

# Overview of Systematic Reviews

Methodology, Evidence Synthesis, Tables

**Appendix 4:**

***Treatment for Pediatric Gender Dysphoria:  
Review of Evidence and Best Practices***

Department of Health and Human Services

May 1, 2025



# 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*.<sup>1</sup>

**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 also conducted in other databases including ACCESSSS (a service providing current evidence for clinical decisions) and Epistemonikos (a database of SRs), and 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. The study population is youth with GD whose age is below 26 years old.<sup>2</sup>

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<sup>1</sup> Higgins et al. (2019).

<sup>2</sup> Empirically, SRs in this area are usually provided for patients under 18 or those under 26. This decision of age 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.

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 ( $\geq 26$  years old) 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.<sup>3</sup>
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<sup>4</sup> 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 as low risk of bias if the SRs have properly addressed these concerns in the evidence interpretation.

**Evidence synthesis and certainty of evidence:** The evidence synthesis summarizes the outcome data across SRs that were published in English and classified as low risk of bias.<sup>5</sup> The evidence synthesis was organized by types of treatment, and the

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<sup>3</sup> The SRs including both  $>26$  years old and  $<26$  years old skew toward the  $>26$  population, and so are less directly applicable to this overview than SRs on youth with GD.

<sup>4</sup> Whiting et al. (2016).

<sup>5</sup> One non-English systematic review was considered eligible and included and classified as low risk of bias. This overview did not summarize the results by outcomes from this review. Nevertheless, its conclusions were similar.

outcomes of interest included GD, mental health and well-being, treatment goal (for example, puberty suppression for puberty blockers), need 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 (or the confidence on the effect estimates, the quality of evidence).

The certainty of evidence was summarized following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.<sup>6</sup> 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).<sup>7</sup> Evidence can be upgraded if there is a large effect size, a clear dose-response relationship, or if confounding factors like would reduce the observed effect but did not do so.<sup>8</sup> Evidence could be classified into four levels of certainty: high, moderate, low, or very low.<sup>9</sup> 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. In the instances where a formal GRADE appraisal had not been performed by the systematic review, but expressions such as “we are very uncertain” and “no conclusions could be drawn” were used in SRs’ conclusions, they were considered equivalent to a “very low quality” GRADE assessment.<sup>10</sup>

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<sup>6</sup> 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).

<sup>7</sup> 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).

<sup>8</sup> Guyatt, Oxman, Sultan, et al. (2011).

<sup>9</sup> 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).

<sup>10</sup> Balshem et al. (2011); Santesso et al. (2020).

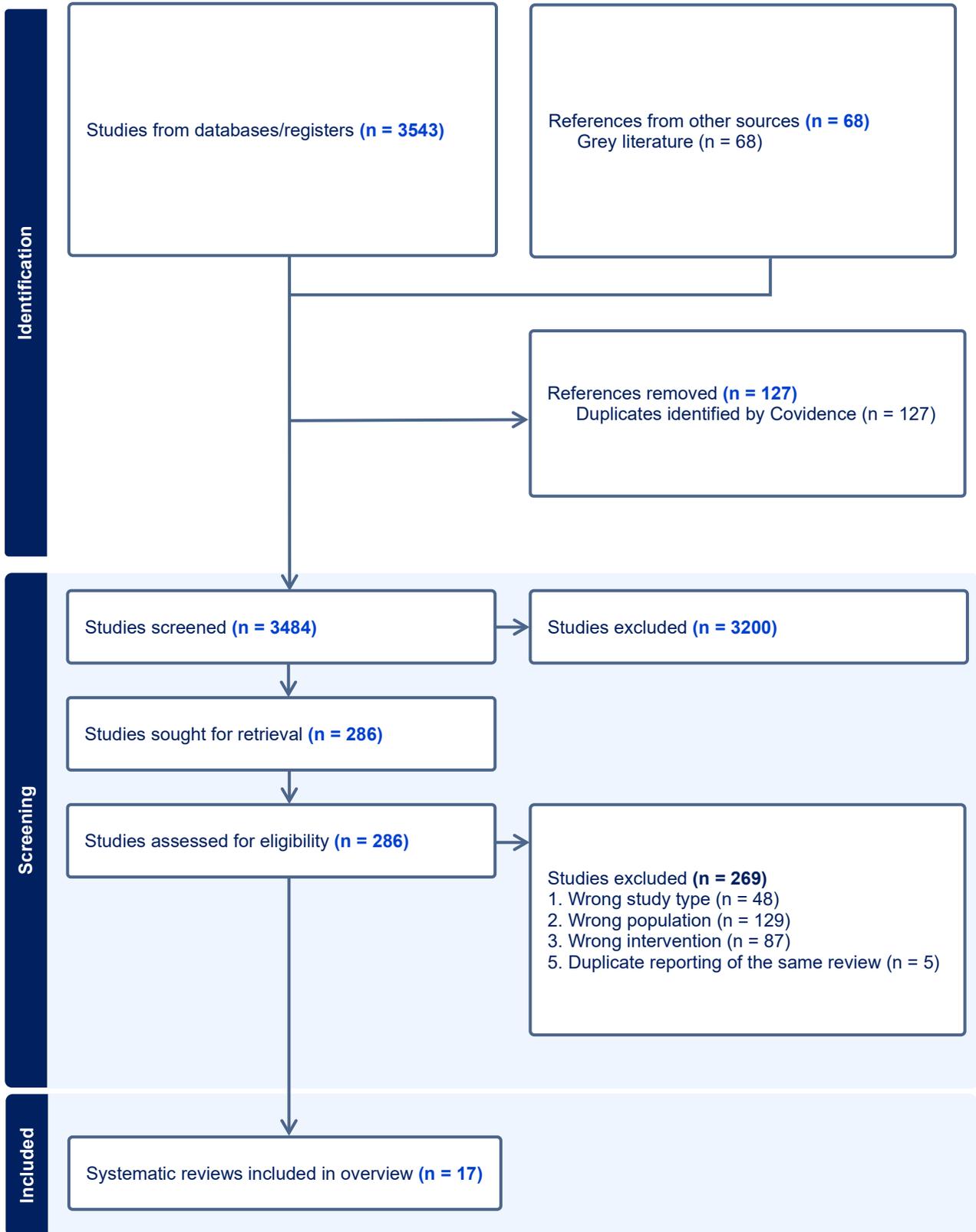
2. If SRs disagreed on GRADE assessment for the same outcome, this overview resolved the disagreement with *de novo* assessment following the GRADE methodology and reported the rationale for the assessment.

**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.  
(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.  
(transgend\* or transex\* or transsex\* or transfem\* or transwom\* or transma\* or transmen\* or transperson\* or transpeopl\*).tw.
- 15 (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  
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/  
(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.  
(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.
- 24 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.
- 25 pediatrics/  
(pediatric\$ or paediatric\$ or peadiatric\$).ti,ab,kf,jn.  
Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Psychology, Adolescent/ or Adolescent Psychiatry/ or Adolescent Health Services/ or Adolescent Medicine/ or Adolescent Development/
- 26 Puberty/  
(adolescens\$ or pubescens\$ or prepubescens\$ or postpubescens\$ or pubert\$ or prepubert\$ or postpubert\$ or teen or teens or teenag\$ or tween\$ or preteen\$ or preadolescens\$ or juvenil\$ or youth\$ or underage\$ or under-age\$).ti,ab,kf,jn.
- 27 Schools/ or Schools, Nursery/
- 28 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 Flow diagram



## 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 5 were excluded due to duplicate reporting (See Figure 7.1). After screening, 17 SRs met the inclusion criteria, examining the effects of psychotherapy (n = 5),<sup>11</sup> social transition (n = 2),<sup>12</sup> PBs (n = 9),<sup>13</sup> CSH (n = 8),<sup>14</sup> and surgeries (n = 3)<sup>15</sup> among children or adolescents with GD.

### 2.1 Risk of bias assessment in included SRs

Of the 17 included SRs, ten were rated as having a low risk of bias in the systematic review (see Table 2.1).<sup>16</sup>

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<sup>17</sup>), CSH (Miroshnychenko 2025b<sup>18</sup>), and mastectomy (Miroshnychenko 2024).
2. The SRs conducted by scholars from University of York to inform the Cass Review, comprising the reviews of PBs (Taylor 2024a<sup>19</sup>), CSH (Taylor 2024b<sup>20</sup>), psychotherapy (Heathcote 2024), and social transition (Hall 2024).

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<sup>11</sup> Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).

<sup>12</sup> Dopp et al. (2024); Hall et al. (2024).

<sup>13</sup> 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).

<sup>14</sup> 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).

<sup>15</sup> Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).

<sup>16</sup> 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).

<sup>17</sup> Miroshnychenko, Roldan, et al. (2025).

<sup>18</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>19</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024).

<sup>20</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

3. The systematic review by researchers from Rand Corporation on all treatment strategies (Dopp 2024<sup>21</sup>).
4. The systematic review by Swedish Agency for Health Technology Assessment and Assessment of Social Services on hormone therapies (Ludvigsson 2023<sup>22</sup>).
5. The systematic review by Zepf et al., which was an update and followed the same methodology of the two SRs and published in German.

SRs within the same group generally followed the same methodological approach. 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.<sup>23</sup> Other SRs rated as 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.<sup>24</sup> 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)<sup>25</sup> review had limitations in the domain of study eligibility criteria as it included case reports and qualitative studies for 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<sup>26</sup> were rated as having a high risk of bias overall, often due to limited or poorly defined research questions and eligibility criteria, lack of risk of bias

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<sup>21</sup> Dopp et al. (2024).

<sup>22</sup> Ludvigsson et al. (2023).

<sup>23</sup> Hall et al. (2024); Heathcote et al. (2024); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>24</sup> 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.

<sup>25</sup> Dopp et al. (2024).

<sup>26</sup> 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).

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 as having high risk of bias.

**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
<b>Chew 2018<sup>27</sup></b>	Y	Y				High risk of bias	Low risk of bias	High risk of bias	High risk of bias	High risk of bias
<b>Dopp 2024<sup>28</sup></b>	Y	Y	Y	Y	Y	High risk of bias	High risk of bias	Low risk of bias	Low risk of bias	<b><u>Low risk of bias</u></b>
<b>Expósito-Campos 2023<sup>29</sup></b>				Y		High risk of bias	High risk of bias	Low risk of bias	High risk of bias	High risk of bias
<b>Hall 2024<sup>30</sup></b>					Y	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	<b><u>Low risk of bias</u></b>
<b>Heathcote 2024<sup>31</sup></b>				Y		Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	<b><u>Low risk of bias</u></b>
<b>Karalexi 2020<sup>32</sup></b>		Y				High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
<b>Ludvigsson 2023<sup>33</sup></b>	Y	Y				Low risk of bias	High risk of bias	Low risk of bias	High risk of bias	<b><u>Low risk of bias</u></b>

<sup>27</sup> Chew et al. (2018).

<sup>28</sup> Dopp et al. (2024).

<sup>29</sup> Expósito-Campos et al. (2023).

<sup>30</sup> Hall et al. (2024).

<sup>31</sup> Heathcote et al. (2024).

<sup>32</sup> Karalexi et al. (2020).

<sup>33</sup> 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 <sup>34</sup>				Y		High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Miroshnychenko 2025a <sup>35</sup>	Y					Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	<b><u>Low risk of bias</u></b>
Miroshnychenko 2025b <sup>36</sup>		Y				Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	<b><u>Low risk of bias</u></b>
Miroshnychenko 2024 <sup>37</sup>			Y			Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	<b><u>Low risk of bias</u></b>
Ramos 2021 <sup>38</sup>	Y					High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Rew 2021 <sup>39</sup>	Y					High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Taylor 2024a <sup>40</sup>	Y					Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	<b><u>Low risk of bias</u></b>

<sup>34</sup> Malpas et al. (2022).

<sup>35</sup> Miroshnychenko, Roldan, et al. (2025).

<sup>36</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>37</sup> Miroshnychenko et al. (2024).

<sup>38</sup> Ramos et al. (2021).

<sup>39</sup> Rew et al. (2021).

<sup>40</sup> 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 <sup>41</sup>		Y				Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	<b><u>Low risk of bias</u></b>
Thompson 2023 <sup>42</sup>	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 <sup>43</sup>	Y	Y				Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	<b><u>Low risk of bias</u></b>

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<sup>41</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>42</sup> Thompson et al. (2023).

<sup>43</sup> 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 Transgender Health*, 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.<sup>44</sup> This was because these two SRs were commissioned by NHS England to inform Dr Hilary Cass' 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 SR by Baker and colleagues,<sup>45</sup> which was funded by the World Professional Association for Transgender Health (WPATH), because it predominantly included studies on mature adults and was therefore too indirect to inform the healthcare of children or adolescents with GD. However, since the Baker et al. review supported 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 excluded studies with follow up less than 3 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.

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<sup>44</sup> National Institute for Health and Care Excellence (2020b, 2020a).

<sup>45</sup> Baker et al. (2021).

### **Data collection and study appraisal: High risk of bias.**

The authors reported 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 described the most important characteristics of the included studies. The results collected, however, are not standardized across studies. For some studies, authors reported magnitudes of effect and confidence intervals, whereas for others they reported only that “no changes were observed.”<sup>46</sup> Although the authors aimed to use the correct tools, when assessing risk of bias they did 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 while it should have been assessed as a case series for the review purposes.

### **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 did 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 did not comment on applicability or address all concerns identified with the evidence.

## **3 Synopses of SRs assessed at low risk of bias**

**Dopp et al. 2024:**<sup>47</sup> This RAND SR examined evidence on interventions for GD and related health problems in youth with GD. The SR applied a strategy of combining

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<sup>46</sup> Baker et al. (2021).

<sup>47</sup> Dopp et al. (2024).

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,<sup>48</sup> Miroshnychenko 2025b,<sup>49</sup> Taylor 2024a,<sup>50</sup> Taylor 2024b<sup>51</sup>), 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 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:**<sup>52</sup> 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) patients under 18 with GD/incongruence. The authors included 11

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<sup>48</sup> Miroshnychenko, Roldan, et al. (2025).

<sup>49</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>50</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024).

<sup>51</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>52</sup> Hall et al. (2024).

studies, most from the US 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:**<sup>53</sup> 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. Ten studies with diverse designs (cohort, pre–post, mixed methods) were included. The literature search was conducted in April 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.

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<sup>53</sup> Heathcote et al. (2024).

**Ludvigsson et al. 2023:**<sup>54</sup> 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:**<sup>55</sup> 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 (3 comparative observational, 2 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 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.

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<sup>54</sup> Ludvigsson et al. (2023).

<sup>55</sup> Miroshnychenko et al. (2024).

**Miroshnychenko et al. 2025a:**<sup>56</sup> This SR evaluated the effects of PBs in individuals under 26 years with GD. The authors searched ten 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 3 comparative observational studies and 7 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:**<sup>57</sup> This SR and meta-analysis assessed the effects of cross-sex hormone therapy in individuals with GD aged under 26 years. The authors searched ten databases through September 2023 and included 24 studies (9 comparative observational, 13 before–after, and 2 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 (Miroshnychenko 2024, Miroshnychenko 2025a<sup>58</sup>). 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 7 to 109 months of follow-up, which was 40 per 1000 following CSH use.

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<sup>56</sup> Miroshnychenko, Roldan, et al. (2025).

<sup>57</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>58</sup> Miroshnychenko, Roldan, et al. (2025).

**Taylor et al. 2024a:**<sup>59</sup> 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 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:**<sup>60</sup> 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, 9 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 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,

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<sup>59</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024).

<sup>60</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

cognitive, and physical health outcomes and concluded that robust evidence is lacking. This conclusion is consistent with other SRs of similar scope (Dopp 2024,<sup>61</sup> Miroshnychenko 2025b<sup>62</sup>), which suggested very low certainty of benefits.

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<sup>61</sup> Dopp et al. (2024).

<sup>62</sup> Miroshnychenko, Ibrahim, et al. (2025).

## 4 Summary of all included SRs

<i>Chew et al. 2018</i> <sup>63</sup>	
<b>Study population description</b>	Young people with gender dysphoria
<b>Intervention</b>	Hormonal treatment including PBs and CSH
<b>Outcomes</b>	Physical effects (including physical sex characteristics, side effects, bone mineral density, etc.), psychological effects, cognitive effects
<b>Included studies</b>	13 studies including 9 on GnRHAs, 3 on estrogen, 5 on testosterone, 1 on antiandrogen (cyproterone acetate), and 1 on progestin (lynestrenol). There were no randomized trials included, and only 2 studies included control groups.
<b>Risk of bias assessment consideration</b>	<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>
<b>Results</b>	<p>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.</p> <p>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.</p>

<sup>63</sup> Chew et al. (2018).

<b>Study population description</b>	Transgender and gender-expansive youth
<b>Intervention</b>	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, other treatments described as "gender identity and expression change efforts."
<b>Outcomes</b>	<p>Psychosocial interventions: suicidality, mental health outcomes (including both depression or mood symptoms, and functioning), regret or dissatisfaction, family support.</p> <p>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.</p> <p>CSH: increase in pubertal changes targeted for initiation, gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility.</p> <p>Surgeries: gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility.</p> <p>Reproductive health interventions: successful cryopreservation of oocytes and embryos, successful cryopreservation of semen.</p> <p>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.</p> <p>"Gender identity and expression change efforts": suicidality, mental health symptoms.</p>
<b>Included studies</b>	<p>Psychosocial interventions: 22 studies, including 1 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),<sup>65</sup> 2 cohort studies, 6 quasi-experimental studies, 9 cross-sectional studies, 3 case reports, and 1 qualitative study.</p> <p>Puberty-suppressing hormones: 49 studies, including 25 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 7 cohort studies, 8 case reports, and 1 qualitative study.</p> <p>CSH: 56 studies, including 26 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 10 cohort studies, 11 case reports, and 1 qualitative study.</p> <p>Surgeries: 18 studies, including 6 cross-sectional studies, 7 quasi-experimental studies, 1 cohort study, 3 case reports, and 1 qualitative study.</p> <p>Reproductive health interventions: 9 studies, using cross-sectional or case report designs with small samples (one to 20 transgender youth per sample).</p> <p>Treatment of co-occurring mental health or developmental disorders: 7 studies, all studies using case report design.</p> <p>"Gender identity and expression change efforts": 4 studies, including 3 using retrospective survey designs with community samples, and 1 case report.</p>

<sup>64</sup> Dopp et al. (2024).

<sup>65</sup> 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.

<p><b>Risk of bias assessment consideration</b></p>	<p>Study eligibility criteria: The review did not include a preregistered protocol. The eligibility criteria focused on youth with gender dysphoria under 26 years old and required post-intervention outcomes. However, case reports and qualitative studies were included, which may be limited in estimating the treatment effects.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>
<p><b>Results</b></p>	<p>Psychosocial interventions: very low certainty evidence for all outcomes.</p> <p>Puberty-suppressing hormones: low certainty evidence for decrease in pubertal changes targeted for suppression, very low certainty evidence for all the other outcomes.</p> <p>CSH: low certainty evidence for increase in pubertal changes targeted for initiation, very low certainty evidence for all the other outcomes.</p> <p>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.</p> <p>Reproductive health interventions: very low certainty evidence for two outcomes.</p> <p>Treatment of co-occurring mental health or developmental disorders: very low certainty for all outcomes.</p> <p>“Gender identity and expression change efforts”: low certainty evidence in increases in suicidality, very low certainty for mental health symptoms.</p>

<b>Expósito-Campos et al. 2023<sup>66</sup></b>	
<b>Study population description</b>	Transgender and non-binary youth and adults
<b>Intervention</b>	Empirically supported affirmative psychological intervention.
<b>Outcomes</b>	Mental health outcomes including anxiety, depression, trauma, suicidality, substance abuse, etc.
<b>Included studies</b>	22 studies, with 10 studies reporting outcome information for transgender and non-binary people (3 randomized controlled trials and 7 uncontrolled before-after studies), while 12 studies reporting mixed outcome information for transgender and non-binary and non-transgender populations.
<b>Risk of bias assessment consideration</b>	<p>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.</p> <p>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.</p> <p>Data collection and study appraisal: Duplicate efforts and consensus process were reported.</p> <p>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.</p> <p>Risk of bias in the review: The interpretation of evidence did not address the concerns in the systematic review process.</p>
<b>Results</b>	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.

<sup>66</sup> Expósito-Campos et al. (2023).

<b>Study population description</b>	Children and adolescents experiencing gender dysphoria or incongruence
<b>Intervention</b>	Social transition
<b>Outcomes</b>	Mental health outcomes including depression, anxiety, substance use, and suicidality, gender identity outcomes (e.g., persistence of gender dysphoria/incongruence)
<b>Included studies</b>	11 studies including 8 cross-sectional studies, 1 reanalysis of previously published cross-sectional data, 1 prospective longitudinal study, and 1 retrospective cohort study
<b>Risk of bias assessment consideration</b>	<p>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.</p> <p>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).</p> <p>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.</p> <p>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.</p> <p>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.</p>
<b>Results</b>	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.

<sup>67</sup> Hall et al. (2024).

*Heathcote et al. 2024<sup>68</sup>*

<b>Study population description</b>	Children and adolescents experiencing gender dysphoria or incongruence
<b>Intervention</b>	Psychosocial support
<b>Outcomes</b>	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).
<b>Included studies</b>	10 studies including 4 cohort studies, 2 pre–post studies, 3 mixed methods, and 1 was a secondary analysis of intervention group data from four randomised controlled trials (these trials were not eligible).
<b>Risk of bias assessment consideration</b>	<p>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.</p> <p>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).</p> <p>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.</p> <p>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.</p> <p>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.</p>
<b>Results</b>	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.

<sup>68</sup> Heathcote et al. (2024).

*Karalexi et al. 2020*<sup>69</sup>

<b>Study population description</b>	Transgender young adults
<b>Intervention</b>	Hormone therapy
<b>Outcomes</b>	Cognitive outcomes including visuospatial ability, verbal memory, verbal reasoning, verbal working memory, computation, motor coordination.
<b>Included studies</b>	10 studies, including 6 cohort studies, 3 cross-sectional studies, and 1 with both longitudinal and cross-sectional analysis.
<b>Risk of bias assessment consideration</b>	<p>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.</p> <p>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.</p> <p>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.</p> <p>Synthesis and findings: Meta-analysis was conducted where appropriate; but the review also conducted narrative synthesis elsewhere. Sources of heterogeneity was assessed using I<sup>2</sup> and this review briefly described the heterogeneity was not evident. No certainty of evidence assessed.</p> <p>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.</p>
<b>Results</b>	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.

<sup>69</sup> Karalexi et al. (2020).

*Ludvigsson et al. 2023*<sup>70</sup>

<b>Study population description</b>	Children with gender dysphoria
<b>Intervention</b>	Hormone therapy
<b>Outcomes</b>	Psychosocial and mental health outcomes (including gender dysphoria, depression, anxiety), cognitive outcomes, bone health outcomes, body composition and metabolic markers.
<b>Included studies</b>	24 studies, all observational studies, including 8 studies on GnRH alone, 13 studies on GnRH and CSH, and 3 studies on cross-sex hormone alone.
<b>Risk of bias assessment consideration</b>	<p>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.</p> <p>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.</p> <p>Data collection and study appraisal: Two independent reviewers extracted data and conducted risk of bias assessment.</p> <p>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.</p> <p>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.</p>
<b>Results</b>	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 GnRHAs 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.

<sup>70</sup> Ludvigsson et al. (2023).

*Malpas et al. 2022<sup>71</sup>*

<b>Study population description</b>	Transgender and gender expansive youth
<b>Intervention</b>	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.
<b>Risk of bias assessment consideration</b>	<p>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."</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Risk of bias in the review: The concerns identified were not addressed in the interpretation of evidence.</p>
<b>Outcomes</b>	No quantitative outcome for effectiveness. This systematic review identified four themes related to family-based intervention.
<b>Included studies</b>	32 studies on clinical practice recommendations for family-based interventions for transgender and gender expansive youth.
<b>Results</b>	This systematic review found that clinical strategies have moved from pathologizing to affirming of transgender and gender expansive youths' gender journey.

<sup>71</sup> Malpas et al. (2022).

<i>Miroshnychenko et al. 2024<sup>72</sup></i>	
<b>Study population description</b>	Individuals aged <26 years experiencing gender dysphoria
<b>Intervention</b>	Mastectomy
<b>Outcomes</b>	Mental health measures (including distress, suicide), gender dysphoria, body satisfaction, and surgical complications (including death, necrosis, and scarring).
<b>Included studies</b>	39 studies, including 3 comparative observational studies, 2 before–after, and 34 case series.
<b>Risk of bias assessment consideration</b>	<p>Study eligibility criteria: The protocol was registered, and the eligibility criteria were clear.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Risk of bias in the review: The interpretation of evidence was appropriately cautious given very low to low certainty of much of the evidence.</p>
<b>Results</b>	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.

<sup>72</sup> Miroshnychenko et al. (2024).

<b><i>Miroshnychenko et al. 2025a</i><sup>73</sup></b>	
<b>Study population description</b>	Individuals aged <26 years experiencing gender dysphoria
<b>Intervention</b>	PBs
<b>Outcomes</b>	Gender dysphoria, global function, depression, bone mineral density, progression to CSH.
<b>Included studies</b>	10 studies, 3 comparative observational studies, and 7 before–after design studies.
<b>Risk of bias assessment consideration</b>	Same as Miroshnychenko 2024 <sup>74</sup>
<b>Results</b>	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.

<sup>73</sup> Miroshnychenko, Roldan, et al. (2025).

<sup>74</sup> Miroshnychenko et al. (2024).

<b>Miroshnychenko et al. 2025b<sup>75</sup></b>	
<b>Study population description</b>	Individuals aged <26 years experiencing gender dysphoria
<b>Intervention</b>	CSH
<b>Outcomes</b>	Gender dysphoria, global function, depression, death by suicide, bone mineral density, sexual dysfunction, cardiovascular events.
<b>Included studies</b>	24 studies, including 9 comparative observational studies, 13 before–after studies, and 2 case series.
<b>Risk of bias assessment consideration</b>	Same as Miroshnychenko 2024 <sup>76</sup>
<b>Results</b>	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.

<sup>75</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>76</sup> Miroshnychenko et al. (2024).

**Ramos et al. 2021<sup>77</sup>**

<b>Study population description</b>	Adolescents with gender incongruity
<b>Intervention</b>	PBs
<b>Outcomes</b>	Gender dysphoria, bone mineral density, side effects.
<b>Included studies</b>	11 studies including 9 observational studies and 2 qualitative studies.
<b>Risk of bias assessment consideration</b>	<p>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.</p> <p>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.</p> <p>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.</p> <p>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."</p> <p>Risk of bias in the review: The concerns identified were not addressed.</p>
<b>Results</b>	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."

<sup>77</sup> Ramos et al. (2021).

<b>Study population description</b>	Transgender and gender diverse youth
<b>Intervention</b>	PBs
<b>Outcomes</b>	Anthropomorphic measurements, sexual characteristics, mental health functioning, depression, emotional and behaviour problems, suicide, and side effects.
<b>Included studies</b>	9 studies including 6 observational studies, 1 cross-sectional study, and 2 case reports.
<b>Risk of bias assessment consideration</b>	<p>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."</p> <p>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.</p> <p>Data collection and study appraisal: A data extraction form was developed, but approach to data extraction was not described.</p> <p>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'.</p> <p>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.</p>
<b>Results</b>	<p>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.</p>

<sup>78</sup> Rew et al. (2021).

**Taylor et al. 2024a<sup>79</sup>**

<b>Study population description</b>	Adolescents with gender dysphoria or gender incongruence
<b>Intervention</b>	PBs
<b>Outcomes</b>	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.).
<b>Included studies</b>	50 studies, including 11 cohorts, 8 cross-sectional and 31 before-after studies. The descriptive evidence synthesis included 1 high quality cross-sectional study, and 25 moderate observational studies.
<b>Risk of bias assessment consideration</b>	<p>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.</p> <p>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).</p> <p>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.</p> <p>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.</p> <p>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.</p>
<b>Results</b>	This systematic review did not identify high-quality studies with appropriate designs (only 1 "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.

<sup>79</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024).

**Taylor et al. 2024b<sup>80</sup>**

<b>Study population description</b>	Adolescents with gender dysphoria or gender incongruence
<b>Intervention</b>	CSH
<b>Outcomes</b>	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.
<b>Included studies</b>	53 studies including 12 cohort, 9 cross-sectional, 32 pre–post studies. This systematic review included 1 high quality cohort study.
<b>Risk of bias assessment consideration</b>	Same as Taylor 2024a. <sup>81</sup>
<b>Results</b>	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 <sup>82</sup> mental health may be improved during treatment.

<sup>80</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>81</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024).

<sup>82</sup> 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<sup>83</sup>**

<b>Study population description</b>	Adolescents with gender dysphoria
<b>Intervention</b>	Psychosocial only PBs CSH Surgeries
<b>Outcomes</b>	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.
<b>Included studies</b>	19 studies, including 13 retrospective studies and no randomized controlled trial.
<b>Risk of bias assessment consideration</b>	<p>Study eligibility criteria: The eligibility criteria were clear.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Risk of bias in the review: The interpretation of evidence did not address the concerns identified.</p>
<b>Results</b>	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.”

<sup>83</sup> Thompson et al. (2023).

<b>Study population description</b>	Children/adolescents with gender dysphoria
<b>Intervention</b>	PBs CSH
<b>Outcomes</b>	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.
<b>Included studies</b>	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.
<b>Risk of bias assessment consideration</b>	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.
<b>Results</b>	This systematic review concluded that the evidence on the effectiveness of PBs and/or CSH in children and adolescents with gender dysphoria remains inadequate.

<sup>84</sup> 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.<sup>85</sup> 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

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<sup>85</sup> 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., König, 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 Übersicht zur Evidenzlage der Pubertätsblockade und Hormongabe bei Minderjährigen mit Geschlechtsdysphorie.*, 52(3), 167-187.

## 5.2 Low risk of bias SRs

Four English language SRs were classified as low risk of bias.<sup>86</sup> 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<sup>87</sup> included most studies: 50 studies including 11 cohorts, 8 cross-sectional, and 31 before-after studies. This SR synthesized only study results from high or moderate quality studies. Dopp 2024<sup>88</sup> included 49 studies including 25 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 7 cohort studies, 8 case reports, and 1 qualitative study (case reports and qualitative studies are inadequate to provide quantitative information on treatment effects). In contrast, Ludvigsson 2023<sup>89</sup> included 21 studies, and Miroshnychenko 2025a<sup>90</sup> included 10 studies (including 3 comparative observational studies and 7 before–after design).

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<sup>86</sup> Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).

<sup>87</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024).

<sup>88</sup> Dopp et al. (2024).

<sup>89</sup> Ludvigsson et al. (2023).

<sup>90</sup> 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,<sup>91</sup> one in the UK<sup>92</sup>), as well as the five before-after studies reported in Canada,<sup>93</sup> Netherlands,<sup>94</sup> and UK.<sup>95</sup>)

### 5.3 Outcome 1. Gender dysphoria

A total of four low risk of bias SRs assessed the impact of PBs on GD.<sup>96</sup> Dopp 2024<sup>97</sup> 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.<sup>98</sup> 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,”<sup>99</sup> 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 wellbeing

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

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<sup>91</sup> Becker-Hebly et al. (2021).

<sup>92</sup> Costa et al. (2015).

<sup>93</sup> Navabi et al. (2021).

<sup>94</sup> Klink et al. (2015); Schagen et al. (2016).

<sup>95</sup> Carmichael et al. (2021); Joseph et al. (2019).

<sup>96</sup> Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).

<sup>97</sup> Dopp et al. (2024).

<sup>98</sup> Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025).

<sup>99</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024).

quality of life.<sup>100</sup> Similar to the reviews on the GD outcome, Dopp 2024<sup>101</sup> 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 or “uncertain.”

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.<sup>102</sup> 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.<sup>103</sup>

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

### **5.6 Outcome 4. Need or progression to further treatment**

Only one systematic review assessed the impact of PBs on proceeding with CSH. Miroshnychenko and colleagues<sup>104</sup> included 2 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.

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<sup>100</sup> Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).

<sup>101</sup> Dopp et al. (2024).

<sup>102</sup> Dopp et al. (2024); Taylor, Mitchell, Hall, Heathcote, et al. (2024).

<sup>103</sup> 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).

<sup>104</sup> 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.<sup>105</sup> Outcomes included overall risk of adverse events, bone health, fertility, anthropometric measures, body composition, growth, and other measures. Dopp 2024<sup>106</sup> 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 puberty blocker treatment. Specifically, Miroshnychenko and colleagues<sup>107</sup> 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<sup>108</sup> (due to risk of bias and imprecision concerns) but very low according to Dopp 2024<sup>109</sup> and Miroshnychenko 2025a.<sup>110</sup> Taylor 2024a<sup>111</sup> 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.<sup>112</sup> In summary, this overview

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<sup>105</sup> Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).

<sup>106</sup> Dopp et al. (2024).

<sup>107</sup> Miroshnychenko, Roldan, et al. (2025).

<sup>108</sup> Ludvigsson et al. (2023).

<sup>109</sup> Dopp et al. (2024).

<sup>110</sup> Miroshnychenko, Roldan, et al. (2025).

<sup>111</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024).

<sup>112</sup> 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.

concludes there is low certainty evidence that PBs may lead to compromised bone density.

Only one systematic review reported on fertility outcomes. Based on two case reports of fertility preservation, Dopp et al<sup>113</sup> 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<sup>114</sup> 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. 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.

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<sup>113</sup> Dopp et al. (2024).

<sup>114</sup> Ludvigsson et al. (2023); Taylor, Mitchell, Hall, Heathcote, et al. (2024).

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. 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,<sup>115</sup> 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, improvement in mental health, and safety.

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<sup>115</sup> 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 <sup>116</sup>	Dopp 2024 <sup>117</sup>	Ludvigsson 2023 <sup>118</sup>	Miroshnychenko 2025a <sup>119</sup>	Ramos 2021 <sup>120</sup>	Rew 2021 <sup>121</sup>	Taylor 2024a <sup>122</sup>	Thompson 2023 <sup>123</sup>	Zepf 2024 <sup>124</sup>
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 <sup>125</sup>	Y	Y			Y		
Chen 2016								Y	
Chiniara 2018							Y		

<sup>116</sup> Chew et al. (2018).

<sup>117</sup> Dopp et al. (2024).

<sup>118</sup> Ludvigsson et al. (2023).

<sup>119</sup> Miroshnychenko, Roldan, et al. (2025).

<sup>120</sup> Ramos et al. (2021).

<sup>121</sup> Rew et al. (2021).

<sup>122</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024).

<sup>123</sup> Thompson et al. (2023).

<sup>124</sup> Zepf et al. (2024).

<sup>125</sup> 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.

	<b>Chew 2018<sup>116</sup></b>	<b>Dopp 2024<sup>117</sup></b>	<b>Ludvigsson 2023<sup>118</sup></b>	<b>Miroshnychenko 2025a<sup>119</sup></b>	<b>Ramos 2021<sup>120</sup></b>	<b>Rew 2021<sup>121</sup></b>	<b>Taylor 2024a<sup>122</sup></b>	<b>Thompson 2023<sup>123</sup></b>	<b>Zepf 2024<sup>124</sup></b>
<b>Cohen-Kettenis 2011<sup>126</sup></b>		Y				Y			
<b>Costa 2015</b>	Y	Y	Y	Y	Y		Y	Y	Y
<b>de Nie 2022</b>							Y		
<b>de Vries 2014</b>	Y		Y		Y		Y		
<b>de Vries 2011</b>	Y	Y		Y	Y	Y	Y	Y	Y
<b>Delemarre-van de Waal 2006</b>	Y	Y					Y		
<b>Donaldson 2018</b>		Y							
<b>Ewan 2014</b>		Y							
<b>Fontanari 2020</b>							Y		
<b>Ghelani 2020</b>							Y		
<b>Giovanardi 2019</b>					Y				
<b>Grannis 2021, Grannis 2023, and Olsavsky 2023</b>		Y <sup>127</sup>							
<b>Grimstad 2021a</b>							Y		
<b>Hisle-Gorman 2021</b>		Y	Y				Y		
<b>Jensen 2019</b>								Y	
<b>Joseph 2019</b>		Y	Y	Y			Y	Y	Y
<b>Karakılıç Özturan 2023</b>				Y					
<b>Khatchadourian 2014</b>		Y			Y	Y	Y		Y
<b>Klaver 2020</b>		Y	Y				Y	Y	
<b>Klaver 2018</b>			Y		Y	Y	Y	Y	

<sup>126</sup> 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.

<sup>127</sup> Dopp et al. (2024) included three citations for one study.

	<b>Chew 2018<sup>116</sup></b>	<b>Dopp 2024<sup>117</sup></b>	<b>Ludvigsson 2023<sup>118</sup></b>	<b>Miroshnychenko 2025a<sup>119</sup></b>	<b>Ramos 2021<sup>120</sup></b>	<b>Rew 2021<sup>121</sup></b>	<b>Taylor 2024a<sup>122</sup></b>	<b>Thompson 2023<sup>123</sup></b>	<b>Zepf 2024<sup>124</sup></b>
<b>Klink 2015</b>	Y	Y	Y	Y	Y		Y		Y
<b>Klink 2013</b>					Y				
<b>Kuper 2020</b>		Y					Y	Y	
<b>Lavender 2023</b>		Y							
<b>Lee 2020</b>			Y					Y	
<b>Lee 2024</b>		Y							
<b>Littman 2021</b>		Y							
<b>Lopez 2018</b>					Y			Y	
<b>López de Lara 2020</b>		Y							
<b>Lynch 2015</b>							Y		
<b>Martin 2021</b>		Y							
<b>McGregor 2024</b>		Y							
<b>Mejia-Otero 2021</b>							Y		
<b>Moussaoui 2023</b>		Y							
<b>Nahata 2017</b>						Y		Y	
<b>Navabi 2021</b>		Y	Y	Y			Y		
<b>Neyman 2019</b>		Y					Y		
<b>Nokoff 2021</b>			Y				Y		
<b>Olson 2022</b>		Y							
<b>Olson-Kennedy 2021</b>							Y		
<b>Pang 2020</b>		Y							

	<b>Chew 2018<sup>116</sup></b>	<b>Dopp 2024<sup>117</sup></b>	<b>Ludvigsson 2023<sup>118</sup></b>	<b>Miroshnychenko 2025a<sup>119</sup></b>	<b>Ramos 2021<sup>120</sup></b>	<b>Rew 2021<sup>121</sup></b>	<b>Taylor 2024a<sup>122</sup></b>	<b>Thompson 2023<sup>123</sup></b>	<b>Zepf 2024<sup>124</sup></b>
<b>Perl 2021<sup>128</sup></b>		Y					Y		
<b>Perl 2020<sup>129</sup></b>		Y	Y				Y	Y	
<b>Pine-Twaddell 2023</b>							Y		
<b>Ristori 2019</b>		Y							
<b>Russell 2021</b>							Y	Y	
<b>Schagen 2016</b>	Y	Y	Y		Y	Y	Y		Y
<b>Schagen 2018</b>							Y		
<b>Schagen 2020</b>		Y	Y	Y			Y	Y	
<b>Schneider 2017</b>		Y				Y			
<b>Schulmeister 2022</b>			Y				Y		
<b>Schwartz 2023</b>		Y							
<b>Segev-Becker 2020</b>							Y		
<b>Staphorsius 2015</b>	Y		Y				Y		Y
<b>Stoffers 2019</b>			Y				Y	Y	
<b>Strang 2022</b>							Y		
<b>Tack 2016</b>		Y					Y	Y	
<b>Tack 2018</b>		Y					Y	Y	
<b>Tack 2017</b>		Y					Y	Y	
<b>Tordoff 2022</b>		Y					Y		
<b>Turban 2020</b>		Y				Y	Y		

<sup>128</sup> 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.

<sup>129</sup> See above note.

	<b>Chew 2018<sup>116</sup></b>	<b>Dopp 2024<sup>117</sup></b>	<b>Ludvigsson 2023<sup>118</sup></b>	<b>Miroshnychenko 2025a<sup>119</sup></b>	<b>Ramos 2021<sup>120</sup></b>	<b>Rew 2021<sup>121</sup></b>	<b>Taylor 2024a<sup>122</sup></b>	<b>Thompson 2023<sup>123</sup></b>	<b>Zepf 2024<sup>124</sup></b>
<b>van de Grift 2020</b>		Y					Y		
<b>van der Loos 2022</b>		Y							
<b>van der Loos 2023</b>		Y							
<b>van der Loos 2021</b>			Y				Y		
<b>van der Miesen 2020</b>		Y					Y		
<b>Vlot 2017</b>	Y	Y	Y		Y	Y	Y		Y
<b>Vrouenraets 2016</b>		Y			Y				
<b>Waldner 2023</b>							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
<b>Dopp 2024</b> <sup>130</sup>	11 studies	_ <sup>131</sup>	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
<b>Ludvigsson 2023</b> <sup>132</sup>	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
<b>Miroshnychenko 2025a</b> <sup>133</sup>	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
<b>Taylor 2024a</b> <sup>134</sup>	2 before-after studies <sup>135</sup>	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
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of PBs on gender dysphoria.	The certainty of evidence is very low.

<sup>130</sup> Dopp et al. (2024).

<sup>131</sup> 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.

<sup>132</sup> Ludvigsson et al. (2023).

<sup>133</sup> Miroshnychenko, Roldan, et al. (2025).

<sup>134</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review only synthesized excluded low quality.

<sup>135</sup> 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
<i>Global function</i>				
<b>Dopp 2024</b> <sup>136</sup>	21 studies	_ <sup>137</sup>	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
<b>Ludvigsson 2023</b> <sup>138</sup>	4 observational cohort studies: 1 prospective and 3 retrospective	254 participants on hormones, <sup>139</sup> 113 were evaluated	Improved global function as assessed with the Children's Global Assessment Scale	Very low certainty <sup>140</sup> due to very serious risk of bias and very serious imprecision
<b>Miroshnychenko 2025a</b> <sup>141</sup>	2 comparative observational studies, and 2 before-after studies	103 participants from 2 comparative observational studies, and 53 participants from 2 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

<sup>136</sup> Dopp et al. (2024).

<sup>137</sup> 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.

<sup>138</sup> Ludvigsson et al. (2023).

<sup>139</sup> In two studies, the participants had also received CSH.

<sup>140</sup> 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.

<sup>141</sup> Miroshnychenko, Roldan, et al. (2025).

<b>Taylor 2024a</b> <sup>142</sup>	1 cohort and 2 before-after studies	174 participants were treated	Three before-after studies reported no clinically significant change	No conclusions can be drawn.
<b>Suicidality</b>				
<b>Ludvigsson 2023</b> <sup>143</sup>	1 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 <sup>144</sup> due to very serious risk of bias and very serious imprecision
<b>Taylor 2024a</b> <sup>145</sup>	1 cross-sectional study and 1 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.
<b>Depression</b>				
<b>Ludvigsson 2023</b> <sup>146</sup>	2 prospective observational cohort studies of which one included mixed treatment	97 participants on hormones, 60 were evaluated	No change in depression	Very low certainty <sup>147</sup> due to very serious risk of bias and very serious imprecision
<b>Miroshnychenko 2025a</b> <sup>148</sup>	1 comparative observational study, and 1 before-after study	26 participants from 1 comparative observational study, and 41 participants from 2 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	Very low certainty due to very serious risk of bias, and serious imprecision

<sup>142</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<sup>143</sup> Ludvigsson et al. (2023).

<sup>144</sup> 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.

<sup>145</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<sup>146</sup> Ludvigsson et al. (2023).

<sup>147</sup> 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.

<sup>148</sup> Miroshnychenko, Roldan, et al. (2025).

			participants; and Mean change -3.36 (95% confidence interval: -3.69 to -3.03) from 1 before-after study (higher score indicating greater depression)	
<b>Taylor 2024a<sup>149</sup></b>	1 before-after study	70 participants were treated	Reduction in depressive symptom	A single study, reporting small to moderate improvement. No conclusion can be drawn.
<b>Anxiety</b>				
<b>Ludvigsson 2023<sup>150</sup></b>	2 prospective observational cohort studies	97 participants on hormones, 60 were evaluated	No change in anxiety	Very low certainty <sup>151</sup> due to very serious risk of bias and very serious imprecision
<b>Taylor 2024a<sup>152</sup></b>	1 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.
<b>Quality of life</b>				
<b>Ludvigsson 2023<sup>153</sup></b>	2 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 <sup>154</sup> due to very serious risk of bias and very serious imprecision.
<b>Taylor 2024a<sup>155</sup></b>	1 before-after study	44 participants were treated	No change in quality of life	A single study, reporting no improvement. No conclusion can be drawn.

<sup>149</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<sup>150</sup> Ludvigsson et al. (2023).

<sup>151</sup> 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.

<sup>152</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<sup>153</sup> Ludvigsson et al. (2023).

<sup>154</sup> 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.

<sup>155</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

<i>Internalising problems</i>				
<b>Taylor 2024a</b> <sup>156</sup>	1 cross-sectional study, and 2 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.
<i>Externalising problems</i>				
<b>Taylor 2024a</b> <sup>157</sup>	1 cross-sectional study, and 2 before-after studies	292 participants were treated	No change to small decrease in externalising problems	No conclusion can be drawn.
<i>Psychological functioning/psychopathology</i>				
<b>Taylor 2024a</b> <sup>158</sup>	2 before-after studies	114 participants were treated	Two before-after studies reported no change to a small change	No conclusions can be drawn.
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of mental health outcomes by PBs.	The certainty of evidence is very low.

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<sup>156</sup> See above note,

<sup>157</sup> See above note.

<sup>158</sup> 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
<b><i>Pubertal progression</i></b>				
<b>Dopp 2024</b> <sup>159</sup>	20 studies	_ <sup>160</sup>	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
<b>Taylor 2024a</b> <sup>161</sup>	4 studies including 2 cohort studies and 2 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 GnRH-a.	Four studies showed that PBs exert its expected physiological effects
<b><i>Hormone level</i></b>				
<b>Taylor 2024a</b> <sup>162</sup>	9 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 GnRH-a	Multiple mainly before-after studies showed that PBs exerts its expected physiological effects

<sup>159</sup> Dopp et al. (2024).

<sup>160</sup> 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., Vrouwenraets et al. 2022). One study included by this review, Grannis 2023, was about CSH not PBs.

<sup>161</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

<sup>162</sup> See note above.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b><i>Menstrual suppression</i></b>				
<b>Taylor 2024a</b> <sup>163</sup>	3 studies including 1 cohort study and 2 before-after studies	202 participants	All studies reported menstrual suppression	Three studies showed that exert its expected physiological effects
<b>Evidence synthesis</b>			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). <sup>164</sup>

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<sup>163</sup> See note above.

<sup>164</sup> 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
<b>Miroshnychenko 2025a</b> <sup>165</sup>	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)
<b>Evidence synthesis</b>			A high proportion of adolescents receiving PBs proceed with cross-sex hormone therapy.	The certainty of evidence is very low.

<sup>165</sup> 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
<b>Overall risk of adverse events</b>				
<b>Dopp 2024</b> <sup>166</sup>	18 studies	- <sup>167</sup>	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
<b>Taylor 2024a</b> <sup>168</sup>	3 before-after studies	109 participants	A cohort study of GnRH-a 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.

<sup>166</sup> Dopp et al. (2024).

<sup>167</sup> 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).

<sup>168</sup> 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
<b>Evidence synthesis</b>			No conclusion can be drawn on the overall risks of side-effects of PBs.	The certainty of evidence is very low.
<b>Bone density</b>				
<b>Dopp 2024</b> <sup>169</sup>	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
<b>Ludvigsson 2023</b> <sup>170</sup>				
<ul style="list-style-type: none"> <li><b>Bone density during PBs treatment (g/cm<sup>2</sup>, g/cm<sup>3</sup>)</b></li> </ul>	5 observational cohort studies (4 retrospective and 1 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
<ul style="list-style-type: none"> <li><b>Bone density during PBs treatment in relation to reference data in the literature (z-score)</b></li> </ul>	5 observational cohort studies (4 retrospective and 1 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

<sup>169</sup> Dopp et al. (2024).

<sup>170</sup> 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
<b>Miroshnychenko 2025a<sup>171</sup></b>				
<ul style="list-style-type: none"> <li><b>Bone mineral density, hip, long term follow-up assessed with: DXA, z scores scale (-3 to 3). Follow-up: 12–36 months</b></li> </ul>	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 3 levels)
<ul style="list-style-type: none"> <li><b>Bone mineral density, lumbar spine, long term follow-up assessed with: DXA, z scores scale (-3 to 3). Follow-up: 12–36 months</b></li> </ul>	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 3 levels)
<ul style="list-style-type: none"> <li><b>Bone mineral density, femoral neck, long term follow-up assessed with: DXA, z scores scale (-3 to 3). Follow-up: 20–24 months</b></li> </ul>	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 3 levels)
<ul style="list-style-type: none"> <li><b>Bone mineral density, lumbar spine, short term follow-up assessed with: DXA, z scores scale (-3 to 3).</b></li> </ul>	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 3 levels)

<sup>171</sup> Miroshnychenko, Roldan, et al. (2025).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b>Follow-up: 6 months</b>				
<b>Taylor 2024a</b>	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
<b>Evidence synthesis</b>			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). <sup>172</sup>
<b>Fertility</b>				
<b>Dopp 2024<sup>173</sup></b>	2 studies	12 participants <sup>174</sup>	Case reports documented healthy, viable oocyte cryopreservation after taking PBs and pausing for at least 3 months	Very low certainty due to very serious risk of bias and very serious indirectness
<b>Evidence synthesis</b>			It is uncertain if 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.
<b>Anthropometric measures</b>				
<b>Ludvigsson 2023<sup>175</sup></b>	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

<sup>172</sup> 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.

<sup>173</sup> Dopp et al. (2024).

<sup>174</sup> This systematic review by Dopp et al reported fertility preservation based on case reports, not fertility outcomes.

<sup>175</sup> Ludvigsson et al. (2023).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b>Body composition</b>				
<b>Ludvigsson 2023</b> <sup>176</sup>	2 prospective observational cohort studies and 1 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
<b>Taylor 2024a</b> <sup>177</sup>	2 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.
<b>Blood pressure</b>				
<b>Ludvigsson 2023</b> <sup>178</sup>	1 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
<b>Taylor 2024a</b> <sup>179</sup>	3 before-after studies	96 participants	Three studies reported no change or small, non-clinically significant change in blood pressure	No conclusions can be drawn.
<b>Metabolic measures</b>				
<b>Ludvigsson 2023</b> <sup>180</sup>	1 retrospective observational cohort study and 1 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
<b>Taylor 2024a</b> <sup>181</sup>	3 before-after studies	127 participants	Three studies reported no change or small change in metabolic measures.	No conclusions can be drawn.
<b>Growth (cm/year)</b>				

<sup>176</sup> Ludvigsson et al. (2023).

<sup>177</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<sup>178</sup> Ludvigsson et al. (2023).

<sup>179</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<sup>180</sup> Ludvigsson et al. (2023).

<sup>181</sup> 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
<b>Ludvigsson 2023</b> <sup>182</sup>	1 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
<b>Taylor 2024a</b> <sup>183</sup>	11 studies, including 1 cohort study, and 10 before-after studies	925 participants	The cohort study found a similar height velocity between the GnRH-a 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.
<b>Evidence synthesis</b>			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.
<b>Cognition</b>				
<b>Ludvigsson 2023</b> <sup>184</sup>	1 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
<b>Taylor 2024a</b> <sup>185</sup>	1 cross-sectional study, and 1 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.
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of PBs on cognitive outcomes.	The certainty of evidence is very low.

<sup>182</sup> Ludvigsson et al. (2023).

<sup>183</sup> Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

<sup>184</sup> Ludvigsson et al. (2023).

<sup>185</sup> 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
<b>Dopp 2024</b> <sup>186</sup>	14 studies	- <sup>187</sup>	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
<b>Evidence synthesis</b>			No conclusion can be drawn on the regret rate after PBs.	The certainty of evidence is very low.

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<sup>186</sup> Dopp et al. (2024).

<sup>187</sup> 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.<sup>188</sup> 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.<sup>189</sup> 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.

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<sup>188</sup> 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).

<sup>189</sup> 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 Übersicht zur Evidenzlage der Pubertätsblockade und Hormongabe bei Minderjährigen mit Geschlechtsdysphorie.*, 52(3), 167-187.

## 6.2 Low risk of bias systematic reviews

Four English SRs were classified as low risk of bias.<sup>190</sup> Of these reviews, the eligibility criteria and number of included studies varied. Dopp 2024<sup>191</sup> included 56 studies including 26 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 10 cohort studies, 11 case reports, and 1 qualitative study. The SR by Taylor and colleagues<sup>192</sup> included 53 studies including 12 cohort, 9 cross-sectional, 32 pre-post studies. This SR excluded results from low quality studies in the evidence synthesis. Ludvigsson 2023<sup>193</sup> included 16 studies and Miroshnychenko 2025b<sup>194</sup> included 24 studies (including 9 comparative observational studies, 13 before-after design, and 2 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,<sup>195</sup> and three before-after studies reported in the US<sup>196</sup> and Netherlands.<sup>197</sup>

## 6.3 Outcome 1. Gender dysphoria

A total of three SRs assessed the impact of CSH on GD.<sup>198</sup> Dopp 2024<sup>199</sup> 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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<sup>190</sup> Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>191</sup> Dopp et al. (2024).

<sup>192</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>193</sup> Ludvigsson et al. (2023).

<sup>194</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>195</sup> Becker-Hebly et al. (2021).

<sup>196</sup> Cantu et al. (2020).

<sup>197</sup> Schagen et al. (2020); Vlot et al. (2017).

<sup>198</sup> Dopp et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>199</sup> 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.<sup>200</sup> Like the SRs on GD, Dopp 2024<sup>201</sup> 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 6 per 1,000 according to Miroshnychenko and colleagues,<sup>202</sup> though the certainty of evidence was very low. According to the review by Taylor and colleagues,<sup>203</sup> 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.<sup>204</sup> SRs showed that the use of cross-sex hormone is consistently associated with physical changes. This overview

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<sup>200</sup> Dopp et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>201</sup> Dopp et al. (2024).

<sup>202</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>203</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>204</sup> 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.<sup>205</sup>

One example of a very large effect pertains to menstrual suppression, which is expected to be rare without CSH. Taylor and colleagues<sup>206</sup> 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.<sup>207</sup> Dopp 2024<sup>208</sup> reported that side effects and complications were limited, and these side effects did not have a major impact on treatment. Taylor 2024b<sup>209</sup> 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<sup>210</sup> 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

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<sup>205</sup> Guyatt, Oxman, Sultan, et al. (2011).

<sup>206</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>207</sup> Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>208</sup> Dopp et al. (2024).

<sup>209</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>210</sup> Miroshnychenko, Ibrahim, et al. (2025).

density decreases relative to reference values (z score). Dopp 2024<sup>211</sup> and Ludvigsson 2023<sup>212</sup> reported that bone density may recover after discontinuation of PBs and initiation of CSH. Miroshnycheko and colleagues<sup>213</sup> reported no changes in bone mineral density for hip, lumbar spine, and femoral neck. Taylor 2024b<sup>214</sup> 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<sup>215</sup> and Miroshnycheko 2025b,<sup>216</sup> but low according to Ludvigsson 2023.<sup>217</sup> Taylor 2024b<sup>218</sup> 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<sup>219</sup> reported cases describing successful cryopreservation of healthy, viable oocytes, embryos, and semen, often after pausing hormone therapy. According to Taylor et al,<sup>220</sup> 1 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.

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<sup>211</sup> Dopp et al. (2024).

<sup>212</sup> Ludvigsson et al. (2023).

<sup>213</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>214</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>215</sup> Dopp et al. (2024).

<sup>216</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>217</sup> Ludvigsson et al. (2023).

<sup>218</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>219</sup> Dopp et al. (2024).

<sup>220</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

Miroshnychenko 2025b<sup>221</sup> included 1 before-after study, reporting no change from baseline in symptoms of vaginal dryness or itch after receiving cross-sex hormone at 6 months or 12 months of follow-up. The certainty of evidence on sexual dysfunction was assessed as very low.

Taylor 2024b<sup>222</sup> 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<sup>223</sup> 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.<sup>224</sup> The certainty of evidence was very low. This overview concludes that the evidence is 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

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<sup>221</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>222</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>223</sup> Ludvigsson et al. (2023).

<sup>224</sup> 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 children or 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 CSHs and the primary studies that these SRs included

	Chew 2018 <sup>225</sup>	Dopp 2024 <sup>226</sup>	Karalexi 2020	Ludvigsson 2023 <sup>227</sup>	Miroshnychenko 2025b <sup>228</sup>	Taylor 2024b <sup>229</sup>	Thompson 2023 <sup>230</sup>	Zepf 2024 <sup>231</sup>
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						

<sup>225</sup> Chew et al. (2018).

<sup>226</sup> Dopp et al. (2024).

<sup>227</sup> Ludvigsson et al. (2023)

<sup>228</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>229</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>230</sup> Thompson et al. (2023).

<sup>231</sup> Zepf et al. (2024).

	<b>Chew 2018<sup>225</sup></b>	<b>Dopp 2024<sup>226</sup></b>	<b>Karalexi 2020</b>	<b>Ludvigsson 2023<sup>227</sup></b>	<b>Miroshnychenko 2025b<sup>228</sup></b>	<b>Taylor 2024b<sup>229</sup></b>	<b>Thompson 2023<sup>230</sup></b>	<b>Zepf 2024<sup>231</sup></b>
<b>Cantu 2020</b>		Y		Y	Y	Y		
<b>Chen 2023</b>		Y			Y			
<b>Chen 2016</b>							Y	
<b>Chiniara 2018</b>						Y		
<b>Cohen-Kettenis 2011<sup>232</sup></b>		Y						
<b>de Nie 2022</b>		Y				Y		
<b>de Vries 2014</b>	Y	Y		Y		Y		
<b>de Vries 2011</b>							Y	
<b>Delemarre-van de Waal 2006</b>		Y				Y		
<b>Donaldson 2018</b>		Y						
<b>Filipov 2023</b>					Y			
<b>Fontanari 2020</b>					Y	Y		
<b>Foster 2021</b>					Y			
<b>Friedman 2000</b>			Y					
<b>Gale 2021</b>		Y						
<b>Gómez-Gil 2009</b>			Y					
<b>Grannis 2021<sup>233</sup></b>		Y				Y		Y
<b>Grannis 2023<sup>234</sup></b>		Y			Y			

<sup>232</sup> 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.

<sup>233</sup> 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.

<sup>234</sup> 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.

	<b>Chew 2018<sup>225</sup></b>	<b>Dopp 2024<sup>226</sup></b>	<b>Karalexi 2020</b>	<b>Ludvigsson 2023<sup>227</sup></b>	<b>Miroshnychenko 2025b<sup>228</sup></b>	<b>Taylor 2024b<sup>229</sup></b>	<b>Thompson 2023<sup>230</sup></b>	<b>Zepf 2024<sup>231</sup></b>
<b>Green 2022</b>		Y			Y	Y		
<b>Grimstad 2021a</b>		Y				Y		
<b>Grimstad 2021b</b>						Y		
<b>Gupta 2023</b>		Y						
<b>Hannema 2017</b>						Y		
<b>Haraldsen 2005</b>			Y		Y			
<b>Hisle-Gorman 2021</b>		Y		Y		Y		
<b>Insogna 2020</b>		Y						
<b>Jarin 2017</b>	Y	Y		Y		Y		
<b>Jensen 2019</b>						Y	Y	
<b>Kaltiala 2020</b>		Y			Y	Y		Y
<b>Khatchadourian 2014</b>		Y				Y		Y
<b>Klaver 2020</b>		Y		Y		Y	Y	Y
<b>Klaver 2018</b>				Y		Y	Y	
<b>Klink 2015</b>	Y	Y		Y		Y		Y
<b>Kuper 2020</b>		Y				Y	Y	Y
<b>Laurenzano 2021</b>		Y				Y		
<b>Lavender 2023</b>		Y						
<b>Lee 2024</b>		Y						
<b>Lierman 2017</b>		Y						
<b>Littman 2021</b>		Y						
<b>López de Lara 2020</b>		Y				Y		Y
<b>Madsen 2021</b>						Y		

	<b>Chew 2018<sup>225</sup></b>	<b>Dopp 2024<sup>226</sup></b>	<b>Karalexi 2020</b>	<b>Ludvigsson 2023<sup>227</sup></b>	<b>Miroshnychenko 2025b<sup>228</sup></b>	<b>Taylor 2024b<sup>229</sup></b>	<b>Thompson 2023<sup>230</sup></b>	<b>Zepf 2024<sup>231</sup></b>
<b>Martin 2021</b>		Y						
<b>Mehringner 2021</b>		Y						
<b>Miles 2006</b>			Y					
<b>Miles 1998</b>			Y					
<b>Millington 2022</b>						Y		
<b>Millington 2021</b>						Y		
<b>Millington 2019</b>						Y		
<b>Morningstar 2023</b>								Y
<b>Mullins 2021</b>		Y		Y		Y		
<b>Nokoff 2020</b>						Y		
<b>Nota 2019</b>					Y			
<b>Olsavsky 2023</b>		Y <sup>235</sup>			Y			
<b>Olson 2014</b>	Y	Y				Y		
<b>Olson 2022</b>		Y						
<b>Olson-Kennedy 2018a</b>		Y				Y		
<b>Perl 2021<sup>236</sup></b>		Y				Y		
<b>Perl 2020<sup>237</sup></b>		Y		Y		Y	Y	
<b>Pyra 2020</b>					Y			
<b>Ristori 2019</b>		Y						

<sup>235</sup> 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.

<sup>236</sup> 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.

<sup>237</sup> See above note.

	<b>Chew 2018<sup>225</sup></b>	<b>Dopp 2024<sup>226</sup></b>	<b>Karalexi 2020</b>	<b>Ludvigsson 2023<sup>227</sup></b>	<b>Miroshnychenko 2025b<sup>228</sup></b>	<b>Taylor 2024b<sup>229</sup></b>	<b>Thompson 2023<sup>230</sup></b>	<b>Zepf 2024<sup>231</sup></b>
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					

	<b>Chew 2018<sup>225</sup></b>	<b>Dopp 2024<sup>226</sup></b>	<b>Karalexi 2020</b>	<b>Ludvigsson 2023<sup>227</sup></b>	<b>Miroshnychenko 2025b<sup>228</sup></b>	<b>Taylor 2024b<sup>229</sup></b>	<b>Thompson 2023<sup>230</sup></b>	<b>Zepf 2024<sup>231</sup></b>
<b>van Goozen 1994</b>			Y					
<b>van Kesteren 1996</b>					Y			
<b>Vlot 2017</b>	Y	Y		Y	Y	Y		Y
<b>Wiepjes 2019</b>					Y			
<b>Wiepjes 2017</b>					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
<b>Dopp 2024</b> <sup>238</sup>	8 studies	_ <sup>239</sup>	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
<b>Miroshnychenko 2025b</b> <sup>240</sup>	1 comparative observational study and 1 before-after study	146 participants from 1 comparative study and 36 from 1 before-after study	Mean difference: -0.4 (95% confidence interval: -0.24 to 0.16) from 1 comparative study and Standardised mean change 0.26 lower (1.64 lower to 1.13 higher) from 1 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
<b>Taylor 2024b</b> <sup>241</sup>	1 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
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of gender dysphoria by CSH.	The certainty of evidence is very low.

<sup>238</sup> Dopp et al. (2024).

<sup>239</sup> 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).

<sup>240</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>241</sup> 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
<i>Global function</i>				
<b>Dopp 2024</b> <sup>242</sup>	21 studies	_243	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
<b>Miroshnychenko 2025b</b> <sup>244</sup>	2 prospective observational cohort studies; 2 before-after studies	125 from 2 prospective observational cohort studies; 73 participants from 2 before-after studies	Standardised mean difference: 0.87 higher (95% confidence interval: 0.25 lower to 2 higher) from 2 prospective observational cohort studies; Standardised mean change 0.25 higher (0.09 higher to 0.4 higher) from 2 before-after studies (higher score indicating better global function)	Very low certainty due to very serious risk of bias, serious imprecision and indirectness

<sup>242</sup> Dopp et al. (2024)

<sup>243</sup> 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.

<sup>244</sup> Miroshnychenko, Ibrahim, et al. (2025)

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b>Death by suicide</b>				
<b>Miroshnychenko 2025b</b> <sup>245</sup>	1 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)
<b>Self-harm and suicide</b>				
<b>Taylor 2024b</b> <sup>246</sup>	2 before-after, and 2 cross-sectional studies	99 participants from 2 before-after studies, and 293 participants from 2 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. <sup>247</sup>
<b>Depression</b>				
<b>Miroshnychenko 2025b</b> <sup>248</sup>	2 prospective observational cohort studies; 2 before-after studies	154 from 2 prospective observational cohort studies; 389 participants from 2 before-after studies	Standardised mean difference: 0.3 lower (95% confidence interval: 0.85 lower to 0.25 higher) from 2 prospective observational cohort studies; Standardised mean change 0.41 lower (0.65 lower to 0.17 lower) from 2 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

<sup>245</sup> Miroshnychenko, Ibrahim, et al. (2025)

<sup>246</sup> Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<sup>247</sup> 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).

<sup>248</sup> Miroshnychenko, Ibrahim, et al. (2025)

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b>Taylor 2024b<sup>249</sup></b>	1 cohort, 1 before-after, and 2 cross-sectional studies	23 participants from 1 cohort, 52 participants from 1 before-after, and 293 participants from 2 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.
<b>Anxiety</b>				
<b>Taylor 2024b<sup>250</sup></b>	1 cohort, 1 before-after, and 1 cross-sectional study	23 participants from 1 cohort, 52 participants from 1 before-after, and 19 participants from 1 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.
<b>Internalising problems</b>				
<b>Taylor 2024b<sup>251</sup></b>	1 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.

<sup>249</sup> Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<sup>250</sup> See above note.

<sup>251</sup> See above note.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b><i>Externalising problems</i></b>				
<b>Taylor 2024b</b> <sup>252</sup>	1 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.
<b><i>Psychological difficulties</i></b>				
<b>Taylor 2024b</b> <sup>253</sup>	1 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.
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of mental health by CSH.	The certainty of evidence is very low. <sup>254</sup>

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<sup>252</sup> See above note.

<sup>253</sup> See above note.

<sup>254</sup> 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
<i>Induced physical changes</i>				
<b>Dopp 2024<sup>255</sup></b>	14 studies	<sup>256</sup>	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
<b>Taylor 2024b<sup>257</sup></b>	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

<sup>255</sup> Dopp et al. (2024).

<sup>256</sup> 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.

<sup>257</sup> Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<b>Hormone level</b>				
<b>Taylor 2024b</b> <sup>258</sup>	15 studies including 2 cohort studies, 12 before-after studies, and 1 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
<b>Menstrual suppression</b>				
<b>Taylor 2024b</b> <sup>259</sup>	3 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
<b>Evidence synthesis</b>			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). <sup>260</sup>

<sup>258</sup> See note above.

<sup>259</sup> Taylor, Mitchell, Hall, Langton, et al. (2024).

<sup>260</sup> 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
<b>Dopp 2024</b> <sup>261</sup>	19 studies	_262	Side effects and complications were limited and did not have a major impact on treatment (e.g., rarely resulted in changed or discontinued medication). <sup>263</sup>	Very low certainty due to very serious risk of bias and serious indirectness
<b>Taylor 2024b</b> <sup>264</sup>	4 studies, including 1 cohort, and 3 before-after studies	17 participants from 1 cohort, and 184 participants from 3 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
<b>Evidence synthesis</b>			No conclusion can be drawn on the overall risks of side-effects of CSH.	The certainty of evidence is very low.
<b>Cardiovascular events</b>				
<b>Miroshnychenko 2025b</b> <sup>265</sup>	2 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

<sup>261</sup> Dopp et al. (2024).

<sup>262</sup> 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.

<sup>263</sup> 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.

<sup>264</sup> Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<sup>265</sup> Miroshnychenko, Ibrahim, et al. (2025).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b>Body mass index</b>				
<b>Taylor 2024b</b> <sup>266</sup>	16 studies (1 cohort, 14 before-after studies, and 1 cross-sectional study)	1275 participants	No change overall but some inconsistencies	There is insufficient evidence about the risks of hormone interventions
<b>Evidence synthesis</b>			For every 1,000 young people receiving CSH, 40 may experience cardiovascular events in 9 years.	The certainty of evidence is moderate to high.
<b>Bone health</b>				
<b>Dopp 2024</b> <sup>267</sup>	7 studies	_ <sup>268</sup>	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
<b>Ludvigsson 2023</b> <sup>269</sup>	3 observational cohort studies (2 retrospective and 1 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

<sup>266</sup> Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<sup>267</sup> Dopp et al. (2024).

<sup>268</sup> 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.

<sup>269</sup> Ludvigsson et al. (2023).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b>Miroshnychenko 2025b270</b>				
<ul style="list-style-type: none"> <li><b>Bone mineral density, femoral neck, long term follow-up assessed with: DXA, z scores scale (-3 to 3). Follow-up: 12 months</b></li> </ul>	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 3 levels)
<ul style="list-style-type: none"> <li><b>Bone mineral density, hip, long term follow-up assessed with: DXA, z scores scale (-3 to 3). Follow-up: 12–36 months</b></li> </ul>	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 3 levels)
<ul style="list-style-type: none"> <li><b>Bone mineral density, lumbar spine, long term follow-up assessed with: DXA, z scores scale (-3 to 3). Follow-up: 12–36 months</b></li> </ul>	2 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 3 levels)
<b>Taylor 2024b<sup>271</sup></b>	4 before-after studies	244 participants from 4 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

<sup>270</sup> Miroshnychenko, Ibrahim, et al. (2025).

<sup>271</sup> 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
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of CSH on bone health.	The certainty of evidence is very low.
<b>Fertility</b>				
<b>Dopp 2024</b> <sup>272</sup>	7 studies	_273	Studies documented healthy, viable oocyte or embryo cryopreservation after taking CSH and pausing for at least 3 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
<b>Taylor 2024b</b> <sup>274</sup>	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
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of CSH on fertility.	The certainty of evidence is very low.
<b>Sexual dysfunction</b> <sup>275</sup>				
<b>Miroshnychenko 2025b</b> <sup>276</sup>	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 6 months or 12 months of follow up.	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of CSH on sexual dysfunction.	The certainty of evidence is very low.

<sup>272</sup> Dopp et al. (2024).

<sup>273</sup> 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.

<sup>274</sup> Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<sup>275</sup> Evidence only on natal females.

<sup>276</sup> Miroshnychenko, Ibrahim, et al. (2025).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b>Cognitive</b>				
<b>Taylor 2024b</b> <sup>277</sup>	4 studies including 2 cohort studies and 2 cross-sectional studies	42 participants from 2 cohort studies and 71 participants from 2 cross-sectional studies	<p>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.</p> <p>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.</p>	There was insufficient evidence regarding changes to cognitive outcomes
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of CSH on cognitive outcomes.	The certainty of evidence is very low.
<b>Height/growth</b>				
<b>Taylor 2024b</b> <sup>278</sup>	7 studies including 1 cohort study and 6 before-after studies	43 participants from 1 cohort study and 563 participants from 6 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

<sup>277</sup> Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

<sup>278</sup> See note above.

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b>Body composition</b>				
<b>Taylor 2024b</b> <sup>279</sup>	2 studies including 1 cohort study and 1 cross-sectional study	28 participants from 1 cohort study and 35 participants from 1 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 2 years, but an increase at 3 years. Fat percentage and lean mass percentage remained stable.	There is insufficient evidence about the risks of hormone interventions
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of CSH on height/growth or body composition.	The certainty of evidence is very low.

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<sup>279</sup> 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
<b>Dopp 2024</b> <sup>280</sup>	13 studies	_281	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
<b>Evidence synthesis</b>			No conclusion can be drawn on the regret rate after CSH.	The certainty of evidence is very low.

<sup>280</sup> Dopp et al. (2024).

<sup>281</sup> 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<sup>282</sup>, 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.<sup>283</sup> 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.00000000000011734>

#### ***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.

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<sup>282</sup> Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).

<sup>283</sup> Becker-Hebly et al. (2021); Olson-Kennedy et al. (2018).

## 7.2 Low risk of bias systematic reviews

Of the two low risk of bias SRs,<sup>284</sup> Dopp 2024<sup>285</sup> included 18 studies (6 cross-sectional studies, 7 quasi-experimental studies, 1 cohort study, 3 case reports, and 1 qualitative study), and included all types of surgeries, though most of the included studies were on mastectomy. Miroshnychenko 2024<sup>286</sup> included 39 studies (3 comparative observational, 2 before–after, and 34 case series), and only assessed the effects of mastectomy. Three studies were included by both reviews.<sup>287</sup>

## 7.3 Outcome 1. Gender dysphoria

Two SRs assessed the impact of surgery on GD. Dopp 2024<sup>288</sup> narratively described that according to 10 studies mastectomy was associated with reduced GD. The certainty of evidence was low. Miroshnychenko and colleagues included 1 comparative observational study with 136 participants and 1 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.<sup>289</sup> Dopp 2024<sup>290</sup> 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<sup>291</sup> reported a lower level of distress measured by Kessler Psychological Distress from one comparative

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<sup>284</sup> Dopp et al. (2024); Miroshnychenko et al. (2024).

<sup>285</sup> Dopp et al. (2024).

<sup>286</sup> Miroshnychenko et al. (2024).

<sup>287</sup> Ascha et al. (2022); Marinkovic & Newfield (2017); Tang et al. (2022).

<sup>288</sup> Dopp et al. (2024).

<sup>289</sup> Dopp et al. (2024); Miroshnychenko et al. (2024).

<sup>290</sup> Dopp et al. (2024).

<sup>291</sup> 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<sup>292</sup> 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<sup>293</sup> concluded that side effects after surgeries, such as scarring or issues with function/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<sup>294</sup> 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,<sup>295</sup> 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

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<sup>292</sup> Miroshnychenko et al. (2024).

<sup>293</sup> Dopp et al. (2024).

<sup>294</sup> Miroshnychenko et al. (2024).

<sup>295</sup> 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 <sup>296</sup>	Miroshnychenko 2024 <sup>297</sup>	Thompson 2023 <sup>298</sup>
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 <sup>299</sup>	Y		
Cohen-Kettenis 1997 <sup>300</sup>	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	

<sup>296</sup> Dopp et al. (2024).

<sup>297</sup> Miroshnychenko et al. (2024).

<sup>298</sup> Thompson et al. (2023).

<sup>299</sup> 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.

<sup>300</sup> 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 <sup>296</sup>	Miroshnychenko 2024 <sup>297</sup>	Thompson 2023 <sup>298</sup>
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	
Mehringier 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	
Sir 2022		Y	
Skorochood 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
<b><i>Mastectomy</i></b>				
<b>Dopp 2024<sup>301</sup></b>	10 studies	_302	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.	Low certainty due to serious risk of bias and serious indirectness
<b>Miroshnychenko 2024<sup>303</sup></b>	1 comparative observational study and 1 before-after study	136 participants from 1 comparative observational study and 35 participants from 1 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
<b><i>Hysterectomy/ovariectomy and/or metoidioplasty or phalloplasty</i></b>				
<b>Dopp 2024<sup>304</sup></b>	4 studies	_305	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

<sup>301</sup> Dopp et al. (2024).

<sup>302</sup> 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).

<sup>303</sup> Miroshnychenko et al. (2024).

<sup>304</sup> Dopp et al. (2024).

<sup>305</sup> 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
<b><i>Vaginoplasty and/or mammoplasty</i></b>				
<b>Dopp 2024</b> <sup>306</sup>	5 studies	_ <sup>307</sup>	Vaginoplasty "bottom surgery" and/or mammoplasty "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
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of surgeries on gender dysphoria.	The certainty of evidence is very low.

<sup>306</sup> Dopp et al. (2024).

<sup>307</sup> 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
<i>Global function</i>				
<b>Dopp 2024</b> <sup>308</sup>	10 studies	_309	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
<b>Miroshnychenko 2024</b> <sup>310</sup>	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

<sup>308</sup> Dopp et al. (2024).

<sup>309</sup> 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).

<sup>310</sup> Miroshnychenko et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b>Depression</b>				
<b>Miroshnychenko 2024</b> <sup>311</sup>	1 before-after study <sup>312</sup>	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
<b>Suicide attempts</b>				
<b>Miroshnychenko 2024</b> <sup>313</sup>	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
<b>Non-suicidal Self-harm</b>				
<b>Miroshnychenko 2024</b> <sup>314</sup>	1 comparative observational study <sup>315</sup>	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
<b>Quality of life</b>				
<b>Miroshnychenko 2024</b> <sup>316</sup>	1 before-after study and 1 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

<sup>311</sup> Miroshnychenko et al. (2024).

<sup>312</sup> The supplementary information of this systematic review reported evidence based on case series, which did not change the certainty of evidence for this outcome.

<sup>313</sup> Miroshnychenko et al. (2024).

<sup>314</sup> Miroshnychenko et al. (2024).

<sup>315</sup> The supplementary information of this systematic review reported evidence based on case series, which did not change the certainty of evidence for this outcome.

<sup>316</sup> Miroshnychenko et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<i>Death by suicide</i>				
<b>Miroshnychenko 2024</b> <sup>317</sup>	1 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
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of mental health by surgeries.	The certainty of evidence is very low.

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<sup>317</sup> 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
<b>Dopp 2024<sup>318</sup></b>	10 studies	_ <sup>319</sup>	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
<b><i>Death as a postoperative complication of mastectomy</i></b>				
<b>Miroshnychenko 2024<sup>320</sup></b>	5 case series studies	3673	0 per 1,000 (0 to 0)	High certainty evidence
<b><i>Necrosis (complete and partial nipple/areola/nipple-areola complex/nipple graft necrosis)</i></b>				
<b>Miroshnychenko 2024<sup>321</sup></b>	8 case series studies	1998	30 per 1,000 (10 to 70)	High certainty evidence
<b><i>Necrosis (complete nipple/areola/nipple-areola complex/nipple graft necrosis)</i></b>				
<b>Miroshnychenko 2024<sup>322</sup></b>	13 case series studies	2236	20 per 1,000 (10 to 30)	High certainty evidence

<sup>318</sup> Dopp et al. (2024).

<sup>319</sup> 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).

<sup>320</sup> Miroshnychenko et al. (2024).

<sup>321</sup> Miroshnychenko et al. (2024).

<sup>322</sup> Miroshnychenko et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<i>Excessive Scarring</i>				
<b>Miroshnychenko 2024</b> <sup>323</sup>	12 case series studies	2405	50 per 1,000 (30 to 80)	High certainty evidence
<b>Evidence synthesis</b>			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.

<sup>323</sup> 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
<b>Dopp 2024</b> <sup>324</sup>	9 studies	_325	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
<b>Miroshnychenko 2024</b> <sup>326</sup>	4 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
<b>Evidence synthesis</b>			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.

<sup>324</sup> Dopp et al. (2024).

<sup>325</sup> 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 (Mehring 2021).

<sup>326</sup> Miroshnychenko et al. (2024).

## 8 Evidence synthesis: psychotherapy

There are five SRs assessing psychotherapy among children or adolescents with GD.<sup>327</sup> Only two were assessed as low risk of bias in the systematic review process.<sup>328</sup>

### 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.

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<sup>327</sup> Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).

<sup>328</sup> 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 systematic reviews**

Evidence on the effects of psychotherapy is limited. Dopp 2024<sup>329</sup> 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<sup>330</sup> 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

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<sup>329</sup> Dopp et al. (2024).

<sup>330</sup> Dopp et al. (2024).

systematic review by Heathcote and colleagues<sup>331</sup> 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.”<sup>35</sup> There has been very limited evidence on the role of psychotherapy in treating mental health problems co-occurring with GD,<sup>36</sup> 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.”<sup>37</sup>

### **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 as 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.

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<sup>331</sup> Heathcote et al. (2024).

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
<i>Peer group intervention</i>				
Dopp 2024 <sup>332</sup>	4 studies	_ <sup>333</sup>	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

<sup>332</sup> Dopp et al. (2024).

<sup>333</sup> 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
<b><i>Professional psychological support as a precondition for additional interventions for gender dysphoria</i></b>				
<b>Dopp 2024<sup>334</sup></b>	2 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
<b><i>Depression</i></b>				
<b>Heathcote 2024<sup>335</sup></b>	6 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.

<sup>334</sup> Dopp et al. (2024).

<sup>335</sup> Heathcote et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b>Anxiety</b>				
<b>Heathcote 2024<sup>336</sup></b>	3 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.
<b>Depression and anxiety combined</b>				
<b>Heathcote 2024<sup>337</sup></b>	1 study	n = 17	no significant, although marginal, difference from baseline to 6 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.

<sup>336</sup> Heathcote et al. (2024).

<sup>337</sup> Heathcote et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b><i>Internalising and externalising symptoms</i></b>				
<b>Heathcote 2024<sup>338</sup></b>	1 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.
<b><i>Emotional dysregulation</i></b>				
<b>Heathcote 2024<sup>339</sup></b>	1 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.

<sup>338</sup> Heathcote et al. (2024).

<sup>339</sup> Heathcote et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b>Suicidality</b>				
<b>Dopp 2024<sup>340</sup></b>	1 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 4 weeks post-intervention and were not large enough to represent clinically significant effects.	Very low certainty due to serious risk of bias and indirectness
<b>Heathcote 2024<sup>341</sup></b>	3 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.

<sup>340</sup> Dopp et al. (2024).

<sup>341</sup> Heathcote et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<b>Family support</b>				
<b>Dopp 2024</b> <sup>342</sup>	2 studies	_343	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
<b>Psychological change</b>				
<b>Heathcote 2024</b> <sup>344</sup>	5 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 3 months for self-compassion and 6 months for self-acceptance, but the difference was no longer observed for resilience at 3-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.

<sup>342</sup> Dopp et al. (2024).

<sup>343</sup> The sample size was not calculated because one study was an individual case report, and another was a report on parental rating.

<sup>344</sup> Heathcote et al. (2024).

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
<i>Psychosocial change</i>				
<b>Heathcote 2024<sup>345</sup></b>	5 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.
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of mental health by psychotherapy.	The certainty of evidence is very low.

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<sup>345</sup> Heathcote et al. (2024).

## 9 Evidence synthesis: social transition

Two SRs assessed the impact of social transition. Both are assessed as low risk of bias.<sup>346</sup>

### 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<sup>347</sup> 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 3 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.

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<sup>346</sup> Dopp et al. (2024); Hall et al. (2024).

<sup>347</sup> Hall et al. (2024).

### 9.3 Outcome 2. Mental health and wellbeing

As for mental health outcomes, Dopp 2024<sup>348</sup> 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<sup>349</sup> highlighted that the evidence on the impact of social transition for children and adolescents with GD is limited and low in quality. Most studies are cross-sectional, US-based, use non-representative samples, and lack 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<sup>350</sup> 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.

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<sup>348</sup> Dopp et al. (2024).

<sup>349</sup> Hall et al. (2024).

<sup>350</sup> 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 as 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
<i>Hall 2024<sup>351</sup></i>				
<b>Children</b>	2 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 3 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.
<b>Adolescents</b>	1 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.
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of social transition on gender dysphoria.	The certainty of evidence is very low. <sup>352</sup>

<sup>351</sup> Hall et al. (2024).

<sup>352</sup> 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
<b>Suicidality</b>				
<b>Dopp 2024</b> <sup>353</sup>	5 studies	_ <sup>354</sup>	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
<b>Hall 2024</b> <sup>355</sup>	2 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 <sup>356</sup> 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.

<sup>353</sup> Dopp et al. (2024).

<sup>354</sup> 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.

<sup>355</sup> Hall et al. (2024); Evidence comparing adolescents with gender dysphoria who have socially-transitioned with those who have not.

<sup>356</sup> 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
<b><i>Psychological functioning</i></b>				
Hall 2024 <sup>357</sup>	3 studies	n = 10,077 <sup>358</sup>	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.
<b><i>Non-clinical depression or mood symptoms</i></b>				
Dopp 2024 <sup>359</sup>	6 studies	_ <sup>360</sup>	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
<b><i>Depressive and anxiety symptoms</i></b>				
Hall 2024 <sup>361</sup>	2 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.

<sup>357</sup> Hall et al. (2024); Evidence comparing children with gender dysphoria who have socially-transitioned with those who have not.

<sup>358</sup> 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.

<sup>359</sup> Dopp et al. (2024).

<sup>360</sup> 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.

<sup>361</sup> 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
<b>Psychological distress</b>				
Hall 2024 <sup>362</sup>	1 study	n = 9,711 <sup>363</sup>	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.
<b>Other mental health outcomes</b>				
Dopp 2024 <sup>364</sup>	7 studies	_ <sup>365</sup>	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
<b>Evidence synthesis</b>			No conclusion can be drawn on the impact of mental health by social transition.	The certainty of evidence is very low. <sup>366</sup>

<sup>362</sup> See above note.

<sup>363</sup> 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.

<sup>364</sup> Dopp et al. (2024).

<sup>365</sup> 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.

<sup>366</sup> 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
<b>Dopp 2024</b> <sup>367</sup>	3 studies	_ <sup>368</sup>	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
<b>Evidence synthesis</b>			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.

<sup>367</sup> Dopp et al. (2024).

<sup>368</sup> 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., Champion, 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., Vrouwenraets, 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.

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