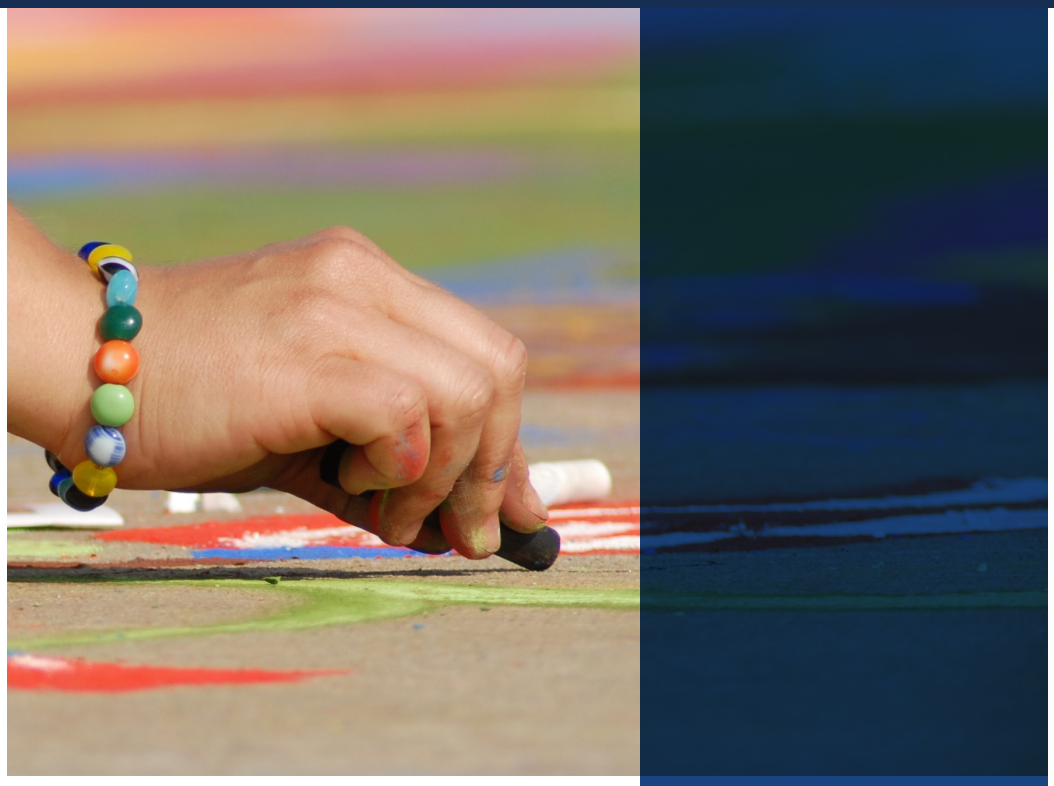
Treatment for Pediatric Gender Dysphoria

Appendix 4: Overview of Systematic Reviews

Methodology, Evidence Synthesis, Tables



Department of Health and Human Services

November 19, 2025

Treatment for Pediatric Gender Dysphoria

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Minor corrections to May 1 document made May 15, 2025; see Errata.

Minor corrections and revisions made November 19, 2025: see Errata and Supplement, which contains peer reviews and replies.

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1 Methodology

The methodology of this overview followed the recommendations for an overview of systematic reviews (SRs) in the *Cochrane Handbook for Systematic Reviews of Interventions*.[1]

Literature search: Medline, Embase, and the psychological database PsycINFO were searched for potentially eligible records. The search strategy included terms related to SRs ("systematic review," "meta-analysis," etc.) and others related to gender dysphoria ("gender incongruence," "gender-affirming hormones," "puberty blockers," etc.), using Boolean operators AND and OR as appropriate. The search was limited to items from 2015 to Feb 20, 2025. A complementary literature search was conducted in other databases including ACCESSSS (a service providing current evidence for clinical decisions) and Epistemonikos (a database of SRs), and a grey literature search was conducted through the systematic review registry PROSPERO and Google Scholar, as well as a manual search of reference lists of eligible SRs. Box 1.1. provides an example of search strategies used in Medline.

Literature screening: After the removal of duplicate records, two reviewers reviewed titles and abstracts and independently determined study eligibility. Once potentially eligible records were identified, a thorough review of full-text articles with a standardized and piloted screening form was performed. Reviewers resolved disagreement by discussion.

A record was included if it met the following criteria:

1. It is an SR.[2]

[1] Higgins et al. (2019).
[2] An SR needs to have: 1) a defined research question according to PICO elements: Population, Intervention, Control/Comparator, Outcome; 2) pre-defined eligibility criteria for studies; 3) adequate systematic search methods that identify all studies that would meet the eligibility criteria; 4) an assessment of the validity of the findings of the included studies, for example through a risk-of-bias assessment; and 5) a systematic presentation and synthesis of the characteristics and findings of the included studies, which may include a meta-analysis. Scoping reviews, overviews of systematic reviews (umbrella reviews), and narrative reviews, are not SRs.

2. The study population is youth with gender dysphoria (GD) whose age is below 26 years.[3]
3. The study assesses at least one of the following: social transition, psychotherapy, puberty blockers (PBs), cross-sex hormones (CSH), or surgery.

The exclusion criteria were the following:

1. Comingling of mature adult (≥ 26 years) and youth, which means systematic reviews with more than 25% of included studies on mature adults were excluded because these reviews were not applicable (too indirect) to inform the outcomes on youths.[4]
2. Overlapping efforts.

Data extraction and appraisal of included reviews: Data extracted included review authors, research team, and research question answered; number and characteristics of included studies; study population; treatment; outcomes of interest; analysis and synthesis strategy; risk of bias assessment used for included studies.

The Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) tool[5] was used to assess the risk of bias for included SRs. The data extraction and risk of bias assessment was completed by one reviewer and checked by a second reviewer. ROBIS assesses the quality of the systematic review according to four domains: 1) study eligibility criteria; 2) identification and selection of studies; 3) data collection and study appraisal; and 4) synthesis of findings. Additionally, ROBIS assesses the overall risk of bias in a systematic review process and SRs with concerns identified in the four domains can still be assessed at low risk of bias if the SRs have properly addressed these concerns in the evidence interpretation.

[3] Empirically, SRs in this area are usually provided for patients under 18 or those under 26. The age cutoff below 26 years balances the comprehensiveness and the directness (applicability) of the evidence review. Though there is a concern regarding the directness of evidence, the evidence for <18 and for <26 years did not identify any significant differences in outcomes.
[4] The SRs including both >26 years and <26 years skew toward the >26 population, and so are less directly applicable to this overview than SRs on youth with GD.
[5] Whiting et al. (2016).

Evidence synthesis and certainty of evidence: The evidence synthesis summarizes the outcome data across SRs that were published in English and classified at low risk of bias.[6] The evidence synthesis was organized by types of treatment, and the outcomes of interest included GD, mental health and well-being, treatment goal (for example, puberty suppression for puberty blockers), need for or progression to further treatment, safety outcomes including side effects and adverse outcomes, and regret. For each outcome, this overview summarized the effect estimates and the certainty of evidence (confidence in the effect estimates, the quality of evidence).

The certainty of evidence was summarized following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.[7] In GRADE, certainty of evidence can be downgraded for: risk of bias (study limitations), inconsistency (unexplained variation in results), indirectness (evidence not directly applicable), imprecision (wide confidence intervals or small samples), and publication bias (selective reporting).[8] Evidence can be upgraded if there is a large effect size, a clear dose-response relationship, or if confounding factors expected to reduce the observed effect did not do so.[9] Evidence could be classified into four levels of certainty: high, moderate, low, or very low.[10] This overview summarized the GRADE rating from the original review for the respective outcome wherever it is available. Nevertheless, there were two modifications made:

1. Where a formal GRADE appraisal had not been performed by the systematic review, but expressions such as “we are very uncertain” and “no conclusions

[6] One non-English systematic review was considered eligible and included and classified at low risk of bias. This overview did not summarize the results by outcomes from this review. Nevertheless, its conclusions were similar.
[7] In GRADE, quality of evidence is equivalent to certainty of evidence. “The quality of evidence is very low” is equivalent to “the certainty of evidence is very low.” See Guyatt et al. (2008), Balshem et al. (2011).
[8] Balshem et al. (2011); Guyatt et al. (2008); Guyatt, Oxman, Kunz, Brozek, et al. (2011); Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Falck-Ytter, et al. (2011); Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Glasziou, et al. (2011); Guyatt, Oxman, Montori, et al. (2011); Guyatt, Oxman, Vist, et al. (2011).
[9] Guyatt, Oxman, Sultan, et al. (2011).
[10] According to GRADE, high certainty evidence means that “we are very confident that the true effect lies close to that of the estimate of the effect” and very low certainty evidence indicates that “we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect” (Balshem et al., 2011).

could be drawn" were used in SRs' conclusions, these statements were considered equivalent to a "very low quality" GRADE assessment.[11]

2. If SRs disagreed on GRADE assessment for the same outcome, this overview resolved the disagreement with *de novo* assessment following the GRADE methodology and reported the rationale for the assessment.

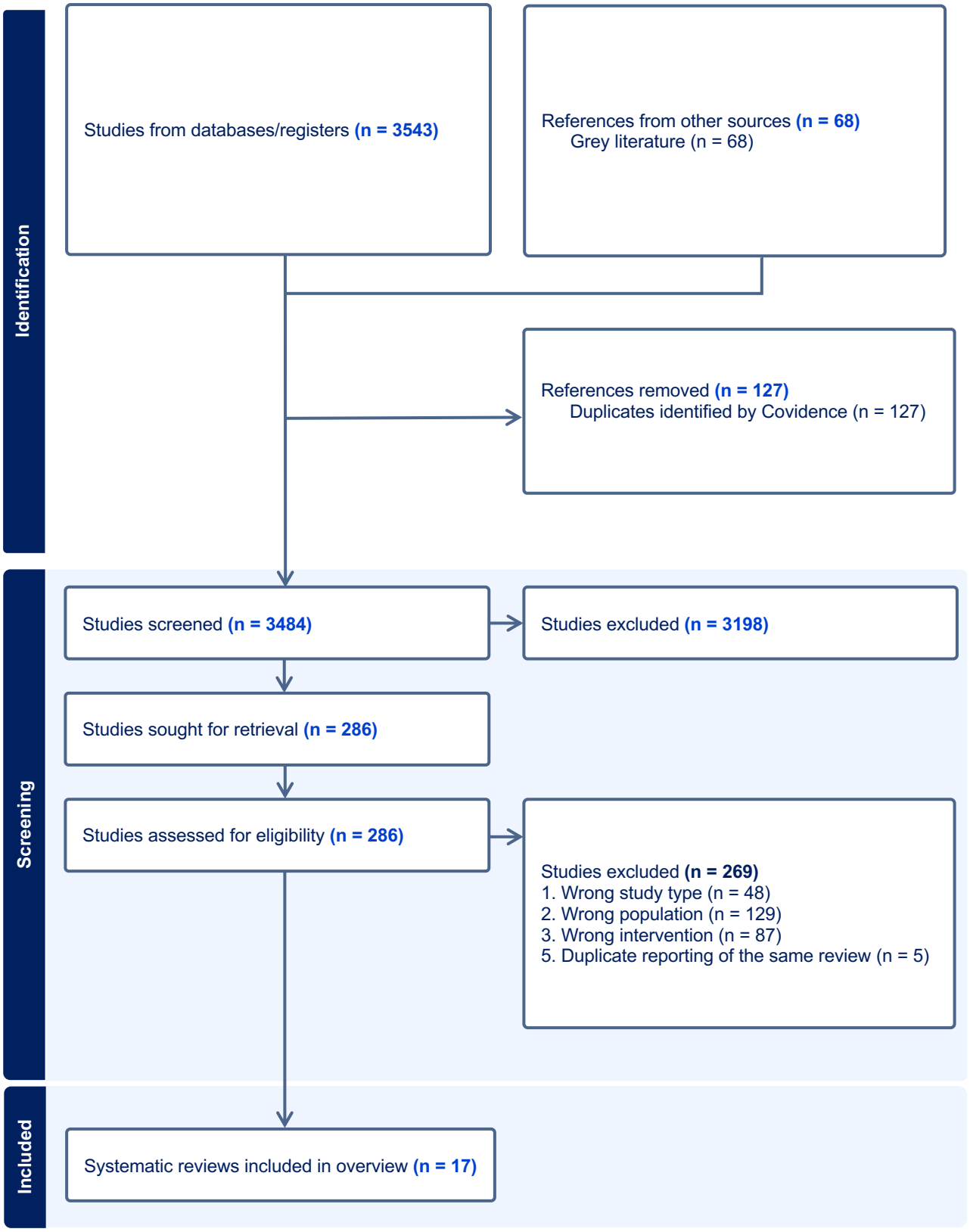
Box 1.1 Search strategy in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, 1996 to Feb 20, 2025

1	exp "Sexual and Gender Minorities"/
2	Gender Dysphoria/
3	Gender Identity/
4	Gender Role/
5	"Sexual and Gender Disorders"/
6	Transsexualism/
7	Transgender Persons/
8	Health Services for Transgender Persons/
9	exp Sex Reassignment Procedures/
10	gender identity disorder.mp.
11	non-binary.mp.
12	transgender.mp.
13	(gender* adj3 (dysphori* or disorder* or distress or nonconform* or non-conform* or atypical or incongru* or identi* or disorder* or confus* or minorit* or queer* or variant or diverse or creative or explor* or question* or expan* or fluid)).tw.
14	((sex or gender*) adj3 (reassign* or chang* or transform* or transition* or expression*)).tw.
15	(transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw.
16	(genderfluid or genderqueer or agender).mp.
17	((correct or chosen) adj3 name).mp.
18	(trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
19	((sex or gender*) adj3 (reassign* or chang* or transform* or transition* or expression*)).tw.
20	(male-to-female or m2f or female-to-male or f2m).tw.
21	or/1-20
22	exp Child/ or Child Behavior/ or Child Health/ or Child Welfare/ or Psychology, Child/ or Child Psychiatry/ or Child Health Services/ or Child Development/
23	Minors/
24	(child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or emerging adult$).ti,ab,kf,jn.
25	(young$ adj (people$ or person$1 or adult$ or man$1 or men$1 or woman$ or women$ or male$1 or female$1)).ti,ab,kf,jn.
26	pediatrics/
27	(pediatric$ or paediatric$ or peadiatric$).ti,ab,kf,jn.
28	Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Psychology, Adolescent/ or Adolescent Psychiatry/ or Adolescent Health Services/ or Adolescent Medicine/ or Adolescent Development/

[11] Balshem et al. (2011); Santesso et al. (2020).

29	Puberty/
30	(adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or underage$ or under-age$).ti,ab,kf,jn.
31	Schools/ or Schools, Nursery/
32	exp Child Day Care Centers/ or Child Care/
33	(school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1).ti,ab,kf,jn.
34	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	systematic review/
36	meta-analysis/
37	(meta anal* or meta-anal* or metaanal*).ti,ab.
38	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
39	((pool* or combined) adj2 (data or trials or studies or results)).ab.
40	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41	(search* adj4 literature).ab.
42	or/35-41
43	21 and 34 and 42

Figure 1.1 Searching, screening, and inclusion process



2 Literature screening results

Following the removal of duplicates, 3,484 records were screened by title and abstract. Of these, 286 full-text articles were assessed for eligibility. A total of 269 full-text articles were excluded for the following reasons: 48 were not SRs (incorrect study type), 129 did not focus on children or adolescents with GD, 87 did not address the treatment of interest, and five were excluded due to duplicate reporting (See Figure 1.1). After screening, 17 SRs met the inclusion criteria, examining the effects of psychotherapy (n = 5),[12] social transition (n = 2),[13] PBs (n = 9),[14] CSH (n = 8),[15] and surgeries (n = 3)[16] among children or adolescents with GD.

2.1 Risk of bias assessment in included SRs

Of the 17 included SRs, 10 were rated as having a low risk of bias (see Table 2.1).[17]

The low risk of bias SRs could be organized into five groups:

1. The SRs by scholars from McMaster University in Canada on PBs (Miroshnychenko 2025a[18]), CSH (Miroshnychenko 2025b[19]), and mastectomy (Miroshnychenko 2024[20]).

[12] Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).
[13] Dopp et al. (2024); Hall et al. (2024).
[14] Chew et al. (2018); Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Ramos et al. (2021); Rew et al. (2021); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Thompson et al. (2023); Zepf et al. (2024).
[15] Chew et al. (2018); Dopp et al. (2024); Karalexi et al. (2020); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024); Thompson et al. (2023); Zepf et al. (2024).
[16] Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[17] Dopp et al. (2024); Hall et al. (2024); Heathcote et al. (2024); Ludvigsson et al. (2023); Miroshnychenko et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024); Zepf et al. (2024).
[18] Miroshnychenko, Roldan, et al. (2025).
[19] Miroshnychenko, Ibrahim, et al. (2025).
[20] Miroshnychenko et al. (2024).

2. The SRs conducted by scholars from University of York to inform the Cass Review, comprising the reviews of PBs (Taylor 2024a[21]), CSH (Taylor 2024b[22]), psychotherapy (Heathcote 2024[23]), and social transition (Hall 2024[24]).
3. The systematic review by researchers from Rand Corporation on all treatment strategies (Dopp 2024[25]).
4. The systematic review by Swedish Agency for Health Technology Assessment and Assessment of Social Services on hormone therapies (Ludvigsson 2023[26]).
5. The systematic review by Zepf et al., which was an update and followed the same methodology of the two SRs published in German.

SRs within each group generally followed the same methodological approach. The three SRs by McMaster University scored as having a low risk of bias across all four domains, as well as low risk of bias overall.[27] Other SRs rated at low risk of bias had limitations in one or more domains. For instance, though published in 2024, the literature search for the University of York SRs was conducted in April 2022. Additionally, there were concerns regarding the risk of bias assessment. Though the Newcastle-Ottawa Scale is an appropriate tool for the study types included in the systematic reviews, the high quality studies (for example, high quality cross-sectional or retrospective studies) are not adequate to provide high certainty evidence on the treatment effect.[28] While narrative descriptors such as “very uncertain” and “no conclusions can be drawn” correspond to the rating of “low/very low certainty” using GRADE, no formal GRADE assessment was performed. The Dopp et al. (2024)[29] review had limitations in the domain of study eligibility criteria as it included case reports and qualitative studies for

[21] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[22] Taylor, Mitchell, Hall, Langton, et al. (2024).
[23] Heathcote et al. (2024).
[24] Hall et al. (2024).
[25] Dopp et al. (2024).
[26] Ludvigsson et al. (2023).
[27] Hall et al. (2024); Heathcote et al. (2024); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024).
[28] van der Miesen 2020 was the only high-quality study in the systematic review on PBs, though it is a cross-sectional study and not adequate to assess treatment effect. Jensen 2019 was assessed as the only high-quality study in the systematic review on CSH, and it was a retrospective chart review and only reported side-effects, not treatment effects.
[29] Dopp et al. (2024).

estimating treatment effects, and in the domain of identification and selection of studies was limited by searching in only one database.

A total of seven SRs[30] were rated at high risk of bias overall, often due to limited or poorly defined research questions and eligibility criteria, lack of risk of bias assessments, and inadequate synthesis of findings. This appendix includes a detailed summary of study characteristics and risk of bias considerations for all included SRs. The variation in methodological rigor highlights the need for cautious interpretation of findings, especially from reviews rated at high risk of bias.

[30] Chew et al. (2018); Expósito-Campos et al. (2023); Karalexi et al. (2020); Malpas et al. (2022); Ramos et al. (2021); Rew et al. (2021); Thompson et al. (2023).

Table 2.1. Scope of included SRs

Review ID	PBs	CSH	Surgeries	Psychotherapy	Social Transition	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Appraisal	Synthesis and Findings	Risk of bias in the review
Chew 2018[31]	Y	Y				High risk of bias	Low risk of bias	High risk of bias	High risk of bias	High risk of bias
Dopp 2024[32]	Y	Y	Y	Y	Y	High risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Expósito-Campos 2023[33]				Y		High risk of bias	High risk of bias	Low risk of bias	High risk of bias	High risk of bias
Hall 2024[34]					Y	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Heathcote 2024[35]				Y		Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Karalexi 2020[36]		Y				High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Ludvigsson 2023[37]	Y	Y				Low risk of bias	High risk of bias	Low risk of bias	High risk of bias	**Low risk of bias**

[31] Chew et al. (2018).
[32] Dopp et al. (2024).
[33] Expósito-Campos et al. (2023).
[34] Hall et al. (2024).
[35] Heathcote et al. (2024).
[36] Karalexi et al. (2020).
[37] Ludvigsson et al. (2023).

Review ID	PBs	CSH	Surgeries	Psychotherapy	Social Transition	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Appraisal	Synthesis and Findings	Risk of bias in the review
Malpas 2022[38]				Y		High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Miroshnychenko 2025a[39]	Y					Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Miroshnychenko 2025b[40]		Y				Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Miroshnychenko 2024[41]			Y			Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Ramos 2021[42]	Y					High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Rew 2021[43]	Y					High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Taylor 2024a[44]	Y					Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**

[38] Malpas et al. (2022).
[39] Miroshnychenko, Roldan, et al. (2025).
[40] Miroshnychenko, Ibrahim, et al. (2025).
[41] Miroshnychenko et al. (2024).
[42] Ramos et al. (2021).
[43] Rew et al. (2021).
[44] Taylor, Mitchell, Hall, Heathcote, et al. (2024).

Review ID	PBs	CSH	Surgeries	Psychotherapy	Social Transition	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Appraisal	Synthesis and Findings	Risk of bias in the review
Taylor 2024b[45]		Y				Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Thompson 2023[46]	Y	Y	Y	Y		Low risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Zepf 2024[47]	Y	Y				Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	**Low risk of bias**

[45] Taylor, Mitchell, Hall, Langton, et al. (2024).
[46] Thompson et al. (2023).
[47] Zepf et al. (2024).

2.2 Excluded SRs

Box 2.1 provides examples of excluded SRs due to focusing on a mixed population or interventions not relevant to this overview.

Box 2.1 Examples of excluded SRs

SRs that were a mixed population (with more than 25% included studies on mature adults):

Baker 2021

Baker, K. E., Wilson, L. M., Sharma, R., Dukhanin, V., McArthur, K., & Robinson, K. A. (2021). Hormone therapy, mental health, and quality of life among transgender people: A systematic review. Journal of the Endocrine Society, 5(4), 1-16.

Doyle 2023

Doyle, D. M., Lewis, T. O. G., & Barreto, M. (2023). A systematic review of psychosocial functioning changes after gender-affirming hormone therapy among transgender people. Nature Human Behaviour.

Dunford 2021

Dunford, C., Bell, K., & Rashid, T. (2021). Genital reconstructive surgery in male to female transgender patients: A systematic review of primary surgical techniques, complication profiles, and functional outcomes from 1950 to present day. European Urology Focus, 7(2), 464-471.

Haupt 2020

Haupt, C., Henke, M., Kutschmar, A., Hauser, B., Baldinger, S., Saenz, S. R., . . . Schreiber, G. (2020). Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women. Cochrane Database of Systematic Reviews(11).

Javier 2022

Javier, C., Crimston, C. R., & Barlow, F. K. (2022). Surgical satisfaction and quality of life outcomes reported by transgender men and women at least one year post

gender-affirming surgery: A systematic literature review. International Journal of , 23(3), 255-273.

Kloer 2021

Kloer, C., Parker, A., Blasdel, G., Kaplan, S., Zhao, L., & Bluebond-Langner, R. (2021). Sexual health after vaginoplasty: A systematic review. Andrology, andr.13022.

Kotamari 2021

Kotamarti, V. S., Greige, N., Heiman, A. J., Patel, A., & Ricci, J. A. (2021). Risk for venous thromboembolism in transgender patients undergoing cross-sex hormone treatment: A systematic review. The Journal of Sexual Medicine, 18(7), 1280-1291.

Thornton 2024

Thornton, S. M., Edalatpour, A., & Gast, K. M. (2024). A systematic review of patient regret after surgery- a common phenomenon in many specialties but rare within gender-affirmation surgery. The American Journal of Surgery.

van Leerdam 2021

van Leerdam, T. R., Zajac, J. D., & Cheung, A. S. (2021). The effect of gender-affirming hormones on gender dysphoria, quality of life, and psychological functioning in transgender individuals: A systematic review. Transgender Health, trgh.2020.0094.

Wilson 2020

Wilson, L. M., Baker, K. E., Sharma, R., Dukhanin, V., McArthur, K., & Robinson, K. A. (2020). Effects of antiandrogens on prolactin levels among transgender women on estrogen therapy: A systematic review. International Journal of Transgender Health, *21*(4), 391–402.

SRs that were not on the interventions of interest:

Diana 2024

Diana, P., Belluzzi, B., Corona, F., Barbi, E., & Tornese, G. (2024). Nonmedical gender-affirming practices in transgender and gender diverse adolescents: A narrative review. Transgender Health.

di Giacomo 2018

di Giacomo, E., Krausz, M., Colmegna, F., Aspesi, F., & Clerici, M. (2018). Estimating the Risk of Attempted Suicide Among Sexual Minority Youths: A Systematic Review and Meta-analysis. *JAMA pediatrics*, *172*(12), 1145–1152.

Notably, this overview excluded two SRs by National Institute for Health and Care Excellence (NICE) in October 2020.[48] This was because these two SRs were commissioned by NHS England to inform Dr Hilary Cass's independent review. In 2024, several SRs funded and commissioned by NHS England to inform the Cass review were published and were more comprehensive and updated than the two NICE SRs.

2.3 Baker et al. 2021

This overview also excluded the systematic review by Baker and colleagues,[49] which was funded by the World Professional Association for Transgender Health (WPATH), because it predominantly includes studies on mature adults and is therefore too indirect to inform the healthcare of adolescents with GD. However, since the Baker et al. review supports the recommendations in the Adolescent chapter of WPATH SOC-8 it was subjected to a separate ROBIS analysis and was found to be at "high risk of bias" due to limitations in data collection and risk of bias assessment, and synthesis of results.

Study eligibility criteria: Low risk of bias.

The systematic review authors registered a protocol and had explicit and appropriate eligibility criteria. The systematic review excludes studies with follow up less than three months and studies that did not provide sufficient information about regimen of intervention.

Identification and selection of studies: Low risk of bias.

The authors searched in several databases and other resources. The authors also reported duplicate screening process.

[48] National Institute for Health and Care Excellence (2020b, 2020a).
[49] Baker et al. (2021).

Data collection and study appraisal: High risk of bias.

Baker et al. report using a standardized form and they performed screening and risk of bias assessment in duplicate, suggesting that data collection was also done in duplicate. The authors describe the most important characteristics of the included studies. The results collected, however, are not standardized across studies. For some studies, authors report magnitudes of effect and confidence intervals, whereas for others they report only that "no changes were observed."[50] Although the authors aimed to use the correct tools, when assessing risk of bias they do not consider that the design of the studies was not the same for the researchers of the primary studies versus the systematic review's question, leading the authors to assess studies using an inappropriate tool: for example, the systematic review authors assessed a primary study as a trial when it should have been assessed as a case series.

Synthesis and findings: High risk of bias.

Although reported per outcome, Baker et al. describe the results at the study level instead of across studies without justifying why they did not conduct a meta-analysis or reporting whether they planned to do so. Therefore, it is challenging for readers to draw any conclusions at the outcome level. While the review used the AHRQ guidelines for assessing strength of evidence, the authors did not comment on a formal assessment of heterogeneity, regardless of apparent between-study variation. The AHRQ guidelines do not consider publication bias. The authors do comment on risk of bias at the outcome level.

Risk of bias in the review: High risk of bias.

While the authors mention some limitations of the evidence, they do not comment on applicability or address all concerns identified with the evidence.

2.4 Utah Review

This document,[51] commissioned by lawmakers in Utah, has been described as a "comprehensive review" and cited by experts as providing evidence of treatment safety.

[50] Baker et al. (2021).
[51] University of Utah College of Pharmacy, Drug Regimen Review Center (2025). This appeared after the initial May 2025 publication of the present Review.

The Utah Review includes evaluations of primary studies, clinical practice guidelines (CPGs), and SRs. The review of CPGs and the review of SRs would not have been eligible for inclusion in the present overview of systematic reviews. The review of primary studies was assessed with ROBIS. This part of the Utah Review was found to be at “high risk of bias” due to limitations in study eligibility criteria, identification and selection of studies, data collection and risk of bias assessment, and synthesis of results. The following analysis is not an exhaustive list of limitations identified in the Utah Review, but a summary of the main issues.

Study eligibility criteria: High risk of bias.

A fundamental requirement of any systematic review is a clearly defined scope, including pre-specified eligibility criteria for the inclusion of studies. This review fails to meet that standard. There was no well-defined research question (Population, Intervention, Comparator, Outcome: see Appendix 3); instead, this review combines puberty blockers and cross-sex hormones as “gender affirming hormonal therapy” and failed to separately assess and summarize the evidence on each. The reviewers also modified the outcomes of interest during the review process. For example, the review notes that “Persistence, desistance, and regret were not among our high-priority outcome categories for this review. However, these concepts were pointedly of interest to the legislature so we examined the evidence in the [previously] retrieved studies.”[52] It is unclear when the decision was made to include these outcomes. It is unclear whether a study only reporting these outcomes would have been excluded from “previously retrieved studies.” Consequently, the eligibility criteria were vague.

Identification and selection of studies: High risk of bias.

Not all relevant databases were searched. While the initial plan included Medline, Embase, CENTRAL, PsycInfo, and ClinicalTrials.gov, the final search was limited to Medline, Embase, and ClinicalTrials.gov. This change compromised the comprehensiveness of the review. It is unclear why some studies were included, as they did not report outcome data which could inform effect estimates. The review includes 134 primary clinical studies involving over 28,000 youth with gender dysphoria from

[52] University of Utah College of Pharmacy, Drug Regimen Review Center (2025, p. 83).

diverse global settings,[53] yet provided no transparent rationale for how such a wide range of study types—all with vastly different designs, populations, and methodological quality—fit within a coherent framework for evidence review. For example, Tables I.8–I.11[54] show the inclusion of everything from cross-sectional internet surveys to single case reports, raising serious questions about what qualified as relevant evidence with respect to treatment effects and how these sources aligned with the stated research objectives. Furthermore, the reviewers report identifying N=134 primary clinical studies,[55] but this number does not appear to match the data in Figure I.3.

Data collection and study appraisal: High risk of bias.

Data collection and study appraisal were similarly problematic. The Utah Review did not follow its own plan for extracting data or assessing risk of bias for all included studies. Initially, the stated intent was to extract information from all descriptive study designs, including case reports that met certain ethical standards. However, due to "time constraints," the review extracted data for 58 observational/experimental studies and 32 single-arm clinical trial/longitudinal, pre-post descriptive studies, while other descriptive studies were relegated to the "bibliography only."[56] This *ad hoc* approach undermines the reliability of the review. This approach was problematic not only because it deviated from the original plan, but also because the reviewers used labels to decide which studies would undergo data extraction/risk of bias assessment. As Chapter 24 of the Cochrane Handbook notes, study labels "are not always clear and can be problematic."[57] Reviews of non-randomized studies of interventions should characterize studies based on specific study design features, as opposed to labels. The decision to perform data extraction based on labels such as "single-arm clinical trials," "observational studies," and "experimental studies"[58] was not justified.

The Utah Review extensively redacts information that is already publicly available in the original academic publications—such as study locations, years, and patient

[53] University of Utah College of Pharmacy, Drug Regimen Review Center (2025, p. 44)
[54] University of Utah College of Pharmacy, Drug Regimen Review Center (2025, pp. 45-53).
[55] University of Utah College of Pharmacy, Drug Regimen Review Center (2025, p. 44).
[56] University of Utah College of Pharmacy, Drug Regimen Review Center (2025, p. 34)
[57] Reeves et al. (2024).
[58] University of Utah College of Pharmacy, Drug Regimen Review Center (2025, p. 34).

characteristics (see Tables I.8–I.11[59]). These redactions do not protect participant privacy, as the data are anonymized and part of the public scientific record, but instead obscure important contextual details necessary for evaluating study relevance.

There are also serious flaws in the risk of bias assessment. The authors used the Newcastle-Ottawa Scale for cohort, case-control, and cross-sectional studies, but the NIH Quality Assessment Tool for before-after studies.[60] The authors could have used the Newcastle-Ottawa scale for before-after studies and presented the risk of bias assessment results in a clearer and more consistent manner. The use of a different risk of bias tool was not justified. Moreover, as with data extraction, the review fails to assess the risk of bias for all studies considered eligible.

Synthesis and findings: High risk of bias.

The review of primary studies did not perform evidence synthesis. Despite citing over 130 clinical studies, the review fails to aggregate findings across studies, compare outcomes by treatment type, or summarize data in a way that explains how they informed conclusions. The results are presented solely as a narrative summary, completely lacking a predefined reporting plan, which hinders clarity and comprehensive understanding. The reviewers state they “were not contracted to include a synthesis of the evidence ... only to assess ROB [risk of bias] and provide evidence tables summarizing safety and efficacy findings."[61] This is inappropriate, because systematic reviews should always involve evidence synthesis. When quantitative evidence synthesis such as meta-analysis is not feasible, systematic review authors should apply other evidence synthesis strategies. If researchers are contracted to conduct SRs, they should include evidence synthesis.

A major methodological shortcoming of the Utah Review is its failure to assess the quality or certainty of the evidence across included studies. Nowhere in the synthesis is a standardized framework—such as GRADE—used to evaluate the strength or reliability of the findings. Despite not performing evidence synthesis and quality of

[59] University of Utah College of Pharmacy, Drug Regimen Review Center (2025, pp. 45-53).
[60] University of Utah College of Pharmacy, Drug Regimen Review Center (2025, p. 29).
[61] University of Utah College of Pharmacy, Drug Regimen Review Center (2025, p. 90).

evidence assessment, the review claims that “rates of depression and suicidal thoughts/self-harm tended to be lower among hormonally treated transgender youth compared to untreated transgender individuals,”[62] and that “the consensus of the evidence supports that the treatments are effective."[63] Given the absence of an evidence synthesis and quality assessment, these statements are unwarranted.

Risk of bias in the review: High risk of bias.

The Utah Review authors claim to have conducted a systematic review; however, this review of primary studies does not properly define the research question, search the literature comprehensively, critically appraise included studies, or properly conduct an evidence synthesis. Therefore, it does not qualify as a systematic review.

Further limitations of the Utah Review

In addition to the limitations in the review of primary studies, there are also problems with the review of clinical practice guidelines and the review of SRs. The review retrieved only four clinical guidelines. (In comparison, the recent systematic guideline appraisal by Taylor et al.[64] included 23 guidelines, with 12 guidelines published no earlier than 2018.) Reviewers do not assess the rigor of guidelines’ development with valid methodological tools, instead relying on the eminence of organizations sponsoring them.

As for the review of SRs, the Utah Review misses the recent systematic reviews commissioned for the Cass Review.[65] The Utah Review also misrepresents standard methodologic practice in claiming that the SR commissioned by Sweden’s National Board of National Health and Welfare ”violate[d] best practices” by excluding high risk of bias studies.[66] This is a valid methodological choice, as outlined in the Cochrane

[62] University of Utah College of Pharmacy, Drug Regimen Review Center (2025, p. 77).
[63] University of Utah College of Pharmacy, Drug Regimen Review Center (2025, p. 90).
[64] Taylor, Hall, et al. (2024).
[65] Taylor, Mitchell, Hall, Heathcote et al. (2024); Taylor, Mitchell, Hall, Langton et al. (2024).
[66] Ludvigsson et al. (2023); University of Utah College of Pharmacy, Drug Regimen Review Center (2025, p. 42).

Handbook.[67] The mischaracterization of a valid approach as methodologically flawed undermines the Utah Review's credibility.

3 Synopses of English language SRs assessed at low risk of bias

Dopp et al. 2024[68] This RAND SR examined evidence on interventions for GD and related health problems in youth with GD. The SR applied a strategy of combining targeted search from existing clinical guidelines, reviews, and legal proceedings, and a broad search from PubMed. It included 105 studies and organized them into seven categories of interventions: psychosocial interventions, PBs, CSH, surgeries, reproductive health interventions, treatment of co-occurring mental health or developmental disorders, and other treatments described as "gender identity and expression change efforts." Although this systematic review is comprehensive (49 studies for PBs, 56 studies for CSH, and 18 studies for surgery), a notable limitation is the inclusion of case reports. Case reports are inherently limited in their ability to establish treatment effects due to the lack of control groups and high risk of bias. The inclusion of case reports inflated the number of included studies but provided no additional benefits in informing about treatment effectiveness, which was reflected by the very low certainty of evidence despite a large number of eligible studies. This SR is limited by having systematically searched PubMed but no other databases. Compared with other low risk of bias SRs on hormonal and surgical treatment (Miroshnychenko 2024, Miroshnychenko 2025a,[69] Miroshnychenko 2025b,[70] Taylor 2024a,[71] Taylor 2024b[72]), the Dopp et al. 2024 review missed more case series and before-after studies while including more case reports. It summarized effect estimates by reviewing all reports of outcomes across studies and applied the GRADE methodology to assess the

[67] E.g., "there will always be a trade-off between restrictive study design criteria (which might result in the inclusion of studies that are at low risk of bias, but very few in number) and more liberal design criteria (which might result in the inclusion of more studies, but at a higher risk of bias)" (McKenzie et al., 2024).
[68] Dopp et al. (2024).
[69] Miroshnychenko, Roldan, et al. (2025).
[70] Miroshnychenko, Ibrahim, et al. (2025).
[71] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[72] Taylor, Mitchell, Hall, Langton, et al. (2024).

certainty of evidence. This SR reported that the evidence was limited by lack of long-term outcomes, lack of randomized controlled trials, and inconsistent measurement of outcomes, concluding that the certainty of evidence was frequently low or very low. For interventions including PBs, CSH, and surgeries, the certainty of evidence was very low for GD and mental health outcomes.

Hall et al. 2024[73] This SR is part of the systematic review effort commissioned by the Cass Review. It assessed the effects of social transition (e.g., name/pronoun use, clothing changes) in patients under 18 with GD/incongruence. The authors included 11 studies, most from the U.S. and of low quality, using cross-sectional and cohort designs. The literature search was conducted in April 2022. The authors used an adapted version of the Newcastle-Ottawa Scale for cohort studies. Notably, the Newcastle-Ottawa Scale is suitable for the study type, but a high-quality study as assessed by this tool may be assessed as having high risk of bias according to other tools such as ROBINS-I, which has been developed to consider both the study design and the appropriateness of a study for answering questions about treatment effects. This SR did not conduct meta-analysis to synthesize evidence quantitatively; instead, it narratively summarized the effect estimates by outcomes. The review authors interpreted the evidence with caution, considering the limitations of the evidence (small sample sizes, lack of longitudinal or controlled designs, and heterogeneous outcomes across included studies), but did not use GRADE methodology to explicitly assess the certainty of evidence. The authors concluded that there is insufficient evidence to determine benefits or harms of social transition.

Heathcote et al. 2024[74] This SR is part of the systematic review effort commissioned by the Cass Review. It evaluated psychosocial support interventions for children and adolescents experiencing GD. 10 studies with diverse designs (cohort, pre–post, mixed methods) were included. The literature search was conducted in April

[73] Hall et al. (2024).
[74] Heathcote et al. (2024).

2022. This SR used the Mixed Methods Appraisal Tool for quality assessment. Although the review followed systematic methods and focused on interventions beyond medical or surgical treatments, the evidence base was limited by the small number of studies, low quality, lack of comparators, and heterogeneity in interventions and outcomes. According to the authors, conclusions were limited due to poor reporting and inconsistent measurement. The authors called for clarity in intervention description and core outcome sets to enhance future research synthesis.

Ludvigsson et al. 2023[75] This systematic review by the Swedish National Board of Health and Welfare synthesized evidence on hormonal and surgical interventions in adolescents with GD. The review conducted a literature search in 2022 and included 24 studies (eight studies on GnRH alone, 13 studies on GnRH and CSH, and three studies on CSH alone). The review applied the GRADE methodology and downgraded the evidence due to concerns related to risk of bias and imprecise outcome measurement. However, the review authors mistakenly concluded that the certainty of evidence "cannot be assessed." Based on the authors' assessment to downgrade the evidence, the certainty of evidence should be "very low" for all outcomes assessed, including global function, suicidal ideation, GD, depression, anxiety, and quality of life. The SR concluded that evidence for benefits and harms of hormonal and surgical interventions remains insufficient for routine clinical use in adolescents.

Miroshnychenko et al. 2024[76] This systematic review and meta-analysis examined the psychological and physical effects of mastectomy in birth-registered females under 26 years with GD. The search included databases through June 2023, yielding 39 studies (three comparative observational, two before-after, and 34 case series). Outcomes included mental health measures, GD, body satisfaction, and surgical complications. The review used ROBINS-I for risk of bias assessment, conducted meta-analyses for evidence synthesis, and applied the GRADE methodology

[75] Ludvigsson et al. (2023).
[76] Miroshnychenko et al. (2024).

for certainty of evidence assessments. Comprehensive and methodologically sound, the SR found the certainty of evidence was limited by a predominance of case series, lack of prospective comparative studies, and other risk of bias concerns in the included studies, as well as small sample sizes. Indirectness was also a concern when participants' age at surgery was above the eligibility threshold. The authors found very low to low certainty evidence regarding mental health outcomes including global functioning, suicide attempt, and non-suicidal self-injuries.

Miroshnychenko et al. 2025a[77] This SR evaluated the effects of PBs in individuals under 26 years with GD. The authors searched 10 databases up to September 2023 and included studies employing observational and interventional designs. Outcomes assessed included psychological functioning, bone health, growth, and progression to CSH. The methodology of this systematic review was the same as that of another systematic review on mastectomy by the same group of researchers (Miroshnychenko 2024). The SR included 10 studies, including three comparative observational studies and seven before-after studies. The review authors concluded that the certainty of evidence for psychological and physical health is very low. This SR found that 92% of individuals who received PBs progressed to receiving CSH, though the evidence on the impact of PBs on this outcome is very uncertain (very low certainty of evidence).

Miroshnychenko et al. 2025b[78] This SR and meta-analysis assessed the effects of cross-sex hormone therapy in individuals with GD aged under 26 years. The authors searched 10 databases through September 2023 and included 24 studies (9 comparative observational, 13 before-after, and two case series). Outcomes assessed included psychological (e.g., depression, global function) and physical effects (e.g., bone mineral density, cardiovascular events). The review followed the same methodology as two other SRs (on PBs and surgery) by the same group of researchers

[77] Miroshnychenko, Roldan, et al. (2025).
[78] Miroshnychenko, Ibrahim, et al. (2025).

(Miroshnychenko 2024, Miroshnychenko 2025a[79]). The review found very low to low certainty evidence for psychological outcomes, and very low certainty evidence on bone mineral density. This SR found high certainty evidence on the proportion of natal females experiencing cardiovascular events during a seven to 109 months of follow-up, which was 40 per 1000 following CSH use.

Taylor et al. 2024a[80] This SR is part of the systematic review effort commissioned by the Cass Review. It focused on the outcomes of puberty blocker treatment in adolescents with GD or gender incongruence. The authors searched the literature through April 2022 and narratively synthesized studies on psychological, physical, and developmental effects. The SR followed the same methodology as the other reviews by the same research group (Hall 2024), including using the Newcastle-Ottawa scale to assess the risk of bias for included studies. This SR included 50 studies, including one high quality cross-sectional study and 25 moderate-quality observational studies. Notably, “moderate-quality observational studies” is not equivalent to “moderate-quality evidence.” Moderate-quality observational studies or high-quality cross-sectional studies are inherently limited in evaluating treatment effects. Moreover, most included studies were observational with small sample sizes and varying outcome definitions. The review employed a narrative synthesis, including only moderate- and high-quality studies but did not explicitly assess the certainty of evidence using the GRADE methodology. The review findings were inconclusive, with inconsistent evidence on psychological benefits and concerns about effects on bone health and growth.

Taylor et al. 2024b[81] This SR is part of the systematic review effort commissioned by the Cass Review. It synthesized studies on the outcomes of masculinising and feminising hormone therapy in adolescents with GD. It included 53 studies (12 cohort, nine cross-sectional, 32 pre–post) identified through a search conducted in April 2022. Of all included studies, there was only one high-quality cohort study, which measured

[79] Miroshnychenko, Roldan, et al. (2025).
[80] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[81] Taylor, Mitchell, Hall, Langton, et al. (2024).

adverse outcomes only. The other included studies were moderate-quality studies. The review employed a narrative synthesis, which was limited by heterogeneity in study designs and outcome measures. Compared with other low risk of bias reviews, not using GRADE methodology to explicitly assess the certainty of evidence is a limitation and creates confusion among users: the review authors discuss “moderate quality” studies, rather than moderate certainty of evidence. The authors found inconsistent or insufficient evidence for the effect of CSH on GD, body satisfaction, psychosocial, cognitive, and physical health outcomes and concluded that robust evidence is lacking. This conclusion is consistent with other SRs of similar scope (Dopp 2024,[82] Miroshnychenko 2025b[83]), which suggested very low certainty of benefits.

[82] Dopp et al. (2024).
[83] Miroshnychenko, Ibrahim, et al. (2025).

4 Summary of all included SRs

Chew et al. 2018[84]	
Study population description	Young people with gender dysphoria
Intervention	Hormonal treatment including PBs and CSH
Outcomes	Physical effects (including physical sex characteristics, side effects, bone mineral density, etc.), psychological effects, cognitive effects
Included studies	13 studies including nine on GnRHas, three on estrogen, five on testosterone, one on antiandrogen (cyproterone acetate), and one on progestin (lynestrenol). There were no randomized trials included, and only two studies included control groups.
Risk of bias assessment consideration	Study eligibility criteria: There was no registration or protocol available, though the authors describe the eligibility criteria with details for the population (age and diagnosis) and intervention, which seem appropriate for the question and are clear and unambiguous. Identification and selection of studies: The authors searched in the largest electronic databases, and although they did not use a formal search strategy, their search terms were broad enough to have likely captured all relevant studies. They also searched the reference list of relevant studies. Data collection and study appraisal: Data extraction captured relevant outcomes including mental health and physical parameters. The authors describe the most important characteristics of the included studies. The results collected, however, are not standardized across studies. Although the authors reported that two reviewers performed risk of bias assessments, they used a tool not designed for these types of study. Synthesis and findings: Only narrative synthesis was used. Although reported per outcome, the authors describe the results at the study level. For some outcomes, they provide a summary that focuses on counting the number of studies with statistically significant results. Risk of bias in the review: The authors mentioned some of the limitations of the evidence; however, they ignored these when interpreting the results and made claims about the presence of associations.
Results	Most of the included studies were assessed as studies with high risk of bias. This systematic review did not conduct evidence synthesis and instead relied on narrative description of individual studies. There was no formal assessment of the certainty of evidence. Nevertheless, the review authors concluded that hormonal treatments effectively achieved their intended physical effects, with GnRHas and cyproterone acetate suppressing sex hormones, and estrogen or testosterone promoting the development of feminized or masculinized secondary sex characteristics. GnRHa treatment was associated with improvements in several domains of psychological functioning, though not in gender dysphoria itself.

[84] Chew et al. (2018).

Dopp et al. 2024[85]	
Study population description	Transgender and gender-expansive youth
Intervention	A health intervention related to recipients' transgender and gender-expansive identity (i.e., targeting gender dysphoria, related health problems, or both): psychosocial interventions, puberty-suppressing hormones, CSH, and surgeries, reproductive health interventions, treatment of co-occurring mental health or developmental disorders, and other treatments described as "gender identity and expression change efforts."
Outcomes	Psychosocial interventions: suicidality, mental health outcomes (including both depression or mood symptoms, and functioning), regret or dissatisfaction, family support. Puberty-suppressing hormones: decrease in pubertal changes targeted for suppression, gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility. CSH: increase in pubertal changes targeted for initiation, gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility. Surgeries: gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility. Reproductive health interventions: successful cryopreservation of oocytes and embryos, successful cryopreservation of semen. Treatment of co-occurring mental health or developmental disorders: eating disorder symptoms co-occurring with gender dysphoria, depression and/or anxiety symptom co-occurring with gender dysphoria, gender dysphoria co-occurring with autism spectrum disorder. "Gender identity and expression change efforts": suicidality, mental health symptoms.
Included studies	Psychosocial interventions: 22 studies, including one randomized controlled trial (intervention as video narratives of lesbian, gay, bisexual, transgender, queer persons or persons with other sexual or gender minority identities of overcoming coming-out-related difficulties),[86] two cohort studies, six quasi-experimental studies, nine cross-sectional studies, three case reports, and one qualitative study. Puberty-suppressing hormones: 49 studies, including 25 quasi-experimental studies (nearly all before-after), eight cross-sectional studies, seven cohort studies, eight case reports, and one qualitative study. CSH: 56 studies, including 26 quasi-experimental studies (nearly all before-after), eight cross-sectional studies, 10 cohort studies, 11 case reports, and one qualitative study. Surgeries: 18 studies, including six cross-sectional studies, seven quasi-experimental studies, one cohort study, three case reports, and one qualitative study. Reproductive health interventions: nine studies, using cross-sectional or case report designs with small samples (one to 20 transgender youth per sample). Treatment of co-occurring mental health or developmental disorders: seven studies, all studies using case report design. "Gender identity and expression change efforts": four studies, including three using retrospective survey designs with community samples, and one case report.

[85] Dopp et al. (2024).
[86] This randomized controlled trial compared "coping-oriented brief videos" as an intervention for suicidality among sexual or gender minority. It was not a trial comparing psychotherapy with no psychotherapy for youth with gender dysphoria.

Dopp et al. 2024[85]	
Risk of bias assessment consideration	Study eligibility criteria: The review did not include a preregistered protocol. The eligibility criteria focused on youth with gender dysphoria under 26 years and required post-intervention outcomes. However, case reports and qualitative studies were included, which may be limited in estimating the treatment effects. Identification and selection of studies: There were two phases of literature search, and a comprehensive search was conducted in PubMed. However, other databases were not searched. Data collection and study appraisal: Data collection followed a structured form with critical appraisal procedures. Reviewers conducted risk of bias assessments using the JBI critical appraisal checklist. The tool was appropriate for the study research design. The reviewers discussed disagreements for consensus. Synthesis and findings: The review synthesized all identified studies for each intervention into a summary of effect estimates for each outcome that had been studied. Results for all prespecified outcomes reported and summarized. However, this review only narratively described the results for each outcome, without details on the evidence synthesis strategy or rationale. The interpretation of review findings were based on study quality and the limitations of included studies. Applicability of evidence was discussed, including study demographics, and statistical results were not overemphasized.
Results	Psychosocial interventions: very low certainty evidence for all outcomes. Puberty-suppressing hormones: low certainty evidence for decrease in pubertal changes targeted for suppression, very low certainty evidence for all the other outcomes. CSH: low certainty evidence for increase in pubertal changes targeted for initiation, very low certainty evidence for all the other outcomes. Surgeries: low certainty evidence for decrease in gender dysphoria after mastectomy, very low certainty evidence for decrease in gender dysphoria after other surgeries and other outcomes. Reproductive health interventions: very low certainty evidence for two outcomes. Treatment of co-occurring mental health or developmental disorders: very low certainty for all outcomes. “Gender identity and expression change efforts”: low certainty evidence in increases in suicidality, very low certainty for mental health symptoms.

Expósito-Campos et al. 2023[87]	
Study population description	Transgender and non-binary youth and adults
Intervention	Empirically supported affirmative psychological intervention.
Outcomes	Mental health outcomes including anxiety, depression, trauma, suicidality, substance abuse, etc.
Included studies	22 studies, with 10 studies reporting outcome information for transgender and non-binary people (3 randomized controlled trials and seven uncontrolled before-after studies), while 12 studies reporting mixed outcome information for transgender and non-binary and non-transgender populations.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criteria were vague, for example, "well-described psychological interventions" introduces subjectivity. It is unclear whether studies following up parallel groups of study participants were considered as "quasi-experimental designs" and included or not. Identification and selection of studies: The search strategy combined five blocks with Boolean logic "AND", including "transgender" "distress" "affirming" "psychotherapy" and "intervention". This strategy was narrow. Data collection and study appraisal: Duplicate efforts and consensus process were reported. Synthesis and findings: The planned meta-analysis was not feasible. However, the narrative synthesis was reported inappropriately. The synthesis was by studies, according to the study population, types of study design, and interventions, while preferably it should be by outcomes and types of interventions. Risk of bias in the review: The interpretation of evidence did not address the concerns in the systematic review process.
Results	This systematic review did not conduct evidence synthesis by outcome, and there was no formal certainty of evidence assessment. The review authors concluded found “improvements in psychological distress, depression, anxiety, suicidality, substance-related risk behaviors, coping skills/emotion regulation, stress appraisal, self-esteem, self-acceptance, social support, minority stress, resilience, hope, positive identity, and identity acceptance” but also noted that conclusions are limited by moderate-to-high risk of bias.

[87] Expósito-Campos et al. (2023).

Hall et al. 2024[88]	
Study population description	Children and adolescents experiencing gender dysphoria or incongruence
Intervention	Social transition
Outcomes	Mental health outcomes including depression, anxiety, substance use, and suicidality, gender identity outcomes (e.g., persistence of gender dysphoria/incongruence)
Included studies	11 studies including eight cross-sectional studies, one reanalysis of previously published cross-sectional data, one prospective longitudinal study, and one retrospective cohort study
Risk of bias assessment consideration	Study eligibility criteria: There is a registered review protocol for the review titled "The epidemiology, management and outcomes of children with gender-related distress/gender dysphoria: a systematic review", including puberty blockers. The eligibility criteria described in the report were clear. Identification and selection of studies: The major issue was that literature search was updated until April 2022, while the review was submitted for publication in July 2023, and published in April 2024. Databases were searched comprehensively and search dates accurately reported. One overarching search was conducted for all relevant efforts (including the other reviews e.g., on cross-sex hormones, psychotherapy, social transition). Data collection and study appraisal: There were duplicate efforts for data collection and study appraisal. The risk of bias tool (adapted version of Newcastle-Ottawa Scale) was acceptable. Synthesis and findings: There was no meta-analysis. Narrative synthesis by outcomes was conducted. Variation in design and measures described qualitatively; Limitations of studies and evidence quality discussed, though no GRADE certainty of evidence was conducted. This review accounted for biases from primary studies by synthesizing only moderate or high-quality studies. Risk of bias in the review: The authors interpreted findings cautiously, highlighting limited strength of evidence. The review also discussed the studies that published after the literature search date. The conclusions were consistent with limitations.
Results	No prospective longitudinal studies with suitable comparator groups have evaluated the effects of social transition on mental health or gender-related outcomes in children and adolescents. Existing studies consistently found no significant differences in mental health outcomes among children who had socially transitioned. For adolescents, the findings were mixed.

[88] Hall et al. (2024).

Heathcote et al. 2024[89]	
Study population description	Children and adolescents experiencing gender dysphoria or incongruence
Intervention	Psychosocial support
Outcomes	Mental health outcomes (including depression, anxiety, combined outcome measurement, emotional dysregulation, suicidality), psychological change (including relationship, resilience, self-compassion, self-care, coping, and problem solving, anger, life satisfaction), psychosocial change (including quality of life, well-being).
Included studies	10 studies including four cohort studies, two pre–post studies, three mixed methods, and one was a secondary analysis of intervention group data from four randomised controlled trials (these trials were not eligible).
Risk of bias assessment consideration	Study eligibility criteria: There is a registered review protocol for the review titled "The epidemiology, management and outcomes of children with gender-related distress/gender dysphoria: a systematic review", including puberty blockers. The eligibility criteria described in the report were clear. Identification and selection of studies: The major issue was that the literature search was updated until April 2022, while the review was submitted for publication in September 2023, and published in April 2024. Databases searched comprehensively and search dates were reported. Though one overarching search was conducted for all relevant efforts (including the other reviews e.g., on cross-sex hormones, psychotherapy, social transition). Data collection and study appraisal: There were duplicate efforts for data collection and study appraisal. The risk of bias tool was Mixed Methods Appraisal Tool. Synthesis and findings: There was no meta-analysis. Narrative synthesis by outcomes was conducted. Variation in design and measures described qualitatively; Limitations of studies and evidence quality discussed, though no GRADE certainty of evidence was conducted. This review accounted for biases from primary studies by synthesizing only moderate or high-quality studies. Risk of bias in the review: The authors interpreted findings cautiously, highlighting limited strength of evidence. The review also discussed the studies that published after the literature search date. The conclusions were consistent with limitations.
Results	Research on the outcomes of psychosocial interventions for children and adolescents with gender dysphoria or incongruence is limited. The risk of bias and poor reporting of the 10 included studies limited the conclusions about the effectiveness of psychosocial support.

[89] Heathcote et al. (2024).

Karalexi et al. 2020[90]	
Study population description	Transgender young adults
Intervention	Hormone therapy
Outcomes	Cognitive outcomes including visuospatial ability, verbal memory, verbal reasoning, verbal working memory, computation, motor coordination.
Included studies	10 studies, including six cohort studies, three cross-sectional studies, and one with both longitudinal and cross-sectional analysis.
Risk of bias assessment consideration	Study eligibility criteria: The review included cohorts and cross-sectional studies. It is unclear whether a single group of participants with before-after study design but not labeled as "cohort" would be included or not. Identification and selection of studies: Literature search was conducted only in one database, MEDLINE. The search strategy included terms for "outcome", which may exclude records that are eligible but not indexed by reported outcomes. The number of records was low compared with other reviews. Data collection and study appraisal: Data collection seemed to be appropriate. Risk of bias was assessed using Newcastle-Ottawa Scale; However, the description of how the assessment was done suggested that the assessment may not be properly done. For example, all cohort studies were awarded with two stars in the ‘’Comparability’’ section. Synthesis and findings: Meta-analysis was conducted where appropriate; but the review also conducted narrative synthesis elsewhere. Sources of heterogeneity was assessed using I^2 and this review briefly described the heterogeneity was not evident. No certainty of evidence assessed. Risk of bias in the review: No discussion or interpretation was included considering the risk of bias of included studies, and the limitation of the evidence.
Results	The review included meta-analyses on the cognitive functions but did not formally assess the certainty of evidence. The systematic review did not identify evidence on adverse impact of hormone therapy on cognitive function.

[90] Karalexi et al. (2020).

Ludvigsson et al. 2023[91]	
Study population description	Children with gender dysphoria
Intervention	Hormone therapy
Outcomes	Psychosocial and mental health outcomes (including gender dysphoria, depression, anxiety), cognitive outcomes, bone health outcomes, body composition and metabolic markers.
Included studies	24 studies, all observational studies, including eight studies on GnRH alone, 13 studies on GnRH and CSH, and three studies on cross-sex hormones alone.
Risk of bias assessment consideration	Study eligibility criteria: This review followed PRISMA and internally register the protocol in the Swedish health technology assessment agency- However, the original protocol was not accessible. Identification and selection of studies: The literature search was comprehensive and reported in detail. However, the search may be outdated when the report was submitted for publication. Data collection and study appraisal: Two independent reviewers extracted data and conducted risk of bias assessment. Synthesis and findings: Narrative synthesis by outcome groups was justified given heterogeneity in studies. Robustness of results was considered through methodological description and bias discussion. Risk of bias in the review: The interpretation of review findings considered study quality and limitations of included studies. Conclusions aligned with evidence and noted significant research gaps. Though the GRADE assessment was labelled as "cannot be assessed", when four or more levels of downgrading happened. It should be very low.
Results	This systematic review did not identify any randomized control trails. The limited number of longitudinal observational studies were constrained by small sample sizes and high dropout rates. The evidence of long-term psychosocial effects of hormone therapy was limited. Treatment with GnRHa was found to delay bone maturation and the accrual of bone mineral density; however, partial recovery was observed during cross-sex hormone therapy when assessed at age 22.

[91] Ludvigsson et al. (2023).

Malpas et al. 2022[92]	
Study population description	Transgender and gender expansive youth
Intervention	Family-based interventions: (1) providing psychoeducation, (2) allowing space for families to express reactions to their child's gender, (3) emphasizing the protective power of family acceptance, (4) utilizing multiple modalities of support, (5) giving families opportunities for allyship and advocacy, (6) connecting families to transgender and gender expansive youth community resources, and (7) centering intersectional approaches and concerns.
Risk of bias assessment consideration	Study eligibility criteria: There was no registration or protocol. This review included three review processes, and the inclusion criteria were vague. For example, for Review 1, the inclusion criteria were: "(1) the article was published in English, and (2) the article provided treatment strategies, best practices, clinical recommendations, or outcome data related to family therapy or interventions to increase family engagement with transgender and gender expansive (TGE) youth." Identification and selection of studies: This review included three stages of search. Review 1 was the part that best met the scope of this overview. However, the number of results was low compared with other reviews. Separating Review 1 and Review 2 may have introduced bias in the review process. Though the search was updated until 2018, while the review was published in 2022. Data collection and study appraisal: No details were reported other than only "Relevant information was then coded ...". There was very brief information for included studies. No formal risk of bias assessment was applied. Synthesis and findings: The review did not identify quantitative outcome information; thus, this review narratively describe the qualitative results. The themes identified through this review included "(1) the change of clinical stance on families of youth with gender dysphoria over time, (2) the theoretical models often cited and used, (3) the most frequently recommended best clinical practices when working with youth with gender dysphoria and their families, and (4) the commonalities of these best practices with outcome data on family therapy with lesbian, gay, and bisexual youth." The review results and analyses deviated from the purpose of summarizing the evidence on family-based intervention. Risk of bias in the review: The concerns identified were not addressed in the interpretation of evidence.
Outcomes	No quantitative outcome for effectiveness. This systematic review identified four themes related to family-based intervention.
Included studies	32 studies on clinical practice recommendations for family-based interventions for transgender and gender expansive youth.
Results	This systematic review found that clinical strategies have moved from pathologizing to affirming of transgender and gender expansive youths' gender journey.

[92] Malpas et al. (2022).

Miroshnychenko et al. 2024[93]	
Study population description	Individuals aged <26 years experiencing gender dysphoria
Intervention	Mastectomy
Outcomes	Mental health measures (including distress, suicide), gender dysphoria, body satisfaction, and surgical complications (including death, necrosis, and scarring).
Included studies	39 studies, including three comparative observational studies, two before-after, and 34 case series.
Risk of bias assessment consideration	Study eligibility criteria: The protocol was registered, and the eligibility criteria were clear. Identification and selection of studies: The literature search covered multiple databases with support from an information specialist. The authors described their duplicate screening and consensus processes. Data collection and study appraisal: Standardized data extraction form and duplicate extraction efforts were used; and a third reviewer was available for consensus. The risk of bias tool was appropriate for the review purpose. Synthesis and findings: Meta-analyses were conducted. When meta-analyses were not feasible, narrative syntheses were conducted. Certainty of evidence was rated using GRADE and considered the heterogeneity and risk of bias in included studies. Risk of bias in the review: The interpretation of evidence was appropriately cautious given very low to low certainty of much of the evidence.
Results	The authors found low certainty evidence on non-suicidal self-injuries, and very low certainty evidence regarding gender dysphoria and other psychological outcomes such as global functioning and suicide attempt. The review also identified high certainty evidence for outcomes of death, necrosis, and excessive scarring after surgery. The numbers of events after mastectomy were estimated to be 0, 10 to 30, and 50 per 1,000 persons for death, necrosis, and excessive scarring, respectively.

[93] Miroshnychenko et al. (2024).

Miroshnychenko et al. 2025a[94]	
Study population description	Individuals aged <26 years experiencing gender dysphoria
Intervention	PBs
Outcomes	Gender dysphoria, global function, depression, bone mineral density, progression to CSH.
Included studies	10 studies, three comparative observational studies, and seven before-after design studies.
Risk of bias assessment consideration	Same as Miroshnychenko 2024[95]
Results	The systematic review identified very low certainty of evidence on the outcomes of gender dysphoria, global function, depression, and bone mineral density. There remains considerable uncertainty regarding the effects of PBs in individuals experiencing gender dysphoria.

[94] Miroshnychenko, Roldan, et al. (2025).
[95] Miroshnychenko et al. (2024).

Miroshnychenko et al. 2025b[96]	
Study population description	Individuals aged <26 years experiencing gender dysphoria
Intervention	CSH
Outcomes	Gender dysphoria, global function, depression, death by suicide, bone mineral density, sexual dysfunction, cardiovascular events.
Included studies	24 studies, including nine comparative observational studies, 13 before-after studies, and two case series.
Risk of bias assessment consideration	Same as Miroshnychenko 2024[97]
Results	This systematic review found very low to low certainty evidence about depression, very low certainty evidence on gender dysphoria, global function, and bone mineral density. The systematic review found moderate to high certainty evidence on the incidence of cardiovascular events after receiving CSH.

[96] Miroshnychenko, Ibrahim, et al. (2025).
[97] Miroshnychenko et al. (2024).

Ramos et al. 2021[98]	
Study population description	Adolescents with gender incongruity
Intervention	PBs
Outcomes	Gender dysphoria, bone mineral density, side effects.
Included studies	11 studies including nine observational studies and two qualitative studies.
Risk of bias assessment consideration	Study eligibility criteria: The authors used study design as a reason for exclusion (e.g., literature reviews, systematic reviews, reports and case series, guidelines, summaries and comments). "Theme" was described as an exclusion reason at full-text screening, but the associated eligibility criterion was not clear. Identification and selection of studies: Search terms, filters, and strategies were reported. However, search strategy included restrictive terms including "NOT" operators that could be related to outcomes of interest (e.g., depressive disorder), which was probably not appropriate as psychosocial functioning is one of the outcomes summarized. The literature search only identified 108 records, which was low compared to other included reviews. Data collection and study appraisal: The study characteristics were not systematically reported. The authors noted using "Cochrane risk of bias assessment for observational and intervention studies", assessing, "bias of selection, performance, selective reporting, detection, attrition, and other (e.g., inadequate control for key confounders) ...", and provided an alphanumeric rating at the study level in Table 1 (e.g., 2B, 2C, 4). There was no legend provided for the meaning of these ratings. It was not clear whether the Cochrane risk of bias tool is referring to ROBINS-I, which does not have these rating categories. At least one of the studies included is a qualitative study, and it was not clear how the risk of bias tool for observational and intervention studies would apply to the qualitative study. There was no mention of whether the assessment was conducted independently, in duplicate. Synthesis and findings: The authors included a narrative synthesis at the study-level highlighting results or conclusions from individual studies. The synthesis was not organized by outcome, and there was high risk of bias for selectively including study results in the narrative synthesis. The authors did not address heterogeneity in the synthesis, rather in the limitations it was noted, "Studies found are heterogeneous (different definitions, population and evaluation techniques) and sometimes based on small sample size, restricting statistical power." Risk of bias in the review: The concerns identified were not addressed.
Results	This systematic review did not conduct evidence synthesis by outcome, rather narratively described results by individual studies. There was no certainty of evidence assessment, but according to the review authors, the use of GnRHa seems to be well tolerated by the studied population, prevent the irreversible phenotypic changes, and “contribute to the mental health.”

[98] Ramos et al. (2021).

Rew et al. 2021[99]	
Study population description	Transgender and gender diverse youth
Intervention	PBs
Outcomes	Anthropomorphic measurements, sexual characteristics, mental health functioning, depression, emotional and behaviour problems, suicide, and side effects.
Included studies	Nine studies including six observational studies, one cross-sectional study, and two case reports.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criterion for outcomes was vague by being specified as studies needing to "identify risks and/or benefits associated with the use of these medications." Identification and selection of studies: The literature search only identified 151 records after de-duplication, which was low compared to other included reviews. The study selection approach was not described. Screening involved multiple reviewers but there was no detailed reporting of calibration or adjudication. Data collection and study appraisal: A data extraction form was developed, but approach to data extraction was not described. Synthesis and findings: Narrative synthesis was justified due to design heterogeneity. Some of the included studies reported the same outcomes (e.g., body composition), but the synthesis (Table 2) was presented at the study-level instead of at the outcome-level, and the summary in the main text was collated under 'risks/adverse outcomes' and 'positive outcomes'. Risk of bias in the review: The interpretation of findings did not address the concerns identified in the process. While the risk of bias was described for the studies, it was not described in relation to the outcomes and findings.
Results	This systematic review did not conduct evidence synthesis by outcome, rather narratively described results. This systematic review listed studies reporting positive outcomes and adverse effects. For example, “positive outcomes were decreased suicidality in adulthood, improved affect and psychological functioning, and improved social life. Adverse factors associated with use were changes in body composition, slow growth, decreased height velocity, decreased bone turnover, cost of drugs, and lack of insurance coverage.” There was no certainty of evidence assessment, and the interpretation did not take into consideration of the strengths and limitations of the evidence.

[99] Rew et al. (2021).

Taylor et al. 2024a[100]	
Study population description	Adolescents with gender dysphoria or gender incongruence
Intervention	PBs
Outcomes	Gender dysphoria and body satisfaction, psychological health (including depression, anxiety, anger, etc.), psychosocial outcomes (including quality of life, peer-relation, etc.), cognitive/neurodevelopmental outcomes, physical health outcomes (including bone health, cardiovascular health, and physiological parameters), side effects, and puberty suppression (including puberty progression, hormone levels, menstrual suppression, height/growth, body composition, bone geometry, etc.).
Included studies	50 studies, including 11 cohorts, eight cross-sectional and 31 before-after studies. The descriptive evidence synthesis included one high quality cross-sectional study, and 25 moderate observational studies.
Risk of bias assessment consideration	Study eligibility criteria: There was a registered review protocol for the review titled "The epidemiology, management and outcomes of children with gender-related distress/gender dysphoria: a systematic review", including puberty blockers. The eligibility criteria described in the report were clear. Identification and selection of studies: The major issue was that literature search was updated until April 2022, while the review was submitted for publication in November 2023, and published in April 2024. Databases searched comprehensively and search dates reported. One overarching search was conducted for all relevant efforts (including the other reviews e.g., on cross-sex hormones, psychotherapy, social transition). Data collection and study appraisal: There were duplicate efforts for data collection and study appraisal. The risk of bias tool (adapted version of Newcastle-Ottawa Scale) was acceptable. Synthesis and findings: There was no meta-analysis. Narrative synthesis by outcomes was conducted. Variation in design and measures described qualitatively; Limitations of studies and evidence quality were discussed, though no GRADE certainty of evidence was conducted. This review accounted for biases from primary studies by synthesizing only moderate or high-quality studies. Risk of bias in the review: The authors interpreted findings cautiously, highlighting limited strength of evidence. The review also discussed the studies that published after the literature search date. The conclusions were consistent with limitations.
Results	This systematic review did not identify high-quality studies with appropriate designs (only one “high-quality” cross-sectional study). Of the 11 cohort studies, only five were rated as moderate in quality. The evidence on the effects of PBs in adolescents with gender dysphoria or incongruence regarding its impact on gender dysphoria, mental or psychosocial health, or cognitive development was limited. Evidence also suggests that bone health and height may be adversely affected during treatment. Recently published studies which were not included in this systematic review align with the findings of this systematic review.

[100] Taylor, Mitchell, Hall, Heathcote, et al. (2024).

Taylor et al. 2024b[101]	
Study population description	Adolescents with gender dysphoria or gender incongruence
Intervention	CSH
Outcomes	Gender dysphoria and body satisfaction, psychological health (including depression, anxiety, anger, etc.), psychosocial outcomes (including quality of life, peer-relation, etc.), cognitive/neurodevelopmental outcomes, physical health outcomes (including bone health, cardiovascular health, and physiological parameters), side effects, and puberty suppression (including induced puberty progression, hormone levels, menstrual suppression, height/growth, body composition/shape, bone geometry, etc.), and fertility.
Included studies	53 studies including 12 cohort, nine cross-sectional, 32 pre–post studies. This systematic review included one high quality cohort study.
Risk of bias assessment consideration	Same as Taylor 2024a.[102]
Results	High-quality research on the outcomes of hormone interventions in adolescents with gender dysphoria or incongruence is lacking, and few studies include long-term follow-up. There is uncertainty regarding their effects on gender-related outcomes, body satisfaction, psychosocial health, cognitive development, or fertility, and the impacts on height, growth, cardiometabolic health, and bone health. The review authors identified "moderate quality" studies[103] mental health may be improved during treatment.

[101] Taylor, Mitchell, Hall, Langton, et al. (2024).
[102] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[103] This review had identified "moderate quality" observational studies. Including "moderate-quality observational studies" is not equivalent to "moderate quality (certainty) evidence." According to the GRADE methodology, the starting point for evidence from observational studies (including high quality observational studies) is generally low quality. To have moderate certainty, the certainty of evidence needs to be upgraded. See Guyatt, Oxman, Sultan, et al. (2011).

Thompson et al. 2023[104]	
Study population description	Adolescents with gender dysphoria
Intervention	Psychosocial only PBs CSH Surgeries
Outcomes	Psychosocial only: mental health. PBs: blood pressure, biochemistry and hematological measurements, anthropometric, bone density and physical changes, mental health. CSH: biochemical and hematological, anthropometric, bone density and physical changes, and mental health. Surgeries: mental health.
Included studies	19 studies, including 13 retrospective studies and no randomized controlled trial.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criteria were clear. Identification and selection of studies: There was no literature search for unpublished literature. Reference list of included studies was checked. But the inclusion criteria also excluded the possibility of searching grey literature. Data collection and study appraisal: Data were comprehensive and tabulated; overlapping samples were identified. All outcome domains from included studies were described, but synthesis was limited to narrative integration. Risk of bias was assessed using Crowe Critical Appraisal Tool, this tool may lack specificity. For example, with this tool, many papers scored lower on was the issue of consent— but many studies were retrospective in nature and the consent process was waived. Synthesis and findings: Narrative synthesis was used by outcomes. However, the syntheses for outcomes were conducted combining both puberty blockers and cross-sex hormones, which may not be appropriate. Heterogeneity was discussed narratively but no subgroup or sensitivity analysis was performed. This review described risk of bias, however, did not account for the limitations of studies in the synthesis. Risk of bias in the review: The interpretation of evidence did not address the concerns identified.
Results	No certainty of evidence assessment was conducted. Most changes to health parameters were inconclusive, “except an observed decrease in bone density z-scores with PBs.” “Some improvements were observed in global functioning and depressive symptoms once treatment was started.”

[104] Thompson et al. (2023).

Zepf et al. 2024[105]	
Study population description	Children/adolescents with gender dysphoria
Intervention	PBs CSH
Outcomes	PBs: gender dysphoria, mental health, quality of life, body image, psychosocial effects, health care utilization, satisfaction with surgery following PBs, and treatment discontinuation. Cross-sex hormone: body image, psychosocial outcomes, treatment discontinuation, and bone metabolism.
Included studies	This systematic review was an update on the systematic review efforts by NICE (National Institute for Health and Care Excellence) – which aimed to "inform Dr Hilary Cass' independent review into gender identity services for children and young people." This updated further included two observational studies on CSH.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criteria were clear. Identification and selection of studies: Five databases were searched; strategy was comprehensive. Screening process was not fully described. Data collection and study appraisal: It is unclear if a structured risk of bias tool was applied. Synthesis and findings: The authors synthesize the results from all studies. They do not describe methods for data analysis. The studies seemed heterogeneous enough that summarizing them narratively is appropriate. Limitations were discussed in detail, including inconsistency and weak study designs. Risk of bias in the review: The authors considered the limitations of the evidence when interpreting the results.
Results	This systematic review concluded that the evidence on the effectiveness of PBs and/or CSH in children and adolescents with gender dysphoria remains inadequate.

[105] Zepf et al. (2024).

5 Evidence synthesis: Puberty blockers

This overview identified nine SRs on the treatment effects of PBs. Across all primary studies included in these SRs, there were no eligible randomized controlled trials. These SRs frequently used the labels based on study design, such as “cohort,” to describe the study design for included studies. However, these labels may be confusing due to the variations in study design with the same label. To address this concern, the researchers from McMaster University used labels such as “comparative observational studies” and “before-after study.” This overview found that across all primary studies in the nine SRs on PBs, only six were observational studies with parallel control groups comparing PBs with no PBs among children or adolescents with GD.[106] The sample sizes in these studies were small: three studies included fewer than 100 participants, ranging from 60 to 438 across these six comparative observational studies. In summary, the methodology of the current studies was insufficient to properly assess the treatment effects of PBs.

5.1 Included SRs on PBs

Chew 2018

Chew, D., Anderson, J., Williams, K., May, T., & Pang, K. (2018). Hormonal treatment in young people with gender dysphoria: A systematic review. *Pediatrics*, *141*(4).

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Ludvigsson 2023

Ludvigsson, J. F., Adolfsson, J., Hoistad, M., Rydelius, P. A., Kristrom, B., & Landen, M. (2023). A systematic review of hormone treatment for children with gender dysphoria

[106] Becker-Hebly et al. (2021); Costa et al. (2015); Grimstad et al. (2021); Jensen et al. (2019); McGregor et al. (2024); Tordoff et al. (2022).

and recommendations for research. *Acta Paediatrica, International Journal of Paediatrics*, *112*(11), 2279-2292.

Miroshnychenko 2025a

Miroshnychenko, A., Roldan, Y., Ibrahim, S., Kulatunga-Moruzi, C., Montante, S., Couban, R., . . . Brignardello-Petersen, R. (2025). Puberty blockers for gender dysphoria in youth: A systematic review and meta-analysis. *Archives of Disease in Childhood*. https://doi.org/https://dx.doi.org/10.1136/archdischild-2024-327909

Ramos 2021

Ramos, G. G. F., Mengai, A. C. S., Daltro, C. A. T., Cutrim, P. T., Zlotnik, E., & Beck, A. P. A. (2021). Systematic review: Puberty suppression with gnrh analogues in adolescents with gender incongruity. *Journal of Endocrinological Investigation*, *44*(6), 1151-1158.

Rew 2021

Rew, L., Young, C. C., Monge, M., & Bogucka, R. (2021). Review: Puberty blockers for transgender and gender diverse youth-a critical review of the literature. *Child and Adolescent Mental Health*, *26*(1), 3-14.

Taylor 2024a

Taylor, J., Mitchell, A., Hall, R., Heathcote, C., Langton, T., Fraser, L., . . . Hewitt, C. E. (2024). Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*, *109*(Suppl 2), s33-s47.

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS Global Public Health*, *3*(8), e0001478.

Zepf 2024

Zepf, F. D., Konig, L., Kaiser, A., Ligges, C., Ligges, M., Roessner, V., . . . Holtmann, M. (2024). [beyond nice: Updated systematic review on the current evidence of using puberty blocking pharmacological agents and cross-sex-hormones in minors with gender dysphoria]. *Beyond NICE: Aktualisierte systematische Ubersicht zur Evidenzlage der Pubertatsblockade und Hormongabe bei Minderjahrigen mit Geschlechtsdysphorie.*, *52*(3), 167-187.

5.2 Low risk of bias SRs

Four English language SRs were classified at low risk of bias.[107] Only SRs with low risk of bias were summarized to assess outcomes.

Of the four low risk of bias SRs, the eligibility criteria and number of included studies varied. Notably, the systematic review by Taylor and colleagues[108] included most studies: 50 studies including 11 cohorts, eight cross-sectional, and 31 before-after studies. This SR synthesized only study results from high or moderate quality studies. Dopp 2024[109] included 49 studies including 25 quasi-experimental studies (nearly all before-after), eight cross-sectional studies, seven cohort studies, eight case reports, and one qualitative study (case reports and qualitative studies are inadequate to provide quantitative information on treatment effects). In contrast, Ludvigsson 2023[110] included 21 studies, and Miroshnychenko 2025a[111] included 10 studies (including three comparative observational studies and seven before-after design).

[107] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[108] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[109] Dopp et al. (2024).
[110] Ludvigsson et al. (2023).
[111] Miroshnychenko, Roldan, et al. (2025).

Only seven studies were included in all four low risk of bias SRs, including two comparative cohorts (one in Germany,[112] one in the UK[113]), as well as the five before-after studies reported in Canada,[114] Netherlands,[115] and UK.[116])

5.3 Outcome 1. Gender dysphoria

A total of four low risk of bias SRs assessed the impact of PBs on GD.[117] Dopp 2024[118] included the most studies, though these included case reports and a qualitative study, which have limited value in estimating treatment effects. This systematic review narratively described that PBs lead to improved GD, without details on its methods for evidence synthesis. In contrast, the other three SRs reported no change in GD associated with PBs.

The interpretation of these results requires caution regarding the certainty of evidence. All three SRs using the GRADE methodology to assess certainty of evidence concluded the certainty of evidence was very low.[119] Taylor 2024a did not formally assess the certainty of evidence but found that “no high-quality studies using an appropriate design were identified, … no conclusions can be drawn,” [120] which is equivalent to very low certainty evidence.

In summary, this overview concludes that the certainty of evidence is very low, and no conclusion could be drawn on the impact of PBs on GD.

5.4 Outcome 2. Mental health and well-being

A total of four SRs assessed the impact of PBs on mental health, using varying measures of mental health such as global function, suicidality, depression, anxiety, and

[112] Becker-Hebly et al. (2021).
[113] Costa et al. (2015).
[114] Navabi et al. (2021).
[115] Klink et al. (2015); Schagen et al. (2016).
[116] Carmichael et al. (2021); Joseph et al. (2019).
[117] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[118] Dopp et al. (2024).
[119] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025).
[120] Taylor, Mitchell, Hall, Heathcote, et al. (2024).

quality of life.[121] Similar to the reviews on the GD outcome, Dopp 2024[122] included more studies than the three other SRs because it included case reports and a qualitative study. It narratively described that PBs lead to improved mental health, though the certainty of evidence was assessed as very low. The remaining three SRs reported either no change or small changes in mental health associated with PBs. The certainty of evidence was very low.

In summary, this overview concludes that no conclusion could be drawn on the impact of PBs on mental health due to very low certainty evidence.

5.5 Outcome 3. Pubertal development

Two SRs assessed the impact of PBs on pubertal development, including pubertal progression, hormone level, and menstrual suppression.[123] SRs showed that the use of PBs is consistently associated with reductions in pubertal development. This overview assessed the certainty of evidence as high due to the observed very large effects.[124]

In summary, this overview finds high certainty evidence showing PBs lead to expected physiological effects on pubertal development.

5.6 Outcome 4. Need for or progression to further treatment

Only one systematic review assessed the impact of PBs on proceeding with CSH. Miroshnychenko and colleagues[125] included two case series and estimated that 92% of children or adolescents with GD proceeded with CSH, suggesting a high proportion of adolescents receiving PBs proceed to CSH. However, due to concerns related to risk of bias, the certainty of evidence regarding the causal role that PBs play in this progression is very low.

[121] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[122] Dopp et al. (2024).
[123] Dopp et al. (2024); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[124] According to GRADE, the evaluation of certainty of evidence based on observational studies starts as low certainty. There is no further downgrade of evidence for this outcome by this overview. The certainty of evidence is upgraded by two levels due to the very large observed effect. See Guyatt, Oxman, Sultan, et al. (2011).
[125] Miroshnychenko, Roldan, et al. (2025).

5.7 Outcome 5. Safety

A total of four low risk of bias SRs reported the safety outcomes for PBs in children or adolescents with GD.[126] Outcomes included overall risk of adverse events, bone health, fertility, anthropometric measures, body composition, growth, and other measures. Dopp 2024[127] included the largest number of eligible studies. The SRs reported side effects including mild headaches or hot flushes, moderate/severe headaches or hot flushes, mild fatigue, mood swings, weight gain and sleep problems. The certainty of evidence on the overall risk of adverse events was very low.

The SRs found no evidence on the long-term safety of PBs.

All four SRs assessed bone health, and the evidence was based primarily on before-after studies. The most frequently reported outcome for bone health was bone mineral density decreases relative to reference values (z score). All SRs reported that bone density is compromised during PB treatment. Specifically, Miroshnycheko and colleagues[128] reported decreases in bone mineral density for hip, lumbar spine, and femoral neck. There was disagreement across SRs on certainty of evidence assessment, which was low according to Ludvigsson 2023[129] (due to risk of bias and imprecision concerns) but very low according to Dopp 2024[130] and Miroshnycheko 2025a.[131] Taylor 2024a[132] did not formally assess the certainty of evidence but concluded that multiple studies found that bone density is compromised. This overview of SRs assessed the certainty of evidence on bone health as low. This was due to the risk of bias in evidence based on observational studies.[133] In summary, this overview concludes there is low certainty evidence that PBs lead to compromised bone density.

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[126] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[127] Dopp et al. (2024).
[128] Miroshnychenko, Roldan, et al. (2025).
[129] Ludvigsson et al. (2023).
[130] Dopp et al. (2024).
[131] Miroshnychenko, Roldan, et al. (2025).
[132] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[133] According to GRADE, the evaluation of certainty of evidence based on observational studies starts as low certainty, due to risk of bias concerns arising from unbalanced prognostic factors and uncontrolled confounding (lack of randomization). There is no further downgrade of evidence by this overview. The certainty of evidence is low.

Only one systematic review reported on fertility outcomes. Based on two case reports of fertility preservation, Dopp et al[134] concluded that there was very low certainty evidence on the risk of infertility after PBs. This overview has not identified empirical evidence on fertility outcomes from included SRs. However, based on high certainty evidence in this overview on PBs' effects on pubertal development and the consideration of fertility preservation in clinical practice, adolescents receiving PBs who then proceed with CSH probably experience infertility, though the impact may depend on natal sex and stage of pubertal development when starting PBs.

Two SRs[135] reported other outcomes such as anthropometric measures, body composition, blood pressure, etc., and found either no change or small changes. The certainty of evidence was judged to be very low. This overview concludes that the certainty of evidence for these outcomes is very low.

5.8 Outcome 6. Regret

Only one SR assessed regret after PBs and reported high satisfaction ratings and low rates of regret. The certainty of evidence was very low, and no conclusions can be reached on the regret rate after PBs.

5.9 Evidence gap

Important gaps remain in both the range and quality of outcomes assessed across the existing literature. Many primary studies were not designed to adequately measure or report on outcomes related to puberty blocker use. For example, only a small number of primary studies included in the SRs assessed the impact of PBs on outcomes such as GD or mental health. Although PBs are frequently described as a "pause button," no studies have systematically examined their role in the decision-making process or the outcomes of those who discontinue treatment.

When outcomes were assessed, the primary focus was on short term psychological or physiological changes, or surrogate outcomes—such as suicidal ideation or bone mineral density—rather than clinically important endpoints like suicide or fractures.

[134] Dopp et al. (2024).
[135] Ludvigsson et al. (2023); Taylor, Mitchell, Hall, Heathcote, et al. (2024).

There is particularly limited evidence on long-term outcomes related to fertility, growth, and cognitive development.

While studies suggest that a high proportion of youth proceed to cross-sex hormones after puberty suppression,[136] there is minimal evidence on the impact of this combined pathway compared to CSH alone, on long-term outcomes such as surgical outcomes, or on the need for future surgery. Furthermore, no studies have clearly examined the physical or psychosocial trajectories of those who stop PBs without transitioning to CSH. As a result, there is little data on what happens after treatment ends, and the assumption of reversibility of all puberty blocker effects remains largely untested. A further important limitation is that most primary studies did not consider the effects of PBs on males versus females. Overall, the absence of long-term, high-certainty evidence on these critical outcomes (including suicide, fractures, fertility, growth, and cognitive development) leaves substantial uncertainty about the effects of PBs.

5.10 Summary

In summary, this overview identified nine SRs addressing the effects of PBs on GD, mental health, safety, pubertal development, and further treatment decisions. There is high certainty evidence that PBs exert physiological effects such as puberty suppression, and that they probably lead to infertility when adolescents receiving PBs go on to receive CSH. PBs may compromise bone health. A high proportion of youth proceed to CSH from PBs. The evidence is very uncertain regarding the effect on GD, mental health, and safety.

[136] Miroshnychenko, Roldan, et al. (2025).

5.11 Evidence mapping: SRs on PBs

Table 5.1. Evidence mapping of the SRs on PBs and the primary studies that these SRs included

	Chew 2018[137]	Dopp 2024[138]	Ludvigsson 2023[139]	Miroshnychenko 2025a[140]	Ramos 2021[141]	Rew 2021[142]	Taylor 2024a[143]	Thompson 2023[144]	Zepf 2024[145]
Achille 2020		Y		Y			Y		
Akgul 2019		Y					Y		
Arcelus 2016							Y		
Arnoldussen 2022		Y							
Barnard 2019		Y							
Becker-Hebly 2021		Y	Y	Y			Y	Y	
Brik 2020		Y							Y
Burke 2020	Y						Y		
Caanen 2017		Y							
Cantu 2020			Y						
Carmichael 2021		Y[146]	Y	Y			Y		
Chen 2016								Y	
Chiniara 2018							Y		

[137] Chew et al. (2018).
[138] Dopp et al. (2024).
[139] Ludvigsson et al. (2023).
[140] Miroshnychenko, Roldan, et al. (2025).
[141] Ramos et al. (2021).
[142] Rew et al. (2021).
[143] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[144] Thompson et al. (2023).
[145] Zepf et al. (2024).
[146] Another citation, McPherson 2023 was provided for this study. This report was a re-analysis of the data collected by the previous report. However, this citation was not included by any other SRs on PBs or CSH.

	Chew 2018[137]	Dopp 2024[138]	Ludvigsson 2023[139]	Miroshnychenko 2025a[140]	Ramos 2021[141]	Rew 2021[142]	Taylor 2024a[143]	Thompson 2023[144]	Zepf 2024[145]
Cohen-Kettenis 2011[147]		Y				Y			
Costa 2015	Y	Y	Y	Y	Y		Y	Y	Y
de Nie 2022							Y		
de Vries 2014	Y		Y		Y		Y		
de Vries 2011	Y	Y		Y	Y	Y	Y	Y	Y
Delemarre-van de Waal 2006	Y	Y					Y		
Donaldson 2018		Y							
Ewan 2014		Y							
Fontanari 2020							Y		
Ghelani 2020							Y		
Giovanardi 2019					Y				
Grannis 2021, Grannis 2023, and Olsavsky 2023		Y[148]							
Grimstad 2021a							Y		
Hisle-Gorman 2021		Y	Y				Y		
Jensen 2019								Y	
Joseph 2019		Y	Y	Y			Y	Y	Y
Karakılıç Özturan 2023				Y					
Khatchadourian 2014		Y			Y	Y	Y		Y
Klaver 2020		Y	Y				Y	Y	
Klaver 2018			Y		Y	Y	Y	Y	

[147] Another citation (Cohen-Kettenis, 1998) was provided for this study. However, this citation was not included by any other SRs on PBs or CSH, although it was included by Dopp et al. (2024) for CSH and surgeries.
[148] Dopp et al. (2024) included three citations for one study.

	Chew 2018[137]	Dopp 2024[138]	Ludvigsson 2023[139]	Miroshnychenko 2025a[140]	Ramos 2021[141]	Rew 2021[142]	Taylor 2024a[143]	Thompson 2023[144]	Zepf 2024[145]
Klink 2015	Y	Y	Y	Y	Y		Y		Y
Klink 2013					Y				
Kuper 2020		Y					Y	Y	
Lavender 2023		Y							
Lee 2020			Y					Y	
Lee 2024		Y							
Littman 2021		Y							
Lopez 2018					Y			Y	
López de Lara 2020		Y							
Lynch 2015							Y		
Martin 2021		Y							
McGregor 2024		Y							
Mejia-Otero 2021							Y		
Moussaoui 2023		Y							
Nahata 2017						Y		Y	
Navabi 2021		Y	Y	Y			Y		
Neyman 2019		Y					Y		
Nokoff 2021			Y				Y		
Olson 2022		Y							
Olson-Kennedy 2021							Y		
Pang 2020		Y							

	Chew 2018[137]	Dopp 2024[138]	Ludvigsson 2023[139]	Miroshnychenko 2025a[140]	Ramos 2021[141]	Rew 2021[142]	Taylor 2024a[143]	Thompson 2023[144]	Zepf 2024[145]
Perl 2021[149]		Y					Y		
Perl 2020[150]		Y	Y				Y	Y	
Pine-Twaddell 2023							Y		
Ristori 2019		Y							
Russell 2021							Y	Y	
Schagen 2016	Y	Y	Y		Y	Y	Y		Y
Schagen 2018							Y		
Schagen 2020		Y	Y	Y			Y	Y	
Schneider 2017		Y				Y			
Schulmeister 2022			Y				Y		
Schwartz 2023		Y							
Segev-Becker 2020							Y		
Staphorsius 2015	Y		Y				Y		Y
Stoffers 2019			Y				Y	Y	
Strang 2022							Y		
Tack 2016		Y					Y	Y	
Tack 2018		Y					Y	Y	
Tack 2017		Y					Y	Y	
Tordoff 2022		Y					Y		
Turban 2020		Y				Y	Y		

[149] Dopp 2024 included two citations for one study, Perl 2021 (19 participants) and Perl 2020 (15 participants). The study population may overlap. Taylor 2024a included the two citations as two moderate quality before-after studies.
[150] See above note.

	Chew 2018[137]	Dopp 2024[138]	Ludvigsson 2023[139]	Miroshnychenko 2025a[140]	Ramos 2021[141]	Rew 2021[142]	Taylor 2024a[143]	Thompson 2023[144]	Zepf 2024[145]
van de Grift 2020		Y					Y		
van der Loos 2022		Y							
van der Loos 2023		Y							
van der Loos 2021			Y				Y		
van der Miesen 2020		Y					Y		
Vlot 2017	Y	Y	Y		Y	Y	Y		Y
Vrouenraets 2016		Y			Y				
Waldner 2023							Y		

5.12 Evidence tables on outcomes for PBs in youth with gender dysphoria

Table 5.2. Summary of evidence on gender dysphoria after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[151]	11 studies	-[152]	PBs lead to improved gender dysphoria. However, reductions in gender dysphoria were measured less consistently than pubertal changes, and almost never in the same study as pubertal changes	Very low certainty due to very serious risk of bias, very serious imprecision, and serious indirectness
Ludvigsson 2023[153]	2 prospective observational cohort studies	145 participants on hormones, 49 were evaluated	Two of these studies observed no statistically significant change in gender dysphoria	Very low certainty due to very serious risk of bias and very serious imprecision
Miroshnychenko 2025a[154]	2 before-after studies	59 participants	Standardised mean change: -0.1 (95% confidence interval: -0.4 to 0.19) (higher score indicating greater gender dysphoria)	Very low certainty due to serious inconsistency and very serious imprecision
Taylor 2024a[155]	2 before-after studies[156]	114 participants were treated	Two before-after studies measured gender dysphoria and reported no change before and after receiving treatment	No high-quality studies using an appropriate design were identified, and only four measured gender dysphoria as an outcome. No conclusions can be drawn
Evidence synthesis			No conclusion can be drawn on the impact of PBs on gender dysphoria.	The certainty of evidence is very low.

[151] Dopp et al. (2024).
[152] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Pang et al. 2020), qualitative studies (e.g., Vrouenraets et al. 2022). One study included by this review, Grannis 2023, was about CSH not PBs.
[153] Ludvigsson et al. (2023).
[154] Miroshnychenko, Roldan, et al. (2025).
[155] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review only synthesized excluded low quality.
[156] Though four studies reported gender dysphoria, only two moderate quality before-after studies were included in evidence synthesis.

Table 5.3. Summary of evidence on mental health and well-being after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Global function				
Dopp 2024[157]	21 studies	-[158]	Receipt of PBs was sometimes associated with improvements in mental health symptoms (depression, anxiety, quality of life, general functioning). In samples that started psychosocial supports prior to starting PBs, however, there were generally no changes in mental health outcomes after PBs began. Effects were also found less consistently for decreases in suicidality, potentially due to the outcome being relatively rare (which makes finding effects more difficult), especially in the younger age range seen in many of these studies.	Very low certainty due to very serious risk of bias, serious imprecision, inconsistency, and indirectness
Ludvigsson 2023[159]	Four observational cohort studies: one prospective and three retrospective	254 participants on hormones,[160] 113 were evaluated	Improved global function as assessed with the Children's Global Assessment Scale	Very low certainty[161] due to very serious risk of bias and very serious imprecision

[157] Dopp et al. (2024).
[158] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Pang et al. 2020). One study included by this review, Grannis 2023, was about CSH not PBs.
[159] Ludvigsson et al. (2023).
[160] In two studies, the participants had also received CSH.
[161] Ludvigsson et al. concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025a[162]	Two comparative observational studies, and two before-after studies	103 participants from two comparative observational studies, and 53 participants from two before-after studies	Difference in mean change from baseline 7.67 (95% confidence interval: -2 to 17.34) in PBs group compared with no PBs group from comparative observational studies; and Mean change 3.63 (95% confidence interval: 3.17 to 4.09) from before-after studies (higher score indicating greater global function)	Very low certainty due to serious risk of bias, inconsistency and imprecision
Taylor 2024a[163]	One cohort and two before-after studies	174 participants were treated	Three before-after studies reported no clinically significant change	No conclusions can be drawn.
Suicidality				
Ludvigsson 2023[164]	One prospective observational cohort study with mixed treatment (38 subjects with no pharmacological treatment)	42 participants on hormones, 28 were evaluated	No change in suicide ideation	Very low certainty[165] due to very serious risk of bias and very serious imprecision
Taylor 2024a[166]	One cross-sectional study and one before-after study	222 participants were treated	The cross-sectional study reported less self-harm/ suicidality in those treated, although similar to group with no gender dysphoria. The before-after study did not report change over time.	No conclusions can be drawn.

[162] Miroshnychenko, Roldan, et al. (2025).
[163] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[164] Ludvigsson et al. (2023).
[165] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[166] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Depression				
Ludvigsson 2023[167]	Two prospective observational cohort studies of which one included mixed treatment	97 participants on hormones, 60 were evaluated	No change in depression	Very low certainty[168] due to very serious risk of bias and very serious imprecision
Miroshnychenko 2025a[169]	One comparative observational study, and one before-after study	26 participants from one comparative observational study, and 41 participants from two before-after study	The comparative observational study with 26 participants (88% using PBs) reported that PBs did not result in a statistically significant decrease in scores in female to male participants; but resulted in a statistically significant decrease in score in male to female participants; and Mean change -3.36 (95% confidence interval: -3.69 to -3.03) from one before-after study (higher score indicating greater depression)	Very low certainty due to very serious risk of bias, and serious imprecision
Taylor 2024a[170]	One before-after study	70 participants were treated	Reduction in depressive symptom	A single study, reporting small to moderate improvement. No conclusion can be drawn.
Anxiety				
Ludvigsson 2023[171]	Two prospective observational cohort studies	97 participants on hormones, 60 were evaluated	No change in anxiety	Very low certainty[172] due to very serious risk of bias and very serious imprecision

[167] Ludvigsson et al. (2023).
[168] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[169] Miroshnychenko, Roldan, et al. (2025).
[170] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[171] Ludvigsson et al. (2023).
[172] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Taylor 2024a[173]	One before-after study	70 participants were treated	No change in anxiety symptom	A single study, reporting small to moderate improvement. No conclusion can be drawn.
Quality of life				
Ludvigsson 2023[174]	Two prospective observational cohort studies, including one retrospective	98 participants on hormones, 46 were evaluated	One study reported improvement in quality of life most pronounced in subjects receiving puberty-blocking hormones, followed by CSH treatment. A second study reported some improvement in quality of life.	Very low certainty[175] due to very serious risk of bias and very serious imprecision.
Taylor 2024a[176]	One before-after study	44 participants were treated	No change in quality of life	A single study, reporting no improvement. No conclusion can be drawn.
Internalising problems				
Taylor 2024a[177]	One cross-sectional study, and two before-after studies	292 participants were treated	No change to small decrease in internalising problems	No high certainty evidence was identified. No conclusion can be drawn.
Externalising problems				
Taylor 2024a[178]	One cross-sectional study, and two before-after studies	292 participants were treated	No change to small decrease in externalising problems	No conclusion can be drawn.

[173] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[174] Ludvigsson et al. (2023).
[175] Ludvigsson et al concluded the review “cannot assess certainty of evidence,” while according to the downgrading process in the review, the certainty of evidence was very low.
[176] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.
[177] See above note,
[178] See above note.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychological functioning/psychopathology				
Taylor 2024a[179]	Two before-after studies	114 participants were treated	Two before-after studies reported no change to a small change	No conclusions can be drawn.
Evidence synthesis			No conclusion can be drawn on the impact of mental health outcomes by PBs.	The certainty of evidence is very low.

[179] See above note.

Table 5.4. Summary of evidence on pubertal development after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Pubertal progression				
Dopp 2024[180]	20 studies	-[181]	Receipt of PBs was consistently associated with reductions in pubertal changes (which were targeted for suppression due to being inconsistent with the youth's gender identity), compared to expected pubertal progress and/or developmental control participants. Various physical and hormonal changes were documented over time, including reductions in endogenous sex-linked hormones, decreased progression (and sometimes regression) of physical sex characteristic development, changes in body hair, changes in height/growth and body fat composition congruent with youths' gender identities, grip strength, vocal register, and cessation of menstruation (both from menstrual suppression treatments and other forms of PBs).	Low certainty due to serious risk of bias, and serious indirectness
Taylor 2024a[182]	Four studies including two cohort studies and two before-after studies	385 participants	In one cohort study, clinical pubertal escape was reported in 2/21 participants. Another cohort study reported that Tanner stage 2/3 treatment resulted in smaller breast size in birth-registered females and lower average penile length and fewer testes descended in birth-registered males, compared with Tanner stage 4/5 or no GnRHa.	Four studies showed that PBs exert their expected physiological effects
Hormone level				
Taylor 2024a[183]	Nine studies including two cohort studies and seven before-after studies	606 participants were treated	Studies reported decreases in luteinising hormone, follicle-stimulating hormone, oestradiol and testosterone after receiving GnRHa	Multiple mainly before-after studies showed that PBs exert their expected physiological effects

[180] Dopp et al. (2024).
[181] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Pang et al. 2020), qualitative studies (e.g., Vrouenraets et al. 2022). One study included by this review, Grannis 2023, was about CSH not PBs.
[182] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.
[183] See note above.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Menstrual suppression				
Taylor 2024a[184]	Three studies including one cohort study and two before-after studies	202 participants	All studies reported menstrual suppression	Three studies showed that PBs exert their expected physiological effects
Evidence synthesis			PBs lead to expected physiological effects	There is high certainty evidence on the physiological effects (High certainty due to very large physiological effects of PBs).[185]

[184] See note above.

[185] According to GRADE, the evaluation of certainty of evidence based on observational studies starts as low certainty. There is no further downgrade of evidence for this outcome by this overview. The certainty of evidence is upgraded by two levels due to very large observed effect. See Guyatt, Oxman, Sultan, et al. (2011). These very large effects on pubertal development would otherwise not have been observed without PBs.

Table 5.5. Summary of evidence on progression to further treatment after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025a[186]	2 case series	65 participants	Proportion 0.92 (95% confidence interval: 0.53 to 0.99)	Very low certainty due to risk of bias concern (rating down by three levels)
Evidence synthesis			A high proportion of adolescents receiving PBs proceed with cross-sex hormone therapy.	The certainty of evidence is very low.

[186] Miroshnychenko, Roldan, et al. (2025).

Table 5.6. Summary of evidence on safety outcomes after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Overall risk of adverse events				
Dopp 2024[187]	18 studies	-[188]	Side effects and complications were limited and did not have a major impact on treatment (e.g., rarely resulted in changed or discontinued medication). Over time, few statistically significant changes were observed in a variety of parameters for cardiovascular health (cholesterol, blood pressure, glucose, lipid levels) and liver enzymes; for the parameters that did show some changes (e.g., body mass index, creatinine levels, hemoglobin/hematocrit levels), values typically remained within the expected or healthy range and thus were not clinically significant. Other minor and infrequent side effects or complications included sterile abscess, headaches, mood changes, hot flashes, decreased libido, and breakthrough menstruation.	Very low certainty due to very serious risk of bias and serious indirectness
Taylor 2024a[189]	3 before-after studies	109 participants	A cohort study of GnRHa reported side effects including mild headaches or hot flushes (~20%) and moderate/severe headaches or hot flushes, mild fatigue, mood swings, weight gain and sleep problems (<10%). Two other studies assessed other medications and reported headaches and hot flushes as common and an increase in acne in a sample of birth-registered females receiving lynestrenol, and complaints of fatigue in birth-registered males receiving cyproterone acetate	No conclusions can be drawn.

[187] Dopp et al. (2024).
[188] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Cohen-Kettenis 2011, Ristori 2019).
[189] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Evidence synthesis			No conclusion can be drawn on the overall risks of side-effects of PBs.	The certainty of evidence is very low.
Bone density				
Dopp 2024[190]	10 studies		The primary concern noted during treatment with PBs was decreases in bone health metrics (e.g., bone mineral density, bone growth markers). These metrics tended to remain stable during PBs treatment but showed decreases relative to age-based reference ranges; as growth rates are slowed during PBs treatment, age-based reference ranges become less relevant, and the clinical significance of these effects is unclear. Bone mineral density generally showed improvement after youth started CSH and initiated puberty consistent with their gender identity; however, it is unclear what the long-term effects on bone health and related functional outcomes (e.g., risk of fracture) would be when a patient desires long-term PBs treatment without future interventions that would enable its discontinuation.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness
Ludvigsson 2023[191]				
• **Bone density during PBs treatment (g/cm2, g/cm3)**	Five observational cohort studies (four retrospective and one prospective)	363 participants on hormones, 297 were evaluated	Unchanged bone density (Dual-Energy X-ray Absorptiometry measurement)	Low certainty due to serious risk of bias and serious imprecision
• **Bone density during PBs treatment in relation to reference data in the literature (z-score)**	Five observational cohort studies (four retrospective and one prospective)	408 participants on hormones, 292 were evaluated	Decreased increase in bone density over time	Low certainty due to serious risk of bias and serious imprecision

[190] Dopp et al. (2024).
[191] Ludvigsson et al. (2023); This review also assessed the effect on bone density when treatment with PBs was followed by CSH.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025a[192]				
• **Bone mineral density, hip, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	2 before-after studies	128 participants	Mean change: -0.71 (95% confidence interval: -1.09 to -0.33)	Very low certainty due to serious risk of bias concern (rating down by three levels)
• **Bone mineral density, lumbar spine, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	5 before-after studies	222 participants	Mean change: -0.72 (95% confidence interval: -0.91 to -0.54)	Very low certainty due to serious risk of bias concern (rating down by three levels)
• **Bone mineral density, femoral neck, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 20–24 months**	1 before-after study	9 participants	Mean change: -1.3 (95% confidence interval: -1.57 to -1.03)	Very low certainty due to serious risk of bias concern (rating down by three levels)
• **Bone mineral density, lumbar spine, short term follow-up assessed with: DXA, z scores scale (−3 to 3).**	2 before-after studies	93 participants	Mean change: -0.7 (95% confidence interval: -1.11 to -0.29)	Very low certainty due to serious risk of bias concern (rating down by three levels)

[192] Miroshnychenko, Roldan, et al. (2025).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Follow-up: six months				
Taylor 2024a	5 before-after studies	331 participants	Five studies found decreases in bone mineral apparent density and z-scores before-after treatment; however, absolute measures generally remained stable or increased/decreased slightly	Multiple studies found that bone density is compromised during PBs treatment
Evidence synthesis			PBs may lead to decreases in bone mineral density (BMD) accumulation that normally occurs during puberty, lowering Z-scores.	The certainty of evidence is low due to evidence based on only observational studies (risk of bias).[193]
Fertility				
Dopp 2024[194]	2 studies	12 participants[195]	Case reports documented healthy, viable oocyte cryopreservation after taking PBs and pausing for at least three months	Very low certainty due to very serious risk of bias and very serious indirectness
Evidence synthesis			It is uncertain of PBs alone will result in impaired fertility once PBs are discontinued and puberty resumes. PBs probably lead to infertility if followed by CSH.	No empirical evidence. Inferred based on high certainty evidence on PBs effects on puberty progression.
Anthropometric measures				
Ludvigsson 2023[196]	1 retrospective observational cohort	192 participants on hormones, 192 were evaluated	Increased weight and body mass index	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision

[193] This overview re-evaluates the certainty of evidence because there was disagreement across the SRs. This overview concludes that the certainty of evidence is low because only evidence based on observational studies is available. Evidence based on observational studies without additional risk of bias concerns is assessed as low certainty of evidence, if there is no sufficient justification to upgrade the certainty of evidence.
[194] Dopp et al. (2024).
[195] This systematic review by Dopp et al reported fertility preservation based on case reports, not fertility outcomes.
[196] Ludvigsson et al. (2023).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Body composition				
Ludvigsson 2023[197]	Two prospective observational cohort studies and one controlled cross-sectional study	325 participants on hormones, 286 were evaluated	Decreased lean body mass	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[198]	Two before-after studies	152 participants	In both sexes, lean body mass percentage or SD score decreased while fat percentage increased	No conclusions can be drawn.
Blood pressure				
Ludvigsson 2023[199]	One retrospective observational cohort	15 participants on hormones, 15 were evaluated	Change in blood pressure	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[200]	Three before-after studies	96 participants	Three studies reported no change or small, non-clinically significant change in blood pressure	No conclusions can be drawn.
Metabolic measures				
Ludvigsson 2023[201]	One retrospective observational cohort study and one controlled cross-sectional study	209 participants on hormones, 209 were evaluated	No change in serum lipids or blood pressure Increased insulin level in natal males Decreased insulin sensitivity	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[202]	Three before-after studies	127 participants	Three studies reported no change or small change in metabolic measures.	No conclusions can be drawn.
Growth (cm/year)				

[197] Ludvigsson et al. (2023).
[198] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[199] Ludvigsson et al. (2023).
[200] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[201] Ludvigsson et al. (2023).
[202] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Ludvigsson 2023[203]	One prospective multicentre observational study	55 participants on hormones, 55 were evaluated	Reduced growth velocity	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[204]	11 studies, including one cohort study, and 10 before-after studies	925 participants	The cohort study found a similar height velocity between the GnRHa group and adolescent controls. Other studies reported no change or small decrease	No high-quality studies using an appropriate design were identified. No conclusions can be drawn.
Evidence synthesis			No conclusion can be drawn on the impact of PBs on anthropometric measures, body composition, blood pressure, and growth.	The certainty of evidence is very low for outcomes such as body composition, anthropometric measures, blood pressure, metabolic measures, and growth.
Cognition				
Ludvigsson 2023[205]	One cross-sectional study	20 participants on hormones, 20 were evaluated	No change in cognition compared with matched controls	Very low certainty due to very serious risk of bias and very serious imprecision
Taylor 2024a[206]	One cross-sectional study, and one before-after study	109 participants	One cross-sectional study measured executive functioning and found no difference between adolescents who were treated for <1 year compared with those not treated, but worse executive functioning in those treated for >1 year compared with those not treated. A before-after study found no differences in features typically associated with autism spectrum condition after treatment	No conclusions can be drawn.
Evidence synthesis			No conclusion can be drawn on the impact of PBs on cognitive outcomes.	The certainty of evidence is very low.

[203] Ludvigsson et al. (2023).
[204] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.
[205] Ludvigsson et al. (2023).
[206] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

Table 5.7. Summary of evidence on regret after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[207]	14 studies	-[208]	High satisfaction ratings and low rates of regret (3.5% or lower) were documented, and most youth who received that intervention progressed to CSH.	Very low certainty due to very serious risk of bias and serious indirectness
Evidence synthesis			No conclusion can be drawn on the regret rate after PBs.	The certainty of evidence is very low.

[207] Dopp et al. (2024).
[208] The number of participants is not calculated because this review included heterogeneous types of studies, including that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Cohen-Kettenis et al. 2011), qualitative studies (e.g., Vrouenraets et al. 2022).

6 Evidence synthesis: Cross-sex hormones

This overview identified eight SRs on the treatment effects of CSH.[209] Across all primary studies included in the eight SRs, there were no eligible randomized controlled trials. Furthermore, this overview found only eight observational studies with parallel comparison groups comparing CSH to no CSH among children or adolescents GD.[210] Generally, the sample size of these studies was small: five studies included fewer than 100 participants. In summary, the methodology of the current studies was insufficient to properly assess the treatment effects of CSH.

6.1 Included SRs on CSH

Chew 2018

Chew, D., Anderson, J., Williams, K., May, T., & Pang, K. (2018). Hormonal treatment in young people with gender dysphoria: A systematic review. *Pediatrics*, *141*(4).

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Karalexi 2020

Karalexi, M. A., Georgakis, M. K., Dimitriou, N. G., Vichos, T., Katsimpris, A., Petridou, E. T., . . . Papadopoulos, F. C. (2020). Gender-affirming hormone treatment and cognitive function in transgender young adults: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *119*, 104721.

[209] Chew et al. (2018); Dopp et al. (2024); Karalexi et al. (2020); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024); Thompson et al. (2023); Zepf et al. (2024).
[210] Becker-Hebly et al. (2021); Filipov et al. (2023); Grannis et al. (2021), (2023); Grimstad et al. (2021); Hisle-Gorman et al. (2021); Jensen et al. (2019); Tordoff et al. (2022).

Ludvigsson 2023

Ludvigsson, J. F., Adolfsson, J., Hoistad, M., Rydelius, P. A., Kristrom, B., & Landen, M. (2023). A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatrica, International Journal of Paediatrics*, *112*(11), 2279-2292.

Miroshnychenko 2025b

Miroshnychenko, A., Ibrahim, S., Roldan, Y., Kulatunga-Moruzi, C., Montante, S., Couban, R., . . . Brignardello-Petersen, R. (2025). Gender affirming hormone therapy for individuals with gender dysphoria aged <26 years: A systematic review and meta-analysis. *Archives of Disease in Childhood*. https://doi.org/https://dx.doi.org/10.1136/archdischild-2024-327921

Taylor 2024b

Taylor, J., Mitchell, A., Hall, R., Langton, T., Fraser, L., & Hewitt, C. E. (2024). Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*, *109*(Suppl 2), s48-s56.

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

Zepf 2024

Zepf, F. D., Konig, L., Kaiser, A., Ligges, C., Ligges, M., Roessner, V., . . . Holtmann, M. (2024). [beyond nice: Updated systematic review on the current evidence of using puberty blocking pharmacological agents and cross-sex-hormones in minors with gender dysphoria]. *Beyond NICE: Aktualisierte systematische Ubersicht zur Evidenzlage der Pubertatsblockade und Hormongabe bei Minderjahrigen mit Geschlechtsdysphorie.*, *52*(3), 167-187.

6.2 Low risk of bias SRs

Four English SRs were classified at low risk of bias.[211] Of these reviews, the eligibility criteria and number of included studies varied. Dopp 2024[212] included 56 studies including 26 quasi-experimental studies (nearly all before-after), eight cross-sectional studies, 10 cohort studies, 11 case reports, and one qualitative study. The SR by Taylor and colleagues[213] included 53 studies including 12 cohort, nine cross-sectional, 32 pre–post studies. This SR excluded results from low quality studies in the evidence synthesis. Ludvigsson 2023[214] included 16 studies and Miroshnychenko 2025b[215] included 24 studies (including nine comparative observational studies, 13 before-after design, and two case series) on CSH. Only four primary studies were included in all four low risk of bias SRs, including one comparative cohort study in Germany,[216] and three before-after studies reported in the US[217] and Netherlands.[218]

6.3 Outcome 1. Gender dysphoria

A total of three SRs assessed the impact of CSH on GD.[219] Dopp 2024[220] included a greater number of studies than three other SRs, though it included case reports and a qualitative study, which inflated the overall number of studies. This systematic review narratively described that therapy with CSH was associated with improved GD and body satisfaction, despite concluding that the certainty of evidence was very low. The other two SRs, based on evidence from observational studies, concluded that the evidence on the effect of CSH on GD and body satisfaction was very uncertain.

In summary, the certainty of evidence is very low, and no conclusion can be drawn on the impact of CSH on GD.

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[211] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[212] Dopp et al. (2024).
[213] Taylor, Mitchell, Hall, Langton, et al. (2024).
[214] Ludvigsson et al. (2023).
[215] Miroshnychenko, Ibrahim, et al. (2025).
[216] Becker-Hebly et al. (2021).
[217] Cantu et al. (2020).
[218] Schagen et al. (2020); Vlot et al. (2017).
[219] Dopp et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[220] Dopp et al. (2024).

6.4 Outcome 2. Mental health and well-being

Three SRs assessed the impact of CSH on mental health, including global function, suicidality, depression, anxiety, and other symptoms.[221] Like the SRs on GD, Dopp 2024[222] included more studies than the other SRs because it included case reports and a qualitative study. This systematic review narratively described that CSH leads to improved mental health, though the certainty of evidence was assessed as very low. Three SRs reported either no change or small changes in mental health associated with CSH. The certainty of evidence was very low or uncertain. In summary, no conclusion could be drawn on the impact of CSH on mental health due to very low certainty evidence.

For suicidality, the risk of death by suicide among hormonally-treated youth was estimated to be six per 1,000 according to Miroshnychenko and colleagues,[223] though the certainty of evidence was very low. According to the review by Taylor and colleagues,[224] two before-after studies reported reduced treatment needs or lower levels of suicidality and self-harm. Two other cross-sectional studies reported mixed findings: one found that adolescents receiving hormones were less likely to have seriously considered or attempted suicide compared to those not receiving hormones, while another found no difference between groups among birth-registered females. It is uncertain whether CSH leads to lower risk of suicide.

In summary, this overview finds the certainty of evidence on mental health and well-being is very low, and no conclusions can be drawn.

6.5 Outcome 3. Pubertal development

Two SRs assessed the impact of CSH on pubertal development, including pubertal progression, hormone level, and menstrual suppression.[225] SRs showed that the use of cross-sex hormone is consistently associated with physical changes. This overview

[221] Dopp et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[222] Dopp et al. (2024).
[223] Miroshnychenko, Ibrahim, et al. (2025).
[224] Taylor, Mitchell, Hall, Langton, et al. (2024).
[225] Dopp et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024).

assessed the certainty of evidence as high due to the observed very large effects.[226] One example of a very large effect pertains to menstrual suppression, which is expected to be rare without CSH. Taylor and colleagues[227] reported that menstrual suppression occurred in most participants on the basis of three before-after studies. In summary, there is high certainty evidence that CSH exerts physiological effects.

6.6 Outcome 4. Safety

Four SRs reported on safety outcomes for CSH in children or adolescents with GD. These included overall risk of adverse events, cardiovascular events, bone health, fertility, sexual dysfunction, body composition, growth, and other measures.[228] Dopp 2024[229] reported that side effects and complications were limited, and these side effects did not have a major impact on treatment. Taylor 2024b[230] listed adverse event types. In birth-registered females, reported adverse events included acne, mood changes, elevated red blood markers, increased appetite, headaches, hot flashes, fatigue, hair loss, and a slight increase in metrorrhagia. In birth-registered males, adverse events included breast tenderness, elevated liver enzymes, mood swings, and increased appetite. The certainty of evidence on the overall risk of adverse events was very low.

There is limited evidence on the long-term safety of CSH among children or adolescents with GD. Based on evidence from retrospective case series, Miroshnychenko 2025b[231] reported that the risk of cardiovascular events after CSH was estimated to be 0 per 1000 (0 to 10) over 26 months, and 40 per 1000 (30 to 50) over a follow up duration of up to 109 months. The certainty of evidence was estimated to be moderate to high, because the SR authors contemplated that a comparison group was not needed to estimate the risk of cardiovascular events following cross-sex hormone.

All four SRs assessed bone health. The evidence was primarily based on before-after studies. The most frequently reported outcome for bone health was bone mineral

[226] Guyatt, Oxman, Sultan, et al. (2011).
[227] Taylor, Mitchell, Hall, Langton, et al. (2024).
[228] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[229] Dopp et al. (2024).
[230] Taylor, Mitchell, Hall, Langton, et al. (2024).
[231] Miroshnychenko, Ibrahim, et al. (2025).

density decreases relative to reference values (z score). Dopp 2024[232] and Ludvigsson 2023[233] reported that bone density may recover after discontinuation of PBs and initiation of CSH. Miroshnycheko and colleagues[234] reported no changes in bone mineral density for hip, lumbar spine, and femoral neck. Taylor 2024b[235] reported conflicting results from four before-after studies: two studies reported an increase in absolute bone density measures and standard deviation (SD) scores at follow-up, with one focusing exclusively on birth-registered females. In contrast, two other studies found no change in bone density or bone biomarkers, though these involved small sample sizes. There was disagreement across SRs on certainty of evidence assessment, which was very low according to Dopp 2024[236] and Miroshnycheko 2025b,[237] but low according to Ludvigsson 2023.[238] Taylor 2024b[239] did not formally assess the certainty of evidence but concluded the evidence was very uncertain. This overview assessed the certainty of evidence for bone health as very low, considering serious risk of bias in included studies, inconsistent findings in included primary studies, and imprecision of evidence (it is unclear whether the difference in bone density is clinically meaningful).

Two SRs reported on fertility outcomes. Dopp et al[240] reported cases describing successful cryopreservation of healthy, viable oocytes, embryos, and semen, often after pausing hormone therapy. According to Taylor et al,[241] one cohort study reported mature spermatozoa observed in patients starting treatment at Tanner stage 4 or higher, but immature germ cells present in all patients treated earlier in puberty. This overview concludes that the evidence is very low for the impact of CSH on fertility.

[232] Dopp et al. (2024).
[233] Ludvigsson et al. (2023).
[234] Miroshnychenko, Ibrahim, et al. (2025).
[235] Taylor, Mitchell, Hall, Langton, et al. (2024).
[236] Dopp et al. (2024).
[237] Miroshnychenko, Ibrahim, et al. (2025).
[238] Ludvigsson et al. (2023).
[239] Taylor, Mitchell, Hall, Langton, et al. (2024).
[240] Dopp et al. (2024).
[241] Taylor, Mitchell, Hall, Langton, et al. (2024).

Miroshnychenko 2025b[242] included one before-after study, reporting no change from baseline in symptoms of vaginal dryness or itch after receiving cross-sex hormone at six months or 12 months of follow-up. The certainty of evidence on sexual dysfunction was assessed as very low.

Taylor 2024b[243] also reported other outcomes such as anthropometric measures, body composition, blood pressure, etc., and found either no change or small changes. The certainty of evidence was judged to be very low or uncertain. Similarly, Ludvigsson et al[244] included three retrospective longitudinal studies assessing CSH in children without prior PBs treatment. Due to small sample sizes and differing outcomes measured (e.g., lipid levels, hemoglobin, blood pressure, metrorrhagia), the studies had low external validity. No overall conclusions could be drawn.

In summary, this overview concludes that the certainty of evidence for these outcomes is very low.

6.7 Outcome 5. Regret

Only one review assessed regret after CSH and reported high satisfaction ratings and low rates of regret.[245] The certainty of evidence was very low. This overview concludes that the evidence is very uncertain, and no conclusion can be drawn on regret rate.

6.8 Evidence gap

Important evidence gaps exist for the effects of CSH. Many studies were not specifically designed to capture the full range of long-term outcomes and have largely concentrated on short-term psychological or physiological changes. Key outcomes such as GD, mental health, and quality of life have been inconsistently measured and, when reported, often are derived from small, observational studies with limited follow-up periods. Critically important long-term outcomes remain poorly understood. Sexual dysfunction, despite being highly relevant to long-term well-being, has been infrequently

[242] Miroshnychenko, Ibrahim, et al. (2025).
[243] Taylor, Mitchell, Hall, Langton, et al. (2024).
[244] Ludvigsson et al. (2023).
[245] Dopp et al. (2024).

assessed. Although a few studies have reported cardiovascular event rates, long-term follow-up is still needed to evaluate cumulative risk.

Evidence on fertility is also sparse, with little data on whether reproductive effects vary by age at treatment initiation and whether these effects are reversible. Furthermore, the compounded effects of sequential treatment with PBs followed by CSH—such as their impact on bone health recovery, final adult height, or likelihood of requiring surgical interventions—have not been investigated adequately. A lack of primary studies that separately evaluate the effects of estrogen in males and testosterone in females is a significant limitation, as hormone-sex interactions may meaningfully influence outcomes.

6.9 Summary

In summary, this overview identified eight SRs addressing the effects of CSH among adolescents with GD. There is high certainty evidence that CSH exerts physiological effects. The evidence is very uncertain regarding effects on GD, mental health, or safety (such as impacts on fertility and bone health).

6.10 Evidence mapping: SRs on CSH

Table 6.1. Evidence mapping of the SRs on CSH and the primary studies that these SRs included

	Chew 2018[246]	Dopp 2024[247]	Karalexi 2020	Ludvigsson 2023[248]	Miroshnychenko 2025b[249]	Taylor 2024b[250]	Thompson 2023[251]	Zepf 2024[252]
Achille 2020		Y			Y	Y		Y
Aldridge 2021					Y			
Allen 2019		Y				Y		Y
Amir 2020		Y						
Arcelus 2016						Y		
Arnoldussen 2022		Y						
Ascha 2022					Y			
Barnard 2019		Y						
Becker-Hebly 2021		Y		Y	Y	Y	Y	
Beking 2020						Y		
Bodlund 1996		Y						
Burke 2016	Y	Y	Y			Y		
Burke 2020						Y		
Caanen 2017		Y						
Campbell 2023		Y						

[246] Chew et al. (2018).
[247] Dopp et al. (2024).
[248] Ludvigsson et al. (2023)
[249] Miroshnychenko, Ibrahim, et al. (2025).
[250] Taylor, Mitchell, Hall, Langton, et al. (2024).
[251] Thompson et al. (2023).
[252] Zepf et al. (2024).

	Chew 2018[246]	Dopp 2024[247]	Karalexi 2020	Ludvigsson 2023[248]	Miroshnychenko 2025b[249]	Taylor 2024b[250]	Thompson 2023[251]	Zepf 2024[252]
Cantu 2020		Y		Y	Y	Y		
Chen 2023		Y			Y			
Chen 2016							Y	
Chiniara 2018						Y		
Cohen-Kettenis 2011[253]		Y						
de Nie 2022		Y				Y		
de Vries 2014	Y	Y		Y		Y		
de Vries 2011							Y	
Delemarre-van de Waal 2006		Y				Y		
Donaldson 2018		Y						
Filipov 2023					Y			
Fontanari 2020					Y	Y		
Foster 2021					Y			
Friedman 2000			Y					
Gale 2021		Y						
Gómez-Gil 2009			Y					
Grannis 2021[254]		Y				Y		Y
Grannis 2023[255]		Y			Y			

[253] Another citation, Cohen-Kettenis 1998 was provided for this study. However, this citation (Cohen-Kettenis 1998) was not included by any other SRs on PBs or CSH. Though this study was included by Dopp 2024 for PBs and surgeries.
[254] Dopp 2024 included three citations for one study, Grannis 2021, Grannis 2023, and Olsavsky 2023. The sample size was 42 for Grannis 2021. The study population may overlap.
[255] Dopp 2024 included three citations for one study, Grannis 2021, Grannis 2023, and Olsavsky 2023. The sample size was 82 for Grannis 2023. This report was an update to Grannis 2021. The study population may overlap.

	Chew 2018[246]	Dopp 2024[247]	Karalexi 2020	Ludvigsson 2023[248]	Miroshnychenko 2025b[249]	Taylor 2024b[250]	Thompson 2023[251]	Zepf 2024[252]
Green 2022		Y			Y	Y		
Grimstad 2021a		Y				Y		
Grimstad 2021b						Y		
Gupta 2023		Y						
Hannema 2017						Y		
Haraldsen 2005			Y		Y			
Hisle-Gorman 2021		Y		Y		Y		
Insogna 2020		Y						
Jarin 2017	Y	Y		Y		Y		
Jensen 2019						Y	Y	
Kaltiala 2020		Y			Y	Y		Y
Khatchadourian 2014		Y				Y		Y
Klaver 2020		Y		Y		Y	Y	Y
Klaver 2018				Y		Y	Y	
Klink 2015	Y	Y		Y		Y		Y
Kuper 2020		Y				Y	Y	Y
Laurenzano 2021		Y				Y		
Lavender 2023		Y						
Lee 2024		Y						
Lierman 2017		Y						
Littman 2021		Y						
López de Lara 2020		Y				Y		Y
Madsen 2021						Y		

	Chew 2018[246]	Dopp 2024[247]	Karalexi 2020	Ludvigsson 2023[248]	Miroshnychenko 2025b[249]	Taylor 2024b[250]	Thompson 2023[251]	Zepf 2024[252]
Martin 2021		Y						
Mehringer 2021		Y						
Miles 2006			Y					
Miles 1998			Y					
Millington 2022						Y		
Millington 2021						Y		
Millington 2019						Y		
Morningstar 2023								Y
Mullins 2021		Y		Y		Y		
Nokoff 2020						Y		
Nota 2019					Y			
Olsavsky 2023		Y[256]			Y			
Olson 2014	Y	Y				Y		
Olson 2022		Y						
Olson-Kennedy 2018a		Y				Y		
Perl 2021[257]		Y				Y		
Perl 2020[258]		Y		Y		Y	Y	
Pyra 2020					Y			
Ristori 2019		Y						

[256] Dopp 2024 included three citations for one study, Grannis 2021, Grannis 2023, and Olsavsky 2023. The sample size was 75 for Olsavsky 2023. This report was a cross-sectional analysis of recruited participants.
[257] Dopp 2024 included two citations for one study, Perl 2021 (19 participants) and Perl 2020 (15 participants). The study population may overlap. Taylor 2024b included the two citations as two moderate quality before-after studies.
[258] See above note.

	Chew 2018[246]	Dopp 2024[247]	Karalexi 2020	Ludvigsson 2023[248]	Miroshnychenko 2025b[249]	Taylor 2024b[250]	Thompson 2023[251]	Zepf 2024[252]
Schagen 2016		Y						
Schagen 2018						Y		
Schagen 2020		Y		Y	Y	Y	Y	
Schöning 2010			Y					
Segev-Becker 2020						Y		
Sequeira 2019						Y		
Slabbekoorn 1999			Y					
Stanley 2018		Y						
Stoffers 2019		Y		Y		Y	Y	Y
Strang 2022						Y		
Tack 2016	Y	Y		Y		Y	Y	
Tack 2017	Y	Y				Y	Y	
Tordoff 2022		Y			Y	Y		
Turan 2018					Y			
Turban 2018		Y						
Turban 2022		Y				Y		
Valentine 2021						Y		
van de Grift 2020						Y		
van der Loos 2022		Y						
van der Loos 2023		Y						
van der Loos 2021				Y		Y		
van Dijk 2019					Y			
van Goozen 2002			Y					

	Chew 2018[246]	Dopp 2024[247]	Karalexi 2020	Ludvigsson 2023[248]	Miroshnychenko 2025b[249]	Taylor 2024b[250]	Thompson 2023[251]	Zepf 2024[252]
van Goozen 1994			Y					
van Kesteren 1996					Y			
Vlot 2017	Y	Y		Y	Y	Y		Y
Wiepjes 2019					Y			
Wiepjes 2017					Y			

6.11 Evidence tables on outcomes for CSH in youth with gender dysphoria

Table 6.2. Summary of evidence on gender dysphoria after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[259]	Eight studies	-[260]	CSH was associated with reduced gender dysphoria and improved body satisfaction in adolescents and young adults with gender dysphoria. Effect sizes for gender dysphoria and body dissatisfaction were the largest observed for any intervention.	Very low certainty due to very serious risk of bias, very serious imprecision, and serious indirectness
Miroshnychenko 2025b[261]	One comparative observational study and one before-after study	146 participants from one comparative study and 36 from one before-after study	Mean difference: -0.4 (95% confidence interval: -0.24 to 0.16) from one comparative study and Standardised mean change 0.26 lower (1.64 lower to 1.13 higher) from one before-after study (higher score indicating higher levels of gender dysphoria)	Very low certainty due to very serious risk of bias (rating down by three levels) and serious imprecision
Taylor 2024b[262]	One before-after study	23 participants from the before-after study	The pre–post study reported a reduction in dysphoria with no participants in clinical range at follow-up.	There was insufficient evidence regarding changes to gender dysphoria
Evidence synthesis			No conclusion can be drawn on the impact of gender dysphoria by CSH.	The certainty of evidence is very low.

[259] Dopp et al. (2024).
[260] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Ristori et al, 2019).
[261] Miroshnychenko, Ibrahim, et al. (2025).
[262] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

Table 6.3. Summary of evidence on mental health and well-being after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Global function				
Dopp 2024[263]	21 studies	-[264]	CSH was associated with improved mental health outcomes in adolescents and young adults with gender dysphoria. The majority of reported outcomes showed statistical significance, and nearly all of those indicated clinical significance as well (measured by effect size or compared to norms). Benefits were most consistent for depression and general functioning or well-being, and sometimes also seen for reductions in outcomes like suicidality, anxiety, and substance use (although these less consistently showed statistically significant changes).	Very low certainty due to very serious risk of bias, serious imprecision, inconsistency, and indirectness
Miroshnychenko 2025b[265]	Two prospective observational cohort studies; two before-after studies	125 from two prospective observational cohort studies; 73 participants from two before-after studies	Standardised mean difference: 0.87 higher (95% confidence interval: 0.25 lower to 2 higher) from two prospective observational cohort studies; Standardised mean change 0.25 higher (0.09 higher to 0.4 higher) from two before-after studies (higher score indicating better global function)	Very low certainty due to very serious risk of bias, serious imprecision and indirectness

[263] Dopp et al. (2024)
[264] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies. For this outcome of mental health, this systematic review included two reports on the same large cross-sectional study (2015 US Transgender Survey, Lee et al. (2024); Turban et al. (2022)). Cross-sectional studies were of limited value in assessing treatment effects, while the reviewers should not include two studies on the same survey.
[265] Miroshnychenko, Ibrahim, et al. (2025)

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Death by suicide				
Miroshnychenko 2025b[266]	One case series study	315 participants	6 per 1000 (1 to 18)	Very low certainty due to very serious risk of bias (rating down by three levels)
Self-harm and suicide				
Taylor 2024b[267]	Two before-after, and two cross-sectional studies	99 participants from two before-after studies, and 293 participants from two cross-sectional studies	Two before-after studies found a reduction in treatment needs for (or lower levels of) suicidality/self-harm, while two cross-sectional studies found conflicting results: those receiving hormones were less likely to have seriously considered/attempted suicide compared with adolescents not receiving hormones, and in birth-registered females there was no difference between groups	Hormone treatment may in the short-term improve psychological health.[268]
Depression				
Miroshnychenko 2025b[269]	Two prospective observational cohort studies; two before-after studies	154 from two prospective observational cohort studies; 389 participants from two before-after studies	Standardised mean difference: 0.3 lower (95% confidence interval: 0.85 lower to 0.25 higher) from two prospective observational cohort studies; Standardised mean change 0.41 lower (0.65 lower to 0.17 lower) from two before-after studies (higher score indicating worse depression)	Very low certainty due to very serious risk of bias (rating down by three levels) and serious imprecision

[266] Miroshnychenko, Ibrahim, et al. (2025)
[267] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[268] This systematic review concluded that there is “moderate-quality evidence from mainly pre–post studies that hormone treatment may in the short-term improve psychological health”. This review had identified “moderate quality” observational studies. Including “moderate-quality observational studies” is not equivalent to “moderate quality (certainty) evidence.” According to the GRADE methodology, the starting point for evidence from observational studies (including high quality observational studies) is generally low quality. To have moderate certainty, the certainty of evidence needs to be upgraded. See Guyatt, Oxman, Sultan, et al. (2011).
[269] Miroshnychenko, Ibrahim, et al. (2025)

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Taylor 2024b[270]	One cohort, one before-after, and two cross-sectional studies	23 participants from one cohort, 52 participants from one before-after, and 293 participants from two cross-sectional studies	Studies found a reduction in depression and anxiety at follow-up (cohort) and for birth-registered females receiving hormones compared with females not receiving hormones (cross-sectional), but levels were higher when compared with adolescents not experiencing gender dysphoria/incongruence (cohort). Lower treatment needs for depression and anxiety were reported after treatment in a pre–post study. A cross-sectional study reported lower levels of depression in adolescents who had received hormones compared with those who had wanted hormones but had not received them.	Hormone treatment may in the short-term improve psychological health.
Anxiety				
Taylor 2024b[271]	One cohort, one before-after, and one cross-sectional study	23 participants from one cohort, 52 participants from one before-after, and 19 participants from one cross-sectional study	Studies found a reduction in depression and anxiety at follow-up (cohort) and for birth-registered females receiving hormones compared with females not receiving hormones (cross-sectional), but levels were higher when compared with adolescents not experiencing gender dysphoria/incongruence (cohort). Lower treatment needs for depression and anxiety were reported after treatment in a pre–post study.	Hormone treatment may in the short-term improve psychological health.
Internalising problems				
Taylor 2024b[272]	One cohort study	23 participants	Emotional symptoms decreased at follow-up and were similar at follow up to adolescents not experiencing gender dysphoria	Hormone treatment may in the short-term improve psychological health.

[270] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[271] See above note.
[272] See above note.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Externalising problems				
Taylor 2024b[273]	One cohort study	23 participants	Conduct problems and hyperactivity decreased and were lower at follow-up compared to adolescents not experiencing gender dysphoria	Hormone treatment may in the short-term improve psychological health.
Psychological difficulties				
Taylor 2024b[274]	One cohort study	23 participants	Difficulties decreased with fewer in borderline/abnormal range at follow-up, and were similar at follow up to adolescents not experiencing gender dysphoria	Hormone treatment may in the short-term improve psychological health.
Evidence synthesis			No conclusion can be drawn on the impact of mental health by CSH.	The certainty of evidence is very low.[275]

[273] See above note.
[274] See above note.
[275] Two systematic reviews assessed reported very low certainty evidence, while another claimed that there was “moderate quality evidence.” This overview assesses the certainty of evidence as very low.

Table 6.4. Summary of evidence on pubertal development after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Induced physical changes				
Dopp 2024[276]	14 studies	-[277]	CSH was associated with physical changes resulting from increased levels of masculinizing hormones (e.g., deeper voice, increased body hair, changes in muscle mass, menstrual suppression) or feminizing hormones (e.g., decreased body hair, changes in body fat distribution, breast growth), which were targeted for initiation due to being consistent with the gender identity of youth with gender dysphoria.	Low certainty due to serious risk of bias, and serious indirectness
Taylor 2024b[278]	4 before-after studies	187 participants were treated	Two observed an increase in breast volume in birth-registered males after hormones, although objectively breast volume was small, and another reported no change in breast volume in birth-registered females. One study of birth-registered females reported an increase in facial, abdominal, chest and extremities hair, and voice deepening in all participants at follow-up. Another reported no change in Tanner genital stage in birth-registered males, and no change in Tanner pubic hair stage for both	Exogenous hormones increase hormone levels and to varying degrees of induced physical changes, with potential differences depending on birth-registered sex and timing of treatment

[276] Dopp et al. (2024).
[277] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.
[278] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

Hormone level				
Taylor 2024b[279]	15 studies including two cohort studies, 12 before-after studies, and one cross-sectional study	1519 participants were treated	All pre–post studies and a cohort reporting pre–post data found increased/heightened testosterone and oestradiol in birth-registered females and males	Exogenous hormones increase hormone levels and to varying degrees induced physical changes, with potential differences depending on birth-registered sex and timing of treatment
Menstrual suppression				
Taylor 2024b[280]	Three before-after studies	387 participants were treated	Three pre–post studies reported suppression in most participants	Exogenous hormones increase hormone levels and to varying degrees induced physical changes, with potential differences depending on birth-registered sex and timing of treatment
Evidence synthesis			CSH lead to expected physiological effects	There is high certainty evidence on the physiological effects (High certainty due to very large physiological effects of CSH).[281]

[279] See note above.
[280] Taylor, Mitchell, Hall, Langton, et al. (2024).
[281] According to the GRADE methods, evidence based on observational studies can be upgraded. See Guyatt, Oxman, Sultan, et al. (2011); This overview assessed the certainty of evidence as high, upgraded by two levels due to very large effects on physical changes, hormone level, and menstrual suppression that would otherwise not be observed without CSH.

Table 6.5. Summary of evidence on safety outcomes after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[282]	19 studies	-[283]	Side effects and complications were limited and did not have a major impact on treatment (e.g., rarely resulted in changed or discontinued medication).[284]	Very low certainty due to very serious risk of bias and serious indirectness
Taylor 2024b[285]	Four studies, including one cohort, and three before-after studies	17 participants from one cohort, and 184 participants from three before-after studies	In birth-registered females, three studies noted increased acne; one also reported mood changes, elevated red blood markers, increased appetite, and less commonly, headaches, hot flashes, fatigue, and hair loss. Another study found a slight rise in metrorrhagia after adding testosterone to <6 months of lynestrenol. In birth-registered males, two studies commonly reported breast tenderness. Less common effects included elevated liver enzymes and high oestradiol levels, while mood swings and increased appetite were frequent.	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			No conclusion can be drawn on the overall risks of side-effects of CSH.	The certainty of evidence is very low.
Cardiovascular events				
Miroshnychenko 2025b[286]	Two case series studies	5768 participants	0 per 1000 (0 to 10) over 26 months, and 40 per 1000 (30 to 50) over a follow up duration of up to 109 months	Moderate to high certainty

[282] Dopp et al. (2024).
[283] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.
[284] This systematic review qualitatively described the types of side effects, such as parameters for cardiovascular health, liver enzyme, etc., but did not provide detailed, separate description for these outcomes.
[285] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[286] Miroshnychenko, Ibrahim, et al. (2025).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Body mass index				
Taylor 2024b[287]	16 studies (1 cohort, 14 before-after studies, and one cross-sectional study)	1275 participants	No change overall but some inconsistencies	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			For every 1,000 young people receiving CSH, 40 may experience cardiovascular events in nine years.	The certainty of evidence is moderate to high.
Bone health				
Dopp 2024[288]	Seven studies	-[289]	CSH was associated with improved bone density in adolescents and young adults who experienced decreases in bone density during PBs treatment. Bone density values after CSH returned to pre-treatment levels or fell within the age-based reference range for some participants.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness
Ludvigsson 2023[290]	Three observational cohort studies (two retrospective and one prospective)	268 participants on hormones, 165 were evaluated	Bone density after 1–3 years (up to 22 years of age) of CSH, which had been preceded by puberty-blocking hormonal treatment in relation to reference data in the literature: After group median five years with CSH, bone density recovered in hip but not in lumbar spine compared to data at start of treatment (z-score)	Low certainty due to serious risk of bias and serious imprecision

[287] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[288] Dopp et al. (2024).
[289] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.
[290] Ludvigsson et al. (2023).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025b[291]				
• **Bone mineral density, femoral neck, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12 months**	1 before-after study	199 participants	Mean change: 0 (0.01 lower to 0)	Very low certainty due to serious risk of bias concern (rating down by three levels)
• **Bone mineral density, hip, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	1 before-after study	199 participants	Mean change: 0.01 higher (0.01 higher to 0.01 higher)	Very low certainty due to serious risk of bias concern (rating down by three levels)
• **Bone mineral density, lumbar spine, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	Two before-after studies	234 participants	Mean change: 0.01 higher (0 to 0.01 higher)	Very low certainty due to serious risk of bias concern (rating down by three levels)
Taylor 2024b[292]	Four before-after studies	244 participants from four before-after studies	Two studies reported increased bone density and SD scores at follow-up (one study included birth-registered females only), while two others found no change in bone density or biomarkers, though sample sizes were small.	There is insufficient evidence about the risks of hormone interventions

[291] Miroshnychenko, Ibrahim, et al. (2025).
[292] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Evidence synthesis			No conclusion can be drawn on the impact of CSH on bone health.	The certainty of evidence is very low.
Fertility				
Dopp 2024[293]	7 studies	-[294]	Studies documented healthy, viable oocyte or embryo cryopreservation after taking CSH and pausing for at least three months; a case report documented that a transgender young adult man cryopreserved viable oocytes without pausing CSH, and two other case reports documented viable semen cryopreservation after pausing CSH.	Very low certainty due to very serious risk of bias, serious imprecision, and very serious indirectness
Taylor 2024b[295]	1 cohort study	78 participants	Mature spermatozoa only observed in those starting treatment at Tanner stage 4 or higher. Immature germ cells present in all treated in early puberty.	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			No conclusion can be drawn on the impact of CSH on fertility.	The certainty of evidence is very low.
Sexual dysfunction[296]				
Miroshnychenko 2025b[297]	1 before-after study	193 participants	A linear regression analysis showed no change from baseline in symptoms of vaginal dryness or itch after receiving cross-sex hormone at six months or 12 months of follow up.	Very low certainty due to serious risk of bias concern (rating down by three levels)
Evidence synthesis			No conclusion can be drawn on the impact of CSH on sexual dysfunction.	The certainty of evidence is very low.

[293] Dopp et al. (2024).
[294] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies. This review assessed fertility preservation outcomes, not fertility outcome.
[295] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[296] Evidence only on natal females.
[297] Miroshnychenko, Ibrahim, et al. (2025).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Cognitive				
Taylor 2024b[298]	Four studies including two cohort studies and two cross-sectional studies	42 participants from two cohort studies and 71 participants from two cross-sectional studies	Two cohort studies of birth-registered females explored testosterone's impact on brain activity. One found no performance differences in visuospatial working memory across groups but noted stronger frontal and parietal activation in treated individuals and male controls. The other observed slightly more rightward amygdala lateralisation post-treatment, aligning with patterns in male and female controls. A cross-sectional study also found greater amygdala activation and stronger amygdala–prefrontal connectivity in those on hormones. Another study reported better executive function, cognitive flexibility, and working memory in hormone-treated individuals.	There was insufficient evidence regarding changes to cognitive outcomes
Evidence synthesis			No conclusion can be drawn on the impact of CSH on cognitive outcomes.	The certainty of evidence is very low.
Height/growth				
Taylor 2024b[299]	Seven studies including one cohort study and six before-after studies	43 participants from one cohort study and 563 participants from six before-after studies	For birth-registered males, two studies reported an increase in height SD score and one no change. Three studies reported an increase in absolute height. For birth-registered females, two studies reported no change in height SD score, and three reported an increase in absolute height. One study reported that birth-registered females who received hormones earlier and for longer, were taller than those who started treatment later.	There is insufficient evidence about the risks of hormone interventions

[298] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[299] See note above.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Body composition				
Taylor 2024b[300]	Two studies including one cohort study and one cross-sectional study	28 participants from one cohort study and 35 participants from one cross-sectional study	Birth-registered females on testosterone had lower body fat and higher lean mass than female controls. Birth-registered males had higher body fat and lower lean mass after hormone treatment than male controls. A pre–post study in birth-registered males found no fat mass change at two years, but an increase at three years. Fat percentage and lean mass percentage remained stable.	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			No conclusion can be drawn on the impact of CSH on height/growth or body composition.	The certainty of evidence is very low.

[300] See above note.

Table 6.6. Summary of evidence on regret after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[301]	13 studies	-[302]	Findings suggest high levels of satisfaction and low rates of regret with CSH, and most youth who received that intervention did not discontinue it.	Very low certainty due to very serious risk of bias and serious indirectness
Evidence synthesis			No conclusion can be drawn on the regret rate after CSH.	The certainty of evidence is very low.

[301] Dopp et al. (2024).
[302] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.

7 Evidence synthesis: Surgeries

This overview identified three SRs on surgeries for children or adolescents with GD[303], with most of the evidence considering mastectomy only. Across all primary studies included in the three SRs, there were no eligible randomized controlled trials. Furthermore, this overview found that only two observational studies with parallel control groups comparing surgery with no surgery among youth with GD.[304] Generally, the sample size of these studies was small: one study included 75 participants and another included 136 participants.

7.1 Included SRs on surgeries

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Miroshnychenko 2024

Miroshnychenko, A., Roldan, Y. M., Ibrahim, S., Kulatunga-Moruzi, C., Dahlin, K., Montante, S., . . . Brignardello-Petersen, R. (2024). "Mastectomy for individuals with gender dysphoria below 26 years of age: A systematic review and meta-analysis". *Plast Reconstr Surg*. https://doi.org/10.1097/prs.0000000000011734

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

[303] Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[304] Becker-Hebly et al. (2021); Olson-Kennedy et al. (2018).

7.2 Low risk of bias SRs

Of the two low risk of bias SRs,[305] Dopp 2024[306] included 18 studies (six cross-sectional studies, seven quasi-experimental studies, one cohort study, three case reports, and one qualitative study), and included all types of surgeries, though most of the included studies were on mastectomy. Miroshnychenko 2024[307] included 39 studies (three comparative observational, two before-after, and 34 case series), and only assessed the effects of mastectomy. Three studies were included by both reviews.[308]

7.3 Outcome 1. Gender dysphoria

Two SRs assessed the impact of surgery on GD. Dopp 2024[309] narratively described that according to 10 studies mastectomy was associated with reduced GD. The certainty of evidence was low. Miroshnychenko and colleagues included one comparative observational study with 136 participants and one before-after study with 35 participants and concluded that the certainty of evidence was very low. The authors concluded that no conclusion could be drawn on the effect of surgery in improving GD.

In conclusion, this overview finds that the certainty of evidence is very low.

7.4 Outcome 2. Mental health and well-being

The SRs assessed the impact of surgery on mental health, including global functioning, suicidality, non-suicidal self-harm, depression, and quality of life.[310] Dopp 2024[311] reported that adolescents and young adults generally showed improved mental health after surgery, with about half the outcomes showing clinically significant gains (e.g., self-perception, distress, functioning, quality of life). This systematic review acknowledged that most patients had prior interventions or were already high functioning, making it hard to isolate the effects of surgery. The other systematic review[312] reported a lower level of distress measured by Kessler Psychological Distress from one comparative

[305] Dopp et al. (2024); Miroshnychenko et al. (2024).
[306] Dopp et al. (2024).
[307] Miroshnychenko et al. (2024).
[308] Ascha et al. (2022); Marinkovic & Newfield (2017); Tang et al. (2022).
[309] Dopp et al. (2024).
[310] Dopp et al. (2024); Miroshnychenko et al. (2024).
[311] Dopp et al. (2024).
[312] Miroshnychenko et al. (2024).

observational study. However, both SRs assessed the certainty of evidence as very low. In summary, no conclusion could be drawn on the impact of surgery on global function due to very low certainty evidence.

Miroshnychenko et al[313] reported very low certainty evidence for the effect of mastectomy on outcomes such as quality of life, depression, suicide attempts and death by suicide compared with no mastectomy. Low certainty evidence suggested that mastectomy may be associated with a lower risk of non-suicidal self-injury.

In summary, this overview suggests that it is unclear whether mastectomy leads to benefits in mental health due to very low certainty evidence.

7.5 Outcome 3. Safety

Dopp 2024[314] concluded that side effects after surgeries, such as scarring or issues with function or appearance, were generally limited. Most complications (e.g., fluid buildup, pain, bruising, infection) were minor and resolved naturally or with simple follow-up care. Miroshnychenko and colleagues[315] found high certainty evidence showing no increased risk of death following the surgery as well as high-certainty evidence for necrosis and excessive scarring after surgery.

7.6 Outcome 4. Regret

Both SRs reported a low level of regret,[316] albeit both reviews found the certainty of evidence was very low. The current evidence basis is not sufficient to reach a conclusion on the regret rate after surgery.

7.7 Evidence gap

There are substantial gaps in the evidence on surgeries for adolescents with GD. Most existing studies are case series or small observational designs, with limited or no comparator groups, and thus are unable to isolate the effects of surgery from prior

[313] Miroshnychenko et al. (2024).
[314] Dopp et al. (2024).
[315] Miroshnychenko et al. (2024).
[316] Dopp et al. (2024); Miroshnychenko et al. (2024).

medical or psychosocial interventions. Outcomes such as GD, mental health, and quality of life are inconsistently reported and often lack validated measures.

Long-term outcomes, including the durability of psychological benefits, sexual function, need for revision surgeries, and satisfaction and well-being into adulthood, remain poorly characterized. Furthermore, while regret is a frequent topic of public discussion, existing studies do not provide robust data on the factors influencing regret. There are also knowledge gaps for other types of surgeries, including genital surgeries

7.8 Summary

In summary, this overview identified three systematic reviews addressing the effects of surgeries among children or adolescents with GD. There is high certainty evidence that mastectomy is associated with predictable surgical complications such as necrosis and scarring. The evidence is very uncertain regarding the effect of surgery on GD, improvement in mental health including suicidality, depression, and long-term outcomes such as sexual function, quality of life, and regret.

7.9 Evidence mapping: SRs on surgeries

Table 7.1. Evidence mapping of the SRs on surgeries and the primary studies that these SRs included

	Dopp 2024[317]	Miroshnychenko 2024[318]	Thompson 2023[319]
Arnoldussen 2022	Y		
Ascha 2022	Y	Y	
Ayyala 2020		Y	
Becker-Hebly 2021	Y		Y
Berry 2012		Y	
Bodlund 1996	Y		
Boskey 2023	Y		
Bungener 2020	Y		
Bustos 2020		Y	
Caro 2024		Y	
Cohen-Kettenis 2011[320]	Y		
Cohen-Kettenis 1997[321]	Y		
Cuccolo 2019		Y	
de Vries 2014	Y		
Donaldson 2018	Y		
Donato 2017		Y	
Ederer 2023		Y	
Elfering 2020		Y	
Frederick 2017		Y	
Gold 2021		Y	
Jolly 2023		Y	
Junn 2021		Y	
Kääriäinen 2017		Y	

[317] Dopp et al. (2024).
[318] Miroshnychenko et al. (2024).
[319] Thompson et al. (2023).
[320] Another citation, Cohen-Kettenis 1998 was provided for this study. However, this citation (Cohen-Kettenis 1998) was not included by any other SRs on PBs or CSH. Though this study was included by Dopp 2024 for PBs and CSH.
[321] Two other citations were included for this study, Smith 2021 and Smith 2022. Neither citation was included by other reviews on PBs, CSH, or surgeries.

	Dopp 2024[317]	Miroshnychenko 2024[318]	Thompson 2023[319]
Kamali 2021		Y	
Kaur 2023		Y	
Kelly-Schuette 2022		Y	
Kuper 2020	Y		Y
Lane 2023		Y	
Lang 2021		Y	
Lee 2024	Y		
Littman 2021	Y		
Marinkovic 2017	Y	Y	
McEvenue 2017		Y	
Mehringer 2021	Y		
Naides 2021		Y	
Namba 2009		Y	
Olson-Kennedy 2018a	Y		
Olson-Kennedy 2018b		Y	
Perez-Alvarez 2021		Y	
Robinson 2023		Y	
Rothenberg 2021		Y	
Rothenberg 2018		Y	
Sır 2022		Y	
Skorochod 2023	Y		
Stein 2021		Y	
Stojanovic 2017		Y	
Tan 2023		Y	
Tang 2022	Y	Y	
Top 2017		Y	
van de Grift 2017		Y	
van de Grift 2018		Y	
van de Grift 2016		Y	
Wolf 2021		Y	
Wolter 2018		Y	

7.10 Evidence tables on outcomes for surgeries in youth with gender dysphoria

Table 7.2. Summary of evidence on gender dysphoria after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Mastectomy				
Dopp 2024[322]	10 studies	-[323]	Mastectomy was associated with reduced gender dysphoria (including specifically chest dysphoria), and related improvements with body satisfaction for primary and sometimes secondary sex characteristics, in natal female adolescents and young adults with gender dysphoria.	Low certainty due to serious risk of bias and serious indirectness
Miroshnychenko 2024[324]	One comparative observational study and one before-after study	136 participants from one comparative observational study and 35 participants from one before-after study	Mean difference 26.3 lower (28.84 lower to 23.76 lower) from the comparative observational study; mean change 28 lower (28.33 lower to 27.67 lower) for gender dysphoria related to chest, and mean change 9.1 higher (8.74 higher to 9.46 higher) according to participant reported transgender congruence scale from the before-after study (higher score indicating greater gender dysphoria)	Very low certainty due to serious risk of bias, imprecision, and indirectness
Hysterectomy/ovariectomy and/or metoidioplasty or phalloplasty				
Dopp 2024[325]	Four studies	-[326]	Hysterectomy/ovariectomy and/or metoidioplasty or phalloplasty was associated with reduced gender dysphoria, and related improvements with body satisfaction related to primary and secondary sex characteristics, in natal female young adults with gender dysphoria.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness

[322] Dopp et al. (2024).
[323] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).
[324] Miroshnychenko et al. (2024).
[325] Dopp et al. (2024).
[326] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Vaginoplasty and/or mammaplasty				
Dopp 2024[327]	5 studies	-[328]	Vaginoplasty "bottom surgery" and/or mammaplasty "top surgery" was associated with reduced gender dysphoria, and related improvements with body satisfaction related to primary and secondary sex characteristics, in natal male adolescents and young adults with gender dysphoria.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness
Evidence synthesis			No conclusion can be drawn on the impact of surgeries on gender dysphoria.	The certainty of evidence is very low.

[327] Dopp et al. (2024).
[328] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).

Table 7.3. Summary of evidence on mental health and well-being after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Global function				
Dopp 2024[329]	10 studies	-[330]	Across surgeries, adolescents and young adults with gender dysphoria generally showed improvement in mental health outcomes, with clinically significant effect sizes for about half of reported outcomes; examples of outcomes measured include self-perception, psychological distress, mental health symptoms, global functioning, and quality of life. In cases where improvement was not found, average scores on outcomes were maintained at the same level as pre-surgery. No evidence of mental health harms was found. In most studies, patients had received numerous interventions and/or been required to demonstrate high levels of functioning prior to receiving surgery, which made it difficult to assess mental health outcomes of surgery, and they are considered secondary intervention benefits.	Very low certainty due to very serious risk of bias, very serious imprecision, serious inconsistency and indirectness
Miroshnychenko 2024[331]	1 comparative observational study	299	16.39% participants had mastectomy. A multivariate analysis showed that those who received mastectomy (chest reconstruction surgery) scored an average of -7.13 (CI= -10.25 to -4.02) points lower on the Kessler Psychological Distress.	Very low certainty due to very serious risk of bias and serious indirectness

[329] Dopp et al. (2024).
[330] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011), or cross-sectional study (Lee 2024).
[331] Miroshnychenko et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Depression				
Miroshnychenko 2024[332]	1 before-after study[333]	68	mean change 3.16 lower (3.35 lower to 2.97 lower) (higher score indicating greater depression)	Very low certainty due to very serious risk of bias and serious indirectness and imprecision
Suicide attempts				
Miroshnychenko 2024[334]	1 comparative observational study	299	16.39% participants had mastectomy. Individuals who underwent mastectomy had 0.39 times the odds of non-suicidal self-injury compared to individuals who did not undergo mastectomy (adjusted odds ratio 0.39 [95% confidence interval 0.11 to 1.45]).	Very low certainty due to very serious risk of bias and serious imprecision
Non-suicidal Self-harm				
Miroshnychenko 2024[335]	One comparative observational study[336]	299	16.39% participants had mastectomy. Individuals who underwent mastectomy had 0.47 times the odds of non-suicidal self-injury compared to individuals who did not undergo mastectomy (adjusted odds ratio 0.47 [95% confidence interval 0.22 to 0.97])	Low certainty due to very serious risk of bias
Quality of life				
Miroshnychenko 2024[337]	One before-after study and one case series	80 participants from the before-after study and 34 participants from the case series	mean change 5.74 higher (5.29 higher to 6.19 higher lower) (higher score indicating better quality of life)	Very low certainty due to serious risk of bias, indirectness, and imprecision

[332] Miroshnychenko et al. (2024).
[333] The supplementary information of this systematic review reported evidence based on case series, which did not change the certainty of evidence for this outcome.
[334] Miroshnychenko et al. (2024).
[335] Miroshnychenko et al. (2024).
[336] The supplementary information of this systematic review reported evidence based on case series, which did not change the certainty of evidence for this outcome.
[337] Miroshnychenko et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Death by suicide				
Miroshnychenko 2024[338]	One case series	464 participants from the case series	10 per 1,000 (0 to 20)	Very low certainty due to serious very serious risk of bias and serious indirectness
Evidence synthesis			No conclusion can be drawn on the impact of mental health by surgeries.	The certainty of evidence is very low.

[338] Miroshnychenko et al. (2024).

Table 7.4. Summary of evidence on safety after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[339]	10 studies	-[340]	Across types of surgery, side effects (e.g., scarring, issues with functioning and/or appearance) were limited and primarily would be resolved through improved surgical techniques; concerns about sexual functioning were often noted, but overall sexual functioning tended to improve from pre-surgery. Complications were also generally minor (e.g., blood fluid collection, pain, bruising, infection) and resolved through natural healing or non-invasive follow-up procedures.	Very low certainty due to very serious risk of bias and serious indirectness
Death as a postoperative complication of mastectomy				
Miroshnychenko 2024[341]	Five case series studies	3673	0 per 1,000 (0 to 0)	High certainty evidence
Necrosis (complete and partial nipple/areola/nipple-areola complex/nipple graft necrosis)				
Miroshnychenko 2024[342]	Eight case series studies	1998	30 per 1,000 (10 to 70)	High certainty evidence
Necrosis (complete nipple/areola/nipple-areola complex/nipple graft necrosis)				
Miroshnychenko 2024[343]	13 case series studies	2236	20 per 1,000 (10 to 30)	High certainty evidence

[339] Dopp et al. (2024).
[340] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that are not typically included a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).
[341] Miroshnychenko et al. (2024).
[342] Miroshnychenko et al. (2024).
[343] Miroshnychenko et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Excessive Scarring				
Miroshnychenko 2024[344]	12 case series studies	2405	50 per 1,000 (30 to 80)	High certainty evidence
Evidence synthesis			Surgery is generally safe and the risk of dying from surgery is low. There are risks of complications such as necrosis, scarring, sexual function impairment, and other functional impairment.	The evidence for mastectomy is high certainty. The evidence for other surgeries is very low certainty.

[344] Miroshnychenko et al. (2024).

Table 7.5. Summary of evidence on regret after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[345]	Nine studies	-[346]	Across types of surgeries, high satisfaction ratings and low rates of regret (<2%) were documented. Comparisons between adolescents and young adults with gender dysphoria suggested rates of regret and satisfaction that were equal or better in youth younger than 18.	Very low certainty due to very serious risk of bias and serious indirectness
Miroshnychenko 2024[347]	Four case series studies	775	10 per 1,000 (0 to 20)	Very low certainty due to very serious risk of bias (rating down for three levels) and serious indirectness
Evidence synthesis			There are cases of regret after surgeries. No conclusion can be drawn on the regret rate after surgery.	The certainty of evidence on regret rate is very low.

[345] Dopp et al. (2024).
[346] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011), and qualitative studies (Mehringer 2021).
[347] Miroshnychenko et al. (2024).

8 Evidence synthesis: Psychotherapy

There are five SRs assessing psychotherapy among children or adolescents with GD.[348] Only two were assessed at low risk of bias in the systematic review process.[349]

8.1 Included SRs on psychotherapy

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Expósito-Campos 2023

Expósito-Campos, P., Pérez-Fernández, J. I., & Salaberria, K. (2023). Empirically supported affirmative psychological interventions for transgender and non-binary youth and adults: A systematic review. *Clinical Psychology Review*, *100*, 102229.

Heathcote 2024

Heathcote, C., Taylor, J., Hall, R., Jarvis, S. W., Langton, T., Hewitt, C. E., . . . Fraser, L. (2024). Psychosocial support interventions for children and adolescents experiencing gender dysphoria or incongruence: A systematic review. *Arch Dis Child*, *109*(Suppl 2), s19-s32.

Malpas 2022 – family-based intervention (social and psychological)

Malpas, J., Pellicane, M. J., & Glaeser, E. (2022). Family-based interventions with transgender and gender expansive youth: Systematic review and best practice recommendations. *Transgend Health*, *7*(1), 7-29.

[348] Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).
[349] Dopp et al. (2024); Heathcote et al. (2024).

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

8.2 Low risk of bias SRs

Evidence on the effects of psychotherapy is limited. Dopp 2024[350] included one randomized controlled trial evaluating the effects of “coping-oriented brief videos” on suicidality. There are no other randomized controlled trials. Both SRs found that psychotherapy interventions were delivered through a range of formats, highlighting considerable heterogeneity in delivery. Most were conducted face-to-face or online. Formats for both face-to-face and online interventions varied widely, including individual, group, family-based, and combined approaches. Face-to-face interventions took place in diverse settings, such as specialist gender services, community programs, community mental health clinics, a weekend retreat, and an acute residential treatment program. These heterogeneities limit the generalizability of evidence.

8.3 Outcome 1. Gender dysphoria

There was no evidence on the impact of psychotherapy on GD.

8.4 Outcome 2. Mental health and well-being

Dopp and colleagues[351] reported that peer group interventions were associated with improvements in general mental health functioning, but professional psychosocial support as a precondition for additional interventions was not associated with any improvements on broad measures of mental health symptoms or functioning. The certainty of evidence was very low. Heathcote and colleagues included 10 studies and found that research on psychosocial interventions for children and adolescents with GD is limited. The 10 included studies were generally low in quality and poorly reported. Most lacked clear participant selection criteria, used varied interventions, applied inconsistent outcome measures, and did not include appropriate comparators. This

[350] Dopp et al. (2024).
[351] Dopp et al. (2024).

systematic review by Heathcote and colleagues[352] underscored a lack of robust research and the use of inadequate methodologies. In summary, the certainty of evidence for benefits of psychotherapy is very low.

8.5 Outcome 3. Safety

Neither systematic review found any indication of harm from psychotherapy.

8.6 Evidence gap

The evidence base for psychotherapy in children and adolescents with GD is marked by substantial gaps. This may be due to the inappropriate conflation of psychotherapy with "conversion therapy." As noted by the Cass Review, "[the] role of psychological therapies in supporting children and young people with gender incongruence or distress has been overshadowed by an unhelpfully polarised debate around conversion practices."[353] There has been very limited evidence on the role of psychotherapy in treating mental health problems co-occurring with GD, including depression, anxiety, eating disorders, self-harm, and suicidality. Studies often did not isolate the effects of psychotherapy from those of other concurrent interventions such as social transition, PBs, or CSH, making it difficult to attribute observed outcomes to psychotherapy alone. There is little understanding of which therapeutic approaches may be more effective for specific subgroups. The lack of robust research was acknowledged by the Cass Review, which noted that "there has been a failure to systematically consider how psychosocial interventions should be used and to research their efficacy."[354]

8.7 Summary

In summary, this overview identified five systematic reviews assessing the effects of psychotherapy among children or adolescents with GD. Only two reviews were rated at low risk of bias. The available evidence on psychotherapy is limited and highly heterogeneous in terms of intervention format, delivery setting, and target population. This overview finds no evidence on the impact of psychotherapy on GD from the SRs.

[352] Heathcote et al. (2024).
[353] Cass (2024, p. 150).
[354] Cass (2024, p. 155).

For mental health outcomes, the certainty of evidence is very low. No harms were reported.

8.8 Evidence tables on outcomes for psychotherapy in youth with gender dysphoria

Table 8.1. Summary of evidence on mental health and well-being after psychotherapy

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Peer-group intervention				
Dopp 2024[355]	Four studies	-[356]	Peer-group interventions were associated with improvements in general mental health functioning in adolescents and young adults with gender dysphoria; examples of outcomes studied include mental health symptoms, well-being/quality of life, and self-esteem. All studies showed benefits on some reported outcomes, but about half of the reported outcomes did not show significant changes, and in one case the effect was not clinically significant (Austin, Craig, and D'Souza, 2018). Furthermore, a group intervention for youth with autism spectrum disorder and gender dysphoria (Brandsma et al., 2022) was associated with increases in gender dysphoria and showed benefits on only one-third of reported outcomes.	Very low certainty due to very serious risk of bias and imprecision, and serious indirectness and inconsistency

[355] Dopp et al. (2024).
[356] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Professional psychological support as a precondition for additional interventions for gender dysphoria				
Dopp 2024[357]	Two studies	135 participants	Professional psychosocial support as a precondition for additional interventions was not associated with any improvements on broad measures of mental health symptoms or functioning in adolescents with gender dysphoria who have started puberty. Youth remained in the clinical range on mental health symptom measures post-intervention (compared to norms) and did not show statistically or clinically significant changes over time.	Very low certainty due to very serious risk of bias, and serious indirectness
Depression				
Heathcote 2024[358]	Six studies	n = 226	Four studies found significant reductions in depression levels post-intervention and/or at a later timepoint. Two studies found non-significant differences in depression levels during mid-treatment and/or post-intervention	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[357] Dopp et al. (2024).
[358] Heathcote et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Anxiety				
Heathcote 2024[359]	Three studies	n = 218	All three studies found significant reductions in anxiety levels post-intervention	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.
Depression and anxiety combined				
Heathcote 2024[360]	One study	n = 17	no significant, although marginal, difference from baseline to six months	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[359] Heathcote et al. (2024).
[360] Heathcote et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Internalising and externalising symptoms				
Heathcote 2024[361]	One study	n = 64	Improvement in internalising and externalising symptoms	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.
Emotional dysregulation				
Heathcote 2024[362]	One study	n = 35	Significant reductions post-intervention and at a later timepoint (1 month)	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[361] Heathcote et al. (2024).
[362] Heathcote et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Suicidality				
Dopp 2024[363]	One randomized controlled trial	483 LGBTQ+ youth (“lesbian, gay, bisexual, transgender, queer persons or persons with other sexual or gender minority identities”)	A randomized controlled trial found that coping-oriented brief videos ("It Gets Better" project) led to short-term decreases in suicidality and increases in help-seeking intentions with personal contacts in young adults with gender dysphoria, but these benefits were not maintained at four weeks post-intervention and were not large enough to represent clinically significant effects.	Very low certainty due to serious risk of bias and indirectness
Heathcote 2024[364]	Three studies	n = 193	Two studies found significant decreases in suicidality scores from baseline to mid-treatment and/or post-intervention, and/or at a later timepoint. One study found no difference in the proportion of patients at high suicide risk before and after the intervention.	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[363] Dopp et al. (2024).
[364] Heathcote et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Family support				
Dopp 2024[365]	Two studies	-[366]	Professional psychosocial support in the form of family and/or caregiver therapy was associated with increased family support for youth with gender dysphoria, with small but clinically significant effect sizes; similar effects were also described in one case report.	Very low certainty due to very serious risk of bias and imprecision, and serious indirectness
Psychological change				
Heathcote 2024[367]	Five studies	n = 219	For resilience, self-compassion and self-acceptance, there were significant increases in scores between baseline and post-intervention, and between baseline and three months for self-compassion and six months for self-acceptance, but the difference was no longer observed for resilience at three-month follow-up. Participants reported more positive coping and problem-solving and increased confidence. Participants also talked about being more comfortable and accepting of their identity, having a better sense of self and self-worth, and reduced feelings of isolation and distrust towards others.	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[365] Dopp et al. (2024).
[366] The sample size was not calculated because one study was an individual case report, and another was a report on parental rating.
[367] Heathcote et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychosocial change				
Heathcote 2024[368]	Five studies	n = 412	Three studies found significant improvements in quality of life/global functioning/well-being post-intervention and/or at later timepoints. Participants reported having better peer relationships and increased acceptance and/or support from peers (from meeting and forging relationships with others in the same situation).	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.
Evidence synthesis			No conclusion can be drawn on the impact of mental health by psychotherapy.	The certainty of evidence is very low.

[368] Heathcote et al. (2024).

9 Evidence synthesis: Social transition

Two SRs assessed the impact of social transition. Both are assessed at low risk of bias.[369]

9.1 Included SRs on social transition

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Hall 2024

Hall, R., Taylor, J., Hewitt, C. E., Heathcote, C., Jarvis, S. W., Langton, T., . . . Fraser, L. (2024). Impact of social transition in relation to gender for children and adolescents: A systematic review. *Arch Dis Child*, *109*(Suppl 2), s12-s18.

9.2 Outcome 1. Gender dysphoria

Hall 2024[370] reported the impact of social transition on GD based on two observational studies. One study found that children who had socially transitioned were more likely to experience persistence of GD into adolescence compared to those who had not. Another study reported that 92.7% of children who socially transitioned between ages three and 12 continued to experience GD an average of 5.4 years later. The systematic review authors did not assess the certainty of evidence, though reported a “lack of robust evidence.”

This overview finds the certainty of evidence for effects of social transition on GD is very low.

[369] Dopp et al. (2024); Hall et al. (2024).
[370] Hall et al. (2024).

9.3 Outcome 2. Mental health and well-being

As for mental health outcomes, Dopp 2024[371] reported that social transition among children or adolescents with GD was associated with reduced suicidality and mixed outcomes for depression or mood symptoms. However, associations with other mental health symptoms (e.g., anxiety, substance use, or overall functioning) were inconsistent. The certainty of evidence was very low. The systematic review by Hall 2024[372] highlighted that the evidence on the impact of social transition for children and adolescents with GD is limited and low in quality. Most studies were cross-sectional, US-based, used non-representative samples, and lacked appropriate comparator groups. No prospective studies with suitable comparators exist. Furthermore, findings are inconsistent and should be interpreted with caution. For example, some studies suggest benefits from using a chosen name in adolescence, while another found higher rates of suicide attempts and ideation among those who socially transitioned during adolescence compared to those who socially transitioned in adulthood.

In summary, this overview concludes that the certainty of evidence for effects of social transition on mental health and well-being is very low.

9.4 Outcome 3. Regret

There was no evidence on side effects, and Dopp 2024[373] was the only review reporting the regret outcome. Though this systematic review found a low level of regret, the certainty of evidence was assessed as very low.

In conclusion, the evidence is uncertain to determine the regret rate associated with social transition.

9.5 Evidence gap

The impact of social transition on long-term GD, psychological outcomes and well-being, and future treatment decisions such as CSH or surgeries remains poorly understood. Evidence on regret is extremely limited.

[371] Dopp et al. (2024).
[372] Hall et al. (2024).
[373] Dopp et al. (2024).

Significant evidence gaps remain in the evaluation of social transition as an intervention for children and adolescents with GD. Most available studies are cross-sectional and there are no prospective longitudinal studies with appropriate comparison groups, making it unclear whether observed associations reflect the effects of social transition or other underlying factors. Additionally, studies often did not disentangle the effects of social transition from concurrent interventions such as psychotherapy or medical treatments, further complicating interpretation.

9.6 Summary

In summary, this overview identified two systematic reviews addressing the effects of social transition among children or adolescents with GD. Both reviews were assessed at low risk of bias. The studies reviewed were largely cross-sectional and no high-quality prospective studies with appropriate comparators were identified. This overview finds that the overall certainty of evidence for effects of social transition on children and adolescents with GD is very low, and no reliable conclusions could be drawn regarding the benefits or risks of this intervention.

9.7 Evidence tables on outcomes for social transition in youth with gender dysphoria

Table 9.1. Summary of evidence on gender dysphoria after social transition

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Hall 2024[374]				
Children	Two studies	n = 444	One study found a higher odd of persistence of gender dysphoria/incongruence in adolescence for children who had socially transitioned compared with those who had not socially transitioned. Another study found that 92.7% of those who socially transitioned between ages three and 12 continued to experience gender dysphoria/incongruence at the end of the study (on average, 5.4 years after socially transitioning).	There is little evidence of the benefits or harms of social transition in children and adolescents.
Adolescents	One study	350 participants	Adolescents who preferred to be called by another name compared with no preferred name use reported higher levels of gender distress.	There is little evidence of the benefits or harms of social transition in children and adolescents.
Evidence synthesis			No conclusion can be drawn on the impact of social transition on gender dysphoria.	The certainty of evidence is very low.[375]

[374] Hall et al. (2024).
[375] Very low certainty due to very serious risk of bias (no prospective longitudinal studies with appropriate comparator group) and serious indirectness concern.

Table 9.2. Summary of evidence on mental health and well-being after social transition

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Suicidality				
Dopp 2024[376]	Five studies	-[377]	Social transition was associated with decreased suicidality in children, adolescents, and young adults with gender dysphoria. The extent to which youth in a sample or subsample were in supportive environments moderated suicidality outcomes in several studies (Campbell, Mann, Rodgers, and Tran, 2023; Turban et al., 2021), such that social transition was associated with greater decreases in suicidality in less supportive environments. An effect size metric was available for about half of reported outcomes, all of which were clinically significant except for the impacts on suicidality in adulthood (Turban et al., 2021) which were statistically but not clinically significant.	Very low certainty due to serious risk of bias, inconsistency, and indirectness
Hall 2024[378]	Two studies	n = 9,840	A cross-sectional study reported that using a chosen name in more contexts was associated with lower suicidal thoughts and behaviors. However, another cross-sectional study[379] found that social transition during adolescence was tied to higher odds of past-year suicidal ideation and lifetime suicide attempts compared to adulthood.	There is little evidence of the benefits or harms of social transition in children and adolescents.

[376] Dopp et al. (2024).
[377] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, cross-sectional studies.
[378] Hall et al. (2024); Evidence comparing adolescents with gender dysphoria who have socially-transitioned with those who have not.
[379] This study (Turban et al. (2021)) reported results from 9,711 socially-transitioned individuals, however, the majority socially-transitioned as adults (n = 8,350), with only 1,196 socially-transitioned as children.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychological functioning				
Hall 2024[380]	Three studies	n = 10,077[381]	The studies comparing children experiencing gender dysphoria/incongruence who have socially transitioned with who have not socially transitioned found that the social transition status was not associated with psychological functioning or self-perception.	There is little evidence of the benefits or harms of social transition in children and adolescents.
Non-clinical depression or mood symptoms				
Dopp 2024[382]	Six studies	-[383]	Social transition was associated with a mix of depression or mood symptom outcomes that showed clinically significant decreases and/or showed a lack of statistically significant effects in children, adolescents, and young adults with gender dysphoria. An effect size metric was available for the majority of reported outcomes, all of which were clinically significant or in the nonclinical range (compared to norms or matched samples of cisgender youth) post-intervention.	Very low certainty due to very serious risk of bias and serious indirectness
Depressive and anxiety symptoms				
Hall 2024[384]	Two studies	n = 479	A cross-sectional study reported that adolescents using a preferred name reported fewer depressive symptoms, with no significant difference in anxiety. Another cross-sectional study found that using a chosen name in more social settings was linked to lower depression levels.	There is little evidence of the benefits or harms of social transition in children and adolescents.

[380] Hall et al. (2024); Evidence comparing children with gender dysphoria who have socially-transitioned with those who have not.
[381] One study (Turban et al. (2021)) reported results from 9,711 socially-transitioned individuals, however, the majority socially-transitioned as adults (n = 8,350), with only 165 socially-transitioned as children.
[382] Dopp et al. (2024).
[383] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, cross-sectional study.
[384] Hall et al. (2024); Evidence comparing adolescents with gender dysphoria who have socially-transitioned with who have not

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychological distress				
Hall 2024[385]	One study	n = 9,711[386]	A cross-sectional study found no significant link between social transition timing (adolescence vs. adulthood) and severe psychological distress.	There is little evidence of the benefits or harms of social transition in children and adolescents.
Other mental health outcomes				
Dopp 2024[387]	Seven studies	-[388]	Social transition did not show consistent associations with other mental health symptoms (beyond depression or mood)—such as anxiety, substance use, or broad measures of mental health symptoms or functioning—in children, adolescents, and young adults with gender dysphoria. Some measures showed a lack of statistically significant change or scores that remained elevated (compared to norms or matched samples of cisgender youth) post-intervention, and/or clinically significant improvements or scores in the nonclinical range. The high level of inconsistency suggests that these outcomes are not a core benefit of social transition. No evidence of mental health harms (e.g., increased symptoms) was found.	Very low certainty due to very serious risk of bias, and serious inconsistency and indirectness
Evidence synthesis			No conclusion can be drawn on the impact of mental health by social transition.	The certainty of evidence is very low. [389]

[385] See above note.
[386] This study (Turban et al. (2021)) reported results from 9,711 socially-transitioned individuals, however, the majority socially-transitioned as adults (n = 8,350), with only 1,196 socially-transitioned as children.
[387] Dopp et al. (2024).
[388] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, cross-sectional study.
[389] Very low certainty due to very serious risk of bias (no prospective longitudinal studies with appropriate comparator group) and serious indirectness concern.

Table 9.3. Summary of evidence on regret after social transition

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[390]	Three studies	-[391]	Social transition was found to have a very low rate of detransition to a cisgender identity (3.5%) in children with gender dysphoria, suggesting low rates of regret; data were not available for detransition rates in adolescents or young adults, but rates were lower in older children (Olson et al., 2022). Perspectives among youth who detransitioned were variable, and they did not necessarily regret the transition or reverse all social transition steps (Littman, 2021; Turban, Carswell, and Keuroghlian, 2018).	Very low certainty due to very serious risk of bias, and serious indirectness
Evidence synthesis			There are cases of regret. No conclusion can be drawn on the regret rate after social transition.	The certainty of evidence on regret rate is very low.

[390] Dopp et al. (2024).
[391] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case report.

10 Citations for the primary studies included in the SRs on PBs, CSH, and surgeries

Achille 2020

Achille, C., Taggart, T., Eaton, N. R., Osipoff, J., Tafuri, K., Lane, A., . . . Wilson, T. A. (2020). Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. International Journal of Pediatric Endocrinology, 2020(1), 8. https://doi.org/10.1186/s13633-020-00078-2

Akgul 2019

Akgul, S., Bonny, A. E., Ford, N., Holland-Hall, C., & Chelvakumar, G. (2019). Experiences of gender minority youth with the intrauterine system. J Adolesc Health, 65(1), 32-38. https://doi.org/10.1016/j.jadohealth.2018.11.010

Aldridge 2021

Aldridge, Z., Patel, S., Guo, B., Nixon, E., Pierre Bouman, W., Witcomb, G. L., . . . Arcelus, J. (2021). Long-term effect of gender-affirming hormone treatment on depression and anxiety symptoms in transgender people: A prospective cohort study. Andrology, 9(6), 1808-1816. https://doi.org/https://doi.org/10.1111/andr.12884

Allen 2019

Allen, L. R., Waston, L. B., Egan, A. M., & Moser, C. N. (2019). Well-being and suicidality among transgender youth after gender-affirming hormones. Clinical Practice in Pediatric Psychology, 7(3), 302-311. https://doi.org/https://doi.org/10.1037/cpp0000288

Amir 2020

Amir, H., Yaish, I., Samara, N., Hasson, J., Groutz, A., & Azem, F. (2020). Ovarian stimulation outcomes among transgender men compared with fertile cisgender women. J Assist Reprod Genet, 37(10), 2463-2472. https://doi.org/10.1007/s10815-020-01902-7

Arcelus 2016

Arcelus, J., Claes, L., Witcomb, G. L., Marshall, E., & Bouman, W. P. (2016). Risk factors for non-suicidal self-injury among trans youth. J Sex Med, 13(3), 402-412. https://doi.org/10.1016/j.jsxm.2016.01.003

Arnoldussen 2022

Arnoldussen, M., van der Miesen, A. I. R., Elzinga, W. S., Alberse, A. E., Popma, A., Steensma, T. D., . . . de Vries, A. L. C. (2022). Self-perception of transgender adolescents after gender-affirming treatment: A follow-up study into young adulthood. LGBT Health, 9(4), 238-246. https://doi.org/10.1089/lgbt.2020.0494

Ascha 2022

Ascha, M., Sasson, D. C., Sood, R., Cornelius, J. W., Schauer, J. M., Runge, A., . . . Jordan, S. W. (2022). Top surgery and chest dysphoria among transmasculine and nonbinary adolescents and young adults. JAMA Pediatr, 176(11), 1115-1122. https://doi.org/10.1001/jamapediatrics.2022.3424

Ayyala 2020

Ayyala, H. S., Mukherjee, T. J., Le, T. M., Cohen, W. A., Luthringer, M., & Keith, J. D. (2020). A three-step technique for optimal nipple position in transgender chest masculinization. Aesthet Surg J, 40(11), Np619-np625. https://doi.org/10.1093/asj/sjaa150

Barnard 2019

Barnard, E. P., Dhar, C. P., Rothenberg, S. S., Menke, M. N., Witchel, S. F., Montano, G. T., . . . Valli-Pulaski, H. (2019). Fertility preservation outcomes in adolescent and young adult feminizing transgender patients. Pediatrics, 144(3). https://doi.org/10.1542/peds.2018-3943

Becker-Hebly 2021

Becker-Hebly, I., Fahrenkrug, S., Campion, F., Richter-Appelt, H., Schulte-Markwort, M., & Barkmann, C. (2021). Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: A descriptive study from the hamburg gender identity service. Eur Child Adolesc Psychiatry, 30(11), 1755-1767. https://doi.org/10.1007/s00787-020-01640-2

Beking 2020

Beking, T., Burke, S. M., Geuze, R. H., Staphorsius, A. S., Bakker, J., Groothuis, A. G. G., . . . Kreukels, B. P. C. (2020). Testosterone effects on functional amygdala lateralization: A study in adolescent transgender boys and cisgender boys and girls. Psychoneuroendocrinology, 111, 104461. https://doi.org/https://doi.org/10.1016/j.psyneuen.2019.104461

Berry 2012

Berry, M. G., Curtis, R., & Davies, D. (2012). Female-to-male transgender chest reconstruction: A large consecutive, single-surgeon experience. J Plast Reconstr Aesthet Surg, 65(6), 711-719. https://doi.org/10.1016/j.bjps.2011.11.053

Bodlund 1996

Bodlund, O., & Kullgren, G. (1996). Transsexualism--general outcome and prognostic factors: A five-year follow-up study of nineteen transsexuals in the process of changing sex. Arch Sex Behav, 25(3), 303-316. https://doi.org/10.1007/bf02438167

Boskey 2023

Boskey, E. R., Jolly, D., Kant, J. D., & Ganor, O. (2023). Prospective evaluation of psychosocial changes after chest reconstruction in transmasculine and non-binary youth. J Adolesc Health, 73(3), 503-509. https://doi.org/10.1016/j.jadohealth.2023.04.029

Brik 2020

Brik, T., Vrouenraets, L. J. J. J., de Vries, M. C., & Hannema, S. E. (2020). Trajectories of adolescents treated with gonadotropin-releasing hormone analogues for gender dysphoria. Archives of Sexual Behavior, 49(7), 2611-2618. https://doi.org/10.1007/s10508-020-01660-8

Bungener 2020

Bungener, S. L., de Vries, A. L. C., Popma, A., & Steensma, T. D. (2020). Sexual experiences of young transgender persons during and after gender-affirmative treatment. Pediatrics, 146(6). https://doi.org/10.1542/peds.2019-1411

Burke 2016

Burke, S. M., Kreukels, B. P., Cohen-Kettenis, P. T., Veltman, D. J., Klink, D. T., & Bakker, J. (2016). Male-typical visuospatial functioning in gynephilic girls with gender dysphoria - organizational and activational effects of testosterone. J Psychiatry Neurosci, 41(6), 395-404. https://doi.org/10.1503/jpn.150147

Burke 2020

Burke, S. M., van Heesewijk, J. O., Menks, W. M., Klink, D. T., Kreukels, B. P. C., Cohen-Kettenis, P. T., . . . Bakker, J. (2020). Postnatal effects of sex hormones on click-evoked otoacoustic emissions: A study of adolescents with gender dysphoria. Arch Sex Behav, 49(2), 455-465. https://doi.org/10.1007/s10508-020-01652-8

Bustos 2020

Bustos, S. S., Forte, A. J., Ciudad, P., & Manrique, O. J. (2020). The nipple split sharing vs. Conventional nipple graft technique in chest wall masculinization surgery: Can we improve patient satisfaction and aesthetic outcomes? Aesthetic Plast Surg, 44(5), 1478-1486. https://doi.org/10.1007/s00266-020-01803-1

Caanen 2017

Caanen, M. R., Schouten, N. E., Kuijper, E. A. M., van Rijswijk, J., van den Berg, M. H., van Dulmen-den Broeder, E., . . . Lambalk, C. B. (2017). Effects of long-term exogenous testosterone administration on ovarian morphology, determined by transvaginal (3d) ultrasound in female-to-male transsexuals. Hum Reprod, 32(7), 1457-1464. https://doi.org/10.1093/humrep/dex098

Campbell 2023

Campbell, T., Mann, S., Nguyen, D. H., & Rodgers, Y. v. d. M. (2023). Hormone therapy, suicidal risk, and transgender youth in the united states. AEA Papers and Proceedings, 113, 551–555. https://doi.org/10.1257/pandp.20231057

Cantu 2020

Cantu, A. L., Moyer, D. N., Connelly, K. J., & Holley, A. L. (2020). Changes in anxiety and depression from intake to first follow-up among transgender youth in a pediatric endocrinology clinic. Transgend Health, 5(3), 196-200. https://doi.org/10.1089/trgh.2019.0077

Carmichael 2021

Carmichael, P., Butler, G., Masic, U., Cole, T. J., De Stavola, B. L., Davidson, S., . . . Viner, R. M. (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. PLoS ONE, 16(2), e0243894. https://doi.org/10.1371/journal.pone.0243894

Caro 2024

Caro, C., Florek, A., Hahn, M., & Marx, M. (2024). Color doppler sonography assisted subcutaneous mastectomy with inferior pedicled nipple-areola complex in female-to-male transsexuals: A retrospective cohort analysis. Aesthetic Plast Surg, 48(6), 1126-1132. https://doi.org/10.1007/s00266-022-02945-0

Chen 2016

Chen, M., Fuqua, J., & Eugster, E. A. (2016). Characteristics of referrals for gender dysphoria over a 13-year period. J Adolesc Health, 58(3), 369-371. https://doi.org/10.1016/j.jadohealth.2015.11.010

Chen 2023

Chen, D., Berona, J., Chan, Y. M., Ehrensaft, D., Garofalo, R., Hidalgo, M. A., . . . Olson-Kennedy, J. (2023). Psychosocial functioning in transgender youth after 2 years of hormones. N Engl J Med, 388(3), 240-250. https://doi.org/10.1056/NEJMoa2206297

Chiniara 2018

Chiniara, L. N., Bonifacio, H. J., & Palmert, M. R. (2018). Characteristics of adolescents referred to a gender clinic: Are youth seen now different from those in initial reports? Horm Res Paediatr, 89(6), 434-441. https://doi.org/10.1159/000489608

Cohen-Kettenis 1997 (three citations)

- Cohen-Kettenis, P. T., & van Goozen, S. H. (1997). Sex reassignment of adolescent transsexuals: A follow-up study. J Am Acad Child Adolesc Psychiatry, 36(2), 263-271.
- Smith, Y. L., Cohen, L., & Cohen-Kettenis, P. T. (2002). Postoperative psychological functioning of adolescent transsexuals: a Rorschach study. *Archives of sexual behavior*, *31*(3), 255–261.
- Smith, Y. L., van Goozen, S. H., & Cohen-Kettenis, P. T. (2001). Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*(4), 472–481.

Cohen-Kettenis 2011 (two citations)

- Cohen-Kettenis, P. T., Schagen, S. E. E., Steensma, T. D., de Vries, A. L. C., & Delemarre-van de Waal, H. A. (2011). Puberty suppression in a gender-dysphoric adolescent: A 22-year follow-up. Archives of Sexual Behavior, 40(4), 843-847.
- Cohen-Kettenis, P. T., & van Goozen, S. H. (1998). Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. *European child & adolescent psychiatry*, *7*(4), 246–248.

Costa 2015

Costa, R., Dunsford, M., Skagerberg, E., Holt, V., Carmichael, P., & Colizzi, M. (2015). Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. J Sex Med, 12(11), 2206-2214. https://doi.org/10.1111/jsm.13034

Cuccolo 2019

Cuccolo, N. G., Kang, C. O., Boskey, E. R., Ibrahim, A. M. S., Blankensteijn, L. L., Taghinia, A., . . . Ganor, O. (2019). Mastectomy in transgender and cisgender patients: A comparative analysis of epidemiology and postoperative outcomes. Plast Reconstr Surg Glob Open, 7(6), e2316. https://doi.org/10.1097/gox.0000000000002316

de Nie 2022

de Nie, I., Mulder, C. L., Meißner, A., Schut, Y., Holleman, E. M., van der Sluis, W. B., . . . van Mello, N. M. (2022). Histological study on the influence of puberty suppression and hormonal treatment on developing germ cells in transgender women. Hum Reprod, 37(2), 297-308. https://doi.org/10.1093/humrep/deab240

de Vries 2011

de Vries, A. L., Steensma, T. D., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2011). Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. J Sex Med, 8(8), 2276-2283. https://doi.org/10.1111/j.1743-6109.2010.01943.x

de Vries 2014

de Vries, A. L., McGuire, J. K., Steensma, T. D., Wagenaar, E. C., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2014). Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics, 134(4), 696-704. https://doi.org/10.1542/peds.2013-2958

Delemarre-van de Waal 2006

Delemarre-van de Waal, H. A., & Cohen-Kettenis, P. T. (2006). Clinical management of gender identity disorder in adolescents: A protocol on psychological and paediatric endocrinology aspectsthis paper was presented at the 4th ferring pharmaceuticals international paediatric endocrinology symposium, paris (2006). Ferring pharmaceuticals has supported the publication of these proceedings. European Journal of Endocrinology, 155(Supplement_1), S131-S137. https://doi.org/10.1530/eje.1.02231

Donaldson 2018

Donaldson, A. A., Hall, A., Neukirch, J., Kasper, V., Simones, S., Gagnon, S., . . . Forcier, M. (2018). Multidisciplinary care considerations for gender nonconforming adolescents with eating disorders: A case series. Int J Eat Disord, 51(5), 475-479. https://doi.org/10.1002/eat.22868

Donato 2017

Donato, D. P., Walzer, N. K., Rivera, A., Wright, L., & Agarwal, C. A. (2017). Female-to-male chest reconstruction: A review of technique and outcomes. Ann Plast Surg, 79(3), 259-263. https://doi.org/10.1097/sap.0000000000001099

Ederer 2023

Ederer, I. A., Spennato, S., Nguyen, C. T., Wehle, A., Wachtel, C., Kiehlmann, M., . . . Rieger, U. M. (2023). A single-center 10-year experience of 180 transmasculine patients undergoing gender-affirming mastectomy while continuing masculinizing hormone replacement therapy. Aesthetic Plast Surg, 47(3), 946-954. https://doi.org/10.1007/s00266-022-03213-x

Elfering 2020

Elfering, L., van de Grift, T. C., Bouman, M. B., van Mello, N. M., Groenman, F. A., Huirne, J. A., . . . Mullender, M. G. (2020). Combining total laparoscopic hysterectomy and bilateral salpingo-oophorectomy with subcutaneous mastectomy in trans men: The effect on safety outcomes. International Journal of Transgender Health, 21(2), 138-146. https://doi.org/10.1080/26895269.2020.1751014

Ewan 2014

Ewan, L. A., Middleman, A. B., & Feldmann, J. (2014). Treatment of anorexia nervosa in the context of transsexuality: A case report. Int J Eat Disord, 47(1), 112-115. https://doi.org/10.1002/eat.22209

Filipov 2023

Filipov, H., Kavla, Y., Şahin, S., Gökler, M. E., & Turan, Ş. (2023). The effects of gender-affirming hormone therapy on body satisfaction, self-esteem, quality of life, and psychopathology in people with female-to-male gender dysphoria. Transgend Health, 8(2), 168-174. https://doi.org/10.1089/trgh.2021.0139

Fontanari 2020

Fontanari, A. M. V., Vilanova, F., Schneider, M. A., Chinazzo, I., Soll, B. M., Schwarz, K., . . . Brandelli Costa, A. (2020). Gender affirmation is associated with transgender and gender nonbinary youth mental health improvement. LGBT Health, 7(5), 237-247. https://doi.org/10.1089/lgbt.2019.0046

Foster 2021

Foster Skewis, L., Bretherton, I., Leemaqz, S. Y., Zajac, J. D., & Cheung, A. S. (2021). Short-term effects of gender-affirming hormone therapy on dysphoria and quality of life in transgender individuals: A prospective controlled study. Front Endocrinol (Lausanne), 12, 717766. https://doi.org/10.3389/fendo.2021.717766

Frederick 2017

Frederick, M. J., Berhanu, A. E., & Bartlett, R. (2017). Chest surgery in female to male transgender individuals. Ann Plast Surg, 78(3), 249-253. https://doi.org/10.1097/sap.0000000000000882

Friedman 2000

Friedman, G. (2000). The effects of estrogen on short-term memory in genetic men. J Am Med Dir Assoc, 1(1), 4-7.

Gale 2021

Gale, J., Magee, B., Forsyth-Greig, A., Visram, H., & Jackson, A. (2021). Oocyte cryopreservation in a transgender man on long-term testosterone therapy: A case report. F S Rep, 2(2), 249-251. https://doi.org/10.1016/j.xfre.2021.02.006

Ghelani 2020

Ghelani, R., Lim, C., Brain, C., Fewtrell, M., & Butler, G. (2020). Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria. Journal of Pediatric Endocrinology and Metabolism, 33(1), 107-112. https://doi.org/doi:10.1515/jpem-2019-0045

Giovanardi 2019

Giovanardi, G., Morales, P., Mirabella, M., Fortunato, A., Chianura, L., Speranza, A. M., . . . Lingiardi, V. (2019). Transition memories: Experiences of trans adult women with hormone therapy and their beliefs on the usage of hormone blockers to suppress puberty. J Endocrinol Invest, 42(10), 1231-1240. https://doi.org/10.1007/s40618-019-01045-2

Gold 2021

Gold, D., Galvez, M. B. Y., Laback, C., Hartleb, R., Tomasch, G., Schöpfer, S., . . . Tamussino, K. (2021). Combined mastectomy and laparoscopic hysterectomy with salpingo-oophorectomy in transgender men: A cohort study. Reprod Sci, 28(12), 3515-3518. https://doi.org/10.1007/s43032-021-00724-x

Gómez-Gil 2009

Gómez-Gil, E., Cañizares, S., Torres, A., de la Torre, F., Halperin, I., & Salamero, M. (2009). Androgen treatment effects on memory in female-to-male transsexuals. Psychoneuroendocrinology, 34(1), 110-117. https://doi.org/https://doi.org/10.1016/j.psyneuen.2008.08.017

Grannis 2021

Grannis, C., Leibowitz, S. F., Gahn, S., Nahata, L., Morningstar, M., Mattson, W. I., . . . Nelson, E. E. (2021). Testosterone treatment, internalizing symptoms, and body image dissatisfaction in transgender boys. Psychoneuroendocrinology, 132, 105358. https://doi.org/10.1016/j.psyneuen.2021.105358

Grannis 2023

Grannis, C., Mattson, W. I., Leibowitz, S. F., Nahata, L., Chen, D., Strang, J. F., . . . Nelson, E. E. (2023). Expanding upon the relationship between gender-affirming hormone therapy, neural connectivity, mental health, and body image dissatisfaction. Psychoneuroendocrinology, 156, 106319. https://doi.org/https://doi.org/10.1016/j.psyneuen.2023.106319

Green 2022

Green, A. E., DeChants, J. P., Price, M. N., & Davis, C. K. (2022). Association of gender-affirming hormone therapy with depression, thoughts of suicide, and attempted suicide among transgender and nonbinary youth. J Adolesc Health, 70(4), 643-649. https://doi.org/10.1016/j.jadohealth.2021.10.036

Grimstad 2021a

Grimstad, F. W., Knoll, M. M., & Jacobson, J. D. (2021). Oxandrolone use in trans-masculine youth appears to increase adult height: Preliminary evidence. LGBT Health, 8(4), 300-306. https://doi.org/10.1089/lgbt.2020.0355

Grimstad 2021b

Grimstad, F., Kremen, J., Shim, J., Charlton, B. M., & Boskey, E. R. (2021). Breakthrough bleeding in transgender and gender diverse adolescents and young adults on long-term testosterone. J Pediatr Adolesc Gynecol, 34(5), 706-716. https://doi.org/10.1016/j.jpag.2021.04.004

Gupta 2023

Gupta, P., Patterson, B. C., Chu, L., Gold, S., Amos, S., Yeung, H., . . . Tangpricha, V. (2023). Adherence to gender affirming hormone therapy in transgender adolescents and adults: A retrospective cohort study. J Clin Endocrinol Metab, 108(11), e1236-e1244. https://doi.org/10.1210/clinem/dgad306

Hannema 2017

Hannema, S. E., Schagen, S. E. E., Cohen-Kettenis, P. T., & Delemarre-van de Waal, H. A. (2017). Efficacy and safety of pubertal induction using 17β-estradiol in transgirls. J Clin Endocrinol Metab, 102(7), 2356-2363. https://doi.org/10.1210/jc.2017-00373

Haraldsen 2005

Haraldsen, I. R., Egeland, T., Haug, E., Finset, A., & Opjordsmoen, S. (2005). Cross-sex hormone treatment does not change sex-sensitive cognitive performance in gender identity disorder patients. Psychiatry Research, 137(3), 161-174. https://doi.org/https://doi.org/10.1016/j.psychres.2005.05.014

Hisle-Gorman 2021

Hisle-Gorman, E., Schvey, N. A., Adirim, T. A., Rayne, A. K., Susi, A., Roberts, T. A., . . . Klein, D. A. (2021). Mental healthcare utilization of transgender youth before and after affirming treatment. J Sex Med, 18(8), 1444-1454. https://doi.org/10.1016/j.jsxm.2021.05.014

Insogna 2020

Insogna, I. G., Ginsburg, E., & Srouji, S. (2020). Fertility preservation for adolescent transgender male patients: A case series. J Adolesc Health, 66(6), 750-753. https://doi.org/10.1016/j.jadohealth.2019.12.004

Jarin 2017

Jarin, J., Pine-Twaddell, E., Trotman, G., Stevens, J., Conard, L. A., Tefera, E., . . . Gomez-Lobo, V. (2017). Cross-sex hormones and metabolic parameters in adolescents with gender dysphoria. Pediatrics, 139(5). https://doi.org/10.1542/peds.2016-3173

Jensen 2019

Jensen, R. K., Jensen, J. K., Simons, L. K., Chen, D., Rosoklija, I., & Finlayson, C. A. (2019). Effect of concurrent gonadotropin-releasing hormone agonist treatment on dose and side effects of gender-affirming hormone therapy in adolescent transgender patients. Transgend Health, 4(1), 300-303. https://doi.org/10.1089/trgh.2018.0061

Jolly 2023

Jolly, D., Boskey, E. R., & Ganor, O. (2023). Racial disparities in the 30-day outcomes of gender-affirming chest surgeries. Annals of Surgery, 278(1), e196-e202. https://doi.org/10.1097/sla.0000000000005512

Joseph 2019

Joseph, T., Ting, J., & Butler, G. (2019). The effect of gnrh analogue treatment on bone mineral density in young adolescents with gender dysphoria: Findings from a large national cohort. Journal of Pediatric Endocrinology and Metabolism, 32(10), 1077-1081. https://doi.org/doi:10.1515/jpem-2019-0046

Junn 2021

Junn, A., Khetpal, S., Smetona, J., Dinis, J., Hirschman, A., Mozaffari, M. A., . . . Persing, J. A. (2021). Hockey stick incision: A modified technique for chest wall masculinization. Ann Transl Med, 9(7), 600. https://doi.org/10.21037/atm-20-7678

Kääriäinen 2017

Kääriäinen, M., Salonen, K., Helminen, M., & Karhunen-Enckell, U. (2017). Chest-wall contouring surgery in female-to-male transgender patients: A one-center retrospective analysis of applied surgical techniques and results. Scand J Surg, 106(1), 74-79. https://doi.org/10.1177/1457496916645964

Kaltiala 2020

Kaltiala, R., Heino, E., Työläjärvi, M., & Suomalainen, L. (2020). Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. Nord J Psychiatry, 74(3), 213-219. https://doi.org/10.1080/08039488.2019.1691260

Kamali 2021

Kamali, A., Sigurjónsson, H., Gran, I., Farnebo, F., Conneryd Lundgren, K., Granath, F., . . . Sommar, P. (2021). Improved surgical outcome with double incision and free nipple graft in gender confirmation mastectomy. Plast Reconstr Surg Glob Open, 9(7), e3628. https://doi.org/10.1097/gox.0000000000003628

Karakılıç Özturan 2023

Karakılıç Özturan, E., Öztürk, A. P., Baş, F., Erdoğdu, A. B., Kaptan, S., Kardelen Al, A. D., . . . Darendeliler, F. (2023). Endocrinological approach to adolescents with gender dysphoria: Experience of a pediatric endocrinology department in a tertiary center in turkey. J Clin Res Pediatr Endocrinol, 15(3), 276-284. https://doi.org/10.4274/jcrpe.galenos.2023.2023-1-13

Kaur 2023

Kaur, M. N., Gallo, L., Wang, Y., Rae, C., McEvenue, G., Semple, J., . . . Klassen, A. F. (2023). Health state utility values in patients undergoing chest masculinization surgery. J Plast Reconstr Aesthet Surg, 81, 26-33. https://doi.org/10.1016/j.bjps.2023.02.004

Kelly-Schuette 2022

Kelly-Schuette, K. A., Wempe, K., Fritz, G. D., Hop, A., & Wright, G. P. (2022). Masculinizing chest surgery for gender affirmation: A retrospective study of outcomes and patient reported satisfaction. Am J Surg, 223(3), 577-580. https://doi.org/10.1016/j.amjsurg.2021.12.032

Khatchadourian 2014

Khatchadourian, K., Amed, S., & Metzger, D. L. (2014). Clinical management of youth with gender dysphoria in vancouver. J Pediatr, 164(4), 906-911. https://doi.org/10.1016/j.jpeds.2013.10.068

Klaver 2018

Klaver, M., de Mutsert, R., Wiepjes, C. M., Twisk, J. W. R., den Heijer, M., Rotteveel, J., . . . Klink, D. T. (2018). Early hormonal treatment affects body composition and body shape in young transgender adolescents. J Sex Med, 15(2), 251-260. https://doi.org/10.1016/j.jsxm.2017.12.009

Klaver 2020

Klaver, M., de Mutsert, R., van der Loos, M. A. T. C., Wiepjes, C. M., Twisk, J. W. R., den Heijer, M., . . . Klink, D. T. (2020). Hormonal treatment and cardiovascular risk profile in transgender adolescents. Pediatrics, 145(3). https://doi.org/10.1542/peds.2019-0741

Klink 2015

Klink, D., Caris, M., Heijboer, A., van Trotsenburg, M., & Rotteveel, J. (2015). Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. J Clin Endocrinol Metab, 100(2), E270-275. https://doi.org/10.1210/jc.2014-2439

Klink 2013

Klink, D., Caris, M., van Trotsenburg, M., & Rotteveel, J. (2013). Bone mineral density in late adolescence of transsexuals treated with gnrh-analogues in their teens. *Endocr Rev*, *34*(Supp. 1), 3.

Kuper 2020

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. Pediatrics, 145(4). https://doi.org/10.1542/peds.2019-3006

Lane 2023

Lane, M., Kirsch, M. J., Sluiter, E. C., Svientek, S. R., Hamill, J. B., Morrison, S. D., . . . Wilkins, E. G. (2023). Gender affirming mastectomy improves quality of life in transmasculine patients: A single-center prospective study. Ann Surg, 277(3), e725-e729. https://doi.org/10.1097/sla.0000000000005158

Lang 2021

Lang, C. L., Day, D. L., Klit, A., Mejdahl, M. K., & Holmgaard, R. (2021). Low risk of persistent pain, sensory disturbances, and complications following mastectomy after gender-affirming surgery. Transgend Health, 6(4), 188-193. https://doi.org/10.1089/trgh.2020.0070

Laurenzano 2021

Laurenzano, S. E., Newfield, R. S., Lee, E., & Marinkovic, M. (2021). Subcutaneous testosterone is effective and safe as gender-affirming hormone therapy in transmasculine and gender-diverse adolescents and young adults: A single center's 8-year experience. Transgend Health, 6(6), 343-352. https://doi.org/10.1089/trgh.2020.0103

Lavender 2023

Lavender, R., Shaw, S., Maninger, J. K., Butler, G., Carruthers, P., Carmichael, P., . . . Masic, U. (2023). Impact of hormone treatment on psychosocial functioning in gender-diverse young people. LGBT Health, 10(5), 382-390. https://doi.org/10.1089/lgbt.2022.0201

Lee 2020

Lee, J. Y., Finlayson, C., Olson-Kennedy, J., Garofalo, R., Chan, Y. M., Glidden, D. V., . . . Rosenthal, S. M. (2020). Low bone mineral density in early pubertal transgender/gender diverse youth: Findings from the trans youth care study. J Endocr Soc, 4(9), bvaa065. https://doi.org/10.1210/jendso/bvaa065

Lee 2024

Lee, M. K., Yih, Y., Willis, D. R., Fogel, J. M., & Fortenberry, J. D. (2024). The impact of gender affirming medical care during adolescence on adult health outcomes among transgender and gender diverse individuals in the united states: The role of state-level policy stigma. LGBT Health, 11(2), 111-121. https://doi.org/10.1089/lgbt.2022.0334

Lierman 2017

Lierman, S., Tilleman, K., Braeckmans, K., Peynshaert, K., Weyers, S., T'Sjoen, G., . . . De Sutter, P. (2017). Fertility preservation for trans men: Frozen-thawed in vitro matured oocytes collected at the time of ovarian tissue processing exhibit normal meiotic spindles. J Assist Reprod Genet, 34(11), 1449-1456. https://doi.org/10.1007/s10815-017-0976-5

Littman 2021

Littman, L. (2021). Individuals treated for gender dysphoria with medical and/or surgical transition who subsequently detransitioned: A survey of 100 detransitioners. Arch Sex Behav, 50(8), 3353-3369. https://doi.org/10.1007/s10508-021-02163-w

Lopez 2018

Lopez, C. M., Solomon, D., Boulware, S. D., & Christison-Lagay, E. R. (2018). Trends in the use of puberty blockers among transgender children in the united states. J Pediatr Endocrinol Metab, 31(6), 665-670. https://doi.org/10.1515/jpem-2018-0048

López de Lara 2020

López de Lara, D., Pérez Rodríguez, O., Cuellar Flores, I., Pedreira Masa, J. L., Campos-Muñoz, L., Cuesta Hernández, M., . . . Ramos Amador, J. T. (2020). [psychosocial assessment in transgender adolescents]. An Pediatr (Engl Ed), 93(1), 41-48. https://doi.org/10.1016/j.anpedi.2020.01.019 (Evaluación psicosocial en adolescentes transgénero.)

Lynch 2015

Lynch, M. M., M., K. M., & and Meyer Iii, W. J. (2015). Retrospective study of the management of childhood and adolescent gender identity disorder using medroxyprogesterone acetate. International Journal of Transgenderism, 16(4), 201-208. https://doi.org/10.1080/15532739.2015.1080649

Madsen 2021

Madsen, M. C., van Dijk, D., Wiepjes, C. M., Conemans, E. B., Thijs, A., & den Heijer, M. (2021). Erythrocytosis in a large cohort of trans men using testosterone: A long-term follow-up study on prevalence, determinants, and exposure years. J Clin Endocrinol Metab, 106(6), 1710-1717. https://doi.org/10.1210/clinem/dgab089

Marinkovic 2017

Marinkovic, M., & and Newfield, R. S. (2017). Chest reconstructive surgeries in transmasculine youth: Experience from one pediatric center. International Journal of Transgenderism, 18(4), 376-381. https://doi.org/10.1080/15532739.2017.1349706

Martin 2021

Martin, C. E., Lewis, C., & Omurtag, K. (2021). Successful oocyte cryopreservation using letrozole as an adjunct to stimulation in a transgender adolescent after gnrh

agonist suppression. Fertil Steril, 116(2), 522-527. https://doi.org/10.1016/j.fertnstert.2021.02.025

McEvenue 2017

McEvenue, G., Xu, F. Z., Cai, R., & McLean, H. (2017). Female-to-male gender affirming top surgery: A single surgeon's 15-year retrospective review and treatment algorithm. Aesthet Surg J, 38(1), 49-57. https://doi.org/10.1093/asj/sjx116

McGregor 2024

McGregor, K., McKenna, J. L., Williams, C. R., Barrera, E. P., & Boskey, E. R. (2024). Association of pubertal blockade at tanner 2/3 with psychosocial benefits in transgender and gender diverse youth at hormone readiness assessment. J Adolesc Health, 74(4), 801-807. https://doi.org/10.1016/j.jadohealth.2023.10.028

Mehringer 2021

Mehringer, J. E., Harrison, J. B., Quain, K. M., Shea, J. A., Hawkins, L. A., & Dowshen, N. L. (2021). Experience of chest dysphoria and masculinizing chest surgery in transmasculine youth. Pediatrics, 147(3). https://doi.org/10.1542/peds.2020-013300

Mejia-Otero 2021

Mejia-Otero, J. D., White, P., & Lopez, X. (2021). Effectiveness of puberty suppression with gonadotropin-releasing hormone agonists in transgender youth. Transgend Health, 6(1), 31-35. https://doi.org/10.1089/trgh.2020.0007

Miles 1998

Miles, C., Green, R., Sanders, G., & Hines, M. (1998). Estrogen and memory in a transsexual population. Hormones and Behavior, 34(2), 199-208. https://doi.org/https://doi.org/10.1006/hbeh.1998.1478

Miles 2006

Miles, C., Green, R., & Hines, M. (2006). Estrogen treatment effects on cognition, memory and mood in male-to-female transsexuals. Hormones and Behavior, 50(5), 708-717. https://doi.org/https://doi.org/10.1016/j.yhbeh.2006.06.008

Millington 2019

Millington, K., Liu, E., & Chan, Y. M. (2019). The utility of potassium monitoring in gender-diverse adolescents taking spironolactone. J Endocr Soc, 3(5), 1031-1038. https://doi.org/10.1210/js.2019-00030

Millington 2021

Millington, K., & Chan, Y. M. (2021). Lipoprotein subtypes after testosterone therapy in transmasculine adolescents. J Clin Lipidol, 15(6), 840-844. https://doi.org/10.1016/j.jacl.2021.09.051

Millington 2022

Millington, K., Barrera, E., Daga, A., Mann, N., Olson-Kennedy, J., Garofalo, R., . . . Chan, Y. M. (2022). The effect of gender-affirming hormone treatment on serum creatinine in transgender and gender-diverse youth: Implications for estimating gfr. Pediatr Nephrol, 37(9), 2141-2150. https://doi.org/10.1007/s00467-022-05445-0

Morningstar 2023

Morningstar, M., Thomas, P., Anderson, A. M., Mattson, W. I., Nahata, L., Leibowitz, S. F., . . . Nelson, E. E. (2023). Exogenous testosterone administration is associated with differential neural response to unfamiliar peer's and own caregiver's voice in transgender adolescents. Dev Cogn Neurosci, 59, 101194. https://doi.org/10.1016/j.dcn.2022.101194

Moussaoui 2023

Moussaoui, D., O'Connell, M. A., Elder, C. V., Grover, S. R., & Pang, K. C. (2023). Characteristics of menstrual suppression and its association with mental health in transgender adolescents. Obstet Gynecol, 142(5), 1096-1104. https://doi.org/10.1097/aog.0000000000005317

Mullins 2021

Mullins, E. S., Geer, R., Metcalf, M., Piccola, J., Lane, A., Conard, L. A. E., . . . Mullins, T. L. K. (2021). Thrombosis risk in transgender adolescents receiving gender-affirming hormone therapy. Pediatrics, 147(4). https://doi.org/10.1542/peds.2020-023549

Nahata 2017

Nahata, L., Quinn, G. P., Caltabellotta, N. M., & Tishelman, A. C. (2017). Mental health concerns and insurance denials among transgender adolescents. LGBT Health, 4(3), 188-193. https://doi.org/10.1089/lgbt.2016.0151

Naides 2021

Naides, A. I., Schultz, J. J., Shulzhenko, N. O., & Keith, J. D. (2021). Chest masculinization technique and outcomes in 72 double-incision chest-contouring procedures with free nipple grafting. Plast Reconstr Surg Glob Open, 9(3), e3459. https://doi.org/10.1097/gox.0000000000003459

Namba 2009

Namba, Y., Watanabe, T., & Kimata, Y. (2009). Mastectomy in female-to-male transsexuals. Acta Med Okayama, 63(5), 243-247. https://doi.org/10.18926/amo/31841

Navabi 2021

Navabi, B., Tang, K., Khatchadourian, K., & Lawson, M. L. (2021). Pubertal suppression, bone mass, and body composition in youth with gender dysphoria. Pediatrics, 148(4). https://doi.org/10.1542/peds.2020-039339

Neyman 2019

Neyman, A., Fuqua, J. S., & Eugster, E. A. (2019). Bicalutamide as an androgen blocker with secondary effect of promoting feminization in male-to-female transgender adolescents. J Adolesc Health, 64(4), 544-546. https://doi.org/10.1016/j.jadohealth.2018.10.296

Nokoff 2020

Nokoff, N. J., Scarbro, S. L., Moreau, K. L., Zeitler, P., Nadeau, K. J., Juarez-Colunga, E., . . . Kelsey, M. M. (2020). Body composition and markers of cardiometabolic health in transgender youth compared with cisgender youth. J Clin Endocrinol Metab, 105(3), e704-714. https://doi.org/10.1210/clinem/dgz029

Nokoff 2021

Nokoff, N. J., Scarbro, S. L., Moreau, K. L., Zeitler, P., Nadeau, K. J., Reirden, D., . . . Kelsey, M. M. (2021). Body composition and markers of cardiometabolic health in transgender youth on gonadotropin-releasing hormone agonists. Transgend Health, 6(2), 111-119. https://doi.org/10.1089/trgh.2020.0029

Nota 2019

Nota, N. M., Wiepjes, C. M., de Blok, C. J. M., Gooren, L. J. G., Kreukels, B. P. C., & den Heijer, M. (2019). Occurrence of acute cardiovascular events in transgender individuals receiving hormone therapy. Circulation, 139(11), 1461-1462. https://doi.org/10.1161/circulationaha.118.038584

Olsavsky 2023

Olsavsky, A. L., Grannis, C., Bricker, J., Chelvakumar, G., Indyk, J. A., Leibowitz, S. F., . . . Nahata, L. (2023). Associations among gender-affirming hormonal interventions, social support, and transgender adolescents' mental health. J Adolesc Health, 72(6), 860-868. https://doi.org/10.1016/j.jadohealth.2023.01.031

Olson 2014

Olson, J., Schrager, S. M., Clark, L. F., Dunlap, S. L., & Belzer, M. (2014). Subcutaneous testosterone: An effective delivery mechanism for masculinizing young transgender men. LGBT Health, 1(3), 165-167. https://doi.org/10.1089/lgbt.2014.0018

Olson 2022

Olson, K. R., Durwood, L., Horton, R., Gallagher, N. M., & Devor, A. (2022). Gender identity 5 years after social transition. Pediatrics, 150(2). https://doi.org/10.1542/peds.2021-056082

Olson-Kennedy 2018a

Olson-Kennedy, J., Okonta, V., Clark, L. F., & Belzer, M. (2018). Physiologic response to gender-affirming hormones among transgender youth. J Adolesc Health, 62(4), 397-401. https://doi.org/10.1016/j.jadohealth.2017.08.005

Olson-Kennedy 2018b

Olson-Kennedy, J., Warus, J., Okonta, V., Belzer, M., & Clark, L. F. (2018). Chest reconstruction and chest dysphoria in transmasculine minors and young adults: Comparisons of nonsurgical and postsurgical cohorts. JAMA Pediatr, 172(5), 431-436. https://doi.org/10.1001/jamapediatrics.2017.5440

Olson-Kennedy 2021

Olson-Kennedy, J., Streeter, L. H., Garofalo, R., Chan, Y. M., & Rosenthal, S. M. (2021). Histrelin implants for suppression of puberty in youth with gender dysphoria: A comparison of 50 mcg/day (vantas) and 65 mcg/day (supprelinla). Transgend Health, 6(1), 36-42. https://doi.org/10.1089/trgh.2020.0055

Pang 2020

Pang, K. C., Notini, L., McDougall, R., Gillam, L., Savulescu, J., Wilkinson, D., . . . Lantos, J. D. (2020). Long-term puberty suppression for a nonbinary teenager. Pediatrics, 145(2). https://doi.org/10.1542/peds.2019-1606

Perez-Alvarez 2021

Perez-Alvarez, I. M., Zolper, E. G., Schwitzer, J., Fan, K. L., & Del Corral, G. A. (2021). Incidence of complications in chest wall masculinization for the obese female-to-male transgender population: A case series. World J Plast Surg, 10(2), 14-24. https://doi.org/10.29252/wjps.10.2.14

Perl 2021

Perl, L., Elkon-Tamir, E., Segev-Becker, A., Israeli, G., Brener, A., & Oren, A. (2021). Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogs followed by estradiol treatment in transgender female adolescents: A pilot study. Journal of Pediatric Endocrinology and Metabolism, 34(6), 741-745. https://doi.org/doi:10.1515/jpem-2021-0172

Perl 2020

Perl, L., Segev-Becker, A., Israeli, G., Elkon-Tamir, E., & Oren, A. (2020). Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogs followed by testosterone treatment in transgender male adolescents: A pilot study. LGBT Health, 7(6), 340-344. https://doi.org/10.1089/lgbt.2020.0026

Pine-Twaddell 2023

Pine-Twaddell, E., Newfield, R. S., & Marinkovic, M. (2023). Extended use of histrelin implant in pediatric patients. Transgend Health, 8(3), 264-272. https://doi.org/10.1089/trgh.2021.0130

Pyra 2020

Pyra, M., Casimiro, I., Rusie, L., Ross, N., Blum, C., Keglovitz Baker, K., . . . Schneider, J. (2020). An observational study of hypertension and thromboembolism among transgender patients using gender-affirming hormone therapy. Transgend Health, 5(1), 1-9. https://doi.org/10.1089/trgh.2019.0061

Ristori 2019

Ristori, J., Fisher, A. D., Castellini, G., Sensi, C., Cipriani, A., Ricca, V., . . . Maggi, M. (2019). Gender dysphoria and anorexia nervosa symptoms in two adolescents. Arch Sex Behav, 48(5), 1625-1631. https://doi.org/10.1007/s10508-019-1396-7

Robinson 2023

Robinson, I. S., Rifkin, W. J., Kloer, C., Parker, A., Blasdel, G., Shakir, N., . . . Bluebond-Langner, R. (2023). Perioperative hormone management in gender-affirming mastectomy: Is stopping testosterone before top surgery really necessary? Plast Reconstr Surg, 151(2), 421-427. https://doi.org/10.1097/prs.0000000000009858

Rothenberg 2021

Rothenberg, K. A., Gologorsky, R. C., Hojilla, J. C., Tang, A., Cohan, C. M., Beattie, G., . . . Yokoo, K. M. (2021). Gender-affirming mastectomy in transmasculine patients: Does obesity increase complications or revisions? Ann Plast Surg, 87(1), 24-30. https://doi.org/10.1097/sap.0000000000002712

Rothenberg 2018

Rothenberg, K. A., Tong, W. M. Y., & Yokoo, K. M. (2018). Early experiences with the buttonhole modification of the double-incision technique for gender-affirming mastectomies. Ann Plast Surg, 81(6), 642-645. https://doi.org/10.1097/sap.0000000000001617

Russell 2021

Russell, I., Pearson, B., & Masic, U. (2021). A longitudinal study of features associated with autism spectrum in clinic referred, gender diverse adolescents accessing puberty suppression treatment. Journal of Autism and Developmental Disorders, 51(6), 2068-2076. https://doi.org/10.1007/s10803-020-04698-8

Schagen 2016

Schagen, S. E., Cohen-Kettenis, P. T., Delemarre-van de Waal, H. A., & Hannema, S. E. (2016). Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents. J Sex Med, 13(7), 1125-1132. https://doi.org/10.1016/j.jsxm.2016.05.004

Schagen 2018

Schagen, S. E. E., Lustenhouwer, P., Cohen-Kettenis, P. T., Delemarre-van de Waal, H. A., & Hannema, S. E. (2018). Changes in adrenal androgens during puberty suppression and gender-affirming hormone treatment in adolescents with gender dysphoria. J Sex Med, 15(9), 1357-1363. https://doi.org/10.1016/j.jsxm.2018.07.017

Schagen 2020

Schagen, S. E. E., Wouters, F. M., Cohen-Kettenis, P. T., Gooren, L. J., & Hannema, S. E. (2020). Bone development in transgender adolescents treated with gnrh analogues and subsequent gender-affirming hormones. J Clin Endocrinol Metab, 105(12), e4252-4263. https://doi.org/10.1210/clinem/dgaa604

Schneider 2017

Schneider, M. A., Spritzer, P. M., Soll, B. M. B., Fontanari, A. M. V., Carneiro, M., Tovar-Moll, F., . . . Lobato, M. I. R. (2017). Brain maturation, cognition and voice pattern in a gender dysphoria case under pubertal suppression [Case Report]. Frontiers in Human Neuroscience, 11. https://doi.org/10.3389/fnhum.2017.00528

Schöning 2010

Schöning, S., Engelien, A., Bauer, C., Kugel, H., Kersting, A., Roestel, C., . . . Konrad, C. (2010). Original research—intersex and gender identity disorders: Neuroimaging differences in spatial cognition between men and male-to-female transsexuals before and during hormone therapy. The Journal of Sexual Medicine, 7(5), 1858-1867. https://doi.org/https://doi.org/10.1111/j.1743-6109.2009.01484.x

Schulmeister 2022

Schulmeister, C., Millington, K., Kaufman, M., Finlayson, C., Kennedy, J. O., Garofalo, R., . . . Rosenthal, S. M. (2022). Growth in transgender/gender-diverse youth in the first year of treatment with gonadotropin-releasing hormone agonists. J Adolesc Health, 70(1), 108-113. https://doi.org/10.1016/j.jadohealth.2021.06.022

Schwartz 2023

Schwartz, B. I., Bear, B., Short, V. L., & Kazak, A. E. (2023). Outcomes of menstrual management use in transgender and gender-diverse adolescents. Obstet Gynecol, 141(4), 748-755. https://doi.org/10.1097/aog.0000000000005123

Segev-Becker 2020

Segev-Becker, A., Israeli, G., Elkon-Tamir, E., Perl, L., Sekler, O., Amir, H., . . . Oren, A. (2020). Children and adolescents with gender dysphoria in Israel: Increasing referral and fertility preservation rates. Endocr Pract, 26(4), 423-428. https://doi.org/10.4158/ep-2019-0418

Sequeira 2019

Sequeira, G. M., Kidd, K., El Nokali, N. E., Rothenberger, S. D., Levine, M. D., Montano, G. T., . . . Rofey, D. (2019). Early effects of testosterone initiation on body mass index in transmasculine adolescents. J Adolesc Health, 65(6), 818-820. https://doi.org/10.1016/j.jadohealth.2019.06.009

Sır 2022

Sır, E., & Tuluy, Y. (2022). Evaluation of life improvement in trans men after mastectomy: A prospective study using the trans-q. Aesthetic Plast Surg, 46(5), 2556-2561. https://doi.org/10.1007/s00266-022-02907-6

Skorochod 2023

Skorochod, R., Rysin, R., & Wolf, Y. (2023). Age-related outcomes of chest masculinization surgery: A single-surgeon retrospective cohort study. Plast Reconstr Surg Glob Open, 11(2), e4799. https://doi.org/10.1097/gox.0000000000004799

Slabbekoorn 1999

Slabbekoorn, D., van Goozen, S. H. M., Megens, J., Gooren, L. J. G., & Cohen-Kettenis, P. T. (1999). Activating effects of cross-sex hormones on cognitive functioning: A study of short-term and long-term hormone effects in transsexuals.

Psychoneuroendocrinology, 24(4), 423-447. https://doi.org/https://doi.org/10.1016/S0306-4530(98)00091-2

Stanley 2018

Stanley, K., & Cooper, J. (2018). Hormone therapy and venous thromboembolism in a transgender adolescent. J Pediatr Hematol Oncol, 40(1), e38-e40. https://doi.org/10.1097/mph.0000000000000984

Staphorsius 2015

Staphorsius, A. S., Kreukels, B. P., Cohen-Kettenis, P. T., Veltman, D. J., Burke, S. M., Schagen, S. E., . . . Bakker, J. (2015). Puberty suppression and executive functioning: An fmri-study in adolescents with gender dysphoria. Psychoneuroendocrinology, 56, 190-199. https://doi.org/10.1016/j.psyneuen.2015.03.007

Stein 2021

Stein, M. J., Grigor, E., Hardy, J., & Jarmuske, M. (2021). Surgical and patient-reported outcomes following double incision and free nipple grafting for female to male gender affirmation: Does obesity make a difference? J Plast Reconstr Aesthet Surg, 74(8), 1743-1751. https://doi.org/10.1016/j.bjps.2020.12.004

Stoffers 2019

Stoffers, I. E., de Vries, M. C., & Hannema, S. E. (2019). Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. J Sex Med, 16(9), 1459-1468. https://doi.org/10.1016/j.jsxm.2019.06.014

Stojanovic 2017

Stojanovic, B., Bizic, M., Bencic, M., Kojovic, V., Majstorovic, M., Jeftovic, M., . . . Djordjevic, M. L. (2017). One-stage gender-confirmation surgery as a viable surgical procedure for female-to-male transsexuals. J Sex Med, 14(5), 741-746. https://doi.org/10.1016/j.jsxm.2017.03.256

Strang 2022

Strang, J. F., Chen, D., Nelson, E., Leibowitz, S. F., Nahata, L., Anthony, L. G., . . . Kenworthy, L. (2022). Transgender youth executive functioning: Relationships with anxiety symptoms, autism spectrum disorder, and gender-affirming medical treatment status. Child Psychiatry Hum Dev, 53(6), 1252-1265. https://doi.org/10.1007/s10578-021-01195-6

Tack 2016

Tack, L. J. W., Craen, M., Dhondt, K., Vanden Bossche, H., Laridaen, J., & Cools, M. (2016). Consecutive lynestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: A retrospective analysis. Biology of Sex Differences, 7(1), 14. https://doi.org/10.1186/s13293-016-0067-9

Tack 2018

Tack, L. J. W., Craen, M., Lapauw, B., Goemaere, S., Toye, K., Kaufman, J. M., . . . Cools, M. (2018). Proandrogenic and antiandrogenic progestins in transgender youth: Differential effects on body composition and bone metabolism. J Clin Endocrinol Metab, 103(6), 2147-2156. https://doi.org/10.1210/jc.2017-02316

Tack 2017

Tack, L. J. W., Heyse, R., Craen, M., Dhondt, K., Bossche, H. V., Laridaen, J., . . . Cools, M. (2017). Consecutive cyproterone acetate and estradiol treatment in late-pubertal transgender female adolescents. J Sex Med, 14(5), 747-757. https://doi.org/10.1016/j.jsxm.2017.03.251

Tan 2023

Tan, K. K. H., Byrne, J. L., Treharne, G. J., & Veale, J. F. (2023). Unmet need for gender-affirming care as a social determinant of mental health inequities for transgender youth in aotearoa/new zealand. J Public Health (Oxf), 45(2), e225-e233. https://doi.org/10.1093/pubmed/fdac131

Tang 2022

Tang, A., Hojilla, J. C., Jackson, J. E., Rothenberg, K. A., Gologorsky, R. C., Stram, D. A., . . . Yokoo, K. M. (2022). Gender-affirming mastectomy trends and surgical outcomes in adolescents. Ann Plast Surg, 88(4 Suppl), S325-s331. https://doi.org/10.1097/sap.0000000000003135

Top 2017

Top, H., & Balta, S. (2017). Transsexual mastectomy: Selection of appropriate technique according to breast characteristics. Balkan Med J, 34(2), 147-155. https://doi.org/10.4274/balkanmedj.2016.0093

Tordoff 2022

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. JAMA Network Open, 5(2), e220978-e220978. https://doi.org/10.1001/jamanetworkopen.2022.0978

Turan 2018

Turan, Ş., Aksoy Poyraz, C., Usta Sağlam, N. G., Demirel Ö, F., Haliloğlu, Ö., Kadıoğlu, P., . . . Duran, A. (2018). Alterations in body uneasiness, eating attitudes, and psychopathology before and after cross-sex hormonal treatment in patients with female-to-male gender dysphoria. Arch Sex Behav, 47(8), 2349-2361. https://doi.org/10.1007/s10508-018-1189-4

Turban 2018

Turban, J. L., Carswell, J., & Keuroghlian, A. S. (2018). Understanding pediatric patients who discontinue gender-affirming hormonal interventions. JAMA Pediatr, 172(10), 903-904. https://doi.org/10.1001/jamapediatrics.2018.1817

Turban 2020

Turban, J. L., King, D., Carswell, J. M., & Keuroghlian, A. S. (2020). Pubertal suppression for transgender youth and risk of suicidal ideation. Pediatrics, 145(2). https://doi.org/10.1542/peds.2019-1725

Turban 2022

Turban, J. L., King, D., Kobe, J., Reisner, S. L., & Keuroghlian, A. S. (2022). Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. PLoS ONE, 17(1), e0261039. https://doi.org/10.1371/journal.pone.0261039

Valentine 2021

Valentine, A., Nokoff, N., Bonny, A., Chelvakumar, G., Indyk, J., Leibowitz, S., . . . Nahata, L. (2021). Cardiometabolic parameters among transgender adolescent males on testosterone therapy and body mass index-matched cisgender females. Transgend Health, 6(6), 369-373. https://doi.org/10.1089/trgh.2020.0052

van de Grift 2017

van de Grift, T. C., Elfering, L., Bouman, M. B., Buncamper, M. E., & Mullender, M. G. (2017). Surgical indications and outcomes of mastectomy in transmen: A prospective study of technical and self-reported measures. Plast Reconstr Surg, 140(3), 415e-424e. https://doi.org/10.1097/prs.0000000000003607

van de Grift 2016

van de Grift, T. C., Kreukels, B. P., Elfering, L., Özer, M., Bouman, M. B., Buncamper, M. E., . . . Mullender, M. G. (2016). Body image in transmen: Multidimensional measurement and the effects of mastectomy. J Sex Med, 13(11), 1778-1786. https://doi.org/10.1016/j.jsxm.2016.09.003

van de Grift 2018

van de Grift, T. C., Elfering, L., Greijdanus, M., Smit, J. M., Bouman, M. B., Klassen, A. F., . . . Mullender, M. G. (2018). Subcutaneous mastectomy improves satisfaction with body and psychosocial function in trans men: Findings of a cross-sectional study using the body-q chest module. Plast Reconstr Surg, 142(5), 1125-1132. https://doi.org/10.1097/prs.0000000000004827

van de Grift 2020

van de Grift, T. C., van Gelder, Z. J., Mullender, M. G., Steensma, T. D., de Vries, A. L. C., & Bouman, M.-B. (2020). Timing of puberty suppression and surgical options for transgender youth. Pediatrics, 146(5). https://doi.org/10.1542/peds.2019-3653

van der Loos 2022

van der Loos, M., Hannema, S. E., Klink, D. T., den Heijer, M., & Wiepjes, C. M. (2022). Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: A cohort study in the Netherlands. Lancet Child Adolescent Health, 6(12), 869-875. https://doi.org/10.1016/s2352-4642(22)00254-1

van der Loos 2023

van der Loos, M., Vlot, M. C., Klink, D. T., Hannema, S. E., den Heijer, M., & Wiepjes, C. M. (2023). Bone mineral density in transgender adolescents treated with puberty suppression and subsequent gender-affirming hormones. JAMA Pediatr, 177(12), 1332-1341. https://doi.org/10.1001/jamapediatrics.2023.4588

van der Loos 2021

van der Loos, M. A., Hellinga, I., Vlot, M. C., Klink, D. T., den Heijer, M., & Wiepjes, C. M. (2021). Development of hip bone geometry during gender-affirming hormone therapy in transgender adolescents resembles that of the experienced gender when pubertal suspension is started in early puberty. J Bone Miner Res, 36(5), 931-941. https://doi.org/10.1002/jbmr.4262

van der Miesen 2020

van der Miesen, A. I. R., Steensma, T. D., de Vries, A. L. C., Bos, H., & Popma, A. (2020). Psychological functioning in transgender adolescents before and after gender-affirmative care compared with cisgender general population peers. J Adolesc Health, 66(6), 699-704. https://doi.org/10.1016/j.jadohealth.2019.12.018

van Dijk 2019

van Dijk, D., Dekker, M., Conemans, E. B., Wiepjes, C. M., de Goeij, E. G. M., Overbeek, K. A., . . . T'Sjoen, G. (2019). Explorative prospective evaluation of short-term subjective effects of hormonal treatment in trans people-results from the European network for the investigation of gender incongruence. J Sex Med, 16(8), 1297-1309. https://doi.org/10.1016/j.jsxm.2019.05.009

van Goozen 2002

van Goozen, S. H., Slabbekoorn, D., Gooren, L. J., Sanders, G., & Cohen-Kettenis, P. T. (2002). Organizing and activating effects of sex hormones in homosexual transsexuals. Behav Neurosci, 116(6), 982-988. https://doi.org/10.1037//0735-7044.116.6.982

van Goozen 1994

Van Goozen, S. H. M., Cohen-Kettenis, P. T., Gooren, L. J. G., Frijda, N. H., & Van de Poll, N. E. (1994). Activating effects of androgens on cognitive performance: Causal evidence in a group of female-to-male transsexuals. Neuropsychologia, 32(10), 1153-1157. https://doi.org/https://doi.org/10.1016/0028-3932(94)90099-X

van Kesteren 1996

van Kesteren, P., Lips, P., Deville, W., Popp-Snijders, C., Asscheman, H., Megens, J., . . . Gooren, L. (1996). The effect of one-year cross-sex hormonal treatment on bone metabolism and serum insulin-like growth factor-1 in transsexuals. J Clin Endocrinol Metab, 81(6), 2227-2232. https://doi.org/10.1210/jcem.81.6.8964856

Vlot 2017

Vlot, M. C., Klink, D. T., den Heijer, M., Blankenstein, M. A., Rotteveel, J., & Heijboer, A. C. (2017). Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (bmad) in transgender adolescents. Bone, 95, 11-19. https://doi.org/10.1016/j.bone.2016.11.008

Vrouenraets 2016

Vrouenraets, L. J., Fredriks, A. M., Hannema, S. E., Cohen-Kettenis, P. T., & de Vries, M. C. (2016). Perceptions of sex, gender, and puberty suppression: A qualitative analysis of transgender youth. Arch Sex Behav, 45(7), 1697-1703. https://doi.org/10.1007/s10508-016-0764-9

Waldner 2023

Waldner, R. C., Doulla, M., Atallah, J., Rathwell, S., & Grimbly, C. (2023). Leuprolide acetate and qtc interval in gender-diverse youth. Transgend Health, 8(1), 84-88. https://doi.org/10.1089/trgh.2021.0102

Wiepjes 2019

Wiepjes, C. M., de Jongh, R. T., de Blok, C. J., Vlot, M. C., Lips, P., Twisk, J. W., . . . den Heijer, M. (2019). Bone safety during the first ten years of gender-affirming hormonal treatment in transwomen and transmen. J Bone Miner Res, 34(3), 447-454. https://doi.org/10.1002/jbmr.3612

Wiepjes 2017

Wiepjes, C. M., Vlot, M. C., Klaver, M., Nota, N. M., de Blok, C. J., de Jongh, R. T., . . . den Heijer, M. (2017). Bone mineral density increases in trans persons after 1 year of hormonal treatment: A multicenter prospective observational study. J Bone Miner Res, 32(6), 1252-1260. https://doi.org/10.1002/jbmr.3102

Wolf 2021

Wolf, Y., & Kwartin, S. (2021). Classification of transgender man's breast for optimizing chest masculinizing gender-affirming surgery. Plast Reconstr Surg Glob Open, 9(1), e3363. https://doi.org/10.1097/gox.0000000000003363

Wolter 2018

Wolter, A., Scholz, T., Pluto, N., Diedrichson, J., Arens-Landwehr, A., & Liebau, J. (2018). Subcutaneous mastectomy in female-to-male transsexuals: Optimizing perioperative and operative management in 8 years clinical experience. J Plast Reconstr Aesthet Surg, 71(3), 344-352. https://doi.org/10.1016/j.bjps.2017.09.003

11 Bibliography

Ascha, M., Sasson, D. C., Sood, R., Cornelius, J. W., Schauer, J. M., Runge, A., Muldoon, A. L., Gangopadhyay, N., Simons, L., Chen, D., Corcoran, J. F., & Jordan, S. W. (2022). Top surgery and chest dysphoria among transmasculine and nonbinary adolescents and young adults. *JAMA Pediatrics*, *76*(11), 1115–1122. https://doi:10.1001/jamapediatrics.2022.3424

Baker, K. E., Wilson, L. M., Sharma, R., Dukhanin, V., McArthur, K., & Robinson, K. A. (2021). Hormone therapy, mental health, and quality of life among transgender people: A systematic review. *Journal of the Endocrine Society*, *5*(4), 1–16. https://doi.org/10.1210/jendso/bvab011

Balshem, H., Helfand, M., Schünemann, H. J., Oxman, A. D., Kunz, R., Brozek, J., Vist, G. E., Falck-Ytter, Y., Meerpohl, J., & Norris, S. (2011). GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology*, *64*(4), 401–406. https://doi.org/10.1016/j.jclinepi.2010.07.01

Becker-Hebly, I., Fahrenkrug, S., Campion, F., Richter-Appelt, H., Schulte-Markwort, M., & Barkmann, C. (2021). Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: A descriptive study from the Hamburg Gender Identity Service. *European Child & Adolescent Psychiatry*, *30*(11), 1755–1767. https://doi.org/10.1007/s00787-020-01640-2

Cantu, A. L., Moyer, D. N., Connelly, K. J., & Holley, A. L. (2020). Changes in anxiety and depression from intake to first follow-up among transgender youth in a pediatric endocrinology clinic. *Transgender Health*, *5*(3), 196–200. https://doi.org/10.1089/trgh.2019.0077

Carmichael, P., Butler, G., Masic, U., Cole, T. J., De Stavola, B. L., Davidson, S., Skageberg, E. M., Khadr, S., & Viner, R. M. (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. *PLoS ONE*, *16*(2), e0243894. https://doi.org/10.1371/journal.pone.0243894

Cass, H. (2024). *Independent Review of Gender Identity Services for Children and Young People: Final Report*.

https://webarchive.nationalarchives.gov.uk/ukgwa/20250310143933/https://cass.independent-review.uk/home/publications/final-report/

Chew, D., Anderson, J., Williams, K., May, T., & Pang, K. (2018). Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. *Pediatrics*, *141*(4), e20173742. https://doi.org/10.1542/peds.2017-3742

Costa, R., Dunsford, M., Skagerberg, E., Holt, V., Carmichael, P., & Colizzi, M. (2015). Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. *Journal of Sexual Medicine*, *12*(11), 2206–2214. https://doi.org/10.1111/jsm.13034

Dopp, A. R., Peipert, A., Buss, J., De Jesus-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). *Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research*. RAND. https://www.rand.org/pubs/research_reports/RRA3223-1.html

Expósito-Campos, P., Pérez-Fernández, J. I., & Salaberria, K. (2023). Empirically supported affirmative psychological interventions for transgender and non-binary youth and adults: A systematic review. *Clinical Psychology Review*, *100*, 102229. https://doi.org/10.1016/j.cpr.2022.102229

Filipov, H., Kavla, Y., Şahin, S., Gökler, M. E., & Turan, Ş. (2023). The Effects of Gender-Affirming Hormone Therapy on Body Satisfaction, Self-Esteem, Quality of Life, and Psychopathology in People with Female-to-Male Gender Dysphoria. *Transgender Health*, *8*(2), 168–174. https://doi.org/10.1089/trgh.2021.0139

Grannis, C., Leibowitz, S., Gahn, S., Nahata, L., Morningstar, M., Mattson, W. I., Chen, D., Strang, J. F., & Nelson, E. E. (2021). Testosterone Treatment, Internalizing Symptoms, and Body Image Dissatisfaction in Transgender Boys. *Psychoneuroendocrinology*, 105358. https://doi.org/10.1016/j.psyneuen.2021.105358

Grannis, C., Mattson, W. I., Leibowitz, S. F., Nahata, L., Chen, D., Strang, J. F., Thobe, H., Indyk, J. A., & Nelson, E. E. (2023). Expanding upon the relationship between gender-affirming hormone therapy, neural connectivity, mental health, and body

image dissatisfaction. *Psychoneuroendocrinology*, *156*, 106319. https://doi.org/10.1016/j.psyneuen.2023.106319

Grimstad, F. W., Knoll, M. M., & Jacobson, J. D. (2021). Oxandrolone Use in Trans-Masculine Youth Appears to Increase Adult Height: Preliminary Evidence. *LGBT Health*, *8*(4), 300–306. https://doi.org/10.1089/lgbt.2020.0355

Guyatt, G. H., Oxman, A. D., Kunz, R., Brozek, J., Alonso-Coello, P., Rind, D., Devereaux, P. J., Montori, V. M., Freyschuss, B., Vist, G., Jaeschke, R., Williams, J. W., Murad, M. H., Sinclair, D., Falck-Ytter, Y., Meerpohl, J., Whittington, C., Thorlund, K., Andrews, J., & Schünemann, H. J. (2011). GRADE guidelines: 6. Rating the quality of evidence—Imprecision. Journal of Clinical Epidemiology, 64(12), 1283–1293. https://doi.org/10.1016/j.jclinepi.2011.01.012

Guyatt, G. H., Oxman, A. D., Kunz, R., Woodcock, J., Brozek, J., Helfand, M., Alonso-Coello, P., Falck-Ytter, Y., Jaeschke, R., Vist, G., Akl, E. A., Post, P. N., Norris, S., Meerpohl, J., Shukla, V. K., Nasser, M., & Schünemann, H. J. (2011). GRADE guidelines: 8. Rating the quality of evidence—indirectness. Journal of Clinical Epidemiology, 64(12), 1303–1310. https://doi.org/10.1016/j.jclinepi.2011.04.014

Guyatt, G. H., Oxman, A. D., Kunz, R., Woodcock, J., Brozek, J., Helfand, M., Alonso-Coello, P., Glasziou, P., Jaeschke, R., Akl, E. A., Norris, S., Vist, G., Dahm, P., Shukla, V. K., Higgins, J., Falck-Ytter, Y., & Schünemann, H. J. (2011). GRADE guidelines: 7. Rating the quality of evidence—inconsistency. Journal of Clinical Epidemiology, 64(12), 1294–1302. https://doi.org/10.1016/j.jclinepi.2011.03.017

Guyatt, G. H., Oxman, A. D., Montori, V., Vist, G., Kunz, R., Brozek, J., Alonso-Coello, P., Djulbegovic, B., Atkins, D., Falck-Ytter, Y., Williams, J. W., Meerpohl, J., Norris, S. L., Akl, E. A., & Schünemann, H. J. (2011). GRADE guidelines: 5. Rating the quality of evidence—publication bias. Journal of Clinical Epidemiology, 64(12), 1277–1282. https://doi.org/10.1016/j.jclinepi.2011.01.011

Guyatt, G. H., Oxman, A. D., Sultan, S., Glasziou, P., Akl, E. A., Alonso-Coello, P., Atkins, D., Kunz, R., Brozek, J., Montori, V., Jaeschke, R., Rind, D., Dahm, P., Meerpohl, J., Vist, G., Berliner, E., Norris, S., Falck-Ytter, Y., Murad, M. H., & Schünemann, H. J. (2011). GRADE guidelines: 9. Rating up the quality of

evidence. *Journal of Clinical Epidemiology, 64*(12), 1311–1316. https://doi.org/10.1016/j.jclinepi.2011.06.004

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., & Schünemann, H. J. (2008). GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ, 336*(7650), 924–926. https://doi.org/10.1136/bmj.39489.470347.AD

Guyatt, G. H., Oxman, A. D., Vist, G., Kunz, R., Brozek, J., Alonso-Coello, P., Montori, V., Akl, E. A., Djulbegovic, B., & Falck-Ytter, Y. (2011). GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). Journal of Clinical Epidemiology, 64(4), 407–415. https://doi.org/10.1016/j.jclinepi.2010.07.017

Hall, R., Taylor, J., Hewitt, C. E., Heathcote, C., Jarvis, S. W., Langton, T., & Fraser, L. (2024). Impact of social transition in relation to gender for children and adolescents: A systematic review. *Archives of Disease in Childhood*. https://doi.org/10.1136/archdischild-2023-326112

Heathcote, C., Taylor, J., Hall, R., Jarvis, S. W., Langton, T., Hewitt, C. E., & Fraser, L. (2024). Psychosocial support interventions for children and adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*, *109*, s19–s32. https://doi.org/10.1136/archdischild-2023-326347

Higgins, J. P. T., Chandler, J., Cumpston, J., Li, T., Page, M. J., & Welch, V. A. (Eds.). (2019). *Cochrane Handbook for Systematic Reviews of Interventions* (2nd ed.). John Wiley & Sons Ltd. https://training.cochrane.org/handbook/current

Hisle-Gorman, E., Schvey, N. A., Adirim, T. A., Rayne, A. K., Susi, A., Roberts, T. A., & Klein, D. A. (2021). Mental healthcare utilization of transgender youth before and after affirming treatment. *The Journal of Sexual Medicine*, *18*(8), 1444-1454. https://doi.org/10.1016/j.jsxm.2021.05.014

Jensen, R. K., Jensen, J. K., Simons, L. K., Chen, D., Rosoklija, I., & Finlayson, C. A. (2019). Effect of Concurrent Gonadotropin-Releasing Hormone Agonist Treatment on Dose and Side Effects of Gender-Affirming Hormone Therapy in Adolescent Transgender Patients. *Transgender Health*, *4*(1), 300–303. https://doi.org/10.1089/trgh.2018.0061

Joseph, T., Ting, J., & Butler, G. (2019). The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: Findings from a large national cohort. *Journal of Pediatric Endocrinology and Metabolism*, *32*(10), 1077–1081. https://doi.org/10.1515/jpem-2019-0046

Karalexi, M. A., Georgakis, M. K., Dimitriou, N. G., Vichos, T., Katsimpris, A., Petridou, E. Th., & Papadopoulos, F. C. (2020). Gender-affirming hormone treatment and cognitive function in transgender young adults: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *119*, 104721. https://doi.org/10.1016/j.psyneuen.2020.104721

Klink, D., Caris, M., Heijboer, A., van Trotsenburg, M., & Rotteveel, J. (2015). Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria. *The Journal of Clinical Endocrinology & Metabolism*, *100*(2), E270–E275. https://doi.org/10.1210/jc.2014-2439

Lee, W. Y., Hobbs, J. N., Hobaica, S., DeChants, J. P., Price, M. N., & Nath, R. (2024). State-level anti-transgender laws increase past-year suicide attempts among transgender and non-binary young people in the USA. *Nature Human Behaviour*. https://doi.org/10.1038/s41562-024-01979-5

Ludvigsson, J. F., Adolfsson, J., Höistad, M., Rydelius, P.-A., Kriström, B., & Landén, M. (2023). A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatrica*, *112*(11), 2279–2292. https://doi.org/10.1111/apa.16791

Malpas, J., Pellicane, M. J., & Glaeser, E. (2022). Family-Based Interventions with Transgender and Gender Expansive Youth: Systematic Review and Best Practice Recommendations. *Transgender Health*, *7*(1), 7–29. https://doi.org/10.1089/trgh.2020.0165

Marinkovic, M., & Newfield, R. S. (2017). Chest reconstructive surgeries in transmasculine youth: Experience from one pediatric center. *International Journal of Transgenderism*, *18*(4), 376–381. https://doi.org/10.1080/15532739.2017.1349706

McGregor, K., McKenna, J. L., Williams, C. R., Barrera, E. P., & Boskey, E. R. (2024). Association of pubertal blockade at Tanner 2/3 with psychosocial benefits in transgender and gender diverse youth at hormone readiness assessment. *Journal of Adolescent Health*, S1054139X23005608. https://doi.org/10.1016/j.jadohealth.2023.10.028

McKenzie, J. E., Brennan, S. E., Ryan, R., Thomson, Hilary J., Johnston, R. V., & Thomas, J. (2024). Defining the criteria for including studies and how they will be grouped for the synthesis. In Higgins J. P. T., Thomas J., Chandler J., Cumpston M., Li T., Page M. J., Welch V. A. (Eds.). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.5. Available from cochrane.org/handbook.

Miroshnychenko, A., Ibrahim, S., Roldan, Y., Kulatunga-Moruzi, C., Montante, S., Couban, R., Guyatt, G., & Brignardello-Petersen, R. (2025). Gender affirming hormone therapy for individuals with gender dysphoria aged <26 years: A systematic review and meta-analysis. *Archives of Disease in Childhood*. https://doi.org/10.1136/archdischild-2024-327921

Miroshnychenko, A., Roldan, Y., Ibrahim, S., Kulatunga-Moruzi, C., Montante, S., Couban, R., Guyatt, G., & Brignardello-Petersen, R. (2025). Puberty blockers for gender dysphoria in youth: A systematic review and meta-analysis. *Archives of Disease in Childhood*. https://doi.org/10.1136/archdischild-2024-327909

Miroshnychenko, A., Roldan, Y. M., Ibrahim, S., Kulatunga-Moruzi, C., Dahlin, K., Montante, S., Couban, R., Guyatt, G., & Brignardello-Petersen, R. (2024). Mastectomy for individuals with gender dysphoria below 26 years of age: A systematic review and meta-analysis. *Plastic and Reconstructive Surgery*. https://doi.org/10.1097/PRS.0000000000011734

National Institute for Health and Care Excellence. (2020a). *Evidence review: Gender-affirming hormones for children and adolescents with gender dysphoria*. NICE. https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_Gender-affirming-hormones_For-upload_Final.pdf

National Institute for Health and Care Excellence. (2020b). *Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with*

gender dysphoria. NICE. https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_GnRH-analogues_For-upload_Final.pdf

Navabi, B., Tang, K., Khatchadourian, K., & Lawson, M. L. (2021). Pubertal suppression, bone mass, and body composition in youth with gender dysphoria. *Pediatrics*, e2020039339. https://doi.org/10.1542/peds.2020-039339

Olson-Kennedy, J., Warus, J., Okonta, V., Belzer, M., & Clark, L. F. (2018). Chest reconstruction and chest dysphoria in transmasculine minors and young adults: Comparisons of nonsurgical and postsurgical cohorts. *JAMA Pediatrics*, *172*(5), 431. https://doi.org/10.1001/jamapediatrics.2017.5440

Ramos, G. G. F., Mengai, A. C. S., Daltro, C. A. T., Cutrim, P. T., Zlotnik, E., & Beck, A. P. A. (2021). Systematic Review: Puberty suppression with GnRH analogues in adolescents with gender incongruity. *Journal of Endocrinological Investigation*, *44*(6), 1151–1158. https://doi.org/10.1007/s40618-020-01449-5

Reeves B. C., Deeks J. J., Higgins J. P. T., Shea B., Tugwell P., Wells G. A. (2024). Including non-randomized studies on intervention effects. In Higgins J. P. T., Thomas J., Chandler J., Cumpston M., Li T., Page M. J., Welch V. A. (Eds.). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.5. Available from cochrane.org/handbook.

Rew, L., Young, C. C., Monge, M., & Bogucka, R. (2021). Review: Puberty blockers for transgender and gender diverse youth—a critical review of the literature. *Child and Adolescent Mental Health*, *26*(1), 3–14. https://doi.org/10.1111/camh.12437

Santesso, N., Glenton, C., Dahm, P., Garner, P., Akl, E. A., Alper, B., Brignardello-Petersen, R., Carrasco-Labra, A., De Beer, H., & Hultcrantz, M. (2020). GRADE guidelines 26: Informative statements to communicate the findings of systematic reviews of interventions. *Journal of Clinical Epidemiology, 119*, 126–135. https://doi.org/10.1016/j.jclinepi.2019.10.014

Schagen, S. E. E., Cohen-Kettenis, P. T., Delemarre-van de Waal, H. A., & Hannema, S. E. (2016). Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents. *Journal of Sexual Medicine*, *13*(7), 1125–1132. https://doi.org/10.1016/j.jsxm.2016.05.004

Schagen, S. E. E., Wouters, F. M., Cohen-Kettenis, P. T., Gooren, L. J., & Hannema, S. E. (2020). Bone development in transgender adolescents treated with GnRH analogues and subsequent gender-affirming hormones. *Journal of Clinical Endocrinology & Metabolism*, *105*(12), dgaa604. https://doi.org/10.1210/clinem/dgaa604

Tang, A., Hojilla, J. C., Jackson, J. E., Rothenberg, K. A., Gologorsky, R. C., Stram, D. A., Mooney, C. M., Hernandez, S. L., & Yokoo, K. M. (2022). Gender-affirming mastectomy trends and surgical outcomes in adolescents. *Annals of Plastic Surgery*, *88*, 7. https://doi.org/10.1097/SAP.0000000000003135

Taylor, J., Hall, R., Heathcote, C., Hewitt, C. E., Langton, T., & Fraser, L. (2024). Clinical guidelines for children and adolescents experiencing gender dysphoria or incongruence: A systematic review of guideline quality (part 1). *Archives of Disease in Childhood*, *109*(Suppl 2), s65-s72. https://doi.org/10.1136/archdischild-2023-326499

Taylor, J., Mitchell, A., Hall, R., Heathcote, C., Langton, T., Fraser, L., & Hewitt, C. E. (2024). Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*. https://doi.org/10.1136/archdischild-2023-326669

Taylor, J., Mitchell, A., Hall, R., Langton, T., Fraser, L., & Hewitt, C. E. (2024). Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*. https://doi.org/10.1136/archdischild-2023-326670

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Sämfjord, A., & Gillberg, C. (2023). A PRISMA systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS Global Public Health*, *3*(8), e0001478. https://doi.org/10.1371/journal.pgph.0001478

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. *JAMA Network Open*, *5*(2), e220978. https://doi.org/10.1001/jamanetworkopen.2022.0978

Turban, J. L., King, D., Kobe, J., Reisner, S. L., & Keuroghlian, A. S. (2022). Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. *PLOS ONE*, *17*(1), e0261039. https://doi.org/10.1371/journal.pone.0261039

Turban, J. L., King, D., Li, J. J., & Keuroghlian, A. S. (2021). Timing of Social Transition for Transgender and Gender Diverse Youth, K-12 Harassment, and Adult Mental Health Outcomes. *Journal of Adolescent Health*, S1054139X21002834. https://doi.org/10.1016/j.jadohealth.2021.06.001

University of Utah College of Pharmacy, Drug Regimen Review Center. (2025). *Gender-Affirming Medical Treatments for Pediatric Patients with Gender Dysphoria*. Salt Lake City, UT: University of Utah. https://web.archive.org/web/20250601064306/https://le.utah.gov/AgencyRP/reportingDetail.jsp?rid=636

Vlot, M. C., Klink, D. T., den Heijer, M., Blankenstein, M. A., Rotteveel, J., & Heijboer, A. C. (2017). Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone*, *95*, 11–19. https://doi.org/10.1016/j.bone.2016.11.008

Whiting, P., Savović, J., Higgins, J. P. T., Caldwell, D. M., Reeves, B. C., Shea, B., Davies, P., Kleijnen, J., & Churchill, R. (2016). ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *Journal of Clinical Epidemiology*, *69*, 225–234. https://doi.org/10.1016/j.jclinepi.2015.06.005

Zepf, F. D., König, L., Kaiser, A., Ligges, C., Ligges, M., Roessner, V., Banaschewski, T., & Holtmann, M. (2024). Beyond NICE: Aktualisierte systematische Übersicht zur Evidenzlage der Pubertätsblockade und Hormongabe bei Minderjährigen mit Geschlechtsdysphorie. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie*, 1422-4917/a000972. https://doi.org/10.1024/1422-4917/a000972