

## **An Evidence-Based Critique of “The Cass Review” on Gender-affirming Care for Adolescent Gender Dysphoria**

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### **Introduction**

In 2020, the United Kingdom’s National Health Service (NHS) commissioned an inquiry to provide recommendations for the healthcare of transgender adolescents. This process was overseen by a pediatrician named Dr. Hillary Cass and reached completion in April 2024. The final product is a 388-page report called the “Cass Review,”<sup>1</sup> (henceforth “the Review”) and is

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<sup>1</sup> The Cass Review, Final Report: Independent Review of Gender Identity Services for Children and Young People, April 2024, at [https://cass.independent-review.uk/wp-content/uploads/2024/04/CassReview\\_Final.pdf](https://cass.independent-review.uk/wp-content/uploads/2024/04/CassReview_Final.pdf)

accompanied by seven systematic reviews conducted by authors affiliated with the University of York (henceforth “the York SRs”).<sup>2</sup>

As researchers and pediatric clinicians with experience in the field of transgender healthcare, we read the Review with great interest. The degree of financial investment and time spent is impressive. Its ability to publish seven systematic reviews, conduct years’ worth of focus groups and deeply investigate care practices in the UK is admirable. We hoped it would improve the public’s awareness of the health needs of transgender youth and galvanize improvements in delivery of this care. Indeed, statements of the Review favorably describe the individualized, careful approach put forth by the World Professional Association for Transgender Health (WPATH) and the Endocrine Society.<sup>3</sup> Unfortunately, the Review repeatedly misuses data and violates its own evidentiary standards by resting many conclusions on speculation. Many of its statements and the conduct of the York SRs reveal profound misunderstandings of the evidence base and the clinical issues at hand. The Review also subverts widely accepted processes for development of clinical recommendations and repeats spurious, debunked claims about transgender identity and gender dysphoria. *These errors conflict with well-established norms of clinical research and evidence-based healthcare. Further, these errors raise serious concern about the scientific integrity of critical elements of the report’s process and recommendations.*

In the short time since its release, the Review has been used to justify restrictions on healthcare for transgender youth. In March 2024, the NHS announced that it would deny puberty-pausing medications to those under age 18 outside of a research setting.<sup>4</sup> In June 2024, the NHS Health

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<sup>2</sup> Taylor J, Hall R, Langton T, et al. Care pathways of children and adolescents referred to specialist gender services: a systematic review. *Archives of Disease in Childhood* Published Online First: 09 April 2024. doi: 10.1136/archdischild-2023-326760; Taylor J, Hall R, Langton T, et al. Characteristics of children and adolescents referred to specialist gender services: a systematic review. *Archives of Disease in Childhood* Published Online First: 09 April 2024. doi: 10.1136/archdischild-2023-326681; Hall R, Taylor J, Hewitt CE, et al. Impact of social transition in relation to gender for children and adolescents: a systematic review. *Archives of Disease in Childhood* Published Online First: 09 April 2024. doi: 10.1136/archdischild-2023-326112; Heathcote C, Taylor J, Hall R, et al. Psychosocial support interventions for children and adolescents experiencing gender dysphoria or incongruence: a systematic review. *Archives of Disease in Childhood* Published Online First: 09 April 2024. doi: 10.1136/archdischild-2023-326347; Taylor J, Mitchell A, Hall R, et al. Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: a systematic review. *Archives of Disease in Childhood* Published Online First: 09 April 2024. doi: 10.1136/archdischild-2023-326670; Taylor J, Mitchell A, Hall R, et al. Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: a systematic review. *Archives of Disease in Childhood* Published Online First: 09 April 2024. doi: 10.1136/archdischild-2023-326669; ; Taylor J, Hall R, Heathcote C, et al. Clinical guidelines for children and adolescents experiencing gender dysphoria or incongruence: a systematic review of guideline quality (part 1). *Archives of Disease in Childhood* Published Online First: 09 April 2024. doi: 10.1136/archdischild-2023-326499; Taylor J, Hall R, Heathcote C, et al. Clinical guidelines for children and adolescents experiencing gender dysphoria or incongruence: a systematic review of recommendations (part 2). *Archives of Disease in Childhood* Published Online First: 09 April 2024. doi: 10.1136/archdischild-2023-326500

<sup>3</sup> Coleman E, Radix AE, Bouman WP, et al. Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. *Int J Transgend Health*. 2022 Sep 6;23(Suppl 1):S1-S259. doi: 10.1080/26895269.2022.2100644. PMID: 36238954; PMCID: PMC9553112.; Hembree WC, Cohen-Kettenis PT, Louis Gooren L, et al. Endocrine Treatment of Gender Dysphoric/Gender Incongruent Persons: An Endocrine Society Clinical Practice Guideline, *The Journal of Clinical Endocrinology & Metabolism*, Volume 102, Issue 11, 1 November 2017, Pages 3869–3903, <https://doi.org/10.1210/jc.2017-01658>

<sup>4</sup><https://www.nhs.uk/conditions/gender-dysphoria/treatment/>

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Secretary cited the Review as the rationale for emergency regulations that criminalize the supply of puberty-pausing medications to new patients under 18 in England, Scotland, or Wales.<sup>5</sup> This ban, which applies only to the treatment of gender dysphoria, labeled these medications as a “serious danger to health.” These medications remain freely available for other pediatric health needs, of which precocious puberty, endometriosis, and fertility preservation prior to chemotherapy are some.<sup>6</sup>

The Cass Review has already been cited in U.S. legal battles over transgender rights.<sup>7</sup> It is likely to feature heavily in the months and years to come. From 2022 through 2024, twenty-five US states enacted legislation that bans gender-affirming healthcare for transgender youth. Litigation is ongoing in at least ten states, and the nation’s highest court has agreed to hear one case, *United States v Skremetti*, in the fall of 2024 term. Other nations’ health ministries are anticipated to use the Cass Review to inform their own policies on access to youth gender care.<sup>8</sup>

Amongst our author group, we have 86 years of experience in caring for 4800 transgender youth and have published 278 peer-reviewed studies, 168 of which are in the field of gender-affirming care. The holistic care that the clinicians among us provide is rooted in decades of research; it is not controversial in the world-class pediatric health centers where we practice. The research we conduct is ethical and valued by our peers in medicine and epidemiology. We can also speak to how the evidence informs the positive clinical outcomes that our patients experience.

We produced this report to emphasize the Review’s key tenets, to bring the critical yet buried findings to the forefront, and to provide evidence-informed critiques where merited. The transparency and expertise of our group starkly contrast with the Review’s authors. Most of the Review’s known contributors have neither research nor clinical experience in transgender healthcare. The Review incorrectly assumes that clinicians who provide and conduct research in transgender healthcare are biased. Expertise is not considered bias in any other realm of science or medicine, and it should not be here. Further, many of the Review’s authors’ identities are unknown.<sup>9</sup> Transparency and trustworthiness go hand-in-hand, but many of the Review’s authors cannot be vetted for ideological and intellectual conflicts of interest.

Our concerns about the Cass Review reflect the politicized context for transgender healthcare, especially for youth. Transgender people of all ages face a critical inflection point in the UK and across the globe today. If politics continue to interfere with transgender healthcare, clinical

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<sup>5</sup><https://www.gov.uk/government/news/new-restrictions-on-puberty-blockers#:~:text=The%20government%20has%20today%20introduced,June%20to%203%20September%202024.>

<sup>6</sup> <https://www.legislation.gov.uk/ukxi/2024/727/made>

<sup>7</sup> *Poe v Labrador*,

[https://www.supremecourt.gov/DocketPDF/23/23A763/300889/20240220100700247\\_Poe%20v%20Labrador%20SOTUS%20Application%20for%20Stay.pdf](https://www.supremecourt.gov/DocketPDF/23/23A763/300889/20240220100700247_Poe%20v%20Labrador%20SOTUS%20Application%20for%20Stay.pdf)

<sup>8</sup> <https://www.biobiochile.cl/noticias/nacional/chile/2024/05/29/pubertad-interrumpida-ninos-trans-inician-tratamiento-hormonal-en-medio-de-controversias.shtml>

<sup>9</sup> Following the completion of the “research programme” by the University of York, “A Clinical Expert Group (CEG) was established by the Review to help interpret the findings” (p 26), defined as “clinical experts on children and adolescents in relation to gender, development, physical and mental health, safeguarding and endocrinology” (p 62). There is no further information about the qualifications of the members of the CEG, nor how they were selected.

services and research in this field may not recover. Peoples' lives will be drastically—and needlessly—upended. Further, the politicization of healthcare is a concern not just for transgender people, but for all people. Every person deserves the opportunity to make private and deeply personal medical decisions in consultation with healthcare providers whose work is guided by sound evidence, appropriate training, and clinical expertise.

With these stakes in mind, the medical community, policymakers, and the media must understand what the Review is and what it is not. *It is* an important document for those considering the availability of health services for transgender young people in the UK. *It is* an attempt to engage many parties, some of whom have ideological opinions that conflict with medical consensus. *It is not* an authoritative guideline or standard of care, nor is it an accurate restatement of the available medical evidence on the treatment of gender dysphoria. *It is not* an effective framework for enhancing clinical services for a marginalized group of people. *Foremost, it is not an endorsement of a ban on medical care for transgender youth.*

### **Executive Summary:**

Section 1: The Cass Review makes statements that are consistent with the models of gender-affirming medical care described by WPATH and the Endocrine Society. The Cass Review does not recommend a ban on gender-affirming medical care.

Section 2: The Cass Review does not follow established standards for evaluating evidence and evidence quality.

Section 3: The Cass Review fails to contextualize the evidence for gender-affirming care with the evidence base for other areas of pediatric medicine.

Section 4: The Cass Review misinterprets and misrepresents its own data.

Section 5: The Cass Review levies unsupported assertions about gender identity, gender dysphoria, standard practices, and the safety of gender-affirming medical treatments, and repeats claims that have been disproved by sound evidence.

Section 6: The systematic reviews relied upon by the Cass Review have serious methodological flaws, including the omission of key findings in the extant body of literature.

Section 7: The Review's relationship with and use of the York systematic reviews violates standard processes that lead to clinical recommendations in evidence-based medicine.

**Section 1: The Cass Review makes statements that are consistent with the models of gender-affirming medical care described by WPATH and the Endocrine Society. The Cass Review does not recommend a ban on gender-affirming medical care.**

## An Evidence-Based Critique of the Cass Review

The Review concurs with the WPATH Standards of Care and the Endocrine Society Clinical Practice Guidelines that: (1) medical care is appropriate for some transgender youth, (2) a holistic, comprehensive, and individualized assessment is needed, and (3) co-occurring mental health conditions should be properly treated before medically affirming interventions. The Review also cites a York SR that favorably appraises the WPATH Standards of Care 8 and the 2017 Endocrine Society Clinical Practice Guidelines.<sup>10</sup> Exemplary quotes from the Review and the Guidelines in each of these areas appear in Table 1.

The Review *does not* conclude that gender-affirming medical care for adolescent gender dysphoria should be banned. Thus, it should not be cited in support of bans on medical treatments for gender dysphoria. Rather, the Review favorably describes the provision of individualized, evidence-informed clinical care, including robust assessments of the various medical and non-medical domains of support that an adolescent may require.

### *Agreement that certain youth with gender dysphoria benefit from medical care*

The Review explicitly notes that, “for some, the best outcome will be transition” (p 21) while also acknowledging, as the WPATH Standards of Care and the Endocrine Society Clinical Practice Guidelines do, that gender-affirming medical interventions are not appropriate for all transgender adolescents. This is an essential point, as many who criticize this care inappropriately contend that medical consensus endorses medical transition for any minor seeking care. The Review states, and indeed WPATH and the Endocrine Society agree, that “there should be a clear rationale for providing hormones at this stage rather than waiting until an individual reaches 18.” (p 187)

While the Review contains some non-technical language regarding gender-affirming medical interventions (e.g., “the review would recommend extreme caution”), it is essential to note that this language is followed by recommendations to conduct thoughtful, cautious assessments prior to considering medical care, rather than banning care or not providing it altogether.

### *Agreement on the need for a holistic, comprehensive, and individualized assessment and treatment plan*

The WPATH Standards of Care and the Endocrine Society Clinical Practice Guidelines emphasize that an individualized, comprehensive biopsychosocial evaluation should be conducted prior to gender-affirming medical interventions during adolescence.<sup>5,6</sup> These assessments involve a careful evaluation of a young person’s gender history, social supports, fertility considerations, and co-existing mental health challenges, among a broad range of other topics.<sup>11</sup>

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<sup>10</sup> The Review produces data that rates the WPATH Standards of Care 8 and the 2017 Endocrine Society Clinical Practice Guidelines among the top five of 23 analyzed documents (p 129), using the AGREE II tool. Further, the Review appraises these guidelines as particularly high in the areas of “rigor of development” and “editorial independence.”

<sup>11</sup> Turban, J. L., Thornton, J., & Ehrensaft, D. (2024). Biopsychosocial Assessments for Pubertal Suppression to Treat Adolescent Gender Dysphoria. *Journal of the American Academy of Child and Adolescent Psychiatry*, S0890-8567.

The Review reads: “When conducting an assessment, it will be important that clinicians are mindful that presentations, pathways and outcomes for this cohort are very individual, and the focus needs to be on helping each person find the best pathway for them. Assessments should be respectful of the individual’s experience and be developmentally informed.” (p 28) The Review highlights that the assessment process should include, “co-develop[ing] a plan for addressing gender issues, which may involve any combination of social, psychological and physical interventions.” This widely used approach aims to create a comprehensive support plan that may involve non-medical and/or medical interventions, depending on the clinical scenario.

*Agreement that optimized treatment of co-occurring mental health conditions is essential*

WPATH and the Endocrine Society consistently highlight that comprehensive care for transgender youth includes optimal treatment of any other mental health conditions, with appropriate evidence-informed medical and/or non-medical interventions.<sup>5, 6</sup> The Review states, as youth gender experts would agree, “for those young people for whom a medical pathway is clinically indicated, it is not enough to provide this without also addressing wider mental health and/or psychosocially challenging problems such as family breakdown, barriers to participation in school life or social activities, bullying and minority stress.” (p 30) There is no evidence that co-occurring mental health conditions cause a person to adopt a transgender identity, nor is there evidence to support that treatment of co-occurring mental health disorders ameliorates the core symptoms of gender dysphoria. Individual patients require treatment plans that are tailored to the diagnoses made by qualified professionals.

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Table 1: Shared core principles between the Cass Review, the Endocrine Society Clinical Practice Guidelines and WPATH's Standards of Care 8 <sup>12</sup>	
<p><i>Agreement that certain youth with gender dysphoria will benefit from medical aspects of gender affirming care</i></p>	<p>Cass Review: “The skills of those working within the service need to reflect the broad and varied needs of this heterogeneous group and the service needs to include the appropriate skill mix to support both individuals for whom medical intervention is clinically indicated and those for whom it is not.” (p 37)</p> <p>Endocrine Society: “We suggest that adolescents who meet diagnostic criteria for GD [gender dysphoria]/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development.” (p 3871)</p> <p>WPATH SOC 8: “For example, some youth will realize they are transgender or more broadly gender diverse and pursue steps to present accordingly. For some youth, obtaining gender-affirming medical treatment is important while for others these steps may not be necessary. For example, a process of exploration over time might not result in the young person self-affirming or embodying a different gender in relation to their assigned sex at birth and would not involve the use of medical interventions.” (p S51)</p>
<p><i>Agreement regarding the need for a holistic, comprehensive, and individualized assessment and treatment plan</i></p>	<p>Cass Review: “When conducting an assessment, it will be important that clinicians are mindful that presentations, pathways and outcomes for this cohort are very individual, and the focus needs to be on helping each person to find the best pathway for them. Assessments should be respectful of the individual’s experience and be developmentally informed.” (p 28)</p> <p>Endocrine Society: “Gender-affirming treatment is a multidisciplinary effort. After evaluation, education, and diagnosis, treatment may include mental health care, hormone therapy, and/or surgical therapy” (p 3871)</p> <p>WPATH SOC 8: “We recommend health care professionals involve relevant disciplines, including mental health and medical professionals, to reach a decision about whether puberty suppression, hormone initiation, or gender-related surgery for gender diverse and transgender adolescents are appropriate and remain indicated throughout the course of treatment until the transition is made to adult care” (p S48)</p>
<p><i>Agreement that optimized treatment of co-occurring mental health conditions is essential</i></p>	<p>Cass Review: “Standard evidence based psychological and psychopharmacological treatment approaches should be used to support the management of the associated distress and co-occurring conditions. This should include support for parents/carers and siblings as appropriate” (p 31)</p> <p>Endocrine Society: “Adolescents are eligible for GnRH agonist [and subsequent sex hormone] treatment if: any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent’s situation and functioning are stable enough to start treatment.” (p 3878)</p> <p>WPATH SOC 8: “We recommend health care professionals assessing transgender and gender diverse adolescents only recommend gender-affirming medical or surgical treatments requested by the patient when... the adolescent’s mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and/or gender-affirming medical treatments have been addressed.” (p S48)</p>

<sup>12</sup> While not a guideline, the American Academy of Pediatrics (AAP) Practice Statement on Gender Affirming Care is often referenced by policymakers and the media. Its core themes also align with the areas discussed in Table 1. For instance, “The decision of whether and when to initiate gender-affirmative treatment is personal and involves careful consideration of risks, benefits, and other factors unique to each patient and family.” and “Many protocols suggest that clinical assessment of youth who identify as TGD is ideally conducted on an ongoing basis in the

## **Section 2: The Cass Review does not follow established standards for evaluating evidence and evidence quality.**

The Review casually discusses evidence quality and does not define it, contravening standard practice in scientific evaluations of medical research. Here, we compare the Review's approach with one of the most widely accepted frameworks for determining evidence quality: Grading of Recommendations Assessment, Development and Evaluation (GRADE).<sup>13</sup> According to GRADE, *well-conducted* randomized controlled trials (RCTs) and systematic reviews (SRs) are typically considered the highest-quality form of evidence. Observational studies rarely meet the criteria to be considered high quality evidence,<sup>14</sup> and yet they supply most of the evidence that guides clinical care across all fields of medicine.

As the drafters of the GRADE framework have explicitly acknowledged, evidence and its quality are one of many considerations in caring for patients.<sup>15</sup> Clinical practice guidelines throughout medicine consider all relevant factors, but the Review takes the unusual step of elevating its own assessment of evidence quality above the considerations that guideline developers value. The Review also uses misleading, subjective terminology and misuses technical language regarding evidence quality. In any other field of medicine, this practice would be deemed unacceptable and harmful to patients.

### *The Review's discussion of evidence quality is scientifically unsound*

Under GRADE, quality designations such as “high”, “moderate”, “low” and “very low” are used to describe evidence.<sup>10</sup> There is a shared understanding of what these terms mean in medical science, which allows experts to use them in developing clinical recommendations for broad application.

The Review introduces GRADE (p 55) but never evaluates the evidence using the GRADE framework. The Review borrows GRADE terminology in repeatedly expressing a desire to see “high quality” evidence dominate the field of transgender health. Thus, the Review falls seriously short in not describing or applying a formal method for assigning evidence quality.

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setting of a collaborative, multidisciplinary approach, which, in addition to the patient and family, may include the pediatric provider, a mental health provider (preferably with expertise in caring for youth who identify as TGD), social and legal supports, and a pediatric endocrinologist or adolescent-medicine gender specialist, if available.” (p 5)

<sup>13</sup> This is the only evidence grading system that uses quality terminology to our knowledge and is widely respected in the medical community. It was also used by both the Endocrine Society and WPATH in developing the guidelines. The Review describes GRADE (p 55) but does not state that it used this method, or any other method, to appraise evidence. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008 May 3;336(7651):995-8. doi: 10.1136/bmj.39490.551019.BE. PMID: 18456631; PMCID: PMC2364804.

<sup>14</sup> An observational study can be deemed high quality if it shows a large effect, if biases in the study design lead to an underestimation of the treatment effect and if the effect is dose-dependent (meaning the magnitude of effect depends on the amount of intervention). This is often not the case in observational studies.

<sup>15</sup> Balshem H, et al., GRADE Guideline: 3. Rating the Quality, 64 *J. Clin. Epidem.* 401, 402-404 (2011).



Thus, the Review speaks a language that may seem familiar, but its foundations are pseudoscientific and subjective. For instance, unscientific evidence quality descriptors such as “weak” and “poor” were identified 21 times and 10 times respectively.<sup>16</sup> The Review’s reliance on such ambiguous terms leads readers to draw their own conclusions, which may not be scientifically informed. Such terms also undermine the rigor of the actual research, which presents much more nuanced findings than subjective descriptors convey.

*The Review fixates on evidence quality to the exclusion of many other factors that are rigorously considered by the developers of clinical practice guidelines*

In developing guidelines that provide recommendations on clinical care, panels of experts consider the evidence of a treatment’s efficacy. They also consider the benefits and harms of both treatment and no treatment, patients’ values and preferences, and the resources required to offer treatment.<sup>17</sup> *This is precisely why evidence quality is not synonymous with clinical recommendations.*

On the surface, it may seem perplexing that clinical care does not proceed directly from medical evidence. But if this were the case, real patients in the real world would not receive appropriate, feasible care that aligns with their preferences and values. GRADE, for instance, describes four areas that guideline developers should rigorously consider in issuing recommendations: evidence certainty and quality, balance between benefits and harms, patient values and preferences, and resource utilization. Here, we show how the Review’s consideration of three of these areas is inadequate.

1. Evidence certainty and quality: The Review does not describe the positive outcomes of gender-affirming medical treatments for transgender youth, including improved body satisfaction, appearance congruence, quality of life, psychosocial functioning, and mental health, as well as reduced suicidality. *It is highly unusual for a document issuing clinical recommendations to not sufficiently describe of the evidence on the effects of treatment.*
2. Balance of benefits and harms: The Review does not consider the harms of not offering gender-affirming medical care to a young person with gender dysphoria. The most concrete and tangible effect of not providing treatment is the development of permanent physical characteristics that do not align with a person’s gender. These include voice deepening, hair growth, breast tissue development, final height, or body habitus. The Review ignores the significant psychological pain suffered by patients with gender dysphoria, for whom these permanent physical changes are highly distressing. The Review also ignores the consequences for teens who, left untreated, must present to the world a physical appearance that is at odds with their own identity. In adulthood, these physical effects can be ameliorated to some degree with costly and invasive treatments such as surgery, hair removal, and speech therapy. These treatments do not erase the

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<sup>16</sup> “Weak” or “weakness”: p 13, 20, 22, 25 (twice), 31, 33, 36, 44, 47, 77, 163, 164, 184, 196, 202, 210, 222, 229, 231, and 320; “poor”: p 30, 34, 114, 130 (twice), 134, 154, 179, 193, 194, and 385

<sup>17</sup> Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Graham R, Mancher M, Miller Wolman D, et al., editors. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US); 2011. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK209539/> doi: 10.17226/13058

intervening years of psychological distress. The Review also selectively identifies the purported harms of treatment while failing to engage with the harms of no treatment. For example, the Review theorizes that those who have been treated with puberty-pausing medications and wish to pursue vaginoplasty may have a more challenging postoperative course.<sup>18</sup> But the Review does not consider how puberty-pausing medications prevent development of unwanted breast tissue and can prevent the later need for mastectomy, which is a commonly sought surgery by transgender adults.<sup>15</sup>

3. Patient values and preferences: The Review does engage with transgender young people, but it often makes recommendations that conflict with their expressed values and preferences. The prevailing theme of the focus groups with transgender youth is that they want improved access to appropriate gender-affirming medical services from clinicians who have appropriate training and experience. They want their needs and concerns taken seriously. *The Review completely disregards the expressed values and preferences of transgender youth in its most emphatic recommendation, which is to limit care to research settings that do not yet exist.*

#### *The Review solicited invalid professional viewpoints*

The Review conducted a series of focus groups with healthcare workers of varying backgrounds, some of whom are not even clinicians. It is not clear what the expertise of these individuals might be in the field of transgender health. Of note, 34% stated that their understanding of “gender questioning children and young people” came from the public discourse and the media. Further, 32% of respondents strongly agreed or agreed with the statement “There is no such thing as a trans child.”<sup>19,20</sup> *Denying the existence of transgender people of any age is an invalid professional viewpoint. The involvement of those with such extreme viewpoints is a deeply concerning move for a document that issues recommendations on clinical care.* A guideline that solicits opinions from those that will not acknowledge the condition for which care is sought should not be used. These individuals may express these ideological views, but their involvement in a process that led to recommendations for clinical care is a failure of the Review.

#### *The Review fails to recognize the nuances of evidence quality measures*

In fixating on evidence to make recommendations for patient care, the Review bets the house on a concept that itself has flaws. The usefulness of evidence quality terminology is thoughtfully debated in the medical community. Different assessors often disagree and make divergent evidence quality assessments. There are no well-described processes by which such disagreement should be resolved. With more research, the quality of evidence in many fields of medicine does not improve, as the study designs needed to detect smaller and smaller effects

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<sup>18</sup> van de Grift TC, van Gelder ZJ, Mullender MG, et al. Timing of Puberty Suppression and Surgical Options for Transgender Youth. *Pediatrics*. 2020 Nov;146(5):e20193653. doi: 10.1542/peds.2019-3653. PMID: 33106340.

<sup>19</sup> Horton, C. (2024). The Cass Review: Cis-supremacy in the UK’s approach to healthcare for trans children. *International Journal of Transgender Health*, 1–25. <https://doi.org/10.1080/26895269.2024.2328249>

<sup>20</sup> <https://cass.independent-review.uk/wp-content/uploads/2022/03/REPORT-Cass-Review-professional-panel-FINAL.pdf>

become infeasible.<sup>21</sup> Thus, many areas of medicine may have inherent, real-world upper limits on quality of evidence—and that level of quality rarely accords with the theoretical ideal described by evidence-grading methodologies.

Proponents of restrictions on healthcare for transgender youth often call attention to the purported absence of high-quality evidence in this field. If high-quality evidence were a prerequisite for medical care, we would all be worse off. Moderate, low, and very low-quality evidence (using the terms as defined in GRADE) informs necessary, valued care at every stage of life. A review of Cochrane systematic reviews across numerous areas of medicine showed that 86.5% of reviews reported moderate (30.8%), low (31.4%), and very-low (24%) levels of evidence.<sup>17</sup> Less than 1 in 7 systematic reviews had evidence of high quality for a primary outcome and less than 1 in 5 systematic reviews had evidence of high quality for any outcome.<sup>22</sup> The authors found that the quality of evidence in 52 areas of medicine was often not high. These areas included procedures and treatments in fields as diverse as anesthesia, breast cancer, cystic fibrosis, pancreatic disease, blood cancers, multiple sclerosis, obstetrics, schizophrenia, and stroke, among many others. Further, there is no published research showing that evidence quality designations improve patient care.<sup>23</sup>

*The Review's call for "high-quality" evidence is inappropriate*

The Review's calls for "high-quality" evidence in the care of transgender youth cannot be separated from the fact that evidence deemed high-quality by systems like GRADE most often comes from RCTs.<sup>24</sup> In any area of medicine, the presence or absence of "high-quality evidence" alone should not be used to decide whether to offer a treatment that has been shown to be beneficial, and care in any area of medicine should not be stopped while awaiting specific study designs. Moreover, RCTs specifically are ill-suited to studying the effects of many interventions on psychological wellbeing and quality of life of trans people.<sup>25</sup> For the following ethical and methodological reasons, the type of evidence that the Review advocates for is neither possible nor appropriate in the field of gender-affirming care.

1. *Masking*: This is the process that blinds participants and investigators to whether patients receive treatment or placebo. Puberty-pausing medications and gender-affirming

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<sup>21</sup> Howick J, Koletsi D, Pandis N, et al. The quality of evidence for medical interventions does not improve or worsen: a meta-epidemiological study of Cochrane reviews. *J Clin Epidemiol.* 2020 Oct;126:154-159. doi: 10.1016/j.jclinepi.2020.08.005. Epub 2020 Sep 2. PMID: 32890636.

<sup>22</sup> Fleming PS, Koletsi D, Ioannidis JP, Pandis N. High quality of the evidence for medical and other health-related interventions was uncommon in Cochrane systematic reviews. *J Clin Epidemiol.* 2016 Oct;78:34-42. doi: 10.1016/j.jclinepi.2016.03.012. Epub 2016 Mar 29. PMID: 27032875.

<sup>23</sup> Kavanagh BP. The GRADE system for rating clinical guidelines. *PLoS Med.* 2009 Sep;6(9):e1000094. doi: 10.1371/journal.pmed.1000094. Epub 2009 Sep 15. PMID: 19753107; PMCID: PMC2735782.

<sup>24</sup> Guyatt GH, Oxman AD, Kunz R, et al HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? *BMJ.* 2008 May 3;336(7651):995-8. doi: 10.1136/bmj.39490.551019.BE. PMID: 18456631; PMCID: PMC2364804.

<sup>25</sup> This article presents an in-depth analysis of why the RCT model is inappropriate: Ashley, F., Tordoff, D. M., Olson-Kennedy, J., & Restar, A. J. (2023). Randomized-controlled trials are methodologically inappropriate in adolescent transgender healthcare. *International Journal of Transgender Health*, 1–12. <https://doi.org/10.1080/26895269.2023.2218357>

hormones have physiologically evident impact. Those who were randomized into the treatment arm would clearly notice lack of physical change from pausing puberty or physical changes related to hormone therapy. Those in a non-treatment arm would experience obvious gender-incongruent physical change. *Thus, masking is impossible.*

2. *Adherence*: Individuals with gender dysphoria seek a difficult-to-access, much desired treatment. Being placed into the non-treatment arm would likely lead to their discontinuation in the study to pursue treatment elsewhere. *Thus, adherence would be severely compromised.*
3. *Coercion*: Coercion occurs when research participation is one of the only ways to obtain a much-needed treatment. Coercion, even when unintended, should be avoided in study design. An RCT model to assess whether to give medically affirming interventions to youth with gender dysphoria may appeal to those who cannot obtain affirming interventions another way. Per international regulations on medical and scientific ethics, coercion, even when unintended, must be avoided in study design.<sup>26</sup> *Restricting all care to a research setting, as recent UK rules have done based on the Review, is coercive and unethical.*
4. *Generalizability*: Coercion is not only unethical, but it also draws a population into research that likely does not resemble the wider population who may benefit from treatment. *Thus, generalizability is not achievable with a coercive RCT model.*

### **Section 3: The Cass Review fails to contextualize the evidence for gender-affirming care with the evidence base for other areas of pediatric medicine.**

Despite the Review's recommendations, the continuum of research and care for transgender youth is well-aligned with standards across pediatrics. Here, we discuss how the Review fails to recognize the intricacies of pediatric research and how other types of pediatric care have comparable evidence and practices to care for transgender youth but are not targeted for comparable restrictions.

*The Review fails to recognize the realities and nuances of pediatric medical research*

The Review expresses an appropriate desire to see longer, larger studies on the impacts of gender-affirming medical treatment, and this aligns with leading organizations' views. The Review's desire to see only high-quality evidence dominate this field, however, is not realistic or appropriate *because no other area of pediatrics is held to this standard.*

Research in youth gender care involves pediatric patients and thus, is subject to unique, necessary considerations that are not present in adult research. These considerations include:

1. *Consent*: Informed consent and voluntary participation form the bedrock of ethical research. Minors cannot independently consent, and parents must be heavily involved. Many pediatric trials have failed to launch because the necessary but arduous informed consent process meant too few participants were recruited.<sup>13</sup> (RCTs must enroll large numbers of study subjects to detect an effect.) Combining the need for parental

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<sup>26</sup> The Declaration of Helsinki outlines authoritative ethical principles for research with human subjects. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>

involvement and the problem of coercion, issues with consent would most certainly limit large-scale enrollment for an RCT in youth gender care.

2. *Rarity*: Conditions that affect children are often different from and/or rarer than those that affect adults. Thus, these conditions must be studied in different ways.
3. *Different physiology*: Children and adolescents have a different physiology compared to adults. Medications used in a pediatric setting have different pharmacokinetic and pharmacodynamic properties.
4. *Inadequate resources*: Legislative and policy initiatives significantly underfund pediatric research relative to research on adult care. Even with governmental and private sector investment, the annual number of published pediatric RCTs is already far less than amongst adults and is decreasing.<sup>27</sup>

### *Parallels between youth gender care and other aspects of pediatric care*

In an interview, Dr. Cass said, “I can’t think of any other situation where we give life-altering treatments and don’t have enough understanding about what’s happening to those young people in adulthood.”<sup>28</sup> In fact, due to the realities of the research dynamics described above, many pediatric medical treatments are based on limited research.

While no comparison is perfect, parallels between gender-affirming medical care and other areas of pediatrics are abundant. All types of pediatric practices begin with a dearth of evidence and yet must deliver care to a heterogeneous population in need. An exhaustive and nuanced analysis of evidence-based pediatric medicine is outside the scope of this report, but we discuss some practices within pediatric and neonatal critical care. The practices we discuss are based on less-than-high-quality evidence (by definitional standards) and—like gender-affirming care for transgender youth—were guided by informed clinical practice and became accepted in high-stakes scenarios even while long-term data are still in the process of being collected.

Neonatology is the care of critically ill, often preterm infants. Pediatric critical care deals with the care of children and teens with unstable, life-threatening medical conditions, including sepsis, brain injuries, organ failure, and cancer crises. Clinicians in these fields routinely make hundreds (if not thousands) of high-stakes, evidence-informed decisions for their patients each day. These decisions are often not as straightforward as those that are life-or-death:

1. Should a premature infant with respiratory problems be supported with a breathing tube or a non-invasive measure? When and how should that support be weaned to see if the infant can breathe on their own?

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<sup>27</sup> A review of publication trends in adult versus pediatric RCTs demonstrated that adult RCTs increased by 4.71 RCTs/year, while pediatric RCTs only increased by 0.44 RCTs per year from 1985-2004. From 2005-2018, adult RCTs increased by 5.1 RCTs per year, while pediatric RCTs decreased by 0.4 RCTs per year. Cohen E, Uleryk E, Jasuja M, Parkin PC. An absence of pediatric randomized controlled trials in general medical journals, 1985-2004. *J Clin Epidemiol.* 2007 Feb;60(2):118-23. doi: 10.1016/j.jclinepi.2006.03.015. Epub 2006 Nov 13. PMID: 17208117., Groff ML, Offringa M, Emdin A, , et al. Publication Trends of Pediatric and Adult Randomized Controlled Trials in General Medical Journals, 2005–2018: A Citation Analysis. *Children.* 2020; 7(12):293. <https://doi.org/10.3390/children7120293>

<sup>28</sup> Ghorayshi A. “Hilary Cass Says U.S. Doctors Are ‘Out of Date’ on Youth Gender Medicine” *New York Times.* Accessed May 30, 2024.

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2. Should a premature infant whose mother cannot produce breast milk be given synthetic formula or donor breast milk? One predisposes to severe intestinal infections while the other is associated with slow weight gain.
3. What is the best way to manage intravenous fluids to support blood pressure in a child with life-threatening systemic infection (i.e., sepsis)? Too much could tax the heart and the kidneys and too little could limit oxygen delivery to the body's tissues, which are in dire need.

The evidence that helps answer these and other questions is rarely “high quality” (as the term is used in GRADE).<sup>29</sup> And yet, clinical outcomes are good and improving: more children leave intensive care units better off than ever before.<sup>30</sup> Most aspects of neonatal and pediatric critical care became accepted clinical practice because of their immediate and short-term benefits, without following patients into adulthood. Even now, the degree to which children discharged from intensive care achieve full neuro-developmental and functional recovery is not well-known and this is a new, active area of research in the critical care world. The quest for longer and more data is never-ending, but when the answers are not available, patients cannot wait for care.

Perhaps the newest area is in the use of glucagon-like peptide-1 (GLP-1) analogues for treatment of pediatric metabolic syndrome.<sup>31</sup> Children now have pre-diabetes, non-alcoholic fatty liver disease, high blood pressure, sleep apnea and other health issues at higher rates than ever before. We are gravely concerned about a generation of youth aging into adulthood with devastatingly high rates of illnesses that increase the risk of early death. In light of these concerns, these medications are now recommended for children. The evidence on GLP-1s can be critiqued in many of the same ways that transgender healthcare is. GLP-1s in children have only been studied for 1-2 years. We do not yet know what the long-term impacts of profound weight loss in adolescence are on bones and disordered eating. Will they be able to enjoy food in adulthood? Can these medications ever be stopped without rebound weight gain?

In youth gender care, we have evidence that these medications effectively treat gender dysphoria, that young people continue these medications into adulthood, that their satisfaction with gender-

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<sup>29</sup> We sourced literature on evidence quality in many areas of neonatal and pediatric care. In lieu of a thorough inventory, we present evidence quality in the care of neonatal respiratory distress syndrome. In guidelines on the care of premature infants with severe breathing difficulty, 92% of recommendations were based on expert consensus (33%), very low (25%), low (12%), or moderate (16%) quality evidence. Huang Y, Zhao J, Hua X, et al. Guidelines for high-flow nasal cannula oxygen therapy in neonates (2022). *J Evid Based Med*. 2023; 16: 394–413. <https://doi.org/10.1111/jebm.12546>; Zhang, Z., Chen, L., Cai, H. *et al*. Low Quality Evidence Supporting Recommendations in the 2021 Sepsis Guideline: An Indication for Precise Medicine?. *Intensive Care Res* 2, 23–25 (2022). <https://doi.org/10.1007/s44231-022-00007-2>

<sup>30</sup> Pollack MM, Banks R, Holubkov R, Meert KL; and the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Long-Term Outcome of PICU Patients Discharged With New, Functional Status Morbidity. *Pediatr Crit Care Med*. 2021 Jan 1;22(1):27-39. doi: 10.1097/PCC.0000000000002590. PMID: 33027242; PMCID: PMC7790876.; Biban P, Marlow N, Te Pas AB, et al. Advances in Neonatal Critical Care: Pushing at the Boundaries and Connecting to Long-Term Outcomes. *Crit Care Med*. 2021 Dec 1;49(12):2003–2016. doi: 10.1097/CCM.0000000000005251. PMID: 34380942.

<sup>31</sup> Hampl SE, Hassink SG, Skinner AC, et al. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. *Pediatrics*. 2023 Feb 1;151(2):e2022060640. doi: 10.1542/peds.2022-060640. Erratum in: *Pediatrics*. 2024 Jan 1;153(1):e2023064612. doi: 10.1542/peds.2023-064612. PMID: 36622115.

affirming medical treatments is high, that their bone density recovers after puberty-pausing medications, and that their transgender identities persist.

*The point is not to compare to the point of destructive criticism. The point is that careful use of the treatment options we have now, with the best evidence we have, defines pediatric care. We invite those who are interested in the care of transgender youth to consider the wide range of practices within pediatrics where the long-term effects are not well known. Children benefit from innovative medical treatments that improve their survival and quality of life. Pediatric care would all but cease if physicians denied treatments for which the evidence base is imperfect.*

*The Review has outsized and vague concerns about long-term data*

It is difficult to discern validity in the Review's preoccupation with long-term data in youth gender care. It claims there is no long-term data, but does not define what it considers "long-term" to mean; it does not describe what long-term outcomes would satisfy its concerns, and does not consider evidence that has followed patients for over a decade.<sup>32</sup> The Review expects researchers to report on the solitary, long-term impacts of puberty-pausing medications, but these medications are nearly always part of a staged process that includes other treatments. Further, the Review expects an abundance of long-term data on treatments that have only been more readily available for gender-affirming purposes over the past 8-10 years. The medical community's ability to describe transgender patients' experiences is commensurate with the improved access to care over the past decade.

While long-term data is costly and difficult to obtain, the field of transgender health is meeting this challenge at exactly the appropriate time. Clinician researchers representing 39 studies in the US have been awarded \$12.1 million by the National Institutes of Health (NIH) to study the physiologic and psychosocial impacts of this care in thousands of patients over the years to come, with direct applicability to transgender youth.<sup>33</sup>

#### **Section 4. The Cass Review misinterprets and misrepresents its own data.**

The Review leverages the UK's National Health Service (NHS) to gather a great deal of data about youth gender services in the UK. Indeed, the reason that the Review was initially commissioned was to address the failure of the NHS to provide timely, competent, and high-quality care to transgender youth across the country. This valuable information sheds light on the needs of the UK's population of transgender youth, the barriers they face in the pursuit of care, and intricacies of the burdened system. These data, when carefully examined, are a significant

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<sup>32</sup> One of the York systematic reviews omitted a study presenting the longest outcome data regarding bone density. This 2023 study described normal bone density after 11 years of gender affirming hormone treatment. The Review mentions this landmark study only passingly and without recognizing its key findings. van der Loos MATC, Vlot MC, Klink DT, et al. Bone Mineral Density in Transgender Adolescents Treated With Puberty Suppression and Subsequent Gender-Affirming Hormones. *JAMA Pediatr.* 2023 Dec 1;177(12):1332-1341. doi: 10.1001/jamapediatrics.2023.4588. PMID: 37902760; PMCID: PMC10616766.

<sup>33</sup> This is a non-systematic, non-exhaustive search of the NIH RePORTER database of awarded grants. This search does not include any research that may be privately funded.

contribution to the field of transgender health. But the Review’s interpretation and representation of these data are often incorrect.

One of the Review’s central points is that the UK’s rise in referrals is so dramatic that it cannot be explained by social acceptance of transgender identity. This position is repeated throughout its 388 pages and best expressed here:

“While it certainly seems to be the case that there is much greater acceptance of trans identities, particularly among younger generations, which may account for some of the increase in numbers, the exponential change in referrals over a particularly short five-year timeframe is very much faster than would be expected for normal evolution of acceptance of a minority group.” (p 26)

If the expectation is that referral trends conform to the “normal evolution of acceptance for a minority group,” one would expect the Review to define this concept. It does not. This is not surprising: there is no so-called normative pattern of social acceptance for a minority group. This is one of many grave and misleading errors packed into this statement. While we agree that referrals to gender-competent services are increasing, we disagree with the way that increase is described. In this section, we use the Review’s own data to show why.

An increase in referrals is not cause for concern. A referral for evaluation does not equate to the provision of gender-affirming medical care. Some youth who are referred will be treated, while others will not. Each referral signifies at least one thoughtful conversation between a pediatric clinician, a young person, and their family. Pediatric clinicians in the UK who ask thoughtful questions about gender identity should be applauded for considering their patients’ needs in a holistic, patient-centered, and non-judgmental fashion.

*The Review does not accurately describe trends in referrals*

Here, we show the Review’s most complete depiction of GID referral data here with emphasis on our areas of concern.<sup>34</sup> The Review’s interpretation of this data is that it shows an “exponential” increase from 2010-2022, particularly for those assigned female sex at birth. However, this graph clearly depicts a leveling off followed by a decrease in referrals, starting in 2018. This leveling off *predates the COVID-19 pandemic* and cannot be explained by

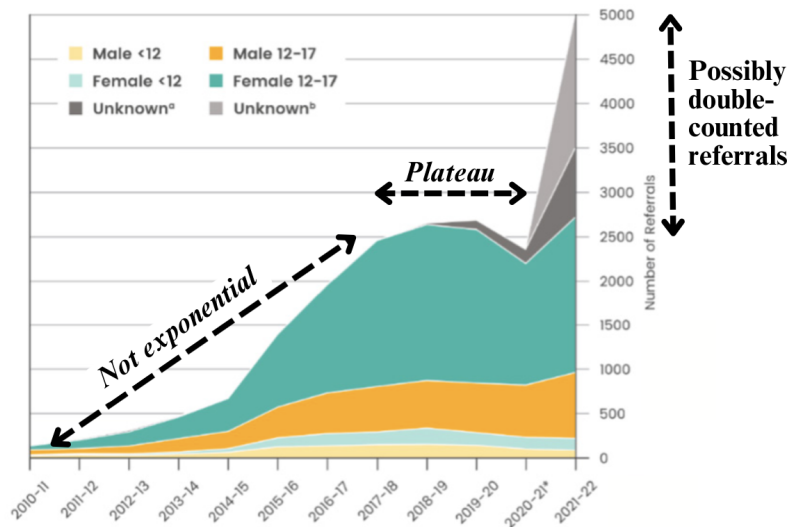


Figure 1: The Review's referral increases are not exponential and do not consistently increase. Graphed data shown above includes double-counted referrals.

<sup>34</sup> Partial reproductions of this data are shown twice in the Review (p 24 and 72). “Figure 11” is the only time that the entire referral dataset is graphically depicted.



the resource limitations imposed by a public health emergency. Further, there is a clear plateau in the *accurately* recorded data from 2017 to 2022. Data shaded in gray are described as potentially representing *double-counted* referrals: the figure caption in the Review states that there “is a strong possibility that there was double counting during 2021/22,” indicated by the gray areas under the curve. Single data points should not be counted multiple times and doing so may overestimate the referral numbers by as much as 100%.

Despite the Review’s repeated claims, the increase in referrals to the UK’s Gender Identity Service *is not exponential*. An exponential increase describes a particular type of growth pattern where there is a fixed time interval over which the quantity increases by a certain factor, and then over that same time interval the quantity again increases by that factor. Even if one considers the double-counted referrals, there is no discernable exponential pattern. A mathematical, logarithmic transformation of the data shows this. While there certainly is an increase in referrals, describing this increase as “exponential” is a serious error that fuels concern that the Review is too often more interested in subjective polemics than in scientific accuracy. This language has been cited in US litigation justifying bans on gender-affirming care.<sup>35</sup>

*What the Review’s data actually describes*

The Review’s referral data demonstrates one objective fact: most transgender adolescents in the UK are not referred for care. There are likely about 44,000 transgender adolescents in the UK based on 2021 census data.<sup>36</sup> Every year people age into and out of this figure. With 3585 referrals reported as in 2021 (and less in years prior), we can safely assume that less than 10% of all youth who may benefit from care have received any opportunity to do so.

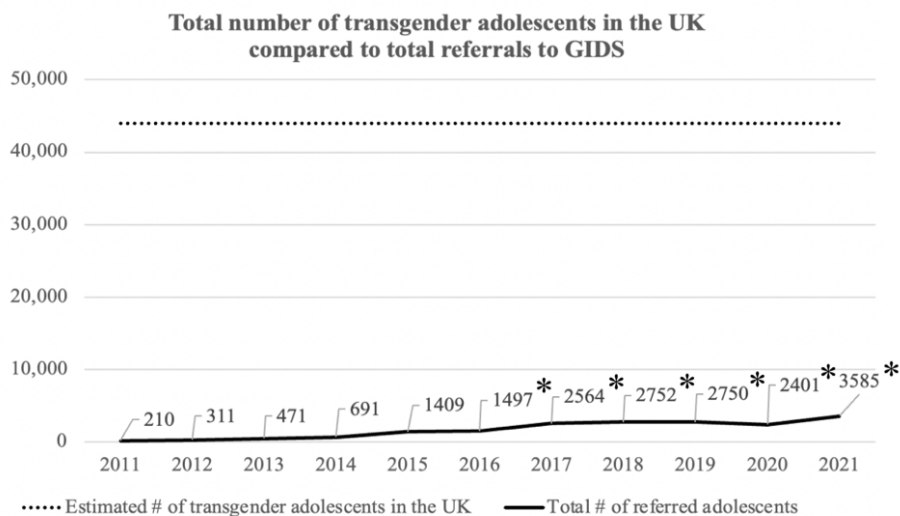


Figure 2: Comparing a population prevalence estimate of transgender-identifying youth in the UK to those who received referrals to GIDS from 2011-2021, \* indicates referrals that may be double-counted

<sup>35</sup> In a filing with the US Supreme Court in *Poe v Labrador*, the Attorney General of Idaho states “For reasons no one knows, gender dysphoria has grown exponentially among young people. App.D.74, 80–82, 84–85, 92, 104–05. Indeed, diagnoses increased ten-fold between 2009 and 2016. Dr. Hilary Cass, Independent Review of Gender Identity Services for Children and Young People: Interim Report 33 (Feb. 2022), <https://bit.ly/4bzkiJI> (“Cass Review”).”

<sup>36</sup> We use a conservative prevalence estimate of 0.6% being transgender, and about 7.4 million adolescents in the UK using Office for National Statistics data. (Other population estimates project that about 1% of people in the UK are transgender.) Youth disclosing self-identification as transgender has likely increased over the past several years. However, this is distinct from our population of interest for this particular point as we seek to describe youth who are transgender and may wish to consider the opportunity to discuss specialized, supportive interventions. Gender

Figure 2 shows a graph plotting total referred adolescents against an estimation of the total population of transgender youth in the UK. One thing is abundantly clear: the gap between youth who may benefit from care and those who receive even the first opportunity to consider this care is astronomical. The Review is overly concerned with overtreating this population, but the data are clear that transgender youth in the UK are vastly underserved, just as they are throughout the world.

*The Review wrongly contends that gender-affirming care is rushed, careless, and common*

Without evidence, the Review states that “practitioners abandoned normal clinical approaches to holistic assessment” (p 13) and that puberty-pausing medications are “available in routine clinical practice.” (p 25) However, the Review’s own data shows that about 178 youth with gender dysphoria in the UK currently receive medications that pause puberty. It is difficult to see how a medication is both “routine” and only in use by 0.0024% of the adolescent population.<sup>31</sup> The Review’s own data lends insight into how hard it is to access care within the UK’s NHS, and the slow, careful decision making that characterizes this care. First, it reports over two years of waiting for assessment. (p 77) Then, of the 3306 patients seen twice in the GIDS clinic or discharged from April 2018-December 2022, only 27% (892) were referred to endocrinology for consideration and consultation of medical interventions.<sup>37</sup> (p 168) Those referrals were preceded by an average of 6.7 appointments, often with several months between each appointment. Of those seen by endocrinology, 81.5% received puberty-pausing treatment (about half of whom were 15-16 years old which is on the upper end of the age spectrum in which these medications are even usable).<sup>38</sup>

These trends are not unique to the UK. Throughout the world, wait lists are long<sup>39,40</sup> and only a small proportion of youth with gender dysphoria receive medical interventions.<sup>41,42</sup> In the United

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identity: age and sex, England and Wales: Census 2021. Accessed June 15, 2024.

<https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/genderidentity/articles/genderidentityageandsexenglandandwalescensus2021/2023-01-25#how-gender-identity-age-and-sex-profiles-varied-across-england-and-wales>

<sup>37</sup> Based on the data provided in Appendix 8 of the Review.

<sup>38</sup> This is not an age at which a patient is likely to benefit from puberty pausing medication, as most youth have completed puberty at this time.

<sup>39</sup> Strauss, P., Winter, S., Waters, Z., Wright Toussaint, D., Watson, V., & Lin, A. (2022). Perspectives of trans and gender diverse young people accessing primary care and gender-affirming medical services: Findings from Trans Pathways. *International Journal of Transgender Health*, 23(3), 295–307. <https://doi.org/10.1080/26895269.2021.1884925>

<sup>40</sup> Reporting wait times globally of several months to several years: Kearns S, Kroll T, O’Shea D, Neff K. Experiences of transgender and non-binary youth accessing gender-affirming care: A systematic review and meta-ethnography. *PLOS ONE*. 2021;16(9). doi:10.1371/journal.pone.0257194; *Reporting an average wait time in a Canadian clinic of 269 days*: Lawson ML, Gotovac S, Couch B, Gale L, Vander Morris A, Ghosh S, Bauer G. Pathways to care for adolescents attending a first hormone appointment at Canadian Gender Affirming Medical Clinics: A cross-sectional analysis from the Trans Youth Can! Study. *Journal of Adolescent Health*. 2024;74(1):140-147. doi:10.1016/j.jadohealth.2023.07.021

<sup>41</sup> Respaut R, Terhune C. Putting numbers on the rise in children seeking gender care. Reuters. October 6, 2022. Accessed May 31, 2024. <https://www.reuters.com/investigates/special-report/usa-transyouth-data/>.

<sup>42</sup> In a large study from the Netherlands, the percentage of evaluated patients who started treatment has decreased over time. Diagnostic criteria for treatment remain stringent, but the threshold for seeking an evaluation is likely

States, an analysis of insurance claims showed that 2-4% of youth diagnosed with gender dysphoria receive puberty-pausing medications or gender-affirming hormones. The data are clear: most transgender youth do not receive medical treatments for gender dysphoria, despite the supportive international medical consensus and evidence documenting the benefits of this care.

**Section 5. The Cass Review levies unsupported assertions about gender identity, gender dysphoria, standard practices, and the safety of gender-affirming medical treatments, and it repeats claims that have been disproved by sound evidence.**

While the Review places a high value on evidence quality and certainty, its recommendations frequently emanate from insufficiently supported assertions that have been disproven by scientific evidence. A recent commentary describes at least eight instances where the Review's citation of a peer-reviewed study was blatantly incorrect.<sup>43</sup> Here, we discuss major areas where unfounded speculation dominates the Review's contents.

*The Review speculates that social transition and puberty-pausing medications may cause harm by putting youth onto a medical path*

The Review expresses concern that early supportive interventions, such as social transition and puberty-pausing medications, lock young people into irreversible care: "...it is clear that social transition is cause for concern for many people," and that it may "[culminate] in medical intervention which will have lifelong implications." (p 158) The Review also states that "those who had socially transitioned at an earlier age and/or prior to being seen in clinic were more likely to proceed to a medical pathway" and that "the vast majority of young people... proceed from puberty blockers to masculinising/feminising hormones." (p 83)

The Review claims that these interventions may "change the trajectory of psychosexual and gender identity development." (p 83) There is no description of how developmental trajectories might be impacted, nor are any data cited. The Review contends that youth who transition may miss a purportedly valuable opportunity to experience adulthood as the gender they do not identify with: "In the absence of any experience as an adult ciswoman, they may have no frame of reference to cause them to regret or detransition, but at the same time they may have had a different outcome without medical intervention and would not have needed to take life-long hormones." (p 195) This statement ties back to our earlier concern that the Review's fixation on over-treating occurs without reciprocal consideration for the harm a transgender youth endures when undergoing puberty that opposes their identity. It is completely unscientific and inappropriate to expect a young person, regardless of their gender identity, "try out" life as a gender they do not identify with - as the Review supposes transgender youth should.

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lower. van der Loos MA, Klink DT, Hannema SE, et al., Children and adolescents in the Amsterdam Cohort of Gender Dysphoria: trends in diagnostic- and treatment trajectories during the first 20 years of the Dutch Protocol The Journal of Sexual Medicine, Volume 20, Issue 3, March 2023, Pages 398–409, <https://doi.org/10.1093/jsxmed/qdac029>

<sup>43</sup> Grijseels, D. M. (2024). Biological and psychosocial evidence in the Cass Review: a critical commentary. *International Journal of Transgender Health*, 1–11. <https://doi.org/10.1080/26895269.2024.2362304>

The Review's own data show that most referred patients are never subsequently referred to pediatric endocrinology and even fewer receive medical interventions (See Section 4). While most who receive puberty-pausing medications do then choose to pursue gender-affirming hormones, not all do.<sup>44</sup> Also, we emphasize that continuation of care is not a negative outcome. The Review does not consider the most likely explanation for why most youth who receive early, supportive interventions continue onto gender-affirming hormone therapy: *that they are indeed transgender*. It is not social transition and puberty-pausing medications that drive a persistent transgender identity. It is a transgender identity that drives social transition and subsequent medical interventions.

### *The Review's statements about "desistance" are unsupported*

Studies in the 1980s demonstrated that most gender non-conforming children would not meet criteria for gender dysphoria after progression through puberty. These studies conflated concepts of gender identity, sexual orientation, and behavior inappropriately. From this arose the concept of "desistance," meant to describe youth who met criteria for a now outdated diagnosis of "gender identity disorder"<sup>45</sup> as pre-pubertal children but no longer did after they entered puberty. *This is not the same as a loss of transgender identity.*

Studies that claim high rates of "desistance" in children rely on data collected before there was a formal definition for gender dysphoria. Children's behaviors<sup>46</sup> were classified as "gender non-conforming" if they did not adhere to gender stereotypes.<sup>47</sup> The Review cites such studies uncritically, even though their findings have no relationship to a contemporary understanding of gender. Concerningly, despite stating opposition to so-called conversion therapy, the Review favorably cites literature proposing methods that claim to suppress transgender identity in

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<sup>44</sup> In these studies, continuation rates range from 96-98%. Wiepjes, C. M., Nota, N. M., de Blok, C. J. M., Klaver, M., de Vries, A. L. C., Wensing-Kruger, S. A., de Jongh, R. T., Bouman, M. B., Steensma, T. D., Cohen-Kettenis, P., Gooren, L. J. G., Kreukels, B. P. C., & den Heijer, M. (2018). The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. *The journal of sexual medicine*, 15(4), 582–590. <https://doi.org/10.1016/j.jsxm.2018.01.016>; Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. *Pediatrics*. 2020 Apr;145(4):e20193006. doi: 10.1542/peds.2019-3006. PMID: 32220906; Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S, Skageberg EM, Khadr S, Viner RM. 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*. 2021 Feb 2;16(2):e0243894. doi: 10.1371/journal.pone.0243894. PMID: 33529227; PMCID: PMC7853497.

<sup>45</sup> "Gender identity disorder" was eliminated from the DSM-V because this diagnosis pathologized gender nonconformity, which is a natural state of being. "Gender dysphoria" is the most contemporary term and guides our modern understanding of distress related to incongruence between gender identity and one's physical body.

<sup>46</sup> Green et al 1987 noted that boys with effeminate traits (i.e. playing with dolls) were more likely to identify as cisgender males with same sex-attraction as adults. Parents provided report, children were never directly observed, and no patients with gender dysphoria are reported to have been enrolled. All early studies on "persistence" of gender identity from childhood to adolescence are reviewed in: Ristori J, Steensma TD. Gender dysphoria in childhood. *Int Rev Psychiatry*. 2016;28(1):13-20. doi: 10.3109/09540261.2015.1115754. Epub 2016 Jan 12. PMID: 26754056.

<sup>47</sup> Temple Newhook, J., Pyne, J., Winters, K., et al (2018). A critical commentary on follow-up studies and "desistance" theories about transgender and gender-nonconforming children. *International Journal of Transgenderism*, 19(2), 212–224. <https://doi.org/10.1080/15532739.2018.1456390>; Ansara, Y. G., & Hegarty, P. (2011). Cisgenderism in psychology: pathologising and misgendering children from 1999 to 2008. *Psychology & Sexuality*, 3(2), 137–160. <https://doi.org/10.1080/19419899.2011.576696>

children<sup>48</sup> and uses the “desistance” data from this literature unquestioningly. One piece of useful information from the older studies on gender identity in childhood bears emphasis here: true cross-gender identification — *being* a different gender rather than *acting* like a different gender — is one of the predictors of persistence of gender identity into adulthood.<sup>49</sup> The Review cites the study that draws this conclusion but does not note this core finding that has been widely acknowledged by those with clinical expertise in the field.

*The Review’s statements about “regret” and “detransition” are unsupported*

Clinicians who work with transgender people of any age, including youth, follow expert standards of care and adhere to ethical practices that guide them in engaging patients in serious discussions of their full range of options and the associated possible outcomes, including the rare possibilities of regret, treatment discontinuation, and re-identification with birth-assigned sex. And while these outcomes are similar, they are not synonymous. A person who regrets receiving care may continue to identify as transgender; another who stops medications may not experience regret, and one who stops identifying as transgender may not regret receiving medical care. It is exceedingly rare that an individual would later determine that they are not transgender.<sup>50</sup>

The Review’s own data contradicts its assertion that “The percentage of people treated with hormones who subsequently detransition remains unknown.” (p 33)<sup>51</sup> In its an audit of 3,306 patient records from its Gender Identity Service, the Review reports that “< 10 patients detransitioned back to their [birth-registered] gender.” (p 168) *This is a “detransition” rate of 0.3%.*

The Review’s data is consistent with robust, long-term studies on regret, medication discontinuation and re-identification with birth-assigned sex. Amongst 882 youth with gender dysphoria in the Netherlands who received puberty suppression, 1% discontinued this medication due to resolution of gender dysphoria.<sup>52</sup> Amongst 720 youth in the Netherlands with gender dysphoria who received puberty suppression and gender-affirming hormones, 98% continued

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<sup>48</sup> Per one such individual: “In my view, offering treatment to a child (either on his or her own or through parental consent) can be justified for a relatively simple reason. Cross gender identification constitutes a potentially problematic developmental condition. Taken to its extreme, the outcome appears to be transsexualism. To make children feel more comfortable about their sex does not, in my view, constitute an unreasonable treatment goal. Although there is considerable disagreement about how one might achieve this aim, the goal itself seems relatively benign.” (Zucker, 1985, p. 117) Zucker, K. J. (1985). Cross-gender-identified children. *Gender Dysphoria*, 75–174. [https://doi.org/10.1007/978-1-4684-4784-2\\_4](https://doi.org/10.1007/978-1-4684-4784-2_4)

<sup>49</sup> Steensma, T. D., McGuire, J. K., Kreukels, B. P., Beekman, A. J., & Cohen-Kettenis, P. T. (2013). Factors associated with desistance and persistence of childhood gender dysphoria: a quantitative follow-up study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 52(6), 582-590.

<sup>50</sup> Cavve et al found that 1% of youth who received gender-affirming medications re-identified with their birth-assigned sex: Cavve BS, Bickendorf X, Ball J, et al. Reidentification With Birth-Registered Sex in a Western Australian Pediatric Gender Clinic Cohort. *JAMA Pediatr*. 2024;178(5):446–453. doi:10.1001/jamapediatrics.2024.0077

<sup>51</sup> The Review defines “detransition” as “the process of discontinuing or reversing a gender transition, often in connection with a change in how the individual identifies or conceptualises their sex or gender since initiating transition.” (p 239)

<sup>52</sup> van der Loos et al. (2023).

gender-affirming hormones as adults.<sup>53</sup> Among 196 youth receiving care in Western Australia's Gender Diversity Service, 1% who received gender-affirming medications re-identified with their birth assigned sex.<sup>54</sup> These studies report findings in well-resourced, nationalized health systems where insurance lapses are rare and care is reliably accessible. These studies could have been systematically reviewed, but they were not.

While no comparable national registry exists in the United States, a survey of 27,715 transgender adults describes the challenges associated with changes in gender expression. Of the 13.1% who reported “living as [their] sex assigned at birth, at least for a while” after pursuing some form of transition, 82.5% reported familial pressure, social pressure, employment difficulty, inability to access care, and financial reasons as influential factors.<sup>55</sup> These reasons do not pertain to a change in identity, but rather the systemic and structural social forces that stigmatize and ostracize transgender people. Other studies have similarly found a variety of reasons that people may temporarily pause or discontinue treatment.<sup>56</sup> These reasons include not only the external pressures cited above but also the fact that, for some transgender people, gender is a journey rather than binary existence or a single destination. People may access hormone therapy for a specific period of time in order to achieve their gender goals—such as feeling comfortable in their body as a non-binary person—and cessation of treatment does not indicate “detransition” or regret, but rather a level of comfort and body satisfaction that could not have been realized without medical treatment.

Rather than consider these studies, the Review relies research plagued by poor methodology, heavy selection bias, and sampling from anti-transgender websites.<sup>57,58</sup> In many of the studies it cites, “detransition” is vaguely defined and incorrectly conflated with discontinuing treatment.<sup>59</sup>

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<sup>53</sup> van der Loos MA, Hannema SE, Klink DT, et al. Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: A cohort study in the Netherlands. *The Lancet Child & Adolescent Health*. 2022;6(12):869-875. doi:10.1016/s2352-4642(22)00254-1 (hereinafter, “van der Loos et al. 2022”).

<sup>54</sup> Cavve BS, Bickendorf X, Ball J, et al. Reidentification With Birth-Registered Sex in a Western Australian Pediatric Gender Clinic Cohort. *JAMA Pediatr*. 2024;178(5):446–453. doi:10.1001/jamapediatrics.2024.0077

<sup>55</sup> Turban JL, Loo SS, Almazan AN, Keuroghlian AS. Factors Leading to "Detransition" Among Transgender and Gender Diverse People in the United States: A Mixed-Methods Analysis. *LGBT Health*. 2021 May-Jun;8(4):273-280. doi: 10.1089/lgbt.2020.0437. Epub 2021 Mar 31. PMID: 33794108; PMCID: PMC8213007.

<sup>56</sup> A qualitative study of 28 adults with heterogeneous gender identities; a majority of respondents reported no decisional regrets about gender-affirming interventions. MacKinnon KR, Kia H, Salway T, et al. Health Care Experiences of Patients Discontinuing or Reversing Prior Gender-Affirming Treatments. *JAMA Netw Open*. 2022;5(7):e2224717. doi:10.1001/jamanetworkopen.2022.24717

<sup>57</sup> Littman 2018 was an anonymous online survey of 100 “detransitioners” who were recruited on social media, professional listservs, and snowball sampling. Many online communities for detransitioned individuals have been co-opted by anti-trans social media users, including the subreddit Littman references r/detrans. With these sampling and recruitment methods, there is a high risk of bias.

<sup>58</sup> Vandebussche through an online survey of 237 self-identified detransitioning respondents. Participants were recruited from r/detrans, private Facebook groups, public Instagram and Twitter posts, and www.post-trans.com, “a platform for female detransitioners.” Vandebussche E. (2022). Detransition-Related Needs and Support: A Cross-Sectional Online Survey. *Journal of homosexuality*, 69(9), 1602–1620. <https://doi.org/10.1080/00918369.2021.1919479>

<sup>59</sup> The Review cites Hall et al. (2021), an adult study where “detransition” is vaguely defined. These authors report that 12/175 “detransitioned” but 4 were later re-referred and two expressed regret about transition. The Review also

The Review criticizes and ultimately discards numerous rigorous research studies on transgender identity and medical treatments for gender dysphoria in youth, while confidently citing pseudoscience in support of outdated and debunked notions around rare phenomena like regret after gender-affirming care.<sup>52,53</sup> In considering the value of the Review's contributions to the field of transgender health, this discrepancy should not be overlooked.

### *The Review reanimates the debunked notion of “social contagion”*

The Review repeatedly describes “peer and socio-cultural influence” as driving the increase in referrals. The theory that such factors influence gender identity development in youth originates from a single article<sup>60</sup> that has been heavily corrected for numerous well-documented fatal flaws.<sup>61</sup> Using sound methods, no link has been found between peer influence and gender identity development.<sup>62</sup> A more plausible and appropriate explanation for the increase in referrals to gender-competent services exists: there is greater awareness and acceptance of gender diversity and improved access to effective medical care with insurance coverage. In some countries, including the UK per the Review's own data (Section 4), referrals to gender services are leveling off.<sup>63</sup> Further, the Review's own data casts doubt on its claims about dramatically increasing referrals (Section 4).

While coming out as transgender may come as a surprise to people in a young person's life, disclosure often occurs several years after a transgender person realizes their gender. A large study of 27,715 transgender adults found that gender identity disclosure predates one's knowledge of gender identity by an average of 14 years.<sup>64</sup> Further, 40.8% of transgender adults reported realizing their gender identity after 10 years of age. A study of 173 adolescents under 16 years attending their first referral visit for hormone suppression or gender-affirming hormones found that the majority of participants (56.4%) had realized their gender identity within three years of their referral.<sup>65</sup> Many factors have been analyzed to see if they correlate with recency of

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cites Boyd et al. (2022), an adult study which found that 8/41 participants ceased hormone therapy, half of whom reported “detransition” or a change in gender identity as a cause.

<sup>60</sup> Littman L. Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. *PLoS One*. 2018 Aug 16;13(8):e0202330. doi: 10.1371/journal.pone.0202330. Erratum in: *PLoS One*. 2019 Mar 19;14(3):e0214157. PMID: 30114286; PMCID: PMC6095578.

<sup>61</sup> Restar AJ. Methodological Critique of Littman's (2018) Parental-Respondents Accounts of "Rapid-Onset Gender Dysphoria". *Arch Sex Behav*. 2020 Jan;49(1):61-66. doi: 10.1007/s10508-019-1453-2. Epub 2019 Apr 22. PMID: 31011991; PMCID: PMC7012957.

<sup>62</sup> Bauer GR, Lawson ML, Metzger DL, Do Clinical Data from Transgender Adolescents Support the Phenomenon of “Rapid Onset Gender Dysphoria”?, *The Journal of Pediatrics*, Volume 243, 2022, Pages 224-227.e2, ISSN 0022-3476, <https://doi.org/10.1016/j.jpeds.2021.11.020>. (hereinafter, “Bauer et al. 2022”).

<sup>63</sup> Indremo M, Jodensvi AC, Arinell H, Isaksson J, Papadopoulos FC. Association of Media Coverage on Transgender Health With Referrals to Child and Adolescent Gender Identity Clinics in Sweden. *JAMA Netw Open*. 2022;5(2):e2146531. doi:10.1001/jamanetworkopen.2021.46531

<sup>64</sup> Turban JL, Dolotina B, Freitag TM, King D, Keuroghlian AS. Age of Realization and Disclosure of Gender Identity Among Transgender Adults. *J Adolesc Health*. 2023 Jun;72(6):852-859. doi: 10.1016/j.jadohealth.2023.01.023. Epub 2023 Mar 17. PMID: 36935303.

<sup>65</sup> Bauer GR, Pcaud D, Couch R, et al. Trans Youth CAN! Research Team. Transgender Youth Referred to Clinics for Gender-Affirming Medical Care in Canada. *Pediatrics*. 2021 Nov;148(5):e2020047266. doi: 10.1542/peds.2020-047266. Epub 2021 Oct 7. PMID: 34620727.

gender knowledge, including having gender-supportive or transgender online friends.<sup>66</sup> And despite the repeated concern that gender diversity amongst youth is somehow new, ethnographic and historical accounts of transgender youth date back to the 19th century and further, youth have sought medically-affirming interventions since the 1920s.<sup>67</sup>

Any discussion of social contagion naturally leads to what *does* shape gender identity. Gender identity has strong biological underpinnings that do not completely overlap with sex assigned at birth. In the truest scientific sense, gender and sex are multidimensional concepts with complex expressions that are related—and distinct from each other—in ways that modern science is still exploring.<sup>68</sup> What we do know, however, is that gender identity is as real for transgender people as it is for cisgender people. Drawing on outdated and biased notions that being transgender is a pathological condition, however, the Review still attempts to find additional explanations for “the cause” of being transgender. It circumvents the known science by drawing a flawed parallel between gender diversity and cancer:

“Expressions of being human vary greatly in how much biological versus psychological versus social (environment) causes contribute. As an unrelated but illustrative example to help explain this, people who carry the BRCA gene have a high genetic risk of breast cancer, whereas for those without the BRCA gene and with no family history, factors like smoking, obesity and lack of exercise play a much greater part. In other words, the end result is the same, but the causes are different.” (p 117)

Many would contest the assertion that breast cancer is “an expression of being human.” Others might balk at using an example of disease to describe gender, which is a natural aspect of human life. But moreover, this is an oversimplification. Many people do develop breast cancer with no known genetic cause, but just because that cause is not known does not mean it does not exist. Investigations into the genetic causes of breast or any other cancer are far from done, and there are many other genes besides BRCA 1 and 2 that are implicated in the development of breast cancer. This example does not cast doubt on the role that biology plays in shaping gender. Most concerningly, its serious lack of scientific rigor should lead readers to question what position the Review is operating from: is it science or is it speculation?

*The Review’s concerns about the cognitive effects of puberty-pausing medications are poorly evidenced and unbalanced*

The Review expresses concern about the safety of puberty-pausing medications. Most of its concern centers on the supposed impact of these medications on adolescent cognitive development. This is an important area of ongoing study, with researchers currently conducting

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<sup>66</sup> Recency of gender knowledge was not associated with any negative issues, including depressive symptoms, mental health issues or neurodevelopmental disorders, severity of gender dysphoria, or gender-related support from parents. Bauer GR, Lawson ML, Metzger DL; Trans Youth CAN! Research Team. Do Clinical Data from Transgender Adolescents Support the Phenomenon of “Rapid Onset Gender Dysphoria”? *J Pediatr.* 2022 Apr;243:224-227.e2. doi: 10.1016/j.jpeds.2021.11.020. Epub 2021 Nov 16. PMID: 34793826.

<sup>67</sup> Gill-Peterson, J. (2018). *Histories of the transgender child.* U of Minnesota Press.

<sup>68</sup> A helpful primer on the multidimensionality of biological sex: Karkazis K. The misuses of “biological sex”. *Lancet.* 2019 Nov 23;394(10212):1898-1899. doi: 10.1016/S0140-6736(19)32764-3. Epub 2019 Nov 21. PMID: 31982044.



some of the largest studies with longest follow up periods to date.<sup>69</sup> The currently available evidence does not support the Review's concern.

The largest and longest study on this topic showed that intelligence quotient and educational achievement amongst youth receiving puberty-pausing medications did not substantially differ from a population of similarly aged Dutch teens.<sup>70</sup> The York SR on puberty-pausing medications misrepresented the evidence by failing to include this study, and also erroneously reported that “the only study [on puberty-pausing medications and cognition] showed worse executive functioning at > 1 year...”. This latter study actually showed significantly better executive functioning in those receiving gender-affirming hormones compared to puberty-pausing medications.<sup>71</sup> Executive functioning was worse amongst those who received puberty-pausing medication for a long time compared to those who received gender-affirming hormones earlier. The appropriate conclusion is not that puberty-pausing medications worsen executive function: rather, it is that cognitive development of transgender youth may be affected in concerning ways by prolonged delays before affirming physical changes with appropriate treatment.

Also, medications to pause puberty have long been used for central precocious puberty without negative impact on cognitive development.<sup>72</sup> Delayed puberty is not associated with delays in cognitive development. In fact, many cisgender youth present after age 14, and not uncommonly at age 16 or 17, for evaluation of absent or delayed puberty, and do not display delays in cognitive development.

There is much uncertainty how about the role of puberty in broader adolescent development. The Review seems bound to the position that sex hormones are the most influential determinants of a healthy adolescence, to the exclusion of so many other complex, interdependent factors.<sup>73</sup> Cognitive development during adolescence is a complex process relying on several different mechanisms, including the psychosocial environment. Chronic stress, particularly during adolescence, does indeed impact cognitive development.<sup>74</sup> Gender diverse youth with dysphoria who are denied the option of medically affirming interventions are thus forced to undergo

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<sup>69</sup> A database of all studies funded by the National Institutes of Health:

<https://reporter.nih.gov/search/sF2XIRReqU-36s8d3bpPOQ/project-details/10883566>

<sup>70</sup> Arnoldussen M, Hooijman EC, Kreukels BP, de Vries AL. Association between pre-treatment IQ and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents. *Clin Child Psychol Psychiatry*. 2022 Oct;27(4):1069-1076. doi: 10.1177/13591045221091652. Epub 2022 May 31. PMID: 35638479; PMCID: PMC9574895.

<sup>71</sup> Strang JF, Chen D, Nelson E, Leibowitz SF, Nahata L, Anthony LG, Song A, Grannis C, Graham E, Henise S, Vilain E, Sadikova E, Freeman A, Pugliese C, Khawaja A, Maisashvili T, Mancilla M, Kenworthy L. Transgender Youth Executive Functioning: Relationships with Anxiety Symptoms, Autism Spectrum Disorder, and Gender-Affirming Medical Treatment Status. *Child Psychiatry Hum Dev*. 2022 Dec;53(6):1252-1265. doi: 10.1007/s10578-021-01195-6. Epub 2021 Jun 19. PMID: 34146208.

<sup>72</sup> Wojniusz S, Callens N, Sütterlin S, Andersson S, De Schepper J, Gies I, Vanbesien J, De Waele K, Van Aken S, Craen M, Vögele C, Cools M, Haraldsen IR. Cognitive, Emotional, and Psychosocial Functioning of Girls Treated with Pharmacological Puberty Blockage for Idiopathic Central Precocious Puberty. *Front Psychol*. 2016 Jul 12;7:1053. doi: 10.3389/fpsyg.2016.01053. PMID: 27462292; PMCID: PMC4940404.

<sup>73</sup> Berenbaum SA, Beltz AM, Corley R. The importance of puberty for adolescent development: conceptualization and measurement. *Adv Child Dev Behav*. 2015;48:53-92. doi: 10.1016/bs.acdb.2014.11.002. Epub 2015 Jan 22. PMID: 25735941.

<sup>74</sup> Eiland L, Romeo RD. Stress and the developing adolescent brain. *Neuroscience*. 2013 Sep 26;249:162-71

unwanted physical development. This can cause significant distress that then limits learning, building friendships, future orientation, and other developmental milestones in adolescence. The harms this poses to healthy cognitive development cannot be ignored. Clinicians, parents, and youth themselves are rightly concerned with the cognitive impact of untreated gender dysphoria, but the Review clearly is not.

*The Review asserts that puberty-pausing medications are not beneficial to transgender youth*

The Review casts doubt on the benefits of puberty-pausing medications for the treatment of gender dysphoria:

“The systematic review undertaken by the University of York found multiple studies demonstrating that puberty blockers exert their intended effect in suppressing puberty, and also that bone density is compromised during puberty suppression... However, no changes in gender dysphoria or body satisfaction were demonstrated.” (p 32)

Here, the Review expresses the expectation that an intervention would lead to an outcome that experts in youth gender care do not: Experts do not expect lessened gender dysphoria or increased body satisfaction with puberty-pausing medications alone, because these medications do not change the *current* physical characteristics of one’s body, they only prevent *future* changes. Puberty-pausing medications only *pause* development of puberty-induced characteristics that might be detrimental to the psychosocial well-being of a transgender young person. For example, puberty-pausing medications halt growth of breasts, but they do not reverse any breast growth that has already occurred; puberty-pausing medications can prevent the deepening of one’s voice, but they will not raise the pitch of a voice that has already deepened.

The Review’s implication that puberty-pausing medication should lead to a reduction in current gender dysphoria or improve one’s current body satisfaction indicates ignorance or misunderstanding at best, and intentional deception about the basic function of these medications at worst. In an era of abundant misinformation, it is important remember the exact function of these medications. The Review, as a document of such influence and importance in the field of transgender health, should not operate from any position of ignorance about this care.

The true effects of puberty-pausing medications are far more nuanced than the Review contends. Some studies show no change in certain mental health scores, which indicates *stability* rather than no effect.<sup>75,76</sup> Stability is a deeply meaningful short-term outcome for youth who are otherwise expected to experience increased gender-related distress without intervention.

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<sup>75</sup> Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S, Skageberg EM, Khadr S, Viner RM. 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. 2021 Feb 2;16(2):e0243894. doi: 10.1371/journal.pone.0243894. PMID: 33529227; PMCID: PMC7853497. (hereinafter, “Carmichael et al. 2021”).

<sup>76</sup> van der Miesen, A. I. R., Steensma, T. D., de Vries, A. L. C., Bos, H., & Popma, A. (2020). Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*, 66(6), 699–704.

Other studies<sup>77,78,79,80</sup> do demonstrate short-term improvement in some mental health scores in relation to treatment with these medications.<sup>81</sup>

Despite its protocol, which claimed the SRs would analyze qualitative data, the SR on puberty-pausing medications did not (See Section 6). Thus, the Review's conclusions are incompletely informed. The studies themselves draw different conclusions from the Review. For example, Carmichael and colleagues describe their nuanced findings: "Participant experience of treatment as reported in interviews was positive for the majority, particularly relating to feeling happier, feeling more comfortable, better relationships with family and peers and positive changes in gender role. Smaller numbers reported having mixed positive and negative changes. A minority (12% at 6–15 months and 17% at 15–24 months) reported only negative changes, which were largely related to anticipated side effects. None wanted to stop treatment due to side effects or negative changes."<sup>82</sup> Newer studies, not analyzed by the Review, demonstrate that avoiding a non-affirming puberty confers benefits that expand and evolve over time.<sup>83</sup>

Importantly, this newer study was able to study the effects of puberty blockers in a cohort of adolescents who started treatment while still in early puberty (and are thus most likely to benefit). This point is highly relevant to assessing the evidence around puberty blockers, since other studies' inclusion of young people who started puberty blockers at a time when they were already in late puberty or had finished puberty – which has been common practice in many places including the UK – will have reduced the chances of seeing benefits from puberty blockers use. Thus, being able to stratify recipients of puberty blockers based on the pubertal

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<sup>77</sup> R. Costa, M. Dunsford, E. Skagerberg, et al. Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria *J Sex Med*, 12 (2015), pp. 2206-2214

<sup>78</sup> C. Achille, T. Taggart, N.R. Eaton, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results *Int J Pediatr Endocrinol*, 2020 (2020)

<sup>79</sup> L.E. Kuper, S. Stewart, S. Preston, et al. Body Dissatisfaction and mental health outcomes of youth on gender-affirming hormone therapy. *Pediatrics*, 145 (2020), Article e20193006

<sup>80</sup> de Vries, A. L., Steensma, T. D., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2011). Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *The journal of sexual medicine*, 8(8), 2276–2283. <https://doi.org/10.1111/j.1743-6109.2010.01943.x>

<sup>81</sup> The Review acknowledges this: "Neither [study] reported any change before or after receiving puberty suppression...the original Dutch protocol (de Vries et al., 2011) found improvements in mental health in a pre-post study without a comparison group, but the GIDS early intervention study (Carmichael et al., 2021) did not replicate this finding. The systematic review on interventions to suppress puberty (Taylor et al: Puberty suppression) identified one other good quality study (van der Miesen et al., 2020), which produced an intermediate result with improvements in some mental health measures but not others." (p 176) The Costa, Achille and Kuper studies were not included in the Review's analysis of puberty-pausing medications, but these studies offer valuable insight.

<sup>82</sup> Regarding the Carmichael study, the Review fails to mention that well-being was not "clinically concerning" at the study start. The authors also address that there is no expectation of profound improvement in mental health scores with a medication that simply pauses the further development: "...the lack of change in an outcome that normally worsens in early adolescence may reflect a beneficial change in trajectory for that outcome, i.e. that GnRHa treatment reduced this normative worsening of problems."

<sup>83</sup> McGregor K, McKenna JL, Williams CR, Barrera EP, Boskey ER. Association of Pubertal Blockade at Tanner 2/3 With Psychosocial Benefits in Transgender and Gender Diverse Youth at Hormone Readiness Assessment. *J Adolesc Health*. 2024 Apr;74(4):801-807. doi: 10.1016/j.jadohealth.2023.10.028. Epub 2023 Dec 13. PMID: 38099903.; Chelliah P, Lau M, Kuper LE. Changes in Gender Dysphoria, Interpersonal Minority Stress, and Mental Health Among Transgender Youth After One Year of Hormone Therapy. *J Adolesc Health*. 2024 Jun;74(6):1106-1111. doi: 10.1016/j.jadohealth.2023.12.024. Epub 2024 Feb 9. PMID: 38340124.

stage at which they started treatment is critical, but neither the Review nor the associated systematic review appear to have considered this.

**Section 6: The systematic reviews relied upon by the Cass Review have serious methodological flaws, including the omission of key findings in the extant body of literature.**

Clinical recommendations should be informed by SRs of the evidence. SRs are a type of research study that combine the findings of multiple individual studies to answer a specific research question, based on a thorough and standardized search of the literature. SRs are considered the strongest form of evidence *if they are well-conducted*.<sup>84</sup> Best practices in conducting SRs aim to minimize bias so that the final product is a clear, precise, and accurate assessment of the body of evidence. These best practices include: (1) Devising, pre-registering, and following a protocol, (2) an exhaustive and up-to-date search of the literature, (3) use of validated assessment tools to examine the quality of individual studies and (4) use of a validated method to describe the quality of the entire body of evidence.

SRs are vulnerable to many forms of bias and are not inherently superior to other forms of evidence.<sup>85</sup> The Review's recommendations are informed by seven SRs,<sup>2</sup> which addressed research questions on gender-affirming hormones, puberty-pausing medications, referral trends to gender-competent services, care pathways, social transition, and psychosocial support for youth with gender dysphoria. In each of the four steps of the process, these reviews (collectively, the "York SRs," because they were conducted by researchers affiliated with the University of York) deviated substantially from standard practices and are rife with bias.

*The York SR protocol is inadequate and deviations from it are not justified*

The York SR authors pre-registered one vague protocol for all seven of their vastly different reviews.<sup>86</sup> The registered protocol bears no relation to what was actually done, and none of the components of the systematic reviews conducted on puberty-pausing medications or gender-affirming hormones were included in the registration. In fact, it is inaccurate to say that the York SRs were pre-registered, given that none of their key methodological details were described.

In the pre-registered protocol, the SR team planned to appraise the quality of studies using the Mixed Methods Appraisal Tool (MMAT).<sup>87</sup> However, they switched to the Newcastle-Ottawa

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<sup>84</sup> Well-conducted SRs use pre-specified, transparent, and reproducible methods to identify relevant studies, determine inclusion/exclusion, extract study data, appraise the risk of bias in included studies, and synthesize results using quantitative (meta-analysis) or qualitative (narrative synthesis) approaches.

<sup>85</sup> Shea B J, Reeves B C, Wells G, Thuku M, Hamel C, Moran J et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both BMJ 2017; 358 :j4008 doi:10.1136/bmj.j4008

<sup>86</sup> Fraser, L. et al. The epidemiology, management, and outcomes of children with gender-related distress / gender dysphoria: a systematic review. PROSPERO. Available at: [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=289659](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=289659). Accessed: May 27, 2024.

<sup>87</sup> Hong QN, Pluye P, Fàbregues S, Bartlett G, Boardman F, Cargo M, Dagenais P, Gagnon M-P, Griffiths F, Nicolau B, O'Cathain A, Rousseau M-C, Vedel I. Mixed Methods Appraisal Tool (MMAT), version 2018. Registration of Copyright (#1148552), Canadian Intellectual Property Office, Industry Canada.

Scale (NOS), but with several adaptations performed by the York SR authors. In their published SRs, they neither mention nor justify this deviation from their protocol. This is a divergence from standard practices designed to minimize bias in systematic reviews and it is not a minor one. This change may have had a decisive impact on the conclusions in the York SRs. In particular, the developers of the MMAT encourage SR authors to include *all* studies in analysis.<sup>88</sup> Using NOS and the arbitrary cutoff that the York SR authors determined, only a portion of the evidence was considered. This is discussed in greater detail as we describe use of the quality appraisal tool below.

*The SR search of the literature is incomplete and outdated*

The York team used a single search strategy for all SRs, which likely excluded many relevant studies in each of the specific areas. Also, SR authors face a challenge in performing a systematic review of the literature while new research is actively being published. SR authors should update their systematic search and apply the same quality appraisal tools to new literature. The York SR team did not systematically search the literature after April of 2022, despite submission for publication 18 months later. In the SRs on puberty-pausing medications and gender-affirming hormone therapy, the authors state that “More recent studies published from April 2022 until January 2024 also support the conclusions of this review.” The authors do not describe how those studies were identified or assessed. Highly impactful studies, such as the longest and largest study to date on gender-affirming medical treatments in youth,<sup>89</sup> received only passing mention: “A single study assessing outcomes during the 2 years after hormone initiation found that scores for gender congruence and life satisfaction increased, but there were differences by birth-registered sex and timing of hormone initiation.” This fails to engage with the study’s core findings that such treatments lead to improved mental health by targeting appearance congruence.

*The York SR team used quality appraisal tools inappropriately*

As we have discussed, quality appraisal tools are used to determine the quality of individual studies. These tools consider a variety of domains of the individual study, including the population selected and the statistical analyses performed on gathered data, among others. The York SRs used two quality appraisal tools incorrectly.

The first is the Appraisal of Guidelines for Research & Evaluation (AGREE) II tool, used in the systematic review of “guidelines” for medical care. The SR team included 23 documents for analysis, but 8 were not guidelines at all. These documents were position papers and affirmative statements that explicitly deferred to actual guidelines. Naturally, such documents fared poorly

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<sup>88</sup> Studies deemed low-quality studies by the modified NOS should have been included and analyzed separately, rather than excluded altogether. A sensitivity analysis could be performed to see if the excluded studies provided relevant information, but this was not done.

<sup>89</sup> Chen D, Berona J, Chan YM, Ehrensaft D, Garofalo R, Hidalgo MA, Rosenthal SM, Tishelman AC, Olson-Kennedy J. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. *N Engl J Med*. 2023 Jan 19;388(3):240-250. doi: 10.1056/NEJMoa2206297. Erratum in: *N Engl J Med*. 2023 Oct 19;389(16):1540. doi: 10.1056/NEJMx230007. PMID: 36652355; PMCID: PMC10081536.

when judged by the standards for clinical guideline development; this is akin to using a diamond quality scale to assess a heterogeneous group of gemstones.

The second quality appraisal tool is NOS and we analyze the Review's misuse of this tool in depth. We first discuss some of the robust criticisms of NOS from others in the field of evidence-based medicine:

1. NOS is not recommended by any leading organizations in the field of evidence-based medicine; is not considered a gold standard or used in guideline development processes.
2. Using NOS, reviewers often come up with different quality appraisals.<sup>90</sup> This is also called “low interobserver reliability” and is precisely why NOS is not recommended by Cochrane.
3. Quality appraisal under NOS leads to a numerical score. Despite a veneer of singular objectivity, numerical scores flatten nuanced assessments and are inherently arbitrary and unreliable.
4. NOS gives equal weight to all scored items equally, though the scientific importance of these items varies.<sup>91</sup>
5. NOS includes items that are immaterial to assessing risk of bias.<sup>80,92</sup> NOS includes an item about representativeness of the study population, which pertains to generalizability of the results to a wider population. While representative samples are critical for estimating population characteristics, they are not essential for determining treatment effectiveness.

Furthermore, the York SR team did not implement the NOS as it is presented by its authors. They modified the scale in an arbitrary way that permitted the exclusion of studies from further consideration, for reasons irrelevant to clinical care. For instance, in the York SR on social transition, the modified NOS asked if study samples were “truly representative of the average child or adolescent with gender dysphoria.” There is no such thing as the “average child or adolescent with gender dysphoria” – this is an inexpertly devised and meaningless concept that is neither defined by the authors nor used in clinical research. And yet it was grounds for excluding several important studies from consideration.

Also, the York SR team made a concerning error in citing NOS. In the SR on social transition, the authors accidentally cite a critical commentary on the scale and *not the scale itself*.<sup>93</sup> The authors of that critical commentary have subsequently written “It appears that the vast majority of systematic review authors who cited this commentary did not read it. Journal reviewers and editors did not recognize and correct these major quotation errors.”<sup>94</sup> The York SR team's error

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<sup>90</sup> Hartling L, Milne A, Hamm MP, et al. Testing the Newcastle Ottawa Scale showed low reliability between individual reviewers. *Journal of clinical epidemiology*. 2013 Sep 1;66(9):982-93.

<sup>91</sup> Jüni P, Witschi A, Bloch R, Egger M. The Hazards of Scoring the Quality of Clinical Trials for Meta-analysis. *JAMA*. 1999;282(11):1054–1060. doi:10.1001/jama.282.11.1054

<sup>92</sup> AHRQ also recommends against considering generalizability when assessing risk of bias. <https://effectivehealthcare.ahrq.gov/products/methods-guidance-bias-individual-studies/methods>

<sup>93</sup> Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5. doi:10.1007/s10654-010-9491

<sup>94</sup> Stang, A., Jonas, S. & Poole, C. Case study in major quotation errors: a critical commentary on the Newcastle–Ottawa scale. *Eur J Epidemiol* 33, 1025–1031 (2018). <https://doi.org/10.1007/s10654-018-0443-3>

calls into question the care with which they approached their task and the thoroughness of the peer review process undertaken by its journal of publication.

*The York SR team does not demonstrate expertise in the clinical matters at hand*

Upon review of the methodology and conclusions of the York SRs, it becomes clear that its authors are unaware of essential concepts in youth gender care.

1. In the SR on puberty-pausing medications, for instance, the authors or the Review's authors (unknown without transparency about the process), determined that a reduction in gender dysphoria was an appropriate outcome. As we discussed in Section 5, puberty-pausing medications themselves are not gender-affirming: they simply aim to pause the anatomical and physiological changes associated with puberty. Thus, the studies on puberty-pausing medications were held to an inappropriate standard.
2. Also, the York SR authors treated puberty-pausing medications and gender-affirming hormone treatments as distinct, reviewed them separately, and excluded studies from analysis that could not comment on the independent impact of each therapy. This is deeply problematic because most patients who receive puberty-pausing medications progress to gender-affirming hormone therapy. The imposition of a strict delineation of the impact of one modality versus another is divorced from the fact that these interventions are part of a continuum of care, and it led to the exclusion of numerous important studies assessing the impacts of this care continuum on the well-being of transgender adolescents.
3. The York SRs do endorse that puberty-pausing medications are effective in temporarily halting puberty and that gender-affirming hormone therapy is effective in developing congruent secondary sex characteristics, *but they do not consider that this is the actual goal of the gender-affirming model*. If the York SRs focused on body satisfaction and appearance congruence, and outcomes were assessed against the avoidance of unwanted pubertal changes and the induction of masculinizing or feminizing body changes, the discussion of the evidence would be quite different — and, indeed, it would be aligned with the goals of gender-affirming medical care.
4. Lastly, there is an undue prioritization of mental health as an expected outcome of all gender-affirming medical treatments, without considering the role that minority stress plays in the psychosocial well-being of young people.

*Using a rigorous assessment tool, the York SRs demonstrate high risk of bias*

Systematic reviews—like the studies they seek to evaluate—are far from perfect. Just as there are bias assessment tools for individual studies, there are also bias assessment tools for systematic reviews. The Cochrane Collaboration encourages use of risk of bias instruments be used in systematic reviews of healthcare interventions. The ROBIS tool is one such instrument rigorously developed to inform those using systematic reviews.<sup>95</sup> This tool considers risk of bias in four areas: (1) study eligibility criteria, (2) identification, and selection of studies, (3) data collection and study appraisal, and (4) synthesis and findings. Noone et al applied ROBIS to the

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<sup>95</sup> Whiting P, Savović J, Higgins JP et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol.* 2016 Jan;69:225-34. doi: 10.1016/j.jclinepi.2015.06.005. Epub 2015 Jun 16. PMID: 26092286; PMCID: PMC4687950.

York SRs and found a high risk of bias in each of these domains.<sup>96</sup> Their findings are described in Table 2.

Table 2: Application of the Cochrane ROBIS tool for bias assessment to the York SRs by Noone et al demonstrates systemic high risk of bias

York SRs and Risk of Bias Determination								
ROBIS Domain	1	2	3	4	5	6	7	Concerns noted
Study eligibility criteria	High	High	High	High	High	High	High	From the outset, “gray” literature, non-English literature, and qualitative research was excluded
Identification and selection of studies	High	High	High	High	High	High	High	Single search strategy used for seven different reviews despite widely divergent topics
Data collection and study appraisal	High	High	Low	High	High	High	High	Misused MMAT and AGREE-II, adapted and non-validated version of NOS used and not justified
Synthesis	High	High	High	High	High	High	High	No method described, 48% of studies on puberty-pausing medications and 36% of studies on hormones excluded from consideration without justification

Method description: “Each of the seven systematic reviews were assessed by two independent assessors using the ROBIS tool. A third and fourth assessor resolved any disagreements by consensus...” (p 3)

1 = SR on hormones; 2 = SR on puberty-pausing medications; 3 = SR on referral trends; 4 = SR on care pathways; 5 = SR on guidelines; 6 = SR on social transition; 7 = SR on psychosocial support

*The York SR team’s findings and conclusions conflict*

Moreover, the York SR team’s evidentiary findings and conclusions conflict. In the SR on gender-affirming hormone therapy, the “moderate and high quality” studies showed improved depression, anxiety, and suicidality (see Supplementary Table). *Every* study showed statistically significant improvements with a substantial magnitude of effect. No study showed a lack of improvement and no study showed worsening outcomes. It is then peculiar that the York SR team concluded that “There was limited evidence regarding gender dysphoria, body satisfaction, psychosocial and cognitive outcomes, and fertility.” There are five studies that were classified as “low quality” and discarded. Of note, Tordoff et al<sup>97</sup> was excluded due to scoring low on the authors’ adapted NOS. However, this study shows statistically significant reductions in depression and suicidality.

<sup>96</sup> Noone, C., Southgate, A., Ashman, A., et al. (2024, June 11). Critically appraising the Cass Report: methodological flaws and unsupported claims. <https://doi.org/10.31219/osf.io/uhndk>

<sup>97</sup> Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K. Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care. *JAMA Netw Open*. 2022 Feb 1;5(2):e220978. doi: 10.1001/jamanetworkopen.2022.0978. Erratum in: *JAMA Netw Open*. 2022 Jul 1;5(7):e2229031. doi: 10.1001/jamanetworkopen.2022.29031. PMID: 35212746; PMCID: PMC8881768.



*No accepted method to determine quality of the entire body of evidence was used*

Once a quality appraisal tool has been used, the quality of the entire body of evidence should be assessed with an accepted method. This is the final product of an SR and, to be sure, it's reason for being conducted. Accepted methods for appraising the entire body of evidence include GRADE and the Agency for Healthcare Research and Quality (AHRQ) approach.<sup>98</sup> This process is not perfect, but it is rigorous, replicable, and widely used by panels of experts who make recommendations. In an SR commissioned by WPATH<sup>99</sup>, the authors describe their application of this process:

“One reviewer graded strength of evidence for each outcome using the Agency for Healthcare Research and Quality Methods Guide for Conducting Comparative Effectiveness Reviews. We considered the directionality and magnitude of effects reported in cross-sectional studies as additional context for our evaluation of evidence from trials and prospective and retrospective cohorts. Each strength of evidence assessment was confirmed by a second reviewer.”

Use of a validated method to translate quality appraisals of individual studies into an assessment of quality for the entire body of evidence is necessary, as is disclosure of that validated method. It is completely unclear and unknown how the York SR team moved from appraising individual studies' quality to the entire body of evidence. Many studies were assessed as being of “moderate” quality according to NOS and it would be incorrect to carry over these designations to the entire body of evidence. But without a clear description of how this occurred, the final conclusions of the York SRs are not justified.

### **Section 7: The Review's relationship with and use of the York systematic reviews violate standard processes that lead to clinical recommendations in evidence-based medicine.**

The University of York was commissioned to conduct a series of SRs to inform the Review, but the York SRs' findings were inappropriately applied to healthcare policy and practice recommendations made in the Review. In Section 2, we discussed how evidence is one of many factors that are considered as clinical recommendations are developed, that the Review failed to consider those factors, and further, that the Review's recommendations are informed by a flawed concept of evidence. Here, we discuss how the Review's relationship with and use of the York SRs goes against the grain of conventional processes used widely in evidence-based medicine.

*The Review subverted the well-established process for making clinical recommendations from systematic review findings*

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<sup>98</sup> [https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/methods-guidance-grading-evidence\\_methods.pdf](https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/methods-guidance-grading-evidence_methods.pdf)

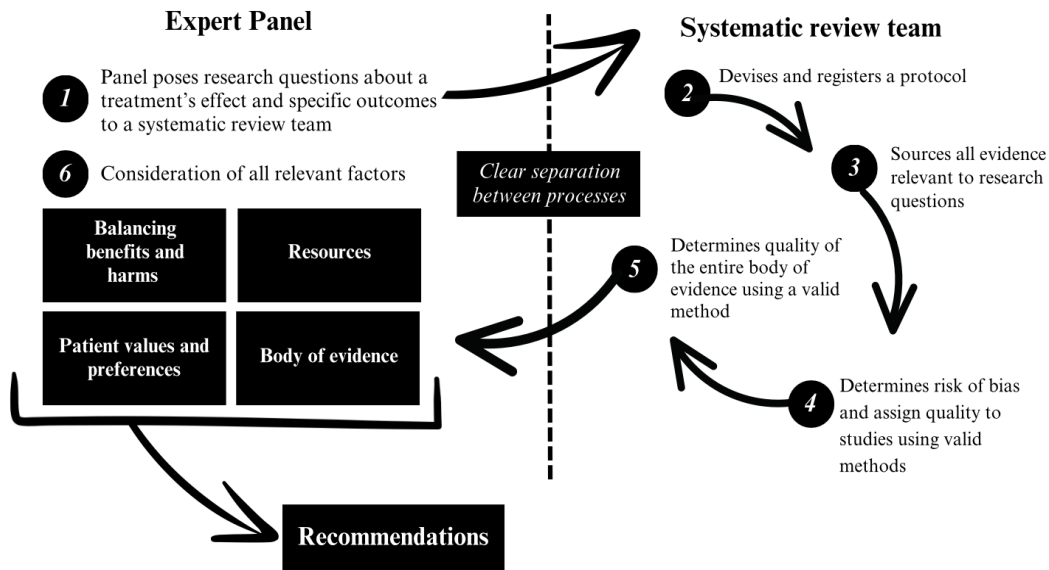
<sup>99</sup> Baker KE, Wilson LM, Sharma R, Dukhanin V, McArthur K, Robinson KA. Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic Review. *J Endocr Soc.* 2021 Feb 2;5(4):bvab011. doi: 10.1210/jendso/bvab011. PMID: 33644622; PMCID: PMC7894249.

## An Evidence-Based Critique of the Cass Review

SRs intended to inform clinical recommendations should follow a standardized and rigorous process that assesses quality of the entire body of evidence. In Section 6, we described many of the ways that the York SR team failed to adhere to such a process.

Here, we discuss the normative process for collaboration between expert panels who issue clinical recommendations and an SR team.

Figure 3: How an expert panel and a systematic review team should collaborate



1. Those who seek to make recommendations should be subject matter experts. Those experts first devise detailed research questions pertinent to a condition and its treatment.
2. A systematic review team then writes and registers a research protocol to answer those questions with the existing evidence. They adhere to this research protocol where possible and justify the need to deviate from it, should that need arise.
3. The SR team sources all evidence relevant to the research questions.
4. It then assigns quality to individual studies using valid methods.
5. The final work of the SR team is determining the quality of the entire body of evidence, again using a valid method. At this point, the work of the systematic review team is done.
6. The expert panel then considers all relevant factors, of which the body of evidence is one.

This process is well-established, in gender-affirming care and beyond.<sup>100</sup> In the SR commissioned by WPATH, the authors state:

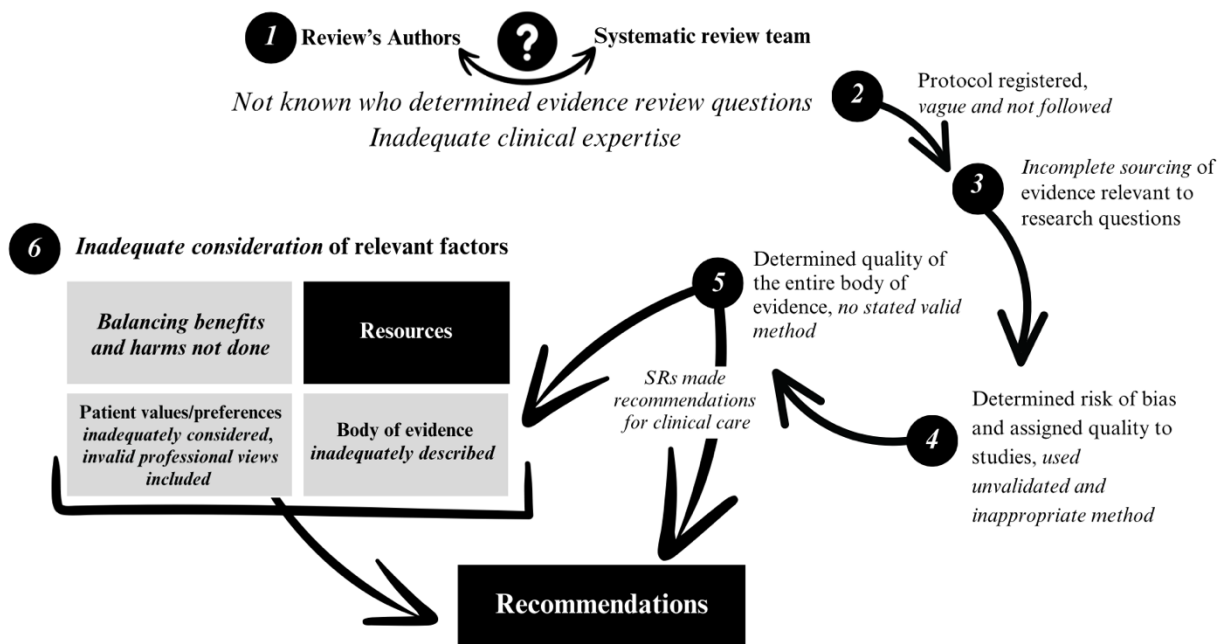
<sup>100</sup> Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Graham R, Mancher M, Miller Wolman D, et al., editors. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US); 2011. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK209539/> doi: 10.17226/13058

“WPATH provided the research question and reviewed the protocol, evidence tables, and report. WPATH had no role in study design, data collection, analysis, interpretation, or drafting... The authors are responsible for all content, and statements in this report do not necessarily reflect the official views of or imply endorsement by WPATH.”

Such descriptions of the relationship between the expert panel forming recommendations and the SR team are conventional in SRs that inform clinical recommendations. Members of expert panels may have authored research that the SR team considers. Members of expert panels may not be familiar with best practices in conducting quality appraisals. The separation between evidence appraisals and the expert panel preserves objectivity and consolidates expertise.

With deviations from normative guideline development at every stage, the Review’s recommendations cannot be given the weight that the authors expect. These deviations are noted at the outset and snowball throughout the process.

Figure 4: The Review's authors and the York systematic review team's processes



1. The earliest flaws in this process begin with ambiguity in how the first steps of the systematic reviews unfolded. The relationship between the Review’s authors and the SR team is unclear. There are no descriptions, either in the Review or the York SRs, about who devised the research questions informing the evidence review. Without disclosure of *all* of the Review’s authors, we cannot say for sure, but inadequate subject matter expertise is quite likely.
2. The SR team did register a protocol, but that protocol was not followed (see Section 6).
3. The SR team did not conduct a complete review of the evidence pertinent to its research questions (see Section 6).
4. The individual studies were assigned a quality designation based on an unvalidated, never-before-used tool that was adapted from a tool with flaws of its own (see Section 7).

5. There is no description of a valid method used to determine quality of the entire body of evidence and, in some cases, recommendations for clinical care were made by the SR authors themselves *in the SRs themselves*.<sup>101</sup>
6. The Review inconsistently used the evidence assessments to inform its recommendations, alongside incomplete or absent analyses of other relevant factors to issue its recommendations (see Section 2).

### Conclusion

The Cass Review was commissioned to address the failure of the UK National Health Service to provide timely, competent, and high-quality care to transgender youth. These failures include long wait times—often years—and resulting delays in timely treatment by skilled providers. Instead of effectively addressing this issue, however, the Review’s process and recommendations stake out an ideological position on care for transgender youth that is deeply at odds with the Review’s own findings about the importance of individualized and age-appropriate approach to medical treatments for gender dysphoria in youth, consistent with the international Standards of Care issued by the World Professional Association for Transgender Health and the Clinical Practice Guidelines issued by the Endocrine Society. Far from evaluating the evidence in a neutral and scientifically valid manner, the Review obscures key findings, misrepresents its own data, and is rife with misapplications of the scientific method. The Review deeply considers the possibility of gender-affirming interventions being given to someone who is not transgender, but without reciprocal consideration for transgender youth who undergo permanent, distressing physical changes when they do not receive timely care. The vast majority of transgender youth in the UK and beyond do not receive an opportunity to even consider clinical care with qualified clinicians—the Review’s data demonstrate this clearly.

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<sup>101</sup> SRs should not make recommendations, but the SR on gender-affirming hormones does: “Clinicians should ensure that adolescents considering hormone interventions are fully informed about the potential risks and benefits including side-effects, and the lack of high-quality evidence regarding these. In response to their own evidence review, the Swedish National Board of Health and Welfare now recommends that hormone treatments should only be provided under a research framework, a key aim for which is to develop a stronger evidence base. As they point out, this approach is common practice in other clinical specialties, where to receive treatments for which the benefits and risks are uncertain, patients must take part in research.” (p 7)

Supplemental Table: Studies on gender-affirming hormones rated by York SR team as high or moderate quality* demonstrate clinically relevant, statistically significant outcomes not adequately discussed	
Study	Findings
López de Lara D et al. <sup>a</sup>	<p>Significant reduction in gender dysphoria in trans group (p&lt;0.001), comparable to cisgender youth after one year</p> <p>Significantly improved anxiety (p&lt;0.001)</p> <p>Significantly improved depression (p&lt;0.001)</p>
Grannis C, et al. <sup>b</sup>	<p>Anxiety &amp; depression significantly lower in testosterone-treated group compared to untreated group</p> <p>Lower suicidality observed</p> <p>Testosterone-treated group - less distress with body features, stronger connectivity within amygdala-prefrontal cortex circuit compared to untreated group</p>
Green AE et al. <sup>c</sup>	<p>Among those who wanted gender-affirming hormones at the start of the study:</p> <ul style="list-style-type: none"> <li>● More depression (77.9% v 60.9%, p&lt;0.001)</li> <li>● More seriously considered suicide (61.6 v 51.1%, p&lt;0.001)</li> <li>● More attempted suicide (27.7 v 16.0%, p&lt;0.001)</li> </ul> <p>After adjustment for covariates, GAHT associated with:</p> <ul style="list-style-type: none"> <li>● Less depression (aOR 0.73, p&lt;0.001)</li> <li>● Less seriously considered suicide (aOR 0.74, p&lt;0.001)</li> <li>● Trend to less attempted suicide (aOR 0.84, p=0.16)</li> <li>● Less attempted suicide in age 13-17 age group (aOR 0.61, p=0.04)</li> </ul>
Kaltiala R, et al. <sup>d</sup>	<p>Significantly less depression, anxiety, suicidality, and self-harm (p &lt; 0.001)</p> <p>Depression 54% v 15%, anxiety 48% v 15%</p> <p>Suicidality/self-harm 35% v 4%</p>
Allen, L. R., et al. <sup>e</sup>	<p>Significantly lower suicidality after gender-affirming hormones (p&lt;0.001)</p> <p>Significantly higher general well-being after gender-affirming hormones (p&lt;0.002)</p>
<p>aOR = adjusted odds ratio, which includes control for confounders</p> <p>a - López de Lara D, et al. Psychosocial assessment in transgender adolescents. <i>An Pediatr (Engl Ed)</i>. 2020 Jul;93(1):41-48. doi: 10.1016/j.anpedi.2020.01.019. Epub 2020 Mar 3.</p> <p>b - Grannis C, et al. Testosterone treatment, internalizing symptoms, and body image dissatisfaction in transgender boys. <i>Psychoneuroendocrinology</i>. 2021 Oct;132:105358. doi: 10.1016/j.psyneuen.2021.105358. Epub 2021 Jul 17.</p>	

c - Green AE et al. Association of Gender-Affirming Hormone Therapy with Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. *J Adolesc Health*. 2022 Apr;70(4):643-649. doi: 10.1016/j.jadohealth.2021.10.036. Epub 2021 Dec 14.

d - Kaltiala R, et al. Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. *Nord J Psychiatry*. 2020 Apr;74(3):213-219. doi: 10.1080/08039488.2019.1691260Epub 2019 Nov 25.

e - Allen, L. R., et al (2019). Well-being and suicidality among transgender youth after gender-affirming hormones. *Clinical Practice in Pediatric Psychology*, 7(3), 302-311. <https://doi.org/10.1037/cpp0000288>

\*In Taylor J, Mitchell A, Hall R, et al (2024) Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: a systematic review. *Archives of Disease in Childhood* Published Online First: 09 April 2024. doi: 10.1136/archdischild-2023-326670