning a diagnosis of GD (6).

The literature uses both the DSM and the ICD definitions of GD, and for the purpose of this evidence brief both have been accepted as valid diagnostic criteria.⁶

Epidemiology

Population data

A study from Sweden (7) used that country’s National Population Health Register (NPR), which made use of ICD-10 codes, to identify individuals with GD. However, as there is no single ICD-10 code for GD, three codes were used (F64.0 transsexualism, F64.8 other gender identity disorders and F64.9 gender identity disorder unspecified). Using at least three diagnostic codes for GD, the study reported that 74% of assigned male at birth (AMAB) individuals and 79% of assigned female at birth (AFAB) individuals underwent gender-affirming medical treatment. Incidence of GD between 2004 and 2015 for individuals aged 10–17 years was reported to be 1.51/10,000 people for AFAB individuals and 0.32/10,000 people for AMAB individuals (7). Over the same duration, the study also reported an increased incidence of GD diagnoses for AMAB from 0.15 to 0.38/10,000 people and for AFAB from 0.07 to 0.47/10,000 people (7).

International survey data

A study from the Appalachian region in the United States used survey data from adolescents aged 13–18 years attending public schools. The aim of the study was to assess the prevalence of self-reported gender incongruence (the text used the term ‘gender diversity’) using a two-staged questionnaire that identified sex assigned at birth and gender identity (8). The study included three categories of gender: cisgender, in which there was congruence between sex assigned at birth and affirmed gender; binary gender diversity, where the sex assigned at birth was opposite to the affirmed gender; and non-binary, where the affirmed gender was neither male nor female. The overall response rate was 69.0%. The study did not disaggregate AMAB and AFAB individuals. The overall prevalence of gender diversity was 7.2%. Of the 202 gender diverse respondents, 46 (22.8%) had a binary identity and 128 (63.3%) had a non-binary identity. The remaining 28 (13.9%) identified as both. By age, the prevalence of gender diversity ranged from 5.7% (in 17–18-year-olds) to 7.7% (in 12–14-year-olds). Prevalence of gender diversity by race and ethnicity was reported to be 4.8% in African American respondents, 6.5% in Caucasian respondents, 9.9% in those with multiple

⁶ The terminology concerning sex, gender and gender identity is inconsistent across the literature. For the purposes of uniformity, this brief uses the terms specified in the glossary where appropriate.

ethnicities, 25.7% in respondents who were Asian, Native Hawaiian and Pacific people combined, and 25.7% in Hispanic respondents.

The quality of the studies was assessed for this evidence brief using the Crowe Critical Appraisal Tool (CCAT) (9) (see 'Supplementary Material 1', published alongside this document). This study rated poorly on the CCAT, with a score of 48%. It did not provide any external validation for the survey responses. Therefore, it is difficult to compare these results with other studies. In addition, the response rate for AMAB individuals (34.2%) was only half that of AFAB individuals (65.8%), suggesting that the sample was not representative of the general population. The prevalence of gender diversity was substantially different from that found in a study of another Appalachian population (which found gender diversity in 1% of the youth population).

In 2022, Turban et al reported on the prevalence of self-reported GD from adolescents aged 12 to 18 years in the United States (10). Data was extracted from the 2017 and 2019 Youth Risk Behaviour Survey, a biennial survey of high school students undertaken by the Centres for Disease Control and Prevention. In the 2019, survey 1.6% (1640/105,437) adolescents reported identifying as gender diverse. This was a decrease from the reported rate of 2.4% (2161/91,937) in 2017.

The study was given a score of 68% on the CCAT but did not score well for either the sample size or the findings. Although the study was large, it was not representative of the population of the United States, as only 16 states contributed data. There was no indication of response rate, nor a clear definition of gender diversity. In addition, there was no analysis to indicate that the two groups were comparable.

New Zealand data

In New Zealand, three recent surveys have collected data about gender diversity in adolescents. The Youth2019 health and wellbeing survey collected data from 7,891 secondary school pupils (aged approximately 12–18 years) in the Auckland, Waikato and Northland regions (11). Of the 7,668 who responded to the question regarding gender identity, 1% (n = 78) reported they were transgender and 0.6% (n = 48) said they were unsure.

Similar results were obtained from the 'What About Me?' survey funded by the Ministry of Social Development, which surveyed 7,209 secondary school students in 2022 (12). Approximately 2% of respondents reported they were gender diverse and 1% were not sure yet or were questioning their gender identity.

The 'Growing up in New Zealand' study follows more than 6,000 ethnically diverse children born in 2009 and 2010 in the Auckland, Counties Manukau and Waikato health districts (13). Of the respondents in the 12-year-old cohort who were AMAB, 91% identified male as their gender, 8% identified as 'mostly a boy' and the remaining 1% identified as 'somewhere in the middle' and 'I don't know'. In comparison, of the AFAB respondents, 78% identified female as their gender, 14% identified as 'mostly a girl', 7% were 'somewhere in the middle' and 1.5% said 'I don't know' (13).

Proportion of people assigned male at birth and assigned female at birth

A systematic review by Thompson et al reported a pooled ratio of 2:1 for AFAB to AMAB individuals (64% AFAB, 36% AMAB) (3). Only one study directly addressed change over time in the ratio of AMAB and AFAB adolescents and found no change from 2014 to 2016 (14). Thompson et al reported that extracting information regarding change in prevalence from the existing published cohorts is difficult, as some studies aggregate information from individuals over a wide time period, and age of onset, referral and assessment of GD is unclear (3). In the population-based study from Sweden, for individuals aged 10–17 years in the period from 2004 to 2015, an increase in the incidence of GD in AMAB individuals was 21% per year, and in AFAB individuals was 33% per year (7).

The survey of Appalachian youth referred to above did not provide data for AMAB and AFAB individuals separately. This precluded an assessment of the ratio of AMAB and AFAB (8). The study reporting data from the Youth Risk Behaviour Survey reported similar proportions of AMAB and AFAB individuals at the two specified time periods; 59.5% (1285/2161) identified as AMAB in 2017 and 52.8% (866/1640) in 2019 (10). For AMAB individuals, the prevalence of GD expressed as a proportion of the population surveyed was 2.8% in 2017 (1,285/45,133) decreasing to 1.7% in 2019 (866/51,484). For AFAB individuals, the prevalence was 1.9% in 2017 (876/47,804) decreasing to 1.4% in 2019 (774/53,953).

Two studies reported referral patterns to gender identity services (GISs). A study from the Netherlands which included data for individuals referred to the Amsterdam GIS from 1998 to 2018 reported a marked increase in the number of AFAB individuals older than 10 years of age referred to the clinic compared to those younger than 10 (Figure 1), although this increase was not quantified (15). However, there was also a marked decrease in referrals in 2018, the last year of reporting, due to the clinic’s inability to manage the ‘overwhelming demand’ (Figure 2).

Figure 1: Number of all AMAB and AFAB referrals to Amsterdam GISs, 1997–2018

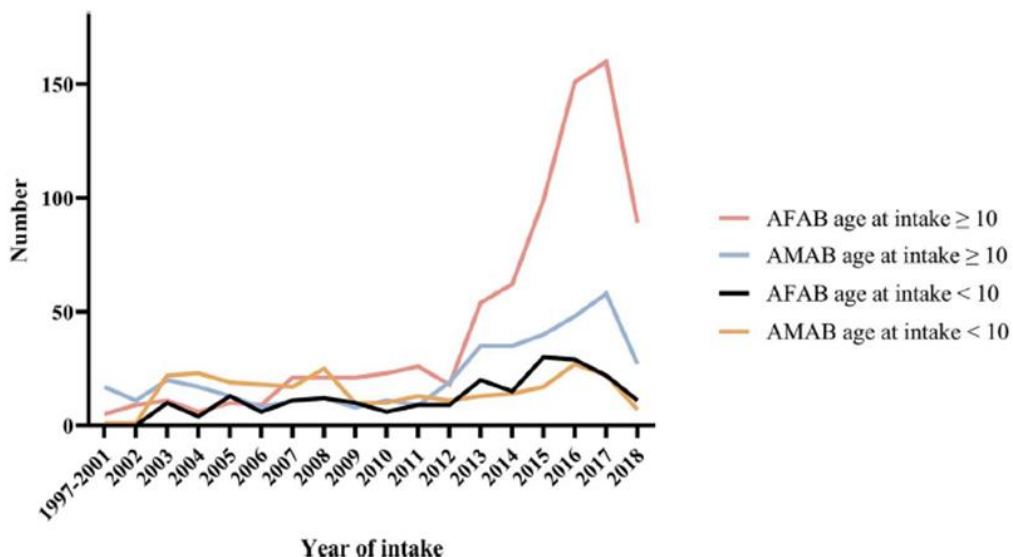
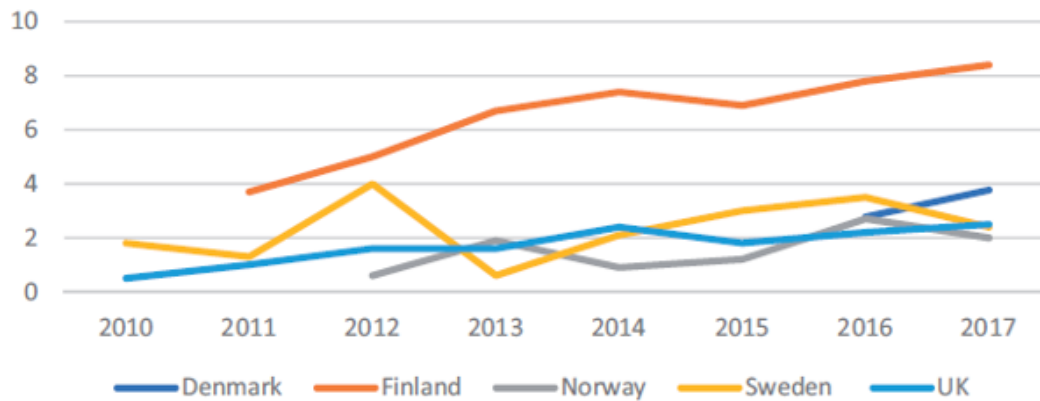
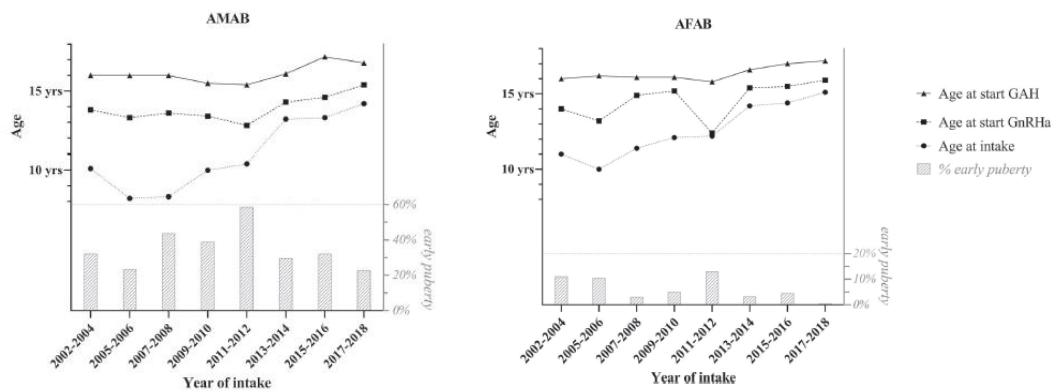


Figure 2: Ratio of AFAB:AMAB in children and adolescents referred to GISs in Denmark, Finland, Norway, Sweden and the United Kingdom, 2010–2017



The other study, a multinational study comparing child and adolescent referral rates from five countries (Denmark, Norway, Sweden, Finland and the United Kingdom) also reported an increase in the proportion of AFAB compared to AMAB individuals referred to GISs between 2010 and 2017 (16). The ratio of AFAB:AMAB individuals referred was 7.1 in Finland, 4.1 in Denmark, 3.2 in Sweden, 2.5 in the United Kingdom and 1.7 in Norway (Figure 3).

Figure 3: Median age at intake, start of GnRH and gender-affirming hormone treatment for AMAB and AFAB individuals



Age of onset, referral and treatment of gender dysphoria

There is limited data available on the age of onset of GD, due to this being a commonly omitted sample characteristic in most of the studies. A single study reported the age of onset of GD with a mean of 6.8 years (standard deviation (SD) 3.9) (range 1–15) among 168 referrals to the London GIS (17). Six studies specifically reported the age at referral (17), (18), (19), (20), (21), (22), giving a pooled mean (\pm SD) age of 13.2 (\pm 0.9) years. The systematic review by Thompson et al noted that age at initial assessment was reported more frequently than the age of onset or referral. In the review, 23 studies reported a mean age at initial assessment of 15.1 (\pm 1.0) years. Of these, the range was included in only 17 studies (6.0 to 18.0 years) (3).

The systematic review noted that given the average age of adolescents receiving an assessment, many individuals might not have received specialist review prior to or early in puberty. Therefore, it was likely that these individuals might have experienced GD for some time prior to assessment and that there might be a decrease in any potential benefits from delaying puberty (3).

The multinational study (16) did not provide information regarding the age of onset, referral for or assessment of GD (15). The Amsterdam Cohort of Gender Dysphoria provided information for the median age (interquartile range) of first visit. The overall median age at first visit for AMAB individuals was 11.5 years (range 8.0–15.2) compared to 14.1 years (range 10.5–16.0) for AFAB. For both groups, the median age at first visit was observed to increase from 2005. For AMAB and AFAB, the median age at start of gonadotrophin-releasing hormone analogues (GnRHa) had risen over time from just under 14 years to over 15 years (Figure 3).

Quality assessment

Of the additional five studies this review identified published after the meta-analysis from Thompson et al (3), only the Swedish population-based study was considered to be of good quality using the CCAT. The international studies using surveys had poor research design and sampling. All surveys used self-reported gender diversity. In addition, the applicability of the sample to the background population was not clear.

Studies reporting referral rates to GISs were not considered suitable evidence with which to estimate the prevalence of GD in the population. This is because a review of the adolescents referred to the Amsterdam GIS found that referral rates had declined markedly in the last year of reporting due to the clinic's excessive workload. While the quality of referral and management data from both studies reporting information from GISs were reasonable quality, the applicability of the data to the questions addressed in this evidence brief was deemed limited.

The medical management of gender dysphoria

Delaying puberty is a medical intervention used to manage GD by suppressing the development of secondary sex characteristics (which are not readily reversible) and delay pubertal progression contrary to the individual's experienced gender (23). GnRHAs are a class of medication commonly prescribed to stop the production of sex hormones. They have thus been termed 'puberty blockers' in the setting of precocious puberty (24), and this term is often also used in the context of the treatment of GD.⁷

In New Zealand, gender-dysphoric adolescents may seek medical affirmation through a range of services, including primary care (25). The use of GnRHa for puberty suppression in the setting of GD is an off-label use under section 25 of the Medicines Act 1981. GnRHAs are available as leuprorelin intramuscular injections or goserelin subcutaneous implants (26). They are approved to treat prostate cancer, breast cancer, endometriosis, uterine fibroids and central precocious puberty. Evidence for the effects of GnRHa in adolescents treated for precocious puberty is available (24), albeit beyond the scope of this brief.

Methods

The methodological details for this systematic review are provided in Appendix 1. The Newcastle-Ottawa Scale (NOS) (27) was used for quality assessment. The assessment undertaken for each study is detailed in 'Supplementary Material 2' (published alongside this document).

Quality and limitations

Fourteen studies reporting on the physical effects of GnRHAs were assessed based on their primary outcomes. The quality of the single study reporting on fertility after GnRHa (28) and the two studies reporting on the efficacy of GnRHa therapy (29, 30) were not assessed for quality given the small number of studies limits the application in a clinical setting.

The three case control studies were assessed for quality using the NOS criteria for case-controlled studies and based on the relevant primary outcome, cardiometabolic health, executive function and the impact of the timing of GnRHa treatment on subsequent gender-affirming surgical treatment (GAST). The eight cohort studies reporting bone mineral density outcomes were assessed for quality using the NOS criteria for cohort studies and based on the data on impact of GnRHa on bone mineral density, and the four cohort studies reporting cardiac and metabolic outcomes were

⁷ There are other medications, such as bicalutamide and progestins, which are not classified as GnRHAs; these can also be used in some cases (25).

assessed for quality using the NOS criteria for cohort studies based on the data related to cardiometabolic health.

A formal quality assessment of studies on the height velocity⁸ of adolescents receiving GnRHa treatment was not undertaken, as this was not the primary outcome in most of the included studies.

Results

Thirteen relevant studies were identified from two recent systematic reviews (31), (32). An additional 12 studies were also identified, resulting in a total of 25 relevant studies. Of these, 20 included the medical complications of GnRHa treatment, four studied the effectiveness of puberty suppression and one studied the impact of GnRHAs on fertility after treatment. A summary of the studies can be found in Appendix 2.

Of the 20 studies investigating clinical outcomes, 12 were from the Netherlands, three from the United Kingdom, two from the United States, one from Israel, one from Belgium and one from Canada. All studies included cohorts from GISs. Fifteen were retrospective studies, four prospective studies and one a cross-sectional cohort study.

Sixteen studies reported anthropometric data.⁹ Eleven studies reported data on bone density or bone morphology, three reported blood pressure measurements, three reported metabolic variables, two reported renal function, one reported executive function and one reported testicular and breast size and development. In 14 studies, triptorelin was used to suppress puberty. Four studies did not report the drug used, and two used leuprolide. Thirteen of the 20 studies provided luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels as evidence of puberty suppression, and one used serum testosterone or oestradiol concentrations.

Anthropometry

Detailed results from studies reporting anthropometric data are summarised in 'Supplementary Material 3' (published alongside this document).

Height / height velocity

A range of variables was used to assess growth. Height velocity and height z-scores were the variables most commonly used, although formulae to predict final height based on parental height were also used. The reference range for height or height z-score was that of either the sex assigned at birth or the affirmed gender or both.

Twelve studies reported height data (n = 918 subjects, AMAB = 457, AFAB = 461). Initially, height SD scores or z-scores and growth velocity appeared to consistently decrease for AMAB adolescents compared to birth-assigned sex based on selected

⁸ Height velocity is the rate of change in height.

⁹ Three studies provided descriptive biometric data but without reference ranges; the remaining study presented data in the form of standard deviation scores (SDSs), z-scores and percentiles.

population growth charts (33, 34, 35, 36). Inconsistent results were reported for AFAB adolescents; some studies reported a significant decrease in expected height (35) and others did not identify any significant difference (34), (37), (38). These studies found that chronological age (38), bone age (36) and Tanner stage¹⁰ (39) at the time of initiation of GnRHa influenced height z-scores, having less impact on older or more mature individuals, in whom linear height was closer to completion. Some studies reported on height data after initiation of gender-affirming hormone treatment (GAHT), but the effects of GAHT after GnRHa treatment are beyond the scope of this review.

No studies reported on the impact of GnRHa alone on linear height and height velocity in individuals who initiated and then ceased GnRHa treatment. Unless GnRHa treatment prior to GAHT results in a substantial alteration of height compared to a desired final height, the implications of alterations in height velocity are difficult to assess. Changes in bone maturation can be measured more accurately by assessing bone mineralisation directly, as discussed below.

Bone density

Bone mineral density was measured by dual-energy X-ray absorptiometry (DEXA),¹¹ which was used to calculate a real or volumetric bone mineral density. All studies included weight-bearing targets such as lumbar spine and femoral neck to measure bone mineral density and then convert into z-scores using accepted reference ranges. One study reported differences over time in hip bone geometry¹² for individuals who had received GnRHa prior to GAHT (40).

Bone-density data was reported in eight studies (n = 517, AMAB = 186, AFAB = 331). Bone-density maturation, usually measured as bone mineral density, was consistently and significantly influenced by GnRHa therapy. Details of changes in bone mineral density z-scores during GnRHa therapy are presented in 'Supplementary Material 3' (published alongside this document), for those studies where the data could be reliably extracted.

While bone mineral density usually increased over the course of GnRHa therapy, the increase was less than that expected for individuals' age or stage of pubertal development by comparison to age-matched controls, resulting in a decrease in bone mineral density z-scores (38, 41, 42, 43, 44, 45, 46, 47, 48). One study did not report data for AMAB and AFAB individuals separately (42), while three reported a statistically significant decrease in z-scores for AMAB individuals but not AFAB individuals (45, 46, 49).

¹⁰ Tanner stages refer to the development of secondary sexual characteristics.

¹¹ Note that a CT scan will provide a more accurate and truer three-dimensional assessment of bone density than a DEXA scan.

¹² Periosteal and endocortical thickness.

In addition, three studies also reported a high incidence of vitamin D deficiency¹³ at the commencement of GnRHa therapy¹⁴ (38, 46, 49). Two studies reported that the bone mineral density of individuals prior to GnRHa treatment was significantly less than that expected for the general population; AMAB individuals had a higher rate of low bone mineral density z-scores than AFAB individuals (49, 50). In multivariate analyses, bone mineral density z-scores at the initiation of treatment were also statistically significantly associated with low body mass index, AFAB individuals and a younger age at initiation of GnRHa therapy (49).

A single study examined hip bone morphology and reported that in both transwomen and transmen, participants resembled the reference curve for the subperiosteal width (SPW) and endocortical diameter (ED) of the experienced gender but only when GnRHa was started during early puberty (51).

Cardiometabolic outcomes

Studies reporting cardiometabolic outcomes are detailed in 'Supplementary Material 3' (published alongside this document).

Blood pressure

Three studies reported blood pressure data (n = 224, AMAB = 79, AFAB = 145). While one study reported no change in systolic or diastolic blood pressure during GnRHa therapy (52), one reported a decrease in systolic blood pressure in both AMAB and AFAB individuals (53). Another reported that in AFAB adolescents treated only with GnRHa for at least two months there was a significant increase in diastolic blood pressure: a mean diastolic blood pressure of 64 ± 10 mm Hg (56 ± 26 percentile) prior to treatment, rising to 74.0 ± 9.0 mm Hg (74.0 ± 9.0 percentile) (p = 0.019) (54). Blood pressure decreased again after initiation of GAHT (testosterone).

Weight, body mass index or body composition

Thirteen studies reported weight, body mass index or body composition data (n = 839, AMAB = 378, AFAB = 461). However, at least two studies used the same or substantially overlapping cohorts (35), (55). Only two of the 13 studies reported significant changes in body mass index z-scores. No significant change in body mass index was reported in the remaining 11 studies. The study investigating prolonged GnRHa treatment reported an increase in body mass index z-score at 36 months but not at 12 or 24 months in a combined group of AMAB and AFAB adolescents (42). The other study identified an increase in body mass index z-score in AFAB adolescents at 12 months (35).

¹³ Vitamin D is measured to understand the level of calcium absorption in the gut and its potential impact on bone mineralisation and hypocalcaemic tetany. Vitamin D measurement is also essential for determining bone growth and bone remodelling.

¹⁴ Lee et al (50) reported that 15% of adolescents had vitamin D levels below 20 ng/ml. Navabi et al (47) reported only 44.7% of adolescents to be vitamin D sufficient (> 50 nmol/L) and Stoffers et al (39) reported that 74% of adolescents were vitamin D deficient at commencement of GnRHa treatment (< 50 nmol/l).

Lipids

Two studies reported lipid data (n = 254, AMAB = 71, AFAB = 183). One study reported a significant increase in total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) in both AMAB and AFAB adolescents (52). The other study reported no significant change in lipid profiles (56).

Glucose/insulin sensitivity

Two studies provided insulin sensitivity and/or glucose concentration data (n = 209, AMAB 79, AFAB = 130). In one study, both AMAB and AFAB individuals receiving GnRHa were reported to have decreased insulin sensitivity compared to cisgender females. This was demonstrated by a lower inverse fasting insulin, higher homeostatic model assessment for insulin resistance (HOMA-IR), higher fasting glucose and higher HbA1c¹⁵ levels (57). The other study did not identify a significant change in glucose concentration or HOMA-IR (52). Neither study reported development of diabetes during GnRHa treatment.

Renal function

Two studies reported on renal function (n = 160, AMAB = 92, AFAB = 68). Neither study found any statistically significant changes in renal function (35, 42).

Liver function tests

One study reported liver function data (n = 44, AMAB = 25, AFAB = 19). No statistically significant change in liver function was reported (42).

Cognition / executive function

Only one study examined executive function in 20 adolescents treated with GnRHa for GD (AFAB = 12, AMAB = 8) (58). Comparisons were made with two groups: one group of gender-dysphoric adolescents not treated with GnRHa and a second group of cisgender adolescents who were friends of the adolescents treated with GnRHa. Tower of London tasks, a validated test for executive function, were undertaken under magnetic resonance imaging of the brain to identify typical or atypical brain activations. The authors found no significant effect of GnRHa on Tower of London performance scores in either AMAB or AFAB adolescents compared to untreated gender-dysphoric controls. They concluded that there were no detrimental effects of GnRHa on executive function. This case-controlled study was assessed to be of good quality given its use of age matched, non-treated individuals with GD as controls, as well as a second group of age-matched, cisgender individuals from the same socio-demographic group.

Efficacy of GnRHa

Two studies assessed the efficacy of puberty suppression using GnRHa (n = 70, AMAB = 54, AFAB = 36). One study reported LH/FSH levels after GnRHa implants, injections or implants after injections (59). The study cohort consisted of individuals with GD and

¹⁵ HbA1c is a measure of glycaemic control over the previous three- month period.

central precocious puberty (CPP). Although the LH/FSH results were pooled for both groups, pubertal suppression (as measured by LH/FSH levels) was achieved for all 40 individuals with GD and 10 of 12 with CPP. Of the two individuals with CPP who did not achieve LH/FSH suppression, one was AFAB and the other was AMAB. The AFAB individual experienced menses suppression and decreased serum oestradiol. The AMAB individual experienced decreased testosterone and growth velocity with a decrease in puberty development.

The second study found that while basal LH levels did not return to prepubertal levels, there was clinical and hormonal evidence of gonadal suppression (29).¹⁶

Two other studies analysing the efficacy of GnRHa included a satisfaction survey of GD youth with GnRHa implants (60), and a study of efficacy and a comparison of two different brands of implants (30).

Serum concentrations of LH and FSH during GnRHa treatment were reported in 13 of the 20 studies assessing the physical effects of GnRHa treatment. Pubertal suppression¹⁷ appeared to have been achieved in all individuals in almost all studies in which this variable was reported.

Fertility

Assigned female at birth

No peer-reviewed studies examining fertility in AFAB individuals were identified. However three conference proceedings have indicated that oocyte retrieval after GnRHa therapy is possible. (61)(62)(63). These studies may be published in due course.

Assigned male at birth

A single study provided an analysis of sperm quality in transwomen (AMAB) who had received GnRHa therapy, although all these individuals had also received GAHT (28). The study found a small number of non-motile spermatozoa at testicular biopsy in only one of six individuals. However, evidence on the impact of GnRHa alone or in combination with GAHT on fertility in AMAB individuals is limited. A conference proceedings report has reported that sperm could be isolated from the ejaculate of 88% of 78 trans girls (64).

¹⁶ FSH levels were lower in the GD group treated with histrelin than in the group treated with leuprolide (0.8–0.8 mIU/mL vs 1.9–1.2 mIU/mL), $p = 0.004$.

¹⁷ More accurate parameters of pubertal suppression are growth rate, physical changes (such as breasts and penile size) and bone age advancement. Other less precise measures of pubertal suppression are oestradiol and testosterone levels.

Impact of puberty blockers on mental health and wellbeing outcomes for gender-dysphoric adolescents

Pubertal delay can be used to manage the mental distress associated with GD. This brief aims to examine the impact on mental health and wellbeing of treating or not treating GD with puberty blockers in adolescents aged 12–18 years.

It was not possible to assess the evidence of specialised clinic-based care compared to community-based care, given the varied methodologies and population cohorts in the available studies.

Methods

Detailed discussion of the methodology of this part of the systematic review is provided in Appendix 3. The quality of the studies was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group methodology for a systematic review (65). An additional risk of bias assessment, the ROBINS-I tool (66), was also used. The quality assessment of each included study can be found in 'Supplementary Material 4' (published alongside this document).

Quality and limitations

Overall, the studies had several limitations. First, the cohorts were usually drawn from a referred population and were not representative of the general population. Second, GD was assessed using a varied range of assessments, including self-reporting and non-standardised or unvalidated assessments. Third, only one study included a control group. The sample sizes for many studies were small, and most of the studies had sub-groups nested within a larger sample of adolescents receiving a range of treatments. Fourth, there were high participant drop-out rates or incomplete follow-up assessments, resulting in a significant proportion of missing data. Fifth, several important variables (such as demographic details, treatment, age and puberty development stage) and co-interventions (such as lack of mental health and wellbeing support)¹⁸ were not adjusted for, making associations unreliable. Finally, most of the

¹⁸ Mental health and wellbeing support includes counselling, family therapy, school-based support, peer support and community group engagement.

literature which met the inclusion criteria was from a medical model standpoint, where diagnosis and treatment can be perceived as a deficit model of characterising mental health and wellbeing.

Results

Three systematic reviews provided background evidence and context. One review reported on mental health prevalence and patterns in gender-dysphoric adolescent populations (67). Two reviews focused on individuals' mental health and wellbeing outcomes after they had received treatment for GD (67), (68).

The systematic review of the prevalence and patterns of mental health needs¹⁹ (67) included 32 studies. It also included a qualitative analysis of 'mental health (MH) status at assessment, pre-intervention, and baseline for adolescents experiencing (clinically likely) GD' (67). The authors of the systematic review used CCAT v1.4 to assess the quality of the studies. The CCAT quality ratings ranged from 45% to 96%; all except one achieved an overall rating of 4 (good) or 5 (very good). An estimated 3,000–4,000 adolescents (aged 12–18 years) were assessed by specialist centres for GD between 1980 and 2020 in the studies reviewed. All but one study was published within the past ten years (2011–2020). The sample sizes in the studies were generally small. A very limited number of studies provided demographic details such as ethnic diversity, socioeconomic status and diversity in gender identity.

Jurisdictions represented in the studies analysed were primarily from Europe: the Netherlands (n = 6), the United Kingdom (n = 6), Belgium (n = 3), Finland (n = 2), Germany (n = 2), Italy (n = 1), Switzerland (n = 1) and Turkey (n = 1). Three other countries were represented: Canada (n = 5), the United States (n = 8) and Australia (n = 1). Some differences in prevalence and patterns of diagnoses were noted by geographic region. There were several reasons for this cited; the cultural norms of the region were noted most often. Other issues raised in the studies were inequitable access to specialised care and length of waiting time for assessment. The underlying level of the mental wellbeing of the regional population may have also influenced prevalence and patterns of diagnoses. Variation between different health systems within a jurisdiction (such as between states in the United States) and discrepancy in funding pathways (involving insurance, for example) may also have impacted access to care.

The analysis of the included literature summarised patterns of mental health needs; the authors identified several limitations (67). Previous or concurrent mental health diagnoses of depression, anxiety, attention deficit disorder, psychoses and autism spectrum disorder; schizophrenia spectrum disorders; and increased suicidal ideation and self-harm were more common in adolescents with GD. There were differences between AFAB and AMAB individuals for many of these diagnoses when compared to a reference sex cohort. There was evidence in many of the studies that AFAB individuals have poorer mental wellbeing. The correlation with the rapid increase of this group of adolescents presenting for treatment for GD was identified as an

¹⁹ The protocol was submitted to PROSPERO and registered on 17 March 2020 (registration number CRD42020162047).

important trend. The analysis concluded by stating 'we understand very little about the development of mental health problems prior to presentation at GD services, and so do not have a clear understanding of the place of GD within the broader context of young people's mental health' (67). The authors concluded that the quality, volume and representation of different population groups in scientific evidence needs to improve if we wish to understand the complexity of young people's lived experiences of GD. Long-term outcomes need to be monitored and should involve qualitative research methods to capture young people's voices.

Two other systematic reviews have included a discrete analysis of mental health and wellbeing outcomes for gender-dysphoric adolescents (aged 12–18 years) receiving puberty blockers. A systematic review commissioned by the Swedish Agency for Health Technology Assessment and Assessment of Social Services focused on four outcomes: psychosocial effects, effects on bone health, effects on body composition and metabolism, and satisfaction and therapy persistence in children aged younger than 18 years with GD undergoing hormone therapy (68). GRADE and ROBINS-I were used for quality appraisal and risk of bias. Six of the 24 studies included examined mental health and wellbeing outcomes. Global function, suicidal ideation, GD, depression, anxiety, cognition and quality of life were individually assessed as treatment outcomes. All the studies had quality and bias limitations, including small numbers of participants, substantial risk of selection bias, and not accounting for co-interventions as a variable. Because of these limitations, the long-term outcomes of puberty blockers on mental health and wellbeing could not be evaluated and remains unknown.

The second systematic review, published in 2023, is the third paper in a series examining the literature on adolescent GD (31). The same methodology and quality review process was used as for the two other publications (3, 67). Literature was searched to November 2020, and 19 studies met the inclusion criteria. Five of these studies included mental health and wellbeing as an outcome of interest. However, there was limited analysis of these by Thompson et al (31) and no comment on the quality of this evidence. The authors suggested that within this small number of studies there were indications of improvement in mental health and wellbeing over the period individuals received puberty blockers. Yet details related to the duration of treatment and the treatment regime, and how these related to the improvement, were not discussed. The review concluded by stating there was a lack of evidence on targeted mental health and wellbeing treatment for GD, and what evidence there was lacked quality or adequate scope to inform clinicians' and communities' decision-making.

Included in this evidence brief

A total of 10 studies have been included in this brief.²⁰ Five studies were from the United States, two from the United Kingdom, and one each from Australia, the Netherlands and Spain.

All studies were observational cohort studies. Eight were prospective cohort studies and two were retrospective. The studies included a total of 600 individuals. Of the 10 studies, six included information on GD (328 subjects), five on suicidality (334 subjects), four on self-harm (245 subjects), six on anxiety (278 subjects), seven on depression (301 subjects) and six on quality of life (326 subjects). Details of each study are included in Appendix 4.

Evidence for mental health and wellbeing outcomes

Gender dysphoria

Six studies assessed GD before and after commencement of puberty blockers. Five of these were from Europe and the United Kingdom; the sixth was from North America. These studies used the Utrecht Gender Dysphoria Scale (UGDS) (71) and Body Image Scale (BIS) (72) to measure levels of GD.

Costa et al (18) (Costa R, Dunsford M, Skagerberg E, Holt V, Carmichael P, Colizzi M. Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria. *The journal of sexual medicine*. 2015;12(11):2206-14.102 used the Children's Global Assessment Scale (73), which is a clinician's assessment of a range of aspects related to a child's psychological and social functioning, as surrogate evidence of improved GD. For this reason, this study has been excluded as evidence for GD but has been included as evidence for quality-of-life outcomes.

Across all the studies, 328 young people received puberty blockers. Of these, 117 individuals had GD directly re-assessed using the UGDS or BIS before commencing cross-sex hormone treatment or after a set time. In the study by López de Lara, Pérez Rodríguez (74), 100% of the 23 participants were retained for follow up. Findings from the study showed that GD had resolved for every one of these young people by the time they were re-assessed 12 months later, prior to commencing GAHT (74). There

²⁰ Eleven articles were deemed to be eligible for inclusion in this brief. Two studies 69. de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. *Journal of Sexual Medicine*. 2011;8(8):2276-83., 70. de Vries ALC, McGuire JK, Steensma TD, Wagenaar ECF, Doreleijers TAH, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*. 2014;134(4):696-704. used the same cohort and have been included as one study. The earlier study assessed mental health and wellbeing at two time points: prior to puberty blockade and prior to GAHT. The more recent study assessed a third time point prior to GAST.

was high attrition in the follow-up periods for all the other studies. The study by López de Lara, Pérez Rodríguez (74) received a moderate quality rating, due to many confounding factors being incorporated in the analysis. However, it still had serious risks of bias, primarily due to the small numbers and enrolment in a program in which the outcomes of intervention were known by participants and researchers. In de Vries, McGuire (70) (n = 33) Lavender, Shaw (75) (n = 38) and Kuper, Stewart (76) (n = 23), GD and body dissatisfaction persisted through puberty suppression treatment, only remitting after commencement of GAHT and eventually gender reassignment surgery.

Suicidality

Five studies assessed suicidality before and after commencement of puberty blockers. All of these were from North America. Only one study (77) used specialised assessments: the Suicide Behaviours Questionnaire-Revised (78) and Columbia Suicide Severity Rating Scale (C-SSRS) (79). However, these assessments were not used in entirety; only one question from each was used as the assessment metric, reducing the validity of the results. The remaining four studies used questions within the Youth Self Report and its caregiver equivalent the Child Behaviour Checklist (80), the Patient Health Questionnaire 9-item scale (81), the Kessler Psychological Distress Scale (82) and a study in which the assessment was not named (76).

Across these five studies, 334 young people received puberty blockers. Of these, follow-up data was reported in subsequent studies for 100 participants. Three of the studies (76, 77, 83) did not separate participants receiving puberty blockers from the wider sample when reporting the findings (likely because the numbers were so low), so were excluded for further analysis. In the two remaining studies there were discrete sub-groups of participants who received puberty blockers only. In Turban, King (84), 89 of 3,494 respondents reported they had received puberty blockers at the time they needed them in adolescence. This large retrospective North American community-based survey found that receiving puberty blockers was associated with decreased odds of lifetime suicidal ideation ($p = 0.001$), but not with past-year suicidal ideation ($p = 0.09$) and past-month severe psychological distress ($p = 0.38$). While this finding was supported by Lavender, Shaw (75) (n = 38), there were serious limitations to that study, as only 11 participants responded to the question related to suicide. In addition, the study combined results on suicide ideation with results on self-harming behaviour, making any distinction between the two impossible. Both studies had a very low-quality rating and serious or critical risks of bias.

Self-harm

Four studies assessed self-harm or non-suicidal self-injury before and after commencement of puberty blockers. These studies were all from North America, and they made no use of specialised or standardised assessments to measure self-harming. Instead, the studies used questions from within the Patient Health Questionnaire 9-item scale (81), the Suicide Behaviours Questionnaire-Revised (78), the Columbia Suicide Severity Rating Scale (79) and the Youth Self Report and its caregiver equivalent, the Child Behaviour Checklist (80) were used.

Across these four studies, 245 young people received puberty blockers. Of the studies, only one (75) (n = 38) reported separate findings for the sub-group of participants who only received puberty blockers. As mentioned in the previous section, that study used a very small sample (11 respondents), and results on self-harm were combined with those on suicidal ideation, making any distinction between the two impossible. In the 11 participants who self-reported self-harm behaviours and suicidality, there were notable improvements from baseline to one year after commencing puberty blockers. All of the four studies were rated as low or very low quality. All had a serious or critical risk of bias.

Anxiety

Six studies assessed levels of anxiety before and after commencement of puberty blockers. These studies were from the Netherlands, Australia, Spain and North America. The studies used three different self-reported assessments to measure anxiety: the Generalized Anxiety Disorder 7-item scale (85), the Screen for Child Anxiety Related Emotional Disorders (86) and the State-Trait Anxiety Inventory (87).

Across the six studies, 278 young people received puberty blockers. Of these, follow-up results for anxiety were collected for a total of 46 participants. Four studies reported findings for the sub-group receiving puberty blockers, three of which (77, 83, 88) combined results for this sub-group with results for the whole sample, which meant that they had to be excluded from further analysis. Although de Vries, McGuire (70) reported results for anxiety (n = 32), they did not comment on these results in their analysis, so this study was also excluded. Kuper, Stewart (76) (n = 25) reported no statistically significant difference in follow-up scores for the 23 participants who completed the assessment; all remained in the clinical range of 'may indicate presence of an anxiety disorder'. In López de Lara, Pérez Rodríguez (74), average baseline anxiety scores (n = 23) were just below the moderate range; they improved significantly after 12 months of receiving puberty blockers but not to the same level as those of the cisgender control group. Three of the six studies were rated as being of moderate quality (74, 76, 83) but had serious risks of bias scores. The remaining three were rated as being of very low quality (70, 77, 88) with a serious or critical risk of bias.

Depression

Seven studies assessed levels of depression before and after commencement of puberty blockers. These studies were from the Netherlands, Australia, Spain and North America. All studies used self-reported assessments. These were the Quick Inventory of Depressive Symptoms (89), the Children's Depression Inventory (90), the Beck Depression Inventory II (91) and the Centre for Epidemiologic Studies Depression Scale (92).

Across the seven studies, 301 young people received puberty blockers. Of these, 68 were followed up. Four studies did not separate the sub-group of those receiving puberty blockers in reporting results (77, 83, 88, 93); these were excluded from further analysis. There were only 13 of 23 responses for the depression questionnaire in Kuper, Stewart (76). Of these, the average score improved at follow-up from baseline but remained within the normal functioning range at both time intervals. A similar finding

was reported in de Vries, McGuire (70) (n = 32). There was a decrease in depression symptoms from baseline to the first follow-up, but at both time points these were within the lowest range (minimal) of depression. López de Lara, Pérez Rodríguez (74) found differently: a significant decrease in symptoms of depression after 12 months of receiving puberty blockers (n = 23). The average score fell from the mild depression range to just within minimal range ($p < .001$); slightly higher than that of the control group. Three of the six studies were rated as being of moderate quality (74, 76, 83) but had serious risks of bias scores. The remaining four were rated as being of very low quality (70, 77, 88, 93) with a serious or critical risk of bias.

Quality of life

Five studies assessed quality of life before and after commencement of puberty blockers. These studies were from the Netherlands, England, Australia, Spain and North America. A broad view of quality-of-life assessment was taken to include all relevant findings. All measurement tools that assessed social skills, behaviour, function and quality of life were included. These included the Quality of Life Enjoyment and Satisfaction Questionnaire (94), the Strengths and Difficulties Questionnaire, Spanish Version (95) the Social Responsiveness Scale-Second Edition (96), the Youth Self Report and Child Behaviour Checklist (80), the World Health Organization's WHOQOL-BREF quality-of-life assessment (97), the Satisfaction With Life Scale (98), the Subjective Happiness Scale (99) and the Children's Global Assessment Scale (73).

Across the five studies, 326 young people received puberty blockers. Of these, 109 participants were followed up to assess their quality of life. Achille, Taggart (93) did not report the sub-group receiving puberty blockers separately from the whole follow-up sample, so this study was excluded from further analysis. López de Lara, Pérez Rodríguez (74) (n = 23), which used the Strengths and Difficulties Questionnaire, found statistically significant improvement between baseline and follow-up in the areas of emotional symptoms, conduct, hyperactivity and prosocial behaviour ($p < 0.001$). No statistically significant change was observed in peer relationships. Average scores ranged from the upper limit of normal scoring towards being clinically significant to being well within normal ranges, comparable to those of the control group. In Lavender, Shaw (75) (n = 38), 19 respondents reported similarly; both baseline and follow-up scores in the Social Responsiveness Scale fell within the non-clinical range. de Vries, Steensma (69) (n = 32) found that global functioning improved over time but was not statistically significant during the period between baseline and follow-up prior to commencing GAHT. A statistically significant ($p=0.0001$) improvement in global functioning was only observed at follow-up prior to gender reassignment surgery. Using the same global functioning assessment as de Vries et al, (18) reported significantly higher functioning at 12 months follow-up ($p = 0.003$) after puberty suppression and psychological support (n=60), and again at 18 months (n = 35). Participants had a score that was five points, on average, higher than that of the non-receipt comparison group. This increase failed to reach statistical significance, likely because of the large reduction in sample size. With the exception of López de Lara, Pérez Rodríguez (74), which was rated as being of moderate quality, all of these studies were rated as being of very low quality, and all had a serious or critical risk of bias.

Targeted mental health and wellbeing interventions for adolescents more likely to experience gender dysphoria

A systematic review of qualitative studies was undertaken to determine the impact of other interventions specifically targeting the mental health and wellbeing of adolescents who may be more likely to experience GD. This review aims to provide a lived experience perspective to the evidence brief. Given the dearth of studies on mental health and wellbeing interventions for GD as a discrete condition, the search was expanded to include studies which have focused on transitioning adolescents and those who identify as transgender or gender diverse.

Methods

The methodological details are provided in Appendix 5. The quality of studies was assessed using the ConQual Approach (100). The quality assessment of each included study can be found in 'Supplementary Material 5' (published alongside this document).

Quality and limitations

In the six studies reviewed, the quality ranged across the ConQual spectrum. Three were rated as being of high or moderate quality and three of low or very low quality. The studies were all small in sample size and/or for limited duration.

Results

Five systematic or comprehensive literature reviews focusing on mental health and wellbeing interventions for transgender adolescents and/or their family were included. These have been summarised as a narrative to provide context and an update of current research. Of the five reviews, only one was a qualitative research review; the remainder were inclusive of quantitative and qualitative research or were evaluations of an intervention.

The only qualitative systematic review identified was also the only one to follow a formal protocol: Psychological/psychosocial interventions for gender diverse youth under 18 years of age and their families: a systematic review: PROSPERO 2020 CRD42020163995 (101). The Mixed Methods Appraisal Tool (102) was used for quality appraisal of the included studies. Lehmann and Leavey (101) identified four studies

which met the inclusion criteria. Due to this limited result, the inclusion criteria were expanded to add an additional four studies, with a caveat that each study had been appraised as being of a low-quality. The review found limited evidence about which family interventions increased resilience in transgender youth or offered protection against adverse mental health outcomes. Group interventions for parents appeared to reduce isolation for most participants by creating a new support network. It was unclear whether parent support groups or the home environment impacted on the mental health outcomes for transgender children living in the home. The review concluded that there was a need for research with families to investigate whether general family approaches or specific gender identity-focused family interventions were most effective to support the mental health and wellbeing of this population (101).

In another systematic review which focused on family interventions to support transgender and gender diverse youth, Malpas, Pellicane (103) followed the Preferred Systematic Reviews and Meta-Analyses guidelines. A quality appraisal of the evidence was not documented as part of the systemic review. The age range of 'youth' was not defined. The review included 32 articles from qualitative and quantitative research studies and coded and thematically organised them for the analysis under the categories 'population of interest', 'treatment modalities used', 'outcome data (if any) and/or empirical support', 'clinical strategies suggested' and 'additional relevant themes explored'. It found there was an absence of youth and family outcome data and empirical research on what constituted effective family therapy and family-based services for transgender and gender expansive youth. In the qualitative research, the most common feature of the various interventions was a combined approach in which close support for the youth was provided at the same time as support for the caregivers or family while community services and systems were also targeted. Malpas, Pellicane (103) concluded with two methodological recommendations related to research involving people from minority communities. The authors called for greater inclusion and reflection of realities and legacies of racial and ethnic systemic inequities within methodologies and research design. These influential socio-cultural factors are often only acknowledged as a limitation of the research findings rather than being seen as important variables.

They recommended future research that is quantitative, qualitative, community-based and participatory, and uses appropriate methodologies, to examine the effectiveness of specific family-based interventions for transgender and gender expansive youth. They also recommended that such future research should also have the primary aim of developing best-practice recommendations to guide practitioners.

In a more specific systematic review, Christensen, Oh (104) examined evidence related to interventions which reduced suicidal ideation and suicide attempt among transgender youth. A systematic review guideline was not referred to, but all studies were appraised with a risk of bias tool (the Newcastle-Ottawa Scale). The overall quality of reviewed evidence was found to be low, and the risk of bias was high. The involvement of youth aged younger than 24 years was one of the inclusion criteria. Primary outcomes of interest were suicide-related thoughts and behaviour. Secondary outcomes of interest were depression severity, anxiety severity, wellbeing measures, global functioning and quality of life. While the review followed a quantitative systematic review methodology, it also included 17 studies as a qualitative synthesis. The review concluded that interventions that might reduce the risk of suicide for

transgender children and adolescents by influencing suicide-related thoughts and behaviours included gender-affirming crisis hotlines, gender-affirming medical care such as GnRHa and GAH, online media-based outreach, interventions fostering safety and connectedness, and family system-based interventions. The review's recommendations highlighted an urgent need for high-quality studies of interventions to reduce risk of suicide among transgender youth.

In a literature review (not a systematic review) about interventions in the United States that have been developed or adapted to treat suicidality among LGBTQIA+ youth (inclusive of lesbian, gay, bisexual, transgender, questioning/queer, intersex and asexual adolescents and young adults), a similar conclusion was made (105). The review analysed interventions that have been developed or adapted to treat suicidality among LGBTQ+ youth using an interpersonal theory of suicide and minority stress theory and incorporating the unique risk factors that affect LGBTQIA+ youth differently. The age range of 'youth' was not defined. A quality appraisal of the evidence was not documented. The review found 35 peer-reviewed intervention studies that met the inclusion criteria. Primary outcomes of interest were studies which focused on psychotherapy treatment studies targeting suicidal ideation, attempts or behaviour and treatments modified or applied intentionally for LGBTQIA+ youth.

The review found that several approaches for suicidality and other mental health concerns have been adapted and tested, but sample sizes have generally been small, and studies have overwhelmingly been focused on sexual minority youth as a whole; few studies have differentiated the needs of transgender youth within this population. Few approaches targeted or engaged families and/or the immediate social networks that may support youth struggling with suicidality. Little attention has been directed toward the implementation of such approaches into service settings and macro-level systems where LGBTQIA+ youth are most likely to receive care. The authors of the study recommended that future research efforts aim to modify promising suicide-specific treatments for LGBTQIA+ youth and seek to evaluate the fit of these treatments in organisations serving this population. Future recommendations were for research to focus on the suicide readiness of settings and organisations that see the majority of LGBTQIA+ populations, continued adaption and testing of promising approaches for specific identities within the LGBTQIA+ 'umbrella' and a better understanding of the systems of care in which these youth receive services.

The final literature review included in this paper examined cognitive behaviour therapy (CBT) as an intervention for adolescents with GD and social anxiety (106). The age range of 'youth' was not defined. No quality appraisal of the evidence was documented. The review found 18 articles that met the inclusion criteria and reviewed each article to assess: (1) the empirical research that has explored mental health disparities in transgender youth, specifically social anxiety; (2) treatment for social anxiety, specifically CBT; and (3) CBT techniques adapted for transgender individuals. The review found that while some studies had researched the efficacy of CBT as an intervention for people who identified as a sexual minority, it was unknown whether this evidence would apply to transgender youth who had social anxiety disorder and/or GD. This lack of empirical support informed the review's recommendations for future research: for more studies about adapting CBT for youth with social anxiety and GD to provide evidence-based guidance for mental health practitioners' work.

In summary, three systematic reviews focused on mental health and wellbeing interventions for GD in youth aged 12–18 years, or their families. There was only one qualitative systematic review, and no reviews focused on the lived experience of receiving a mental health and wellbeing intervention. The reviews generally applied quality appraisal tools and found that the quality of existing research was low. All five reviews concluded that further research is needed for this specific population group, that is rigorous and inclusive of appropriate methodology.

Included in this evidence brief

There were six different interventions in the included studies: online youth self-compassion training (107), a cognitive behaviour and systemic clinic-based therapeutic youth group (108), multi-disciplinary specialised clinic care (109), a six-day residential pride youth camp (110), a parent psychotherapeutic group (111) and a trauma-informed parenting skills group (112). A summary of evidence for each of these is provided in Appendix 6.

Youth-focused

Of the six intervention studies, four were centred on youth voice. Bluth et al found that after completing an online youth self-compassion training programme, 11 transgender young people reported feeling less alone and isolated in a post-evaluation survey Bluth, Lathren (107). A study looking at a nine-week structured youth group involving 11 transgender members (108) found that after the experience the young people reported feeling significantly more included and supported by their peers, less alone and more able to trust people. Interviews with 36 transgender youth who attended a multi-disciplinary gender-affirming health clinic found that most participants had felt that having access to medical intervention, professional support and assistance in coping with their GD at a dedicated clinic a positive experience. Individuals also reported improved overall wellbeing, including feelings of greater happiness, better mental health or better functioning at school (109). Focus groups with eight attendees who had attended a six-day residential camp for gender-diverse adolescents facilitated by gender-diverse young adults found that this environment allowed the young people to further their communication skills and process some of the traumatising experiences they faced in their lives (110).

Parent/carer focused

A study involving 11 parents/carers of gender-diverse youth who attended an 11-month psychology-informed support group (111) found, based on the post-programme evaluation, that attendees reported an improved capacity to empathise with their children. This led to the parents/carers supporting their children and having achieved a deeper understanding of gender diversity and of their children's need for love and support.

The study earlier referred to that involved a nine-week structured youth group (108) also surveyed the parents/carers of attendees. The parents reported that their children felt less alone and that their confidence had improved after attending the group.

Societal impact

Only one study incorporated societal impact into the design of its research. In this study (110), a residential camp for LGBTQ youth was deliberately designed to be held at the campus of a university attendees were likely to consider attending after high school. Campus faculty, staff and students were primarily the coordinators of the camp. Focus groups with the coordinators, found that they had become more educated about LGBTQ issues, and carried this education back to the university environment. In addition the peer counsellors, who were university students, played a key role in facilitating camp attendees' development of confidence and resilience and provided role models for their life at the university.

Key attributes of successful interventions

All studies itemised the key attributes that contributed to the positive impact of an intervention for participants. These included a safe and welcoming space; activities and practices that encouraged body kindness and awareness (107); opportunities to share experiences and learning alongside others in a similar situation (111), (112); enabling the formation of trusted peer relationships (108); group meetings that were scheduled at the right time for a family; having an established gender-affirming approach, policies and practices (110), (109); and timing at a critical juncture of development (110).

Legislation and Governance

International context

Suppressing puberty as part of gender-affirming health care for gender-dysphoric adolescents was first advocated in 1996 (113). However, use of this intervention remained uncommon until the Dutch Protocol²¹ became more widely adopted in the mid-2000s (114). Parental or guardian consent is required. Managing use of the intervention, and accommodating changing views toward the rights of minor adolescents to consent (or not consent) to medical treatment as they develop greater autonomy has necessitated the development of legislative and governance arrangements for access to puberty blockers in many countries. These arrangements are broad and varied.

One legislative example has involved the concept of Gillick competence.²² A court's assessment of Gillick competence is binding in England and Wales, and this has been adopted to varying extents in Australia, Canada and New Zealand (115, 116). In medical situations where there is a dispute between an adolescent, their parents or guardians and/or treating medical practitioners, court involvement may be required to determine whether the proposed medical treatment is in the child's best interests (117). Legal directives about the prescription of puberty blockers control medical decision-making pathways for GD management. Pharmaceutical and medical treatment regulatory authorities may also impose legally binding processes that prescribers are required to adhere to.

To provide a snapshot of current legal, regulatory and governance arrangements, a scan of various international approaches was carried out. Published and grey literature was searched. Due to the multitude of governance structures and funding systems for health care in various countries, it was difficult to produce a comprehensive summary. Many documents related to regulations and legislation were not in English; these have been excluded.²³ The United States, Canada and Australia have many different legal and governance structures, because national and provincial or state structures differ.

World Health Organization

The World Health Organization is in the process of developing a guideline on the health of transgender and gender diverse people, including on health policies and

²¹ The protocol states that individuals presenting with GD should be provided with counselling and advice until such time that they are considered able to provide informed consent to the initiation of GAHT; generally when the adolescent is no longer a legal minor.

²² This term 'Gillick competence' originated in England and Wales in the 1980s after a legal case by claimant Victoria Gillick. Under certain circumstances, 'Gillick competence' can be granted to a child or adolescent under the age of 16, allowing them the right to give consent to medical treatment in lieu of the permission or knowledge of their parent or legal guardian.

²³ Countries searched for and excluded due to language barriers were the Netherlands and Spain.

legal recognition of self-determined gender identity (1). While these are not legally binding, they may influence future governance and legal structures.

United Kingdom

The United Kingdom introduced new legislative requirements in this area in 2020.²⁴ These require a multi-professional review group²⁵ to review all cases being referred by GIs to endocrine services, and all cases to follow an interim clinical guidance specification. The interim specification for children and young people with gender incongruence was published by NHS England in June 2023 (119). It requires the ICD-11 diagnostic criteria to be followed, and states that administration of puberty blockers is not to be commenced before Tanner stage 2²⁶ (119). When considering the validity of consent for medical treatment in the United Kingdom, practitioners are directed to the General Medical Council guidance for decision-making and consent (121). That guidance sets out people's rights to make health care decisions for themselves when their consent is affected by the law ('mental health or other legislation and by common law powers of the courts' (such as the power to assess Gillick competence)) and advises medical practitioners to 'be aware of what treatment is, and is not, legally permissible' (p. 38).²⁷

Finland

Finland does not have any specific laws governing the provision of puberty blockers for GD. The Council for Choices in Health Care in Finland (COHERE Finland) provides governance of public health care decision-making. In 2020, COHERE recommended 'the diagnostics of GD, the assessment of the need for medical treatments, and the planning of their implementation are centralised by law to the multi-professional research clinics of Helsinki University Central Hospital (HUS) and Tampere University Hospital (TAYS)' (122). COHERE has adopted a recommendation on medical treatment methods for GD, but the updated summary within it identifies neither the DSM-5 nor the ICD-11 as endorsed diagnostic criteria (122). The legal age of adulthood is 18 years in Finland. The initiation of hormonal interventions that alter sex characteristics may be considered before a person is 18 years of age only if it can be ascertained that their identification as another gender to their sex assigned as birth is of a permanent nature

²⁴ 'Children and young persons under 18 are not competent to give consent to the administration of puberty blocking drugs. The information given to those under 18 by the defendant [Gender Identity Development Services] is misleading and insufficient to ensure such children or young persons can give informed consent. The absence of procedural safeguards, and the inadequacy of the information provided, results in an infringement of the rights of such children and young persons under Article 8 of the European Convention for the Protection of Human Rights and Fundamental Freedoms' (118. Cass H. Independent review of gender identity services for children and young people: Interim report. National Health Service; 2022.

²⁵ An independent group hosted by NHS England to decide on an individual's gender-affirming care pathway.

²⁶ Tanner stages (also known as 'Sexual Maturity Rating') is a classification system used to assess and monitor the development and sequence of the secondary sex characteristics of children during puberty. Tanner stage 1 corresponds to the pre-pubertal form, and Tanner stage 5 is the final adult form (120. Emmanuel M, BR. B. Tanner Stages. Treasure Island. Florida: Stat pearls publishing; 2023.

²⁷ Following the publication of the final Cass review (April 2024), UK has decided to restrict administration of puberty blockers to clinical trials. While our evidence review refers to the interim Cass report, the final report was outside the review timeframe.

and is causing severe dysphoria. In addition, it must be confirmed that ‘the young person is able to understand the significance of irreversible treatments and the benefits and disadvantages associated with lifelong hormone therapy, and that no contraindications are present’ (123). Further detail related to how these decisions are made was not available.

Sweden

Sweden’s National Board of Health and Welfare updated its guidelines for the care of children and adolescents with GD in 2022 to state: ‘treatment with GnRH analogues, gender-affirming hormones, and mastectomy can be administered in exceptional cases’ (124). The updated guidelines refer to the Dutch Protocol (125). Diagnostic criteria are not specified; however, the Dutch Protocol uses DSM-5 (125). Further detail related to how decisions are made for managing exceptional cases was not available.

Australia

Except in South Australia, in all Australian states the prescription of puberty blockers for GD in people under 18 years requires consent from all parties who have parental responsibility for the young person. In South Australia, the legal age of adulthood is 16 years. This ruling has been applied even when a young person is deemed Gillick competent and consents to their own treatment. If there is any dispute between treating medical practitioners and parents regarding a young person’s Gillick competence or diagnosis or treatment, a court application is required (117).

Canada

The only federal legislation or governance related to use of puberty blockers to manage GD in Canada relates to the regulation of pharmaceuticals. Health Canada, through the Food and Drugs Act 1985, approves pharmaceuticals and audits and monitors their safety, efficacy and quality (126). The Canada Health Act legislates for the provinces and territories to administer and deliver most of Canada’s health care services; all provincial and territorial health insurance plans are expected to meet national principles set out under the Act (127). Further detail related to minors, medical consent and assessing competence, and on how decisions are made related to puberty blockers, was not available.

The United States

In the United States, the US Food and Drug Administration (FDA) functions at the federal level to govern the prescription of puberty blockers for GD. The FDA regulates pharmaceuticals but does not regulate the practice of medicine (128). Many states are currently enacting new legislation addressing access to puberty blockers (129). For example, the Wisconsin Assembly passed legislation in 2023 (in (Bill 465) prohibiting gender transition medical intervention for individuals under 18 years of age.

New Zealand

Currently in New Zealand there is no specific legislation related to the use of puberty blockers. Consent to medical treatment can be given by legal minors of or over the age of 16 years; this is detailed in section 36 of the Care of Children Act 2004. That Act also outlines the process of referral to the Family Court for rulings when there is disagreement between parties. Under common law, Gillick competence is used to establish if an adolescent under 16 years is capable of giving consent to medical treatment (130). The use of these medicines for GD is therefore considered off-label, and it is the medical practitioner's responsibility to manage and monitor treatment regimes. The Medicines Act 1981 allows practitioners to determine the dose and route of a medicine that they prescribe, and the indication for which it is prescribed. However, the prescriber must take responsibility for the safety and long-term impacts of this prescription if it is off-label.

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Appendix 1: Medical Management of GD - systematic review method

Methods

To maximise the identification of relevant publications, a broad search strategy was used based on the PRISMA systematic review of use of GnRHa in adolescents with GD by Thompson et al (Thompson et al 2023) (Supplementary Material 4.5, published alongside this document). Relevant recent studies were identified by extending the search period of that study from November 2020 to September 2023.

Inclusion criteria

- English language publication
- peer reviewed publication
- published between November 2020 - 31 August 2023
- age within 12-18 years, or as discrete age sub-set
- GD diagnosed by clinician OR self-reported
- receiving puberty blockers as an intervention
- pre-GnRHa-treatment assessment.

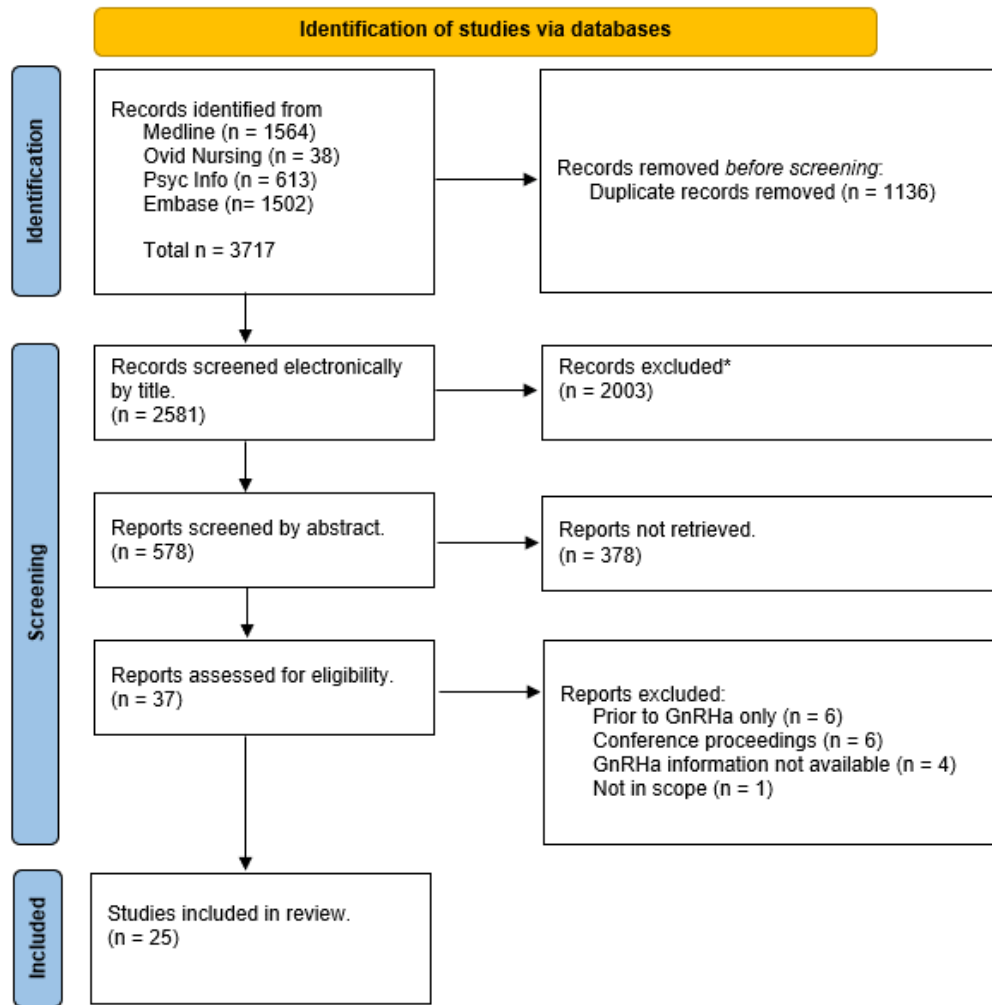
Study selection

The PRISMA systematic review study selection process was used to identify relevant studies. Endnote 20 was used to manage references. After removal of duplicate references, screening, and assessment of papers for inclusion was conducted by the primary reviewer. Papers were excluded based on the title or abstract if they did not clearly report on GD, did not include original data on adolescents aged 12-18 years, or were not in English. Papers were retained if there was not sufficient information to reject them. Full-text files were obtained for the remaining articles. Papers were rejected at this stage if they

- did not contain original data
- were case reports
- did not have identifiable data on individuals with GD aged 12–18 years inclusive
- not peer reviewed
- not obtainable.

Following selection, a second reviewer reviewed all papers to reduce the risk of inclusion bias. Where any disagreement regarding inclusion existed, a discussion was held to reach a consensus. If no agreement could be reached, a third reviewer made a decision regarding inclusion.

Figure 4: PRISMA Study Selection Clinical implications of Puberty Blockers as an intervention for adolescents with gender dysphoria



* Systematic reviews, guidelines, commentaries, errata, not in scope

Quality assessment

The Newcastle Ottawa Scale (NOS) was used to assess the quality of the cohort studies and case control cohort studies selected. NOS uses three domains, each with a variable number of sections, to assess quality (Wells et al 2021). A star rating is used for each section to provide a final rating of Good, Fair or Poor. The criteria for each section was constructed using published guidelines (Wells et al 2021) and agreed upon by the two primary authors (Supplementary Material 2). The quality of each paper was assessed based on the primary outcome of the study.

Appendix 2: Summary of evidence medical management of GD

No	Country / Year	Reference	Design	Setting	Age Range (years)	Date Range	N	Gender		Outcomes
								AMAB	AFAB	
Studies of medical complications of GnRHs										
1	N'lands 2022	(L. S. Boogers et al 2022) Transgender Girls Grow Tall: Adult Height Is Unaffected by GnRH Analogue and Estradiol Treatment	Retrospective, longitudinal	Specialist GIS VU University Centre, Amsterdam	< 18	1972 - 2018	161	161	0	Anthropometry
2	N'lands 2023	(Lidewij Sophia Boogers et al 2023) The dose-dependent effect of estrogen on bone mineral density in trans girls	Retrospective, Longitudinal.	Specialist GIS VU University Centre, Amsterdam	<18	1972 - 2018	87	87	0	Bone density
3	UK 2021	(Carmichael et al 2021) Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK	Prospective, longitudinal.	Speciality GIS Tavistock & UCL London	12 – 15	2011 – 2015	44	25	19	Bone density Liver function Renal Function
4	Belgium 2023	(S. Ciancia, Klink, Craen, et al 2023) Early puberty suppression and gender-affirming hormones do not alter final height in transgender adolescents	Retrospective	Ghent University Ghent	<18	2004 - 2023	32	22	10	Anthropometry
5	UK 2019	(Rahul Ghelani, Lim, Brain, et al 2019) Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria	Retrospective, Longitudinal	Speciality GIS Tavistock & UCL	15 - 17	2013 - 2015	36	11	25	Anthropometry

Not Government Policy

No	Country / Year	Reference	Design	Setting	Age Range (years)	Date Range	N	Gender		Outcomes
								AMAB	AFAB	
6	UK 2019	(Joseph et al 2019) The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort	Retrospective, longitudinal	Speciality GIS Tavistock & UCL	12-14	2011 - 2016	70	31	39	Anthropometry Bone Density
7	N'Lands 2020	(Klaver et al 2020) Hormonal treatment and cardiovascular risk profile in transgender adolescents	Retrospective, longitudinal	Specialist GIS VU University Centre, Amsterdam	GnRHa < 18 FU age 22	1998 - 2015	192	71	121	Cardiovascular
8	N'Lands 2015	(Klink. et al 2015) Bone mass in young adulthood following gonadotropin-releasing hormone analogue treatment and cross-sex hormone treatment in adolescents with gender dysphoria	Retrospective, longitudinal	Specialist GIS VU University Centre, Amsterdam	< 18 years at commencement of GnRHa.	1998 - 2012	34	15	19	Bone Density
9	Canada 2021	(Navabi et al 2021) Pubertal suppression, bone mass, and body composition in youth with gender dysphoria	Retrospective Observational	Specialist GIS Children's Hospital Ontario	< 18	01/2006 - 04/2017	116	36	80	Anthropometry Bone density Vit D
10	USA 2021	(Nokoff et al 2021a) Body composition and markers of cardiometabolic health in transgender youth on gonadotropin-releasing hormone agonists	Prospective observational	Specialist GIS Children's Hospital Colorado	<20	2016 - 2019	17	8	9	Anthropometry Metabolic
11	Israel 2020	(Liat Perl et al 2021) Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogues followed by testosterone treatment in transgender male adolescents: A pilot study	Retrospective Observational Longitudinal	Dana-Dwek Children's Hospital Tel Aviv	Adolescents. Not otherwise specified	2013 - 2018	15	0	15	Cardiovascular
12	N'lands 2016	(S. E. Schagen et al 2016)	Prospective, longitudinal	Specialist GIS VU University Centre, Amsterdam	<18	1998 - 2009	116	49	67	Anthropometry Renal Function Liver function

Not Government Policy

No	Country / Year	Reference	Design	Setting	Age Range (years)	Date Range	N	Gender		Outcomes
								AMAB	AFAB	
		Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents								
13	N'lands 2020	(S. E. E. Schagen et al 2020b) Bone development in transgender adolescents treated with GnRH analogues and subsequent gender-affirming hormones	Prospective, longitudinal	Specialist GIS VU University Centre, Amsterdam	<18	1998 - 2009	121	36	42	Bone Density
14	USA 2021	(Schulmeister et al 2022) Growth in transgender/gender-diverse youth in the first year of treatment with gonadotropin-releasing hormone agonists	Prospective Observational Longitudinal	Speciality GIS Multiple sites	<18	07/2016 – 09/2018	55	26	29	Anthropometry
15	N'lands 2015	(Staphorsius. et al 2015) Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria	Cross-sectional	Specialist GIS VU University Centre, Amsterdam	12 -18	Not stated	20	8	12	Executive Function
16	N'lands 2019	(I. E. Stoffers et al 2019) Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria	Retrospective case series	Speciality GIS VU University Centre, Amsterdam	12 - 18	2010 - 2018	62	0	62	Bone density Metabolic Hormonal
17	N'lands 2020	(van de Grift et al 2020) Timing of puberty suppression and surgical options for transgender youth	Retrospective Observational	Specialist GIS VU University Centre, Amsterdam	All ages	2006 - 2013	300	116	184	Mastectomy
18	N'lands 2021	(M. A. van der Loos et al 2021a) Development of hip bone geometry during gender-affirming hormone therapy in transgender adolescents resembles that of the experienced gender when pubertal suspension is started in early puberty	Retrospective, longitudinal	Specialist GIS VU University Centre, Amsterdam	<18	1972 - 2018	322	106	216	Bone density
19	N'Lands 2017	(Vlot et al 2017)	Retrospective, longitudinal	Specialist GIS VU University Centre, Amsterdam	<18	2001 - 2011	70	28	42	Bone density

Not Government Policy

No	Country / Year	Reference	Design	Setting	Age Range (years)	Date Range	N	Gender		Outcomes
								AMAB	AFAB	
		Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents								
20	N'lands 2022	(Willemsen et al 2023) Just as tall on testosterone; a neutral to positive effect on adult height of GnRHa and testosterone in trans boys	Retrospective, longitudinal	Specialist GIS VU University Centre, Amsterdam	< 16 years	1972 – 2018	146	-	146 TM	Anthropometry
Studies of Fertility and Efficacy										
Efficacy of Gonadotrophin										
P1	USA 2022	(Hobson et al 2022) Transgender youth experiences with implantable GnRH agonists for puberty suppression	Survey	Specialist GIS Children's Hospital Pennsylvania	Mean age 11.5	2008 - 2019	36	15	21	Satisfaction with implant
P2	USA 2023	(Ni et al 2023) Review of implant gonadotrophin-releasing hormone agonist use: experience in a single academic center	Retrospective Comparative	Specialist GIS Multisite Trans Youth Care Study	<18	01/2018 – 03/2021	40	17	23	GnRH implant efficacy
P3	USA 2021	(Olson-Kennedy et al 2021) Histrelin implants for suppression of puberty in youth with gender dysphoria: A comparison of 50 mcg/day (Vantas) and 65 mcg/day (SupprelinLA)	Retrospective Trial	Specialist GIS Children's Hospital LA California	9-15	NS	66	32	34	Gonadotrophin Suppression
P4	USA 2021	(Mejia-Otero et al 2021) Effectiveness of puberty suppression with gonadotropin-releasing hormone agonists in transgender youth	Retrospective Cohort	University Arkansas Arkansas	<18	01/2014 – 06/2018	30	17	13	Gonadotrophin suppression
Fertility Preservation AMAB										
F1	Australia 2021	(Peri et al 2021) Predicting successful sperm retrieval in transfeminine adolescents after testicular biopsy	Retrospective cohort	Specialist GIS Royal Melbourne Melbourne	< 18	2010 - 2019	25	25		Semenalysis Biopsy

Not Government Policy

No	Country / Year	Reference	Design	Setting	Age Range (years)	Date Range	N	Gender		Outcomes
								AMAB	AFAB	
Fertility Preservation AFAB										
No studies were identified										

Appendix 3: Puberty blockers and impact on mental health and wellbeing outcomes systematic review method

Eligibility criteria

A comprehensive search strategy was designed and implemented with a senior Ministry of Health Librarian and is detailed in Supplementary Material 4.5. Key mental health and wellbeing outcomes were identified by a broad reading of the literature and contextual background documents. Mental health and wellbeing outcomes which were most frequently cited, presented the highest risk of harm, and were likely to be important for young people were chosen as the foci of the review, these being: gender dysphoria, suicidality, self-harm, anxiety, depression, and quality of life.

Inclusion criteria

- English language publication
- peer reviewed publication
- published between 1990 and August 2023
- mean age within or 12-18 years as discrete age sub-set
- gender dysphoria diagnosed by clinician OR self-reported
- receiving or not receiving puberty blockers as an intervention
- pre-and post-intervention assessments of at least one of the predetermined outcome measures were available
- statistical analyses of the impact of puberty blockers on predetermined outcomes were available.

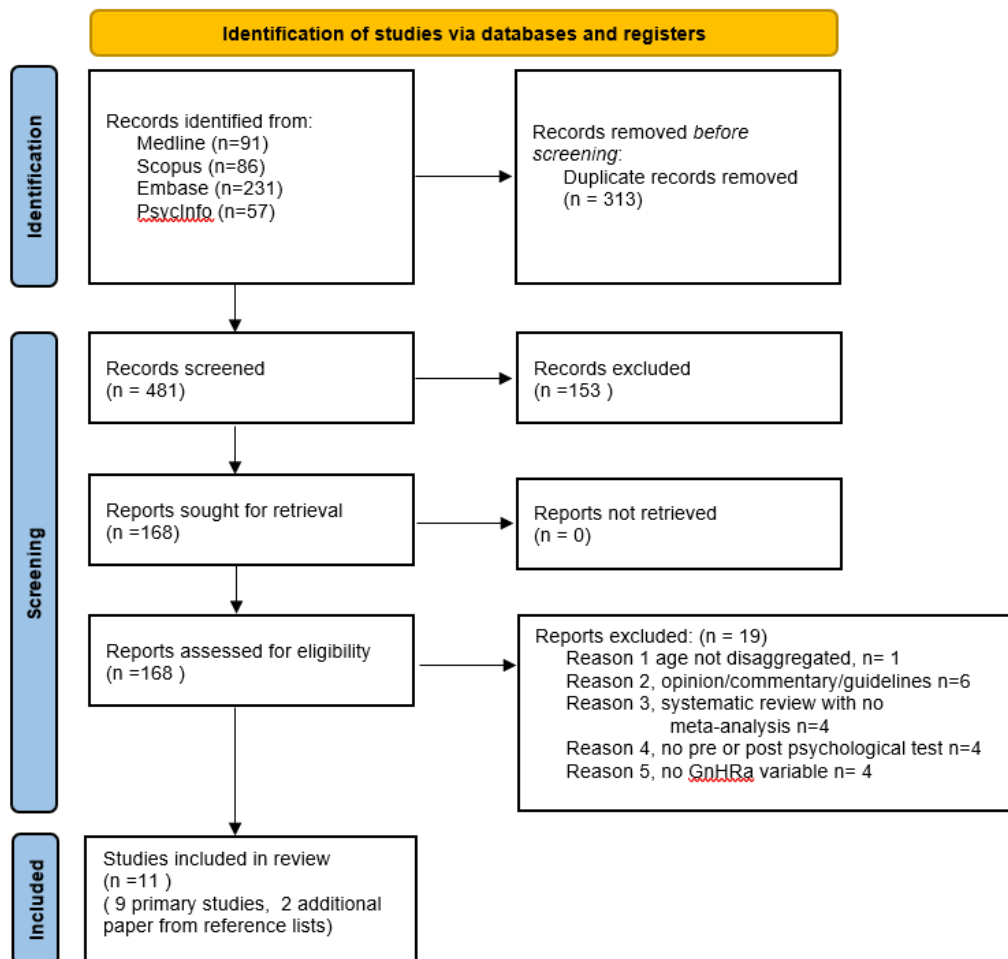
Search and study selection

The final search was undertaken on 3 September 2023. The study selection process is illustrated in Figure 5. Endnote 20 was used to manage references. After removal of duplicate references, screening and assessment of papers for inclusion was conducted by the primary reviewer. Papers were excluded based on the title or abstract if they did not clearly report on gender dysphoria, did not include original data on adolescents, or were not in English. Papers were retained if there was not sufficient information to

retain them. Full-text files were obtained for the remaining articles. Papers were then excluded if they

- were opinion, clinical guidelines, or otherwise did not contain original data
- included conditions other than gender dysphoria (such as autism or eating disorders)
- did not have identifiable data on individuals aged 12–18 years, inclusive
- not peer reviewed (such as pre-prints)
- not obtainable.

Figure 5: PRISMA study selection for mental health and wellbeing outcomes for adolescents with gender dysphoria



Following selection, a second reviewer reviewed all papers to reduce the risk of inclusion bias. Where any disagreement regarding inclusion a discussion was held to reach a consensus. If no agreement could be reached a third reviewer made a decision regarding inclusion.

Quality assessment

All papers were rated by two reviewers for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group methodology for a systematic review (GRADE Handbook 2013). The GRADE

methodology guides the healthcare question, evaluation of the available evidence through a systematic search strategy, and a transparent assessment of the quality of evidence for pre-identified outcomes. An additional Risk of Bias assessment, The ROBINS-I tool (Sterne et al 2016) was also used and has been added into the Summary of Evidence Table. (Supplementary Material 4).

The ROBINS-I protocol requires key co-interventions to be identified to assess the studies against, as this is also an important source of bias. Key co-interventions in the literature that were likely to have an impact on outcomes associated with mental health and wellbeing of the participants, were identified. These were:

- counselling
- family therapy
- school-based support
- peer support
- community group engagement.

We have documented decisions that were made for risk of bias in the supplementary materials published alongside this document.

Appendix 4: Puberty blockers; mental health and wellbeing outcomes for adolescents with gender dysphoria

Summary of Evidence - included studies

Author & Country	Study Design	Sample characteristics	Source of Participants	Age, mean	Puberty blocker	Pre-post intervention follow up (months)	Assessment used	Confounding domains controlled for ¹	Psychosocial outcome ²	GRADE quality of evidence ³	ROBINS-1 Risk of Bias ⁴
Costa et al. (2015) Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria. <i>The journal of sexual medicine</i> , 12(11), 2206-2214. London UK	Longitudinal observational study 2010-2014	201 participants Clinically diagnosed and eligible for PBs Comparison group: n = 169 derived from child and adolescent services cohort in Stockholm	Gender Identity Development Service referrals	12-17 years Mean= 15.52 years AMAB:AFAB ratio = 1:1.6	101 received 100 did not receive	T1 = 6 months T2 = 12 months T3 = 18 months	Utrecht GD Scale (UGDS) Children's Global Assessment Scale (CGAS)	Psychological therapy provided for both cohorts	Gender Dysphoria (UGDS) [40-60 is clinical range] Baseline av score = 54.7 (±12.3) T1 T2 T3 = no follow up assessment QoL (CGAS) Baseline av score = 57.7±12.3 [60-51 score = variable functioning with sporadic difficulties or symptoms in several but not all social areas...] Not received PBs Baseline n = 100, 56.63 T1 n = 100, 60.29 (p = 0.05) T2 n = 61, 62.97 (p = 0.005) T3 n = 36, 62.53 (p=0.02) Significantly higher functioning after 6 mths psychological support only Received PBs Baseline n = 101, 58.72 T1 n = 101, 60.89 (p = 0.19) T2 n = 60, 64.70 (p = 0.003) T3 n = 35, 67.40 (p = <0.001) Significantly higher functioning after 12 months of puberty suppression & psychological support Follow-up at 18 months the PB group had a 5-point higher CGAS score than the non-receipt group, this difference failed to reach significance, possible because of sample size	Gender dysphoria Very Low Suicidity; N/A Self-harm; N/A Anxiety; N/A Depression; N/A Life satisfaction/QoL Very Low	Critical risk of bias Serious risk of bias
deVries et al. (2011) Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. <i>Journal of Sexual Medicine</i> , 8(8), 2276-2283. deVries (2014) Young adult psychological outcome after puberty	Prospective follow-up 2000-2008	70 participants Clinically diagnosed AMAB = 33 Mean age at T0 = 14.25 years AFAB = 37 Mean age at T0 = 15.21 At initial assessment for eligibility AMAB were roughly one year younger than AFAB who had a mean age of 14,	Center of Expertise on Gender Dysphoria [previously Amsterdam Identity Clinic] First 70 of the first cohort of 111 [from 196 referrals, 140 considered eligible] who received PB treatment at the clinic	11-17 years T0 start of PB mean age = 14.75 years T1 start of cross sex hormones (GAHT) Mean age = 16.7 years T2 12 months post gender	T0 n = 70 Only data of adolescents who completed all the questionnaires were reported and these changed between 2011 & 2014 studies n = 41 (2011) n = 33 (2014)	T0 shortly after their attendance at the gender identity clinic T1 shortly before starting GAHT treatment T2 12 months post GRS	Child Behaviour Checklist -parent (CBCL) Youth Self-Report (YSR) Beck Depression Inventory - II (BDI) Trait Anger and Anxiety Scales of the Spielberger State-Trait Personality Inventory (STAI)	2011 only reported not updated for 2014 study: 44/70 lived with both parents 26 lived with 'other' (not defined)	Gender Dysphoria (UGDS) [40-60 is clinical range] n = 33 (2014) T0 = 53.51 (±8.29) [PB only] T1 = 54.39 (±7.70) [PB only] T2 = 15.81 (±2.78) T0-T2 P = <0.001 Gender dysphoria and body image difficulties persisted through puberty suppression (at T0 and T1) and remitted after the administration of GAHT and GRS (at T2) Anxiety (STAI) [temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety Scoring: "no or low anxiety" (20-37), "moderate anxiety" (38-44), and "high anxiety" (45-80).] n = 32 (2014) T0 = 39.57 (±10.53) [PB only]	Gender dysphoria Low Suicidity; N/A Self-harm; N/A Anxiety; Very low Depression; Very low Life satisfaction/QoL Very low	Critical risk of bias N/A N/A Critical risk of bias Critical risk of bias Critical risk of bias

Author & Country	Study Design	Sample characteristics	Source of Participants	Age, mean	Puberty blocker	Pre-post intervention follow up (months)	Assessment used	Confounding domains controlled for ¹	Psychosocial outcome ²	GRADE quality of evidence ³	ROBINS-1 Risk of Bias ⁴
<p>suppression and gender reassignment. <i>Pediatrics</i>, 134(4), 696-704.</p> <p>[2014 publication extends study to early adulthood but does not re-analyse data/findings from 2011]</p> <p>Amsterdam, Netherlands</p>		with most having developed breasts and had their menarche.		reassignment surgery (GRS) Mean age = 19.2 years			<p>Children's Global Assessment Scale (CGAS)</p> <p>Utrecht Gender Dysphoria Scale (UGS)</p> <p>Body Image Scale (BIS)</p> <p>2014 study only:</p> <p>WHOQOL-BREF (quality of life measure World Health Organization)</p> <p>Satisfaction With Life Scale (SWLS)</p> <p>Subjective Happiness Scale (SHS)</p>		<p>T1 = 37.52 (±9.87) [PB only] T2 = 37.61 (10.39) T0-T2 P = 0.45</p> <p>[No analysis of these results present in 2014 study]</p> <p>Depression (BDI- II) [0–13 is considered minimal range, 14–19 is mild, 20–28 is moderate, and 29–63 is severe.] n = 32 (2014) T0 = 7.89 (±7.52) [PB only] T1 = 4.10 (±6.17) [PB only] T2 = 5.44 (±8.40) T0-T2 P = 0.21</p> <p>Quadratic trends revealed decreased depression from T0 to T1, followed by an increase from T1 to T2 in depression</p> <p>Global functioning (CGAS) n = 32 (2014) T0 = 71.13 (±10.46) [PB only] T1 = 74.81 (±9.86) [PB only] T2 = 79.94 (±11.56) T0-T2 P = 0.001</p> <p>Significant linear effects showed improvement over time in global functioning</p> <p>QoL (WHOQOL-BREF) [1–5 range with higher scores indicating better quality of life] [not reported for PB T0 & T1 only] n = 55 (2014) Physical mean score = 15.22 (2.49) Psychological mean score = 14.66 (2.44) Social Relations score = 14.91 (2.35) Environment score = 15.47 (2.06)</p> <p>Mean scores on WHOQOL-BREF had similar scores in all areas except WHOQOL-Environment subdomain, which was higher for the participants than the norm</p> <p>(SWLS) [5–35 range, 20 being neutral] [not reported for PB T0 & T1 only] n = 54 (2014) mean score 24.98 (6.0) slightly satisfied with life) (SHS) [7-point likert scale, 1 not happy - 7 very happy] [not reported for PB T0 & T1 only] n = 54 (2014) Mean score 4.73 (0.77) ()</p> <p>[WHOWOL, SWLS and SHS not reported for T0, T1,T2 follow ups]</p> <p>Social, and global functioning (CBCL - parent) n = 40 (2014) T0 = 60.20 (±12.66) [PB only] T1 =54.70 (± 11.58) [PB only]</p>		

Author & Country	Study Design	Sample characteristics	Source of Participants	Age, mean	Puberty blocker	Pre-post intervention follow up (months)	Assessment used	Confounding domains controlled for ¹	Psychosocial outcome ²	GRADE quality of evidence ³	ROBINS-1 Risk of Bias ⁴
									<p>T2 = 48.10 (±9.30) T0-T2 P = <0.001 (YSR- participant) n = 43 (2014) T0 = 54.72 (±12.08) [PB only] T1 = 49.16 (±11.16) [PB only] T2 = 48.53 (±9.46) T0-T2 P = <0.005</p> <p>For all CBCL and YSR indicators except YSR/ASR externalizing, the percentage in the clinical range dropped significantly (P value ,0.05) from T0 to T1, from T0 to T2, or from T1 to T2.</p>		
<p>Elkadi et al. (2023)</p> <p>Developmental Pathway Choices of Young People Presenting to a Gender Service with Gender Distress: A Prospective Follow-Up Study. <i>Children</i>, 10(2), 314.</p> <p>NSW, Australia</p>	<p>Prospective case-cohort study</p> <p>2013-2018</p>	<p>79 participants</p> <p>Clinically diagnosed</p> <p>33 AMAB</p> <p>46 AFAB</p>	<p>Gender Service at the Sydney Children's Hospitals Network</p>	<p>13-23 years</p> <p>mean = 19 yr</p>	<p>49/79 received PBs</p> <p>Mean age = 13.26</p>	<p>Telephone follow-up after 4-9 years depending on referral date</p> <p>T0 = 79</p> <p>T1 = 50</p>	<p>Multi-disciplinary clinical assessment based on DM-5 criteria for gender dysphoria</p> <p>Custom made 5 self-report questionnaire</p>	<p>[PB group of n = 49 not reported separately for mental health and wellbeing measurements]</p> <p>Self-reported anxiety: T0 = 63.3% T1 = 44%</p> <p>Self-reported depression: T0 = 62.0% T1 = 50%</p> <p>Self-reported education/occupation T1: 48% at school 20% at University 12% employed 4% apprenticeship 4% training programme 12% unemployed</p> <p>Ongoing mental health concerns were reported by 44 of 50 (88.0%) [not just depression and anxiety]. Educational/occupations outcomes varied widely</p>	<p>Anxiety: Very low</p> <p>Depression: Very low</p> <p>Life satisfaction/QoL N/A</p> <p>Gender dysphoria N/A</p> <p>Suicidality; N/A</p> <p>Self-harm; N/A</p>	<p>Critical risk of bias</p> <p>Critical risk of bias</p> <p>N/A</p> <p>N/A</p> <p>N/A</p> <p>N/A</p>	
<p>Lavender et al. (2023)</p> <p>Impact of Hormone Treatment on Psychosocial Functioning in Gender-Diverse Young People. <i>LGBT health</i>.</p> <p>England</p>	<p>Retrospective observational analysis</p> <p>2014-2018</p>	<p>109 participants</p> <p>< 15 years and at Tanner stage 2+,</p> <p>Clinically referred by the Gender Identity Development Service for PB and then and GAH treatment at approx. 16 years</p> <p>Gender 28 AFAB 10 AMAB</p> <p>Ethnicity 29 White 1 Black 3 Mixed 5 unknown</p>	<p>Endocrine clinic</p>	<p>10-14 years</p> <p>AFAB mean age starting PB = 14.19 yr GAH=16.06yr</p> <p>AMAB mean age starting PB =13.51 yr GAH=16.25yr</p>	<p>109 received</p>	<p>N = 38/109</p> <p>71 excluded because of non-completion of questionnaires</p> <p>T0 = first assessment</p> <p>T1 = 12mths after PB</p> <p>T2 = 12 mths after GAH</p>	<p>The Youth Self Report (YSR)</p> <p>Child Behaviour Checklist (CBCL)</p> <p>Body Image Scale (BIS),</p> <p>Utrecht Gender Dysphoria Scale (UGDS)</p> <p>Social Responsiveness Scale-Second Edition (SRS-2)</p>	<p>Participants all continued therapeutic engagement with the Clinic</p>	<p>"No set of young people and their caregivers completed every questionnaire at all time points"</p> <p>Gender Dysphoria (UGDS) [40-60 is clinical range] n = 19 Baseline mean score = 4.70 1 year after PB =4.60 p <0.63 1 year after GAH = 3.97 p <0.02</p> <p>A significant reduction of dissatisfaction with primary sexual characteristics over time was observed, most notably, dissatisfaction at baseline and 1 year after GAH was found</p> <p>Body Image (BIS) n = 21 Baseline mean score = 3.30 1 year after PB = 3.5 p<0.53 1 year after GAH = 3.46 p<0.58</p> <p>Psychological and behaviour function (YSR-participant) n = 20 Baseline mean score = 59.25</p>	<p>Anxiety: N/A</p> <p>Depression: N/A</p> <p>Gender dysphoria Very low</p> <p>Suicidality Very low</p> <p>Self-harm Very low</p> <p>Life satisfaction/QoL Very low</p>	<p>N/A</p> <p>N/A</p> <p>Critical risk of bias</p> <p>Critical risk of bias</p> <p>Critical risk of bias</p> <p>Critical risk of bias</p>

Author & Country	Study Design	Sample characteristics	Source of Participants	Age, mean	Puberty blocker	Pre-post intervention follow up (months)	Assessment used	Confounding domains controlled for ¹	Psychosocial outcome ²	GRADE quality of evidence ³	ROBINS-1 Risk of Bias ⁴
									<p>1 year after PB = 57.44 p < 0.56 1 year after GAH = 55.84 p < 0.28</p> <p>Self-harm/suicidality (YSR) n = 11 Baseline no thoughts/actions = 36% Sometimes/often = 64% 1 year after PB no thought/act = 73% Sometimes/often = 27% 1 year after GAH=no thou/act = 91% Sometimes/often = 9%</p> <p>(CBCL- caregiver) n = 18 Baseline mean score = 57.48 1 year after PB = 39.71 p< 0.07 1 year after GAH = 56.05 p < 0.76</p> <p>Self-harm/suicidality (CBCL) n = 11 Baseline no thoughts/actions = 55% Sometimes/often = 45% 1 year after PB no thought/act=82% Sometimes/often = 18% 1 year after GAH=no thot/act= 100% Sometimes/often = 0%</p> <p>CBCL and YFS mean scores were within the normal ranges using general population reference ranges across both CBCLs and YSRs at baseline.</p> <p>Internalizing T-scores reported from the CBCL (parent) demonstrated a significant reduction across time (p = 0.0). There was a reduction in mean internalizing scores from baseline to 1 year after PB (p = 0.03)</p> <p>There was no significant difference in internalizing and externalizing YSR scores (participant) across time points, although a general improvement over time was evident</p> <p>Of the young people and their caregivers who completed the statements regarding self-harm behaviours and suicidality 1 year after PB, and 1 year after GAH (n = 11), improvements were noted in self-harm and suicidality statements from baseline to PB and further improvements with GAH</p> <p>Social wellbeing/QoL (SRS-2) [<59 designated as normal range, 60–75 considered mild-to-moderate, and a T-score >75 indicating severe impairment] n = 19 Baseline overall mean score = 45.12 1 year after PB = 51.97 p<0.31 1 year after GAH = 56.84 p<0.09</p> <p>SRS-2 scores all lay within the "normal" range</p>		
Lopez de Lara (2020)	Prospective analytical study	53 participants 23 transgender adolescents	Paediatric endocrinology clinic of the	14-18 years	23/23 trans participants	T0 = start PB T1 = 12 months post	Utrecht Gender Dysphoria Scale (UGDS)	Families of transgender participants provided a	<p>Gender Dysphoria (UGDS) [40-60 is clinical range] T0 baseline mean score Trans = 57.1 (±4.1)</p>	<p>Gender dysphoria Moderate</p> <p>Suicidality N/A</p>	<p>Serious risk of bias</p> <p>N/A</p>

Author & Country	Study Design	Sample characteristics	Source of Participants	Age, mean	Puberty blocker	Pre-post intervention follow up (months)	Assessment used	Confounding domains controlled for ¹	Psychosocial outcome ²	GRADE quality of evidence ³	ROBINS-1 Risk of Bias ⁴
Psychosocial assessment in transgender adolescents. <i>Anales de Pediatría</i> , 93(1), 41-48. Spain	2018-2019	30 cisgender comparison group matched for ethnicity, age and socioeconomic status. Trans cohort Gender 16 AFAB 7 AMAB Ethnicity 21 White 1 Black Colombian, 1 Chinese. Socioeconomic 40-50% in middle socioeconomic class with parents who had university education Cisgender Gender 12 AFAB 18 AMAB Ethnicity 30 White Socioeconomic 40-50% in middle socioeconomic class with parents who had university education	Hospital Clínico San Carlos	Mean age =16 years	received whilst < 14 years old	commencement of cross-sex hormone treatment	Strengths and Difficulties Questionnaire, Spanish Version (SDQ-Cas) Family APGAR test State-Trait Anxiety Inventory Beck Depression Inventory II (BDI-II)	highly supportive environment, as demonstrated by the family APGAR scores.	T1 mean score Trans = 14.7 (±3.2) P<0.001 Significant improvement at 12 months of treatment. Every trans participant had gender dysphoria at T0 and none had gender dysphoria at T1 State-Trait Anxiety [temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety"] T0 baseline mean state anxiety: Trans = 33.3 (±9.1) Cis = 11.8 (±3.8) T1 mean state anxiety: Trans = 16.8 (±8.1) P <0.001 Cis = 12.3 (±3.8) P<0.001 State anxiety in the trans group improved significantly, with the mean score decreasing by 16.5 ± 1.1 points (P < .001), corresponding to a decrease from the 75th to 85th percentile at T0 to below the 50th percentile at T1. On the other hand, participants in the control group had similar scores at T0 and T1. Comparing the trans and cis groups at T0, we found a difference in the mean score of 21.5 ± 1.8 (P < .001), and there was still a mean difference at T1, in this case of 4.6 ± 1.6 points (P < .008) There was a higher level of anxiety in cases compared to controls at 1 year despite treatment T0 baseline mean trait anxiety: Trans = 33.0 (±7.2) Cis = 14.2 (±4.8) T1 mean trait anxiety: Trans = 18.5 (±8.4) P <0.001 Cis = 14.2 (±4.8) P<0.001 Trait anxiety decreased by a mean of 14.5 ± 0.9 points between T0 and T1 in the trans group (P < .001), with no difference between time points in the control group. In contrast, controls had similar scores at T0 and T1. Comparing the trans and cis groups at T0, we found a mean difference of 18.8 ± 1.6 points (P < .001), and we also found differences between groups at T1, with a mean difference of 4.3 ± 1.8 points (P < .02). While there was improvement in the score for trait anxiety, the level of anxiety continued to be higher in the trans group compared to the control group at T1 Depression (BDI-II) [>30 severe - 0-9 no depression] T0 baseline mean depression: Trans = 19.3 (±5.5) Cis = 7.2 (±3.9) T1 mean depression: Trans = 9.7 (±3.9) P <0.001 Cis = 7.4 (±3.6) P<0.001	Self-harm N/A Anxiety: Moderate Depression: Moderate Life satisfaction/QoL Moderate	N/A Serious risk of bias Serious risk of bias Serious risk of bias

Author & Country	Study Design	Sample characteristics	Source of Participants	Age, mean	Puberty blocker	Pre-post intervention follow up (months)	Assessment used	Confounding domains controlled for ¹	Psychosocial outcome ²	GRADE quality of evidence ³	ROBINS-1 Risk of Bias ⁴
									<p>We found a decrease in symptoms of depression between T0 and T1 in the trans group, with a mean difference in the BDI-II score of 9.5 ± 0.6 points ($P < .001$), while there were no differences in the control group</p> <p>Comparing the trans and cis groups at T0, we found a mean difference of 12.0 ± 1.3 points in the score ($P < .001$) that had decreased to 2.4 ± 0.7 points at T1 ($P < .034$).</p> <p>Trans participants had more depression symptoms compared to controls at T0 and, despite improvement, also at T1</p> <p>Social wellbeing/QoI (SDQ-Cas) [normal 0-14, abnormal 20-40] T0 baseline mean total difficulties: Trans = 14.7 (± 3.3) 61% normal range, 34.7% borderline, 4.3% abnormal (1 person) Cis = 11.3 (± 2.3) T1 mean total difficulties: Trans = 10.3 (± 2.9) $P < 0.001$ 95.6% normal, 4.3% borderline, 0.5% abnormal Cis = 11.3 (± 2.3) $P < 0.001$</p> <p>When we compared the trans and cis groups at T0, we found significant differences, with a mean difference in the questionnaire score of 3.3 ± 0.7 ($P < .001$), a difference that was nearly reversed after 1 year of treatment (-1.0 ± 0.7; $P = .153$), so that emotional symptoms and conduct problems had both become comparable to those of the control group at T1.</p> <p>Of the 5 groups of difficulties that compose the SDQ, we found significant improvement between T0 and T1 in the trans group in the areas of emotional symptoms, conduct problems, hyperactivity and prosocial behaviour ($P < .001$), with no significant change in the area of peer relationship problems, with similar scores at T0 and T1.</p> <p>Family APGAR [17-20 functional, <9 severely dysf] T0 baseline mean score Trans = 17.9 Cis = "no difference" T1 mean score Trans = 18.0 Cis = "no difference"</p> <p>We did not find differences between T0 and T1 or between the case and control groups.</p>		
Olsavsky (2022) Associations Among Gender-Affirming Hormonal Interventions, Social Support, and Transgender Adolescents' Mental Health <i>The Journal of</i>	Cross sectional study 2018-2022	75 participants Clinically diagnosed Gender 43 AFAB 32 AMAB Ethnicity 1 Asian/Pacific	Children's Hospital, gender-affirming multidisciplinary clinic	11-18 years Mean = 16.39 years	7/39 PBs only 39/75 on gender affirming hormonal intervention 36/75 not receiving any treatment	No follow up	Multidimensional Scale of Perceived Social Support (MSPSS) Screen for Child Anxiety Related Disorders (SCARED)	Peer/other and family support Community based comparison cohort	Anxiety (SCARED) A total score of ≥ 25 may indicate the presence of an Anxiety Disorder Mean score = $43.47 (\pm 16.98)$ [PB only group not reported separately] N = 75 Support from friends ($p = 0.007$) and gender-affirming hormonal (0.046) intervention use were each associated with fewer anxiety symptoms, accounting for all other variables. (mean T-scores not reported) Depression (CDI) >20 indicative of depression	Anxiety Very low Depression Very low Suicidality Very low Self-harm Very low Gender Dysphoria N/A QoI N/A	Serious risk of bias Serious risk of bias Serious risk of bias Serious risk of bias N/A N/A

Author & Country	Study Design	Sample characteristics	Source of Participants	Age, mean	Puberty blocker	Pre-post intervention follow up (months)	Assessment used	Confounding domains controlled for ¹	Psychosocial outcome ²	GRADE quality of evidence ³	ROBINS-1 Risk of Bias ⁴
adolescent health : official publication of the Society for Adolescent Medicine, 72(6), 860-868. Midwest, USA		4 African Am 2 Native Am 58 White 7 Multi-racial 2 not disclosed					Children's Depression Inventory (CDI) (1985) One question based from the Suicide Behaviors Questionnaire-Revised (SBQ-R) and Columbia Suicide Severity Rating Scale(C-SSRS) were used to assess non suicidal self injury (NSSI)		Mean score = 16.33 (±7.92) [PB only group not reported separately] Fewer depressive symptoms were associated with family support (p =0.003) and marginally associated with gender-affirming hormonal intervention use (p = .05), accounting for all other variables. (mean T-score not reported) Suicidality [PB only group not reported separately] 59% all participants reported considering suicide at least once in the past year with non-significant difference between treatment groups Greater friend support (p = 0.03) was significantly associated with less suicidality. Non suicidal self-injury [PB only group not reported separately] 41% all participants reported engaging in NSSI at least once in the past year with non-significant difference between treatment groups Identifying as nonbinary (p = 0 .008) and having greater family support (p = 0 .019) were each significantly associated with fewer reports of NSSI, accounting for all other variables.		
Tordoff, D. M., Wanta, J. W., Collin, A., Stepney, C., Inwards-Breland, D. J., & Ahrens, K. (2022) Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care. <i>JAMA network open</i> , 5(2), e220978. Seattle, USA	Prospective observational cohort study 2017-2018	104 participants Self or clinician referral Gender 33 AMAB 71 AFAB Ethnicity 4 Asian/Pacific 3 African Am 9 Latinx 6 Native Am, Alaskan or Hawaiian 67 White 9 multi-ethnic 6 missing	Enrolled in an urban multidisciplinary gender clinic	13-20 years Mean age = 15.8 years	Over 12 month period: 57 received PB/GAH [5 PB only] 8 not received At T3: 5 PB only 50 GAH 14 PB+GAH 35 no Tx	T0 = 104 T1 = 3 months 84/104 responses T1 = 6 months 84/104 responses T3 = 12 months 65/104 responses	Patient Health Questionnaire 8-item scale (PHQ-8) Patient Health Questionnaire 9-item scale (PHQ-9) [Depression] Generalized Anxiety Disorder 7-item scale (GAD-7) Self-harm and suicidal thoughts were assessed using PHQ-9 question 9 Connor-Davidson Resilience Scale (CD-RISC)	Race and ethnicity Ongoing mental health therapy Tension with parents or guardians Substance use	Depression [PB only group not reported separately] Baseline: 59.7% moderate to severe T3: Received PBs or GAH: 60% lower odds of moderate severe depression (aOR, 0.40; 95%CI, 0.17-0.95) Anxiety [PB only group not reported separately] Baseline: 50.0% moderate to severe T3: There was no association between receipt of PBs or GAHs and moderate to severe anxiety (aOR, 1.01; 95%CI, 0.41-2.51). Self-harm or suicidality [PB only group not reported separately] Baseline: 43.3% reported thoughts T3: 73% lower odds of self-harm or suicidal thoughts (aOR, 0.27; 95%CI, 0.11-0.65) compared with youths who had not yet initiated PBs or GAHs.	Depression Moderate Anxiety Moderate Suicidality Low Self-harm Low Gender Dysphoria N/A QoL N/A	Serious risk of bias Serious risk of bias Serious risk of bias N/A N/A
Turban, J. L., King, D., Carswell, J. M., & Keuroghlian, A. S. (2020). Pubertal Suppression for Transgender Youth and Risk of Suicidal	Retrospective analysis of self-reported cross-sectional survey 2015	3494 individuals between the ages of 18 and 36 who ever wanted pubertal suppression at the time of the survey	2015 US Transgender Survey (USTS) Participants were recruited through community outreach in collaboration with > 400 lesbian, gay,	N = 89 Mean age began PBs = 15.7 years	89/3494 (2.5%) who wanted PBs had received it 3405/3494 (97.5% who wanted PBs did not receive it	Retrospective study, follow up time period varied depending on age of participant Access to pubertal suppression was associated with a	Kessler Psychological Distress Scale [K6], Survey questions: Past-month binge drinking Lifetime illicit drug use (not including marijuana),	All outcomes: Family support, sexual orientation, education level, employment status, and total household income	Suicidality Receiving PBs was associated with decreased odds of past-year: Suicidal ideation (p = 0.09) Lifetime suicidal ideation (0.001) Past-month severe psychological distress (p = 0.38)	Suicidality Very Low Depression N/A Anxiety N/A Self-harm N/A Gender Dysphoria N/A QoL N/A	Serious risk of bias N/A N/A N/A N/A

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Ideation. <i>Pediatrics</i> , 145(2) USA		PBs received n = 89 Gender 50 = AMAB 39 = AFAB Ethnicity racial min = 28 White = 61	bisexual, and transgender organizations			greater total household income, family support Access to pubertal suppression was associated with male sex assignment at birth, heterosexual sexual orientation	Past-year suicidal ideation, Past-year suicidal ideation with a plan, Past-year suicide attempts, Past-year suicide attempts resulting in inpatient care, Lifetime suicidal ideation, Lifetime suicide attempts.	Some outcomes: Age, gender identity, ethnicity and relationship status			
Kuper, L. E., Stewart, S., Preston, S., Lau, M., & Lopez, X. (2020). Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. <i>Pediatrics</i> , 145(4). Texas, USA	Longitudinal cohort study 2014-2018	148 participants Clinically diagnosed Gender 55 AMAB 94 AFAB Ethnicity White 137 (95%) African American 3 (2%) Multiracial 3 (2%) American Indian 1 (1%) Tanner stage I = 3 (2%) II = 6 (4%) III = 5 (4%) IV = 32 (23%) V = 94 (67%)	Multidisciplinary clinic	9-18 years Mean age PB sub-group at start of treatment = 13.7 years	PBs n = 25 (17%) GAH n = 93 (63%) Both n = 30 (20%)	T1 = 11-18mths PBs T1 = 23/25	Body Image Scale (BIS) Screen for Child Anxiety Related Emotional Disorders (SCARED) Quick Inventory of Depressive Symptoms (QIDS)	Tanner stage Therapy received No correlations were found between change scores and demographic and treatment-related characteristics.	No statistical significance in follow up scores found for the PB subgroup alone for any measure Body dissatisfaction (BIS) [score 1-100, >score indicates more disturbance] PB responses n = 10 Baseline = 64.1 (±18.2) Follow up = 53.8 (±20.1) Depression (QIDS) [score 0-27, 0 none, 27 severe] <i>Self-report PB responses n = 13</i> Baseline = 8.2 (±6.1) Follow up = 7.0 (±5.6) <i>Clinician PB responses n = 19</i> Baseline = 5.3 (±4.9) Follow up = 5.5(±4.8) Anxiety (SCARED total score) [total score of >25 may indicate the presence of an Anxiety Disorder] PB responses n = 22 Baseline = 31.8 (±16.6) Follow up = 29.3 (±17.1) Suicidality and self-harm [PB only group not reported separately] n = 148 Of those who experienced suicidal ideation during the follow-up period, 94% had a lifetime history. These figures were 67% for suicide attempt and 87% for non-suicidal self-injury.	Gender Dysphoria Very Low Depression Moderate Anxiety Moderate Self-harm Very Low Suicidality Very Low QoL N/A	Serious risk of bias Serious risk of bias Serious risk of bias Serious risk of bias N/A
Achille, C., Taggart, T., Eaton, N. R., Osipoff, J., Tafuri, K., Lane, A., & Wilson, T. A. (2020). Longitudinal impact of gender-affirming endocrine	Longitudinal cohort study 2013-2018	116 participants 95= 0 Tx 21 = prior Tx Gender 33 AFAB 17 AMAB	Referrals to Paediatric Endocrine Department for gender dysphoria	9-25 years Mean age = 16.2 years	23 Received PBs 46 received GAH or both 3 received no tx	T0 = Baseline T2= 6 mths T3 = 12 mths 50/95 completed all 3 follow up questionnaire waves	Center for Epidemiologic Studies Depression Scale (CESD-R) The Patient Health Questionnaire Modified for Teens (PHQ-9) Quality of Life Enjoyment and	Psychiatric medication Engagement in psychotherapy	Depression (CESD-R) [<16 no clinical depression] [PB only group not reported separately] Mean baseline CESD-R score = 21.4 T3 = 13.9 p < 0.001 (PHQ-9) [0-27 0 being minimal, 27 severe] [PB only group not reported separately] Mean baseline scores =not reported T3 = not reported as number	Depression: Very low QoL: Very low Gender Dysphoria N/A Anxiety N/A Self-harm N/A Suicidality N/A	Critical risk of bias Critical risk of bias N/A N/A N/A N/A

Not Government Policy

Author & Country	Study Design	Sample characteristics	Source of Participants	Age, mean	Puberty blocker	Pre-post intervention follow up (months)	Assessment used	Confounding domains controlled for ¹	Psychosocial outcome ²	GRADE quality of evidence ³	ROBINS-1 Risk of Bias ⁴
intervention on the mental health and well-being of transgender youths: preliminary results. <i>International journal of paediatric endocrinology</i> , 2020, 8. New York, USA							Satisfaction Questionnaire (QLES-Q-SF)		Quality of Life (QLES-Q-SF) [rating scales 1 being poor, 5 being good] [PB only group not reported separately] Mean baseline scores =not reported T3 = not reported as number		

1. Confounding factors controlled for (European/white ethnicity; family support; enrolled in a specialised service; puberty development (Tanner stage)
2. (Gender dysphoria +/-; Suicidality; Self-harm; Anxiety; Depression; Life satisfaction/QoL)
3. High; Moderate; Low; Very Low
4. Low; Moderate; Serious; Critical; No Information

Appendix 5: Targeted mental health and wellbeing interventions for gender dysphoria

Systematic review method

The review question has been formulated using the qualitative research version of the **P**opulation, phenomena of **I**nterest and the **C**ontext (PICo) guidelines recommended for qualitative systematic reviews (Stern, Jordan, McArthur 2014). As advised in the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis on page 8 (Lockwood et al 2020).

The question therefore focuses on which targeted interventions (**C**ontext) do adolescents aged 12-18 years, experiencing gender dysphoria (phenomena of **I**nterest), and their families (**P**opulation), positively impact on mental health and wellbeing outcomes.

The JBI methodology guides the review question, evaluation of the available evidence through a systematic search strategy and a transparent assessment of the quality of evidence. JBI uses a meta-aggregation approach which 'is sensitive to the practicality and usability of the primary author's findings and does not seek to re-interpret those findings...' (Lockwood et al 2020). The quality of research is assessed by the reviewer through close reading of the findings of a paper (such as themes, metaphors or concepts) identified by the researchers (not the reviewer). Verbatim quotations and/or descriptions of participant experiences which support these findings are considered primary evidence for the assessment of quality of evidence.

Eligibility criteria

A comprehensive search strategy was designed and implemented with a senior Ministry of Health librarian and is detailed in Supplementary Material 4.5. Inclusion criteria for the search was:

- English language publication
- academic publications which have been peer reviewed
- studies that focus on qualitative experiential data including, but not limited to, designs such as phenomenology, grounded theory, ethnography, action research and lesbian, gay, bisexual, transgender, queer, intersex and asexual (LGBTQIA+)/queer theory.
- published between 2000 and 31 August 2023 (gender dysphoria interventions just being established in early 2000's)

- age of young people within 12-18 years
- experiencing gender dysphoria diagnosed by clinician OR self-reported
- any intervention targeting mental health or wellbeing intervention for individuals and/or their family
- systematic reviews which meet the above criteria and have qualitative research included.

Study selection

The study selection process is illustrated in below in Figure 6. Endnote 20 was used to manage references. Screening and assessment of papers for inclusion was conducted by the primary reviewer. Papers were excluded on the basis of the title or abstract if they did not clearly report on gender dysphoria, did not include original data on youth aged 12-18 years or were not in English. Papers were retained if there was not sufficient information to exclude them. Full-text files were obtained for the remaining articles.

Paper were rejected at this stage if they

- did not contain original data
- were focussed on populations other than youth who experience gender dysphoria
- did not have identifiable data pertaining to youth aged 12 – 18 years
- were quantitative methodology.

Figure 6: PRISMA study selection (search 1) mental health and wellbeing interventions for adolescents experiencing gender dysphoria

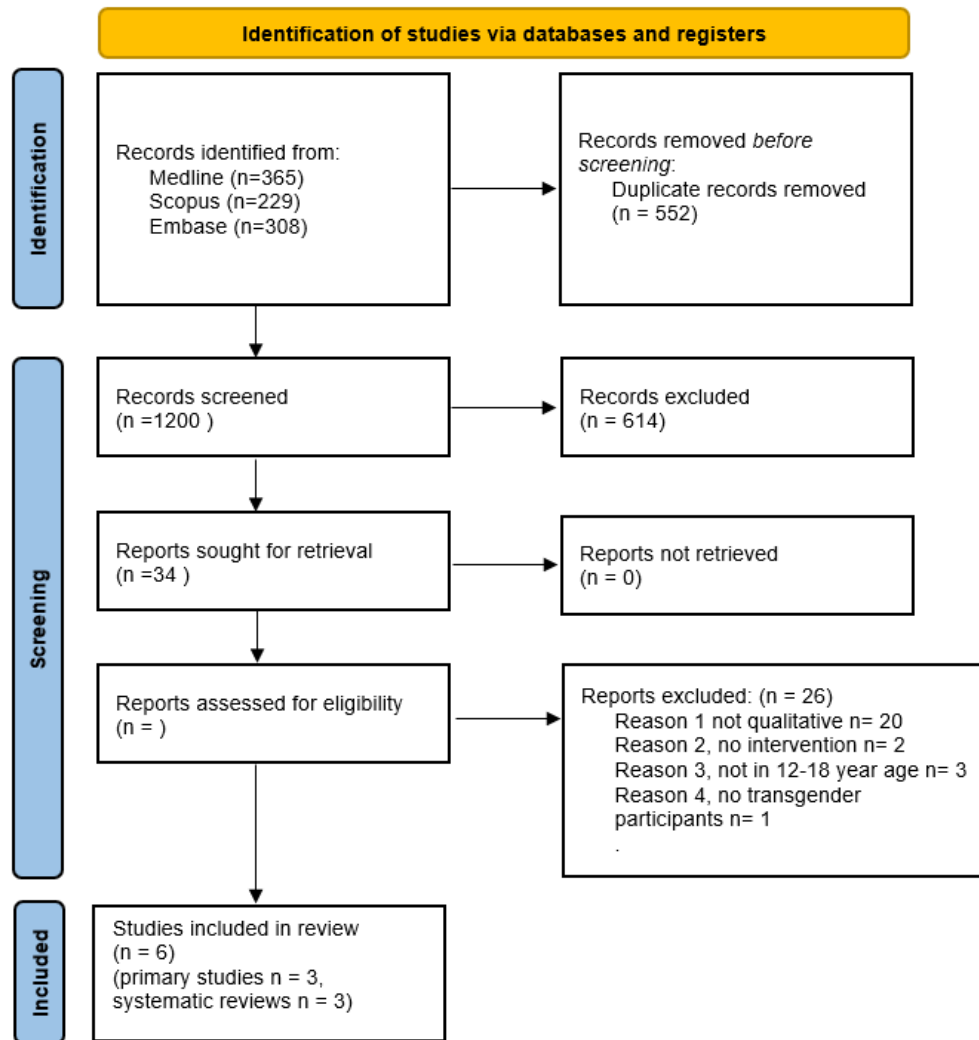
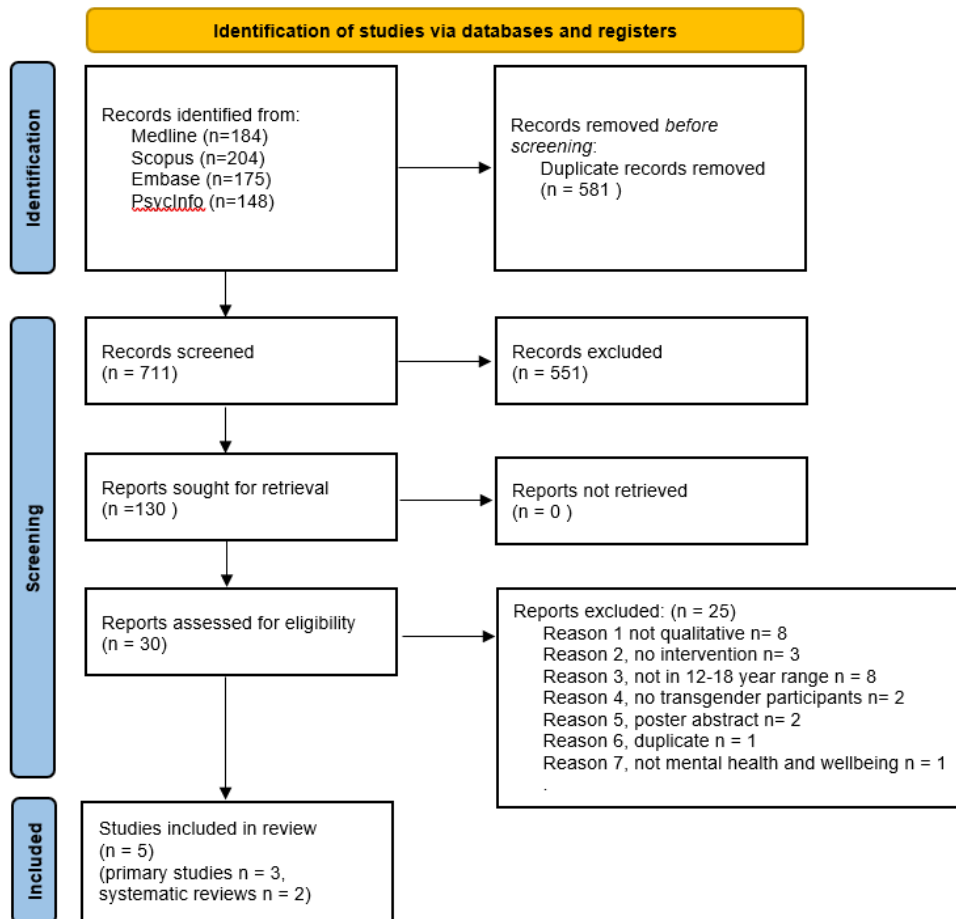


Figure 7: PRISMA study selection (search 2) mental health and wellbeing interventions for adolescents experiencing gender dysphoria



Following selection, all papers were reviewed by a second reviewer to reduce the risk of inclusion bias. Where any disagreement regarding inclusion a discussion was held to reach a consensus. If no agreement could be reached a third reviewer made a decision regarding inclusion. There were 1,133 papers identified for screening and of these there were no papers which met the criteria of ‘experiencing gender dysphoria’. To locate literature which focussed on youth living with gender dysphoria this criterion was expanded to encompass identifying as ‘transgender or gender diverse’. One research paper and one systematic review then met the criteria for inclusion. Due to this paucity, qualitative evaluations and qualitative components of mixed methods studies were then included and two more studies and two systematic reviews were identified. A second more targeted search was then conducted with specific qualitative research terms such as grounded theory, action research, ethnography added to the search terms to ensure we had not missed any publications. The second search identified an additional three studies and two more systematic reviews.

With the two searches a total of six studies were included for the systematic review. To account for the broadening of inclusion criteria in the quality appraisal of the literature being reviewed, qualitative evaluations and mixed methods studies have been rated down one level to reflect the absence of a qualitative research methodology. A

comparison of the methodological base of the included studies is itemised in Table 2 in Appendix 3 and Supplementary Materials 4 and 5.

Quality Appraisal

Quality of evidence was rated using the ConQual Approach (Munn, Porritt, Lockwood, et al 2014) as advised in the JBI qualitative systematic review manual. ConQual scoring is carried out following a process of moving down levels from High to Very Low using the formula in Supplementary Material 5. Findings which provided evidence were collated under headings:

- impact on youth mental health and wellbeing
- key factors of intervention attributed to success
- family/social impact (see Supplementary Material 5).

These were then summarised and graded using the ConQual scoring guide (Supplementary Material 5). The lowest rating of each of these findings has been used as the overall quality rating. To reflect the inclusion of youth and families in the systematic review question and to acknowledge the importance of the social and systemic context of interventions, the findings have been presented as reflecting youth or parent/carer voice, and any societal impact in the summary of findings table (see Appendix 6).

Mental health and wellbeing interventions for gender dysphoria - Methodology and Quality tables

Table 1: Comparison of methodologies of included papers

Included studies for this systematic review	Methodology			
	Qualitative research	Qualitative evaluation	Mixed method research	Mixed method evaluation
Bluth, K., Lathren, C., Clepper-Faith, M., Larson, L. M., Ogunbamowo, D. O., & Pflum, S. (2023). Improving Mental Health Among Transgender Adolescents: Implementing Mindful Self-Compassion for Teens. <i>Journal of Adolescent Research</i> , 38(2), 271-302. USA		√		
Caldarera, A. M., Davidson, S., Vitiello, B., & Baietto, C. (2021). A psychological support group for parents in the care of families with gender diverse children and				√

Included studies for this systematic review	Methodology			
	Qualitative research	Qualitative evaluation	Mixed method research	Mixed method evaluation
adolescents. <i>Clinical child psychology and psychiatry</i> , 26(1), 64-78. Italy & UK				
Dangaltcheva, A., Booth, C., & Moretti, M. M. (2021). Transforming Connections: A Trauma-Informed and Attachment-Based Program to Promote Sensitive Parenting of Trans and Gender Non-conforming Youth. <i>Frontiers in psychology</i> , 12, 643823 Canada	√			
Davidson, S., Morrison, A., Skagerberg, E., Russell, I., & Hames, A. (2019). A therapeutic group for young people with diverse gender identifications. <i>Clinical child psychology and psychiatry</i> , 24(2), 241-257. UK & Sweden			√	
Pullen Sansfacon, A., Temple-Newhook, J., Suerich-Gulick, F., Feder, S., Lawson, M. L., Ducharme, J., . . . Holmes, C. (2019). The experiences of gender diverse and trans children and youth considering and initiating medical interventions in Canadian gender-affirming speciality clinics. <i>The international journal of transgenderism</i> , 20(4), 371-387. Canada	√			
Weinhardt, L. S., Wesp, L. M., Xie, H., Murray, J. J., Martin, J., DeGeorge, S., . . . Stevens, P. (2021). Pride Camp: Pilot study of an intervention to develop resilience and self-esteem among LGBTQ youth. <i>International journal for equity in health</i> , 20(1), 150. USA			√	

Systematic Reviews	Included studies	
Study	Qualitative research	Quantitative and Qualitative research
Malpas, J., Pellicane, M. J., & Glaeser, E. (2022).		√

Systematic Reviews	Included studies	
Study	Qualitative research	Quantitative and Qualitative research
Family-Based Interventions with Transgender and Gender Expansive Youth: Systematic Review and Best Practice Recommendations. <i>Transgender health</i> , 7(1), 7-29.		
Christensen, J. A., Oh, J., Linder, K., Imhof, R. L., Croarkin, P. E., Bostwick, J. M., & McKean, A. J. S. (2023). Systematic Review of Interventions to Reduce Suicide Risk in Transgender and Gender Diverse Youth. <i>Child psychiatry and human development</i> .		√
Lehmann, K., & Leavey, G. (2023). Systematic review: Psychological/psychosocial interventions for the families of gender diverse youth under 18 years old. <i>Clinical child psychology and psychiatry</i> , 28(3), 1160-1174.	√	
Literature Review	Included studies	
Russon, J., Washington, R., Machado, A., Smithee, L., & Dellinger, J. (2022). Suicide among LGBTQIA+ youth: A review of the treatment literature. <i>Aggression and Violent Behavior</i> , 64.		√
Busa, S., Janssen, A., & Lakshman, M. (2018). A Review of Evidence Based Treatments for Transgender Youth Diagnosed with Social Anxiety Disorder. <i>Transgender health</i> , 3(1), 27-33. Review of Evidence Based Treatments for Transgender Youth Diagnosed with Social Anxiety Disorder.		√

Table 2: Summary of included studies

Included studies for this systematic review	Category of findings				Quality rating
Study	Youth voice	Parent/ carer voice	Social impact	Key attributes for success	
Bluth, K., Lathren, C., Clepper-Faith, M., Larson, L. M., Ogunbamowo, D. O., & Pflum, S. (2023). Improving Mental Health Among Transgender Adolescents: Implementing Mindful Self-Compassion for Teens. <i>Journal of Adolescent Research</i> , 38(2), 271-302. USA	√			√	High

Included studies for this systematic review	Category of findings				Quality rating
	Youth voice	Parent/ carer voice	Social impact	Key attributes for success	
<p>Caldarera, A. M., Davidson, S., Vitiello, B., & Baietto, C. (2021). A psychological support group for parents in the care of families with gender diverse children and adolescents. <i>Clinical child psychology and psychiatry</i>, 26(1), 64-78.</p> <p>Italy & UK</p>		√		√	Very Low
<p>Dangaltcheva, A., Booth, C., & Moretti, M. M. (2021). Transforming Connections: A Trauma-Informed and Attachment-Based Program to Promote Sensitive Parenting of Trans and Gender Non-conforming Youth. <i>Frontiers in psychology</i>, 12, 643823</p> <p>Canada</p>		√		√	Moderate
<p>Davidson, S., Morrison, A., Skagerberg, E., Russell, I., & Hames, A. (2019). A therapeutic group for young people with diverse gender identifications. <i>Clinical child psychology and psychiatry</i>, 24(2), 241-257.</p> <p>UK & Sweden</p>	√	√		√	Very Low
<p>Pullen Sansfacon, A., Temple-Newhook, J., Suerich-Gulick, F., Feder, S., Lawson, M. L., Ducharme, J., . . . Holmes, C. (2019). The experiences of gender diverse and trans children and youth considering and initiating medical interventions in Canadian gender-affirming speciality clinics. <i>The international journal of transgenderism</i>, 20(4), 371-387.</p> <p>Canada</p>	√			√	High
<p>Weinhardt, L. S., Wesp, L. M., Xie, H., Murray, J. J., Martin, J., DeGeorge, S., . . . Stevens, P. (2021). Pride Camp: Pilot study of an intervention to develop resilience and self-esteem among LGBTQ youth. <i>International journal for equity in health</i>, 20(1), 150.</p> <p>USA</p>	√		√	√	Low

Appendix 6: Summary of Qualitative Evidence Table

Title Author Country	Study Design	Participant characteristics	Source of Participants	Age, mean	Targeted intervention	Category of findings	ConQual grade
<p>Bluth, K., Lathren, C., Clepper-Faith, M., Larson, L. M., Ogunbamowo, D. O., & Pflum, S. (2023).</p> <p>Improving Mental Health Among Transgender Adolescents: Implementing Mindful Self-Compassion for Teens. <i>Journal of Adolescent Research, 38</i>(2), 271-302.</p> <p>USA</p>	<p>Qualitative evaluation</p> <p>Qualitative component: Thematic Analysis</p> <p>Research questions: (1) Is the program feasible and acceptable? (2) Is program participation associated with improvement in psychosocial outcomes?</p>	<p>11 participants:</p> <p>Gender 0 transboy/man 8 transgirl/woman 2 non-binary 1 gender fluid</p> <p>Ethnicity (total response) 7 White 1 Black/African American 1 Asian 3 Hispanic/Latino/a 1 Mixed ethnicity</p>	<p>Participants were recruited through postings on social media platforms such as Facebook, Twitter, and Instagram, including Facebook groups that were specifically for parents of transgender adolescents and organizations for LGBTQIA+ populations.</p> <p>Flyers providing information for the study were also sent to academic researchers, community psychologists and therapists, LGBTQ advocacy organizations, and three local pediatric and adolescent gender clinics for gender diverse youth.</p>	13-17 years	<p>Mindful Self-Compassion for Teens (MSC-T) training, taught online over eight sessions; each session was 1.50 hours long.</p>	<p>Youth Voice</p> <p>Bolstering self-compassion may be a particularly effective method of addressing the mental health concerns that transgender adolescents face.</p> <p>Feeling less alone and isolated undoubtedly contributed to improved mental health.</p> <p>Key attributes of success:</p> <p>Creation of a safe and welcoming space was crucial for participants to feel comfortable about discussing their experiences and at times being vulnerable to the group was likely an instrumental factor in achieving positive outcomes</p> <p>Practices that encouraged body kindness and awareness were generally well received. encouraging being kind to one's body was helpful for many in that they were accustomed to rejecting and dismissing their body.</p> <p>The presence of supportive instructors also contributed to the sense of safety. Providing an additional staff member to monitor and assist with chats allowed instructors to focus on content.</p>	High
<p>Caldarera, A. M., Davidson, S., Vitiello, B., & Baietto, C. (2021).</p> <p>A psychological support group for parents in the care of families with gender diverse children and adolescents. <i>Clinical child psychology and psychiatry, 26</i>(1), 64-78.</p>	<p>Mixed method evaluation</p> <p>A. Themes: A1. What were the main themes that emerged in the group sessions? A2. Was there an evolution of the themes across time?</p> <p>B. Perceived benefit:</p>	<p>11 caregivers of a children/adolescents aged 8-17 years old who were attending the gender identity service</p>	<p>Parents were offered the possibility of attending the group and informed that it was not mandatory. This information was given to each parent individually, and the child psychiatrist explored with each parent her/ his motivations for attending the group.</p>	8-17 years	<p>Parent group within a specialised service for gender diverse children based at a paediatric hospital.</p> <p>Eleven monthly 90 minute group therapy sessions combining a psychoanalytic therapeutic approach based on Bion's perspective (1961) and psychoeducation techniques.</p>	<p>Parent/Carer Voice</p> <p>Our results show that the participants (1) took a more complex perspective on gender diversity and on the needs of their offspring and (2) became more able to deal with the uncertainty related to the process of their gender development</p> <p>Carers were more open to the process of change.</p>	Very Low

Title Author Country	Study Design	Participant characteristics	Source of Participants	Age, mean	Targeted intervention	Category of findings	ConQual grade
	<p>B1. To what extent was the support group perceived as helpful in</p> <ul style="list-style-type: none"> improving the understanding of gender diversity? meeting with other parents of gender diverse children and thus reducing sense of isolation? changing parents' approach to their child's gender diversity? <p>B2. Which aspects were perceived by the parents as helpful and which ones as involved in the process of change?</p> <p>B3. Which specific benefits and which aspects to be changed were identified by participants in relation to the group?</p>				<p>Delivered by a child psychiatrist and a clinical psychologist</p>	<p>Parents outlined the fact of</p> <ol style="list-style-type: none"> having improved their capacity of empathising with their children and thus supporting them and having achieved a deeper understanding of gender diversity and of their children's need for love and support. <p>Key attributes of success:</p> <p>Participants described all these positive changes as related to the opportunity the group offered of sharing experiences and of being involved in a process of mutual learning</p> <p>Parents who accepted to attend the group might have been, compared to parents who did not, more motivated and willing to question their attitudes and ideas</p> <p>The group process which supported an evolution of personal development and understanding of gender diversity and child development</p>	
<p>Dangaltcheva, A., Booth, C., & Moretti, M. M. (2021).</p> <p>Transforming Connections: A Trauma-Informed and Attachment-Based Program to Promote Sensitive Parenting of Trans and Gender Non-conforming Youth. <i>Frontiers in psychology</i>, 12, 643823</p> <p>Canada</p>	<p>Qualitative research</p> <p>The current study reports on the adaptation of the Connect program to address the needs of parents of gender nonconforming and trans youth and measure the effectiveness of the program.</p>	<p>Participants were 20 parents (14 mothers, 6 fathers) of 16 gender non-conforming youth (ages 12–18),</p> <p>Parents ranged between 32 and 59 years old</p> <p>The majority self-identified as ethnicities: Caucasian (90%; n = 18); 5% as Aboriginal (n = 1); 5% as Asian (n = 1).</p>	<p>Participants of a pilot group delivering an adapted version of the Connect intervention - called Transforming Connections</p>	<p>12-18 years</p> <p>Six youth had begun taking hormones or hormone blockers.</p>	<p>Connect is a trauma-informed intervention that collaboratively engages caregivers and builds sensitive parenting skills that promote attachment security in teens</p> <p>Designed for delivery by a wide-range of mental health and education professionals, this ten-session program (1.5 h weekly) is delivered by two trained facilitators who guide groups of 8–14 parents through emotion-focused, experiential, and reflective exercises that increase their understanding of trauma, attachment, and adolescent mental health.</p> <p>Transforming Connections is an adaptation of the Connect program to address the needs of</p>	<p>Parent/Carer voice</p> <p>Caregiver feedback supported the effectiveness of this intervention.</p> <p>Parents also endorsed rates of positive change in their relationships with their teens as a result of implementing these strategies, comparable to rates reported by parents who completed the Connect program</p> <p>Parents expressed feeling more confident in parenting and expecting more positive changes in their relationship in the future.</p> <p>Key attributes of success</p> <p>Parent attendance and engagement in our groups was high</p>	<p>Moderate</p>

Title Author Country	Study Design	Participant characteristics	Source of Participants	Age, mean	Targeted intervention	Category of findings	ConQual grade
					parents of gender nonconforming and trans youth	<p>Feedback indicated that parents expressed increasing satisfaction as the group progressed and there was a greater emphasis on specific issues related to gender.</p> <p>Parents shared feeling isolated initially and relieved to be able to share their experiences with other parents who were encountering similar challenges.</p> <p>Caregivers in our groups indicated that they liked both the structured and supportive aspects of the group. They reported feeling safe and supported, while also discussing strategies that allowed them to better support their teens.</p>	
<p>Davidson, S., Morrison, A., Skagerberg, E., Russell, I., & Hames, A. (2019).</p> <p>A therapeutic group for young people with diverse gender identifications. <i>Clinical child psychology and psychiatry</i>, 24(2), 241-257.</p> <p>UK & Sweden</p>	<p>Mixed Method research</p> <p>Thematic analysis of: <i>Post-group experiences: young people</i>. A short form with four qualitative questions</p> <p><i>Post-group experiences: parents</i>. A short four-item questionnaire was given to parents/carers</p>	<p>11 participants</p> <p>10 AFAB 1 AMAB</p> <p>[trans identities not referred too]</p>	<p>Gender Identity Development Service</p>	<p>12-18 years</p>	<p>Young Persons' Group over nine consecutive weeks in the school summer holidays in 2011.</p> <p>Each group session lasted for 90 minutes and were held at the same time and on the same day every week; each with a specific theme.</p> <p>A variety of therapeutic techniques were drawn upon, with cognitive and behavioural therapy (CBT) and systemic therapy (ST) being the predominant approaches</p> <p>The co-facilitators were a Consultant Clinical Psychologist, a Trainee Clinical Psychologist, and a Research Psychologist</p>	<p>Youth Voice</p> <p>The findings demonstrated that the group met its aim of providing peer support and was also clearly of value for the young people as evidenced in the high levels of attendance and positive questionnaire feedback.</p> <p>After the group, the young people reported feeling significantly more included and supported by their peers and recognised feeling less alone and more able to trust people.</p> <p>Parent/carer voice</p> <p>The parents believed that their children felt less alone and that their confidence had improved after attending the group.</p> <p>Key attributes of success</p> <p>The group provided an opportunity for those who may have previously struggled to form trusted peer relationships to build valued connections with other young people.</p> <p>An invitation-only group where the readiness for the group was made by</p>	<p>Very Low</p>

Title Author Country	Study Design	Participant characteristics	Source of Participants	Age, mean	Targeted intervention	Category of findings	ConQual grade
						clinicians and who would to be invited to attend	
<p>Pullen Sansfacon, A., Temple-Newhook, J., Suerich-Gulick, F., Feder, S., Lawson, M. L., Ducharme, J., . . . Holmes, C. (2019).</p> <p>The experiences of gender diverse and trans children and youth considering and initiating medical interventions in Canadian gender-affirming speciality clinics. <i>The international journal of transgenderism</i>, 20(4), 371-387.</p> <p>Canada</p>	<p>Qualitative research</p> <p>The objectives of the study were: to explore the experiences of trans youth and their families who access care during prepubertal, pubertal and post-pubertal stages of development, and to understand the motivations and pathways that lead them and their families to seek care, the issues affecting them, and the strategies they use to express and/or address dysphoria with the help of the gender clinics and in larger social contexts.</p>	<p>36 participants</p> <p>Gender 14 transgirl/woman 22 transboy/man</p> <p>Ethnicity 25 White 4 non-white or indigenous 7 not disclosed</p> <p>Age 9-11 years – 4 13-15 years - 14 1-17 years - 17</p> <p>At the time of their interview, youth had been receiving care at the clinic for a period ranging from one month to 6 years, including nine participants who had been attending the clinic for more than two years.</p>	Gender-affirming care clinics	9-17 years	<p>Clinical care from a specialised gender affirming clinic.</p> <p>Clinics aim to provide the youth with “the opportunity to live in the gender that feels most real and/or comfortable for the child and the ability for children to express gender without experiencing restriction, criticism, or ostracism”</p> <p>Clinics differ in terms of staff, resources and protocols for accessing appointments and medical interventions, but they all seek to validate the child/youth’s experience with respect and sensitivity.</p>	<p>Youth Voice</p> <p>Accessing gender-affirming healthcare was a positive experience for youth overall. The youth’s narratives highlighted how having access to medical intervention has improved their overall well-being, including feelings of greater happiness overall, better mental health, or better functioning at school.</p> <p>Key attributes of success:</p> <p>The importance for all professionals providing care to trans and gender diverse youth to maintain a gender-affirming approach that is experienced as inclusive, validating and safe.</p>	High
<p>Weinhardt, L. S., Wesp, L. M., Xie, H., Murray, J. J., Martin, J., DeGeorge, S., . . . Stevens, P. (2021).</p> <p>Pride Camp: Pilot study of an intervention to develop resilience and self-esteem among LGBTQ youth. <i>International journal for equity in health</i>, 20(1), 150.</p>	<p>Mixed Methods research</p> <p>An uncontrolled pilot test of the effects of a six-day on-campus program, called Pride Camp, on resilience and well-being among LGBTQ youth.</p> <p>Qualitative component: Thematic Analysis</p> <p>Two semi-structured focus groups in 2016 to describe the experiences of transgender of nonbinary campers at Pride Camp</p>	<p>8 participants</p> <p>Gender 8 transboy/man</p> <p>Ethnicity 7 non-Hispanic White 1 multiple-ethnicity</p>	Attendance to Pride Camp between 2015- 2017	13-17 years	<p>Pride Camp was situated on a college campus in an urban setting. Our program was designed to build resilience, self-esteem, leadership skills, and other personal strengths, while also encouraging LGBTQ high school students to envision themselves as future college students..</p> <p>Implemented by trained facilitators who were LGBTQ staff of the University of Wisconsin-Milwaukee LGBTQ resource center</p>	<p>Youth voice</p> <p>Youth explained [the environment] allowed them to further their communication skills and process some of the traumatizing experiences they faced in their lives.</p> <p>Society impact</p> <p>Pride Camp is one of few interventions that is situated to support LGBTQ students at a critical juncture of their educational experience: the transition from high school to college</p> <p>Campus faculty, staff, and students were primarily the coordinators, and through this experience, became more educated about LGBTQ issues. Also, peer counsellors, who were university students, played a key role in facilitating youth’s development of confidence</p>	Low

Title Author Country	Study Design	Participant characteristics	Source of Participants	Age, mean	Targeted intervention	Category of findings	ConQual grade
						<p>and resilience. Peer counselors were self-identified LGBTQ individuals</p> <p>Key attributes of success</p> <p>Specific professional development and educational resources for campers (tailored camper programming) and addressing their internal growth, resilience, and mental health.</p> <p>Gender-affirming policies and practices, such as introducing and using pronouns consistently and correctly, ensured that transgender youth were less likely to face stigma or discrimination while they were at camp</p> <p>Pride Camp was situated to support LGBTQ students at a critical juncture of their educational experience: the transition from high school to college</p>	