EXHIBIT 7

Affidavit of Meredithe McNamara, M.D. MSc.

I, Meredithe McNamara, M.D. Msc., state as follows:

1. I know that the facts set forth in this affidavit are true because I have personal knowledge of them.

2. As set forth in earlier affidavits filed in this matter, I am board-certified in both pediatrics and adolescent medicine. I provide full spectrum clinical care to youth aged 12-25 years, which includes youth experiencing gender dysphoria.

3. On February 8, 2023, I provided a report regarding the evidence of the benefits of treatments for youth experiencing gender dysphoria. On March 25, 2024, I provided a supplemental report responding to the rebuttal reports from Defendants' expert witnesses.

4. I am now providing this affidavit evaluating the reliability of the Cass Review. The Cass Review was released on April 10, 2024, after my deposition and previous two reports.

5. I have reviewed and analyzed the Cass Review and the evidence on which it relies and come to the following expert opinions.

6. The Cass Review does not alter the opinions set forth in my initial and rebuttal reports, including my opinions that:

    a. Gender dysphoria is a real and serious condition.
    b. Adolescents with untreated gender dysphoria suffer from a wide array of physical, mental health and psychosocial harms.
    c. Treatments, including puberty blockers and hormone therapy, are effective treatments for gender dysphoria in adolescents, when prescribed consistent with the WPATH Standards of Care and the Endocrine Society Clinical Practice Guidelines.
    d. No study demonstrates that receiving transitioning medications worsens the mental health of youth with gender dysphoria.
    e. There are no evidence-supported, effective alternative treatments for gender dysphoria.

7. In addition, it is my expert opinion that:

    a. The Cass Review does not recommend a ban on gender-affirming medical care for minors nor does it provide support for such a ban.

b. The Cass Review makes some recommendations for the diagnosis and treatment of gender dysphoria in minors that are consistent with international standards of care, including the WPATH and Endocrine Society guidelines.
c. The Cass Review makes some additional recommendations that conflict with international standards of care, including the WPATH and Endocrine Society guidelines.
d. The Cass Review does not follow established standards for evaluating evidence and evidence quality.
e. The Cass Review fails to contextualize the evidence for gender-affirming care with the evidence base for other areas of pediatric medicine.
f. The Cass Review misinterprets and misrepresents its own data.
g. The Cass Review levies unsupported assertions about gender identity, gender dysphoria, standard practices, and safety of gender-affirming medical treatments, and repeats claims that have been disproved by sound evidence.
h. 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.
i. The Cass Review’s relationship with and use of the York systematic reviews contravenes conventional processes used to develop clinical recommendations.

8. These opinions are supported by the scientific literature attached as an appendix to this supplemental affidavit.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed this 28th day of June, 2024.

Meredithe McNamara, M.D. MSc.

Appendix A

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

Meredithe McNamara, MD MSc, Assistant Professor of Pediatrics, Yale School of Medicine

Kellan Baker, PhD, Executive Director of the Whitman-Walker Institute

Kara Connelly, MD, MCR, Associate Professor of Pediatrics, Division of Endocrinology, School of Medicine, Oregon Health & Science University

Aron Janssen, MD, Associate Professor of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine

Johanna Olson-Kennedy, MD, Professor of Clinical Pediatrics, Keck School of Medicine of University of Southern California

Ken C. Pang, FRACP, PhD. NHMRC Leadership Fellow and Senior Principal Research Fellow, Murdoch Children’s Research Institute, VIC Australia

Ayden Scheim, PhD, Assistant Professor of Epidemiology, Dornsife School of Public Health, Drexel University

Jack Turban, MD, MHS, Assistant Professor of Psychiatry & Behavioral Sciences and Affiliate Faculty at the Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco

Anne Alstott, JD, Professor of Law, Yale Law School

We would like to thank Richard Body, MB ChB, MRCSEd (A&E), FRCEM, PhD and Annelou de Vries, MD, PhD for their expert feedback on drafts of this report. We would also like to thank Jay Taimish, Paola Vidal-Espinoza, and Schuylar Bailar for their excellent research support.

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,”[1] (henceforth “the Review”) and is accompanied by seven systematic reviews conducted by authors affiliated with the University of York (henceforth “the York SRs”).[2]

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[1] 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

[2] 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:

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.[3] 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.[4] In June 2024, the NHS Health 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.[5] 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

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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

[3] 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

[4] https://www.nhs.uk/conditions/gender-dysphoria/treatment/

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

needs, of which precocious puberty, endometriosis, and fertility preservation prior to chemotherapy are some.[6]

The Cass Review has already been cited in U.S. legal battles over transgender rights.[7] 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 Skrmetti, 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.[8]

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.[9] 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 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.

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[6] https://www.legislation.gov.uk/uksi/2024/727/made

[7] Poe v Labrador, https://www.supremecourt.gov/DocketPDF/23/23A763/300889/20240220100700247_Poe%20v%20Labrador%20SCOTUS%20Application%20for%20Stay.pdf

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

[9] 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.

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.

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.[10] 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.[5,6] 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.[11]

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

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[10] 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."

[11] 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.

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.[5, 6] 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.

Table 1: Shared core principles between the Cass Review, the Endocrine Society Clinical Practice Guidelines and WPATH's Standards of Care 8[12]

Agreement that certain youth with gender dysphoria will benefit from medical aspects of gender affirming care	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) 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) 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)
Agreement regarding the need for a holistic, comprehensive, and individualized assessment and treatment plan	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) 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) 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)
Agreement that optimized treatment of co-occurring mental health conditions is essential	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) 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) 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)

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[12] 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).[13] 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,[14] 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.[15] 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.[10] 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)

[13] 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.

[14] 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.

[15] 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.[16] 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.[17] *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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[16] "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

[17] 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.[18] 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.[15]

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.”[19,20] *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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[18] 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.

[19] 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

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

become infeasible.[21] 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.[17] 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.[22] 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.[23]

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.[24] 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.[25] 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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[21] 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.

[22] 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.

[23] 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.

[24] 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.

[25] 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.[26] *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.[13] (RCTs must enroll large numbers of study subjects to detect an effect.) Combining the need for parental

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[26] 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.[27]

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."[28] 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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[27] 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

[28] Ghorayshi A. "Hilary Cass Says U.S. Doctors Are 'Out of Date' on Youth Gender Medicine" New York Times. Accessed May 30, 2024.

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).[29] And yet, clinical outcomes are good and improving: more children leave intensive care units better off than ever before.[30] Most aspects of neonatal and pediatric critical care became accepted clinical practice because on 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.[31] 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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[29] 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

[30] 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.

[31] 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.[32] 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.[33]

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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[32] 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.

[33] 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.[34] 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

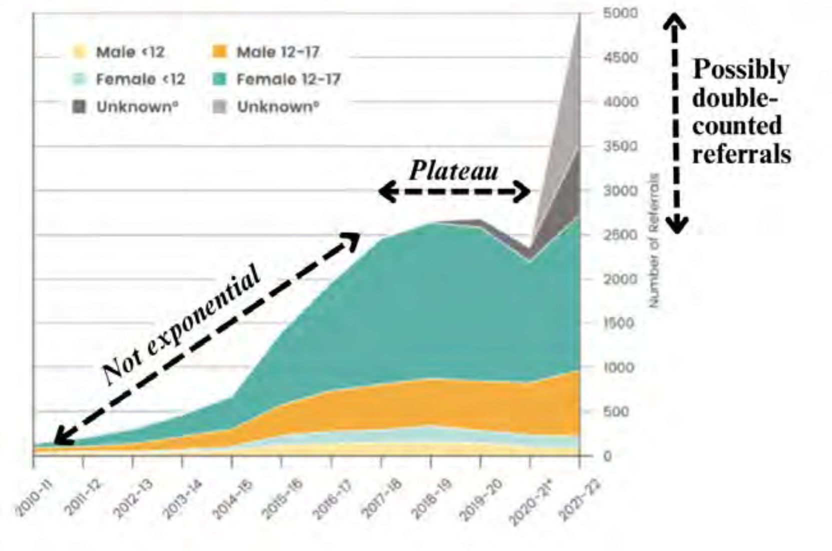

Figure 1: The Review's referral increases are not exponential and do not consistently increase. Graphed data shown above includes double-counted referrals.

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[34] 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 quality 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.[35]

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.[36] 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.

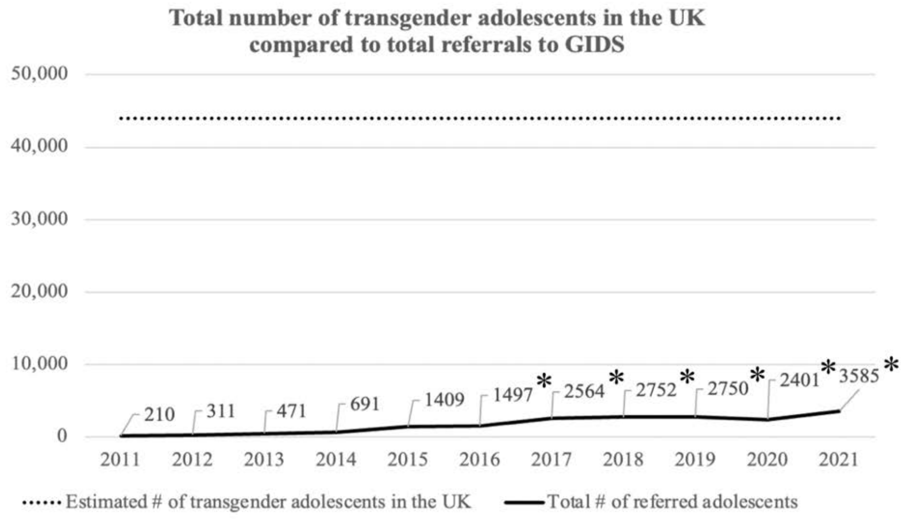

Figure 2: Comparing a population prevalence estimate of transgender-identifying youth in the UK to those who received referrals to GIDS from 2011-2021,
** indicates referrals that may be double-counted*

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[35] 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")."

[36] 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.[31]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.[37] (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).[38]

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

[37] Based on the data provided in Appendix 8 of the Review.

[38] 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.

[39] 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

[40] 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, Vandermorris 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

[41] 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/.

[42] 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.[43] 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

[43] 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.[44] 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"[45] 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[46] were classified as "gender non-conforming" if they did not adhere to gender stereotypes.[47] 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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[44] 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.

[45] "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.

[46] 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.

[47] 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[48] 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.[49] 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.[50]

The Review's own data contradicts its assertion that "The percentage of people treated with hormones who subsequently detransition remains unknown." (p 33)[51] 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.[52] Amongst 720 youth in the Netherlands with gender dysphoria who received puberty suppression and gender-affirming hormones, 98% continued

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[48] 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

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

[50] 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

[51] 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)

[52] van der Loos et al. (2023).

gender-affirming hormones as adults.[53] 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.[54] 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.[55] 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.[56] 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.[57,58] In many of the studies it cites, "detransition" is vaguely defined and incorrectly conflated with discontinuing treatment.[59]

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[53] 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").

[54] 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

[55] 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.

[56] 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

[57] 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.

[58] Vandenbussche 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." Vandenbussche 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

[59] 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.[52,53]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[60] that has been heavily corrected for numerous well-documented fatal flaws.[61] Using sound methods, no link has been found between peer influence and gender identity development.[62] 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.[63] 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.[64] 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.[65] 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.

[60] 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.

[61] 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.

[62] 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").

[63] 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

[64] 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.

[65] Bauer GR, Pacaud 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.[66] 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.[67]

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.[68] 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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[66] 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.

[67] Gill-Peterson, J. (2018). Histories of the transgender child. U of Minnesota Press.

[68] 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.[69] 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.[70] 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.[71] 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.[72] 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.[73] 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.[74] Gender diverse youth with dysphoria who are denied the option of medically affirming interventions are thus forced to undergo

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[69] A database of all studies funded by the National Institutes of Health: https://reporter.nih.gov/search/sF2XlRReqU-36s8d3bpPOQ/project-details/10883566

[70] 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.

[71] 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.

[72] 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.

[73] 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.

[74] 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.[75,76] 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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[75] 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”).

[76] 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[77,78,79,80] do demonstrate short-term improvement in some mental health scores in relation to treatment with these medications.[81]

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."[82] Newer studies, not analyzed by the Review, demonstrate that avoiding a non-affirming puberty confers benefits that expand and evolve over time.[83]

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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[77] 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

[78] 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)

[79] 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

[80] 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

[81] 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.

[82] 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."

[83] 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*.[84] 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.[85] The Review's recommendations are informed by seven SRs,[2] 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.[86] 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).[87] However, they switched to the Newcastle-Ottawa

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[84] 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.

[85] 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

[86] 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. Accessed: May 27, 2024.

[87] 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.[88] 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,[89] 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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[88] 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.

[89] 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.[90] 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.[91]
5. NOS includes items that are immaterial to assessing risk of bias.[80,92] 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*.[93] 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."[94] The York SR team's error

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[90] 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.

[91] 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

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

[93] 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

[94] 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.[95] 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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[95] 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.[96] 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[97] was excluded due to scoring low on the authors' adapted NOS. However, this study shows statistically significant reductions in depression and suicidality.

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[96] 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

[97] 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.[98] 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[99], 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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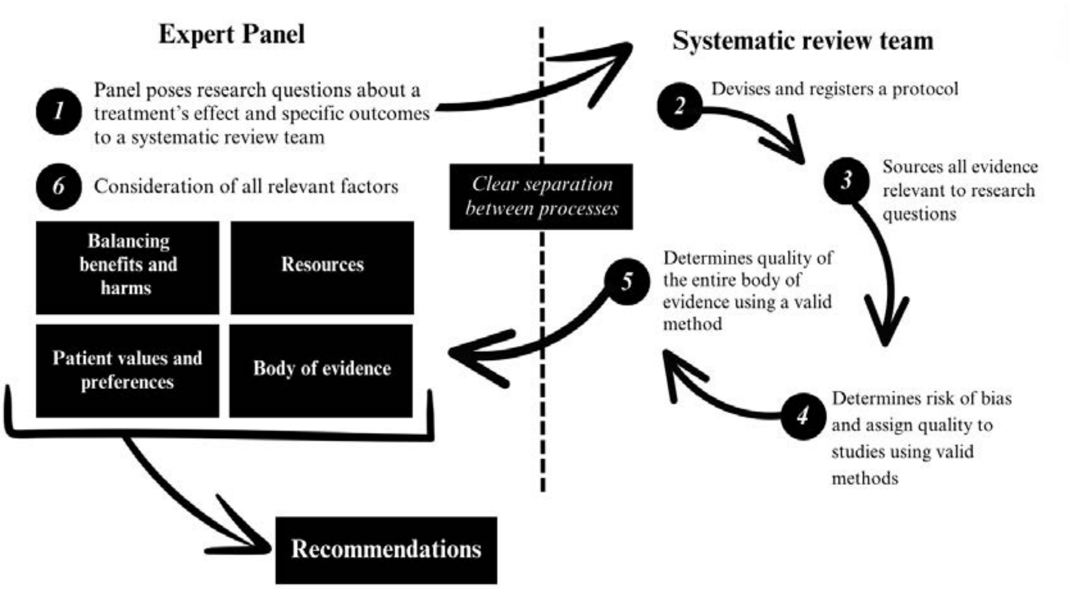
[98] https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/methods-guidance-grading-evidence_methods.pdf

[99] 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.

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.[100] In the SR commissioned by WPATH, the authors state:

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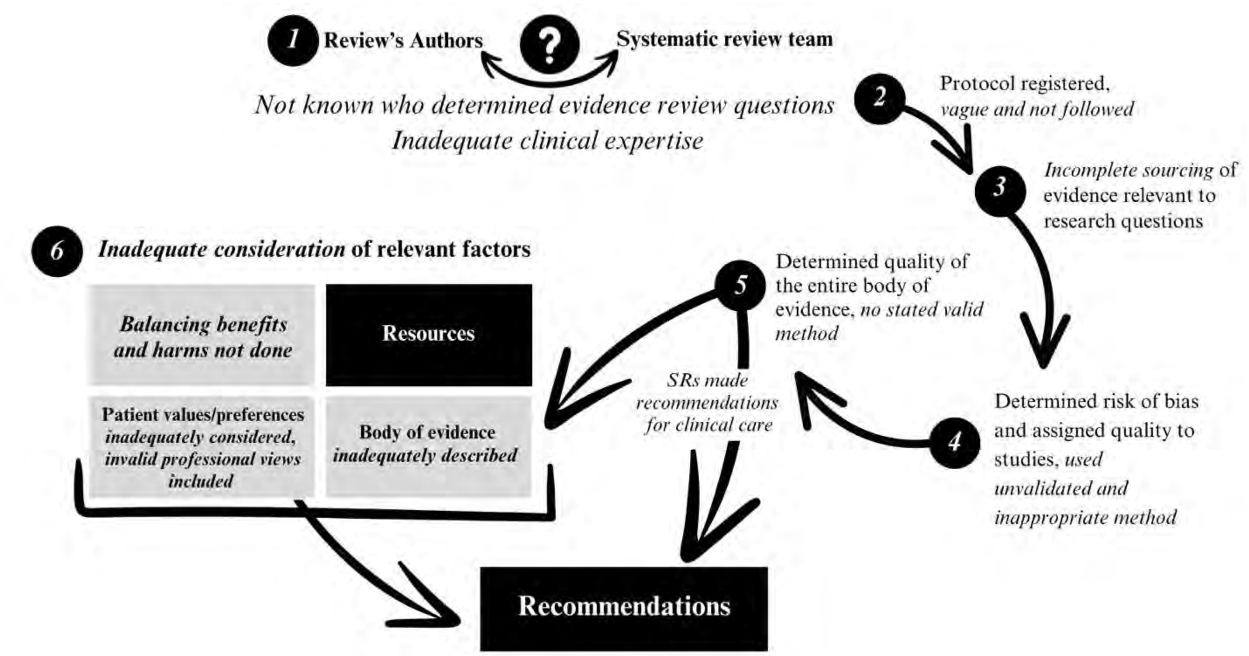
[100] Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Graham R, Mancher M, Miller Wolman D, et al., editors. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US); 2011. Available from: https://www.ncbi.nlm.nih.gov/books/NBK209539/ 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*.[101]
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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[101] 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)

<table>
<tr><td colspan="2">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</td></tr>
<tr><td>Study</td><td>Findings</td></tr>
<tr><td>López de Lara D et al.[a]</td><td>Significant reduction in gender dysphoria in trans group ($p<0.001$), comparable to cisgender youth after one year
Significantly improved anxiety ($p<0.001$)
Significantly improved depression ($p<0.001$)</td></tr>
<tr><td>Grannis C, et al.[b]</td><td>Anxiety & depression significantly lower in testosterone-treated group compared to untreated group
Lower suicidality observed
Testosterone-treated group - less distress with body features, stronger connectivity within amygdala-prefrontal cortex circuit compared to untreated group</td></tr>
<tr><td>Green AE et al. [c]</td><td>Among those who wanted gender-affirming hormones at the start of the study:
- More depression (77.9% v 60.9%, $p<0.001$)
- More seriously considered suicide (61.6 v 51.1%, $p<0.001$)
- More attempted suicide (27.7 v 16.0%, $p<0.001$)
After adjustment for covariates, GAHT associated with:
- Less depression (aOR 0.73, $p<0.001$)
- Less seriously considered suicide (aOR 0.74, $p<0.001$)
- Trend to less attempted suicide (aOR 0.84, $p=0.16$)
- Less attempted suicide in age 13-17 age group (aOR 0.61, $p=0.04$)</td></tr>
<tr><td>Kaltiala R, et al. [d]</td><td>Significantly less depression, anxiety, suicidality, and self-harm ($p < 0.001$)
Depression 54% v 15%, anxiety 48% v 15%
Suicidality/self-harm 35% v 4%</td></tr>
<tr><td>Allen, L. R., et al.[e]</td><td>Significantly lower suicidality after gender-affirming hormones ($p<0.001$)
Significantly higher general well-being after gender-affirming hormones ($p<0.002$)</td></tr>
<tr><td colspan="2">aOR = adjusted odds ratio, which includes control for confounders
a - López de Lara D, et al. Psychosocial assessment in transgender adolescents. An Pediatr (Engl Ed). 2020 Jul;93(1):41-48. doi: 10.1016/j.anpedi.2020.01.019. Epub 2020 Mar 3.
b - Grannis C, et al. Testosterone treatment, internalizing symptoms, and body image dissatisfaction in transgender boys. Psychoneuroendocrinology. 2021 Oct;132:105358. doi: 10.1016/j.psyneuen.2021.105358. Epub 2021 Jul 17.</td></tr>
</table>

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

Appendix B

Critically Appraising the Cass Report: Methodological Flaws and Unsupported Claims

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Abstract

The Cass Report aimed to provide recommendations for how services for gender diverse children and young people should be delivered in England. Our critical appraisal reveals significant methodological and conceptual flaws within the report and the research commissioned to inform the report, which included seven systematic reviews and both quantitative and qualitative primary research. Using the ROBIS tool, we identified a high risk of bias in each of the systematic reviews driven by unexplained protocol deviations, ambiguous eligibility criteria, inadequate study identification, and the failure to integrate consideration of these limitations into the conclusions derived from the evidence syntheses. We also identified potential sources of bias and unsubstantiated claims in the primary research that suggest a double standard in the quality of evidence produced for the Cass Report compared to quality appraisal in the systematic reviews. We discuss these issues in relation to how evidence regarding gender affirming care is framed, the wider political context, and the future for gender affirming care. To uphold evidence-based medicine, future gender-affirming care research must generate robust observational data, involve transgender communities, and prioritise patient-centred outcomes, ensuring validity, generalisability, and cultural relevance. The Cass Report's recommendations, given its methodological flaws and misrepresentation of evidence, warrant critical scrutiny to ensure ethical and effective support for gender-diverse youth.

Keywords: Cass Report, Gender Affirming Care, Gender Dysphoria, Gender Incongruence, Transgender

The Cass Report was commissioned by NHS England and NHS Improvement "to make recommendations on the services provided to children and young people who are exploring their gender identity or experiencing gender incongruence" [1]. These recommendations were informed through seven systematic reviews, a survey of gender services for young people in Europe, two quantitative studies of health records, and a qualitative study on the experience of gender dysphoria (GD) among young people. In this paper, we show that this programme of research has significant methodological problems; that the Cass Report's application of evidence-based medicine (EBM) to Gender-Affirming Care (GAC) is flawed; and that the Review's understanding of transgender identities and experiences deploys a paternalistic lens that disregards the competence of transgender young people. We contend that together these issues undermine the validity of the Review's recommendations and that it has therefore failed to fulfil the commission request. We also make suggestions for how future research and systematic reviews on GAC should develop to ensure evidence-based quality improvement in the provision of GAC for transgender and gender diverse children and young people.

1. The Systematic Reviews

Seven systematic reviews were commissioned by the Cass Report and published in the BMJ Archives of Disease in Childhood[2–8] with a single systematic review protocol registered in PROSPERO for all seven reviews[9]. To evaluate their risk of bias we applied the ROBIS tool[10] as recommended by Cochrane[11,12]. The ROBIS tool considers four domains of risk of bias: (1) study eligibility criteria, (2) identification and selection of studies, (3) data collection and study appraisal, and (4) synthesis and findings. An overall judgement of the risk of bias for a systematic review is also made. 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 (see supplementary material for further information). As we demonstrate for each of the domains described below, our analyses resulted in all of the systematic reviews being judged as at a high risk of bias due to both methodological limitations and failure to adequately address these limitations in their conclusions and interpretations.

1.1. Domain 1: Study eligibility criteria

In this domain, all the systematic reviews were considered to be at high risk of bias because the eligibility criteria in most of the systematic reviews are unacceptably ambiguous, there are significant deviations from the eligibility criteria in the protocol, and the eligibility criteria excluded types of studies that are relevant to the systematic reviews' research questions. These problems are exacerbated by the fact that the protocol was updated on January 23rd 2023 to record that screening against the eligibility criteria had been completed (presumably for all of the systematic reviews) without taking this opportunity to record and explain deviations from the original criteria. Best practice guidelines for systematic reviews require that deviations like this are described and justified[13].

Every systematic review, except one focusing on clinical guidelines, excluded all grey literature (in another deviation from the protocol) and all literature not in English. The exclusion of ”grey” literature (including dissertations, white papers, and government reports) and non-English materials creates concerns that studies relevant to the systematic reviews may have been excluded. While it is true that much of the known scientific literature on this topic is published in English, the Cass Report's team had the opportunity and resources to search for data without language limitations given the support the review process received. If the goal was to conduct a thorough overview of all extant knowledge on the subject, these limitations—apart from being incongruent with best practices in the absence of justification—obstruct that goal.

The exclusion of qualitative research from the overall set of systematic reviews is questionable, especially because qualitative studies were part of the inclusion criteria in the protocol and several of the research questions for the reviews have been investigated using rigorous qualitative methods[14–17]. Given that the Cass Report itself presents qualitative data (anecdotes, quotations, community claims) as evidence and purports to value stakeholder input, the fact that qualitative studies were not reviewed impedes the comprehensiveness of the overall project.

1.2. Domain 2: Identification and selection of studies

For the second domain, all seven systematic reviews were judged to be at high risk of bias since it is likely that the search strategy failed to identify all relevant studies. A single search strategy was used for all systematic reviews without any modifications. This calls into question the appropriateness of the search strategy and its applicability to each specific systematic review. Furthermore, there is no evidence that grey literature was searched for, apart from the systematic review of clinical guidelines (despite the protocol indicating intent to do so).

For some reviews, the selection and identification of studies for inclusion was questionable. The systematic review for social transition excluded studies in which social transition was not treated "as an exposure", and therefore excluded Olson et al. (2018)[18] and Rae et al. (2019)[19]. However, the authors included five other studies from the same ongoing project (the TransYouth Project) ignoring that the same design limitations would also apply to these studies, especially as no differences between the transgender group and the cisgender controls in this group would indicate something very different than no difference between a socially transitioned group and a group denied social transition.

1.3. Domain 3: Data collection and study appraisal

In the third domain, the systematic review of clinical guidelines was judged to have a low risk of bias, and each of the other systematic reviews was judged to be at a high risk of bias. This was due to concerns about whether the inclusion of studies for synthesis in each systematic review depended on how well these studies were reported, as no information was provided about how or whether missing data was sought from study authors, and problems with the application, or lack, of study appraisal.

There were several issues with how study appraisal was conducted in these reviews. In the systematic review of psychosocial support interventions for children and adolescents experiencing gender dysphoria or incongruence, the Mixed Methods Appraisal Tool[20] (MMAT) was used to critically appraise the quality of the primary studies. The reviewers categorised the study quality into three categories (low/medium/high), which is not recommended by the authors of the MMAT. In fact, the authors of the MMAT actively discourage the use of an overall score of quality and state that, if this advice is not followed, a 5-point scale should be used alongside a full description of the MMAT results.[21]

In the systematic review of clinical guidelines, which was not described in the protocol, an appropriate study appraisal tool—the AGREE-II—was used. However, its reliability in this context may be questionable since several other systematic reviews have applied this tool to some of the same studies and arrived at quite different conclusions, with some also criticising the usefulness of AGREE-II for GAC guidelines.[22–24] Notably, the most restrictive guidelines were rated highest in this systematic review, without a clear justification related to how these guidelines were developed,[6,25] while guidelines for more affirmative models of care were judged to be of higher quality in other reviews than by Taylor and colleagues.[22–24]

An adapted version of the Newcastle-Ottawa Quality Assessment Scale[26] (NOS) was used in three of the systematics instead of the MMAT[2,3,7]—a deviation from the protocol that was not explained or clearly reported. The NOS has been highly criticised[27] and the use of an adapted scoring negates any previous attempts to validate the NOS. In fact, one of the systematic reviews[7] cites this critical paper by Stang and colleagues (2010)[27] to support their use of the NOS—a practice its authors that have called out as a major quotation error.[28] The systematic review authors provide no rationale for the threshold scores used to categorise the quality of studies. It is generally accepted that the use of a single score (as used in these systematic reviews) is unacceptable in the assessment of risk of bias of individual studies within systematic reviews.[29,30] Single scores do not capture the nuances of risk of bias, making them difficult to interpret. Additionally, the NOS is considered a quality appraisal scale, but within systematic reviews exploring the effectiveness of interventions (which this review claims to be doing) it is recommended that a domain-based risk of bias assessment tool should be used instead of a quality appraisal tool.[11] The ROBINS-I is an example of an available tool which is more suitable.[31]

1.4. Domain 4: Synthesis and findings

All of the systematic reviews were judged to be at high risk of bias for the synthesis and findings domain. For two of the systematic reviews, this was because of the inappropriate exclusion from the synthesis of studies that were deemed to be of ”low quality” according to the adapted NOS.[2,8] Using this approach, the authors excluded 48% and 36% of studies for puberty blockers and hormone therapy respectively. This practice is not recommended in systematic reviews unless explicitly pre-specified in a protocol with a clear and reasonable rationale, which was not evident in these cases.[32] Instead, the narrative syntheses should have included all studies and integrated observations regarding study quality into the analyses, similar to how a sensitivity analysis would treat study quality in a meta-analysis.[33] In the systematic reviews on the characteristics of children and young people referred for GAC and on care pathways for this population, there was no assessment of study quality or risk of bias so their conclusions could not take these issues into account.

This pattern of deviations from the protocol's plan for quality assessment is striking. The protocol stated that the MMAT would be used to appraise the quality of the studies included in each systematic review. However, only one of the systematic reviews followed the protocol by using the MMAT, but did so inappropriately; the systematic review of clinical guidelines used an appropriate tool for quality assessment, but was not mentioned in the protocol; three of the systematic reviews used a different tool from what was planned in the protocol and altered it in problematic ways; and two of the systematic reviews did not assess study quality at all. It is notable that the combination of using the NOS instead of the MMAT, altering how it is scored, and then excluding evidence on the basis of this altered score only applied to the systematic reviews on what could be considered the three most controversial topics that the Cass Report addressed—puberty blockers, hormone therapy, and social transition. The fact that these decisions were deviations from the protocol and that justifications for them were not provided raises concerns about cherry-picking.

In the synthesis sections, the authors conclude that low quality or even moderate quality evidence indicates that there is insufficient evidence for recommending gender-affirming care practices. For example, in the review on hormone replacement therapy, the authors argue that no conclusions can be drawn regarding any relationships between HRT and psychological health. However, this minimizes their own data. One study showed an improvement in gender dysphoria,[34] one showed an improvement in body satisfaction,[35] four studies showed an improvement in depression-related outcomes,[34–37] three studies showed an improvement in anxiety-related outcomes[34–36] and three studies showed a decrease in suicidality/self-harm related outcomes.[36–38] Here, five distinct studies on 415 trans youth show an improvement in mental health, body satisfaction and/or gender dysphoria. Further, no study demonstrated "consistent" evidence for harm. Therefore, it appears that the body of evidence, despite its limitations, is at least suggestive of a beneficial direction. At minimum, the lack of evidence for harm should have been detailed. Had this been detailed more, the authors still would have likely concluded that more research is necessary for elucidating the impacts of gender-affirming care, but their conclusions would be less likely to be misrepresented to insinuate that GAC is harmful.

1.5. Additional Issues of Concern

Beyond what is captured by our application of ROBIS, there are several other ways in which these systematic reviews deviate from best practice. PRISMA reporting guidelines advise authors to provide a transparent, complete and accurate account of why a review was done, what they did, and what they found. However, as highlighted above, there are several deviations from PRISMA within the systematic reviews.[39] Of particular concern is the lack of explicit, pre-specified methods in a detailed protocol for each separate review resulting in a lack of transparency and reproducibility. The protocol falls short of the PRISMA-P guidelines[40] by failing to document changes to the protocol or how they would be recorded (item 4), specifying ambiguous eligibility criteria (item 8), failing to disclose how the search strategy was developed and the expertise of the searcher (item 10), omitting a description of whether or how information missing from included studies would be obtained (item 11), and neglecting to consider how meta-biases (e.g., publication bias, outcome reporting bias) may have affected the reviews (item 16). Ideally, an adequately detailed protocol should have been written for each individual systematic review and submitted for peer review.

Another deviation from best practice concerns the composition of the review team. Both the Cochrane Handbook[11] and the Institute of Medicine[41] recommend including content area experts on the review team. Initially, the Cass team specifically excluded content experts, but they later added Dr Trilby Langton who is "a former Clinical Psychologist at the Tavistock Gender Identity Development Service".[9] Despite this, there is still a distinct lack of content expertise among the authors on many of the issues examined by the systematic reviews. Ideally, there would also be input to systematic reviews from those affected by the topic, and there is evidence that this practice is becoming common.[42] Given the potential, and now actual, implications of the Cass Report for the gender-diverse communities in the UK and elsewhere, knowledge and experience from community leaders should have formed the basis for each of the systematic reviews.

Finally, it is considered mandatory by Cochrane to rerun searches that are more than 12 months old and to screen the results for eligibility. The search for these systematic reviews was conducted in May 2021 and updated in April 2022 and was therefore 24 months old on publication. This means that the most recent eligible research is not included in these reviews.

Not only were these systematic reviews out of date and conducted in a manner that is likely to have biased their conclusions, but their necessity is also questionable in some cases. Several previous studies had addressed similar research questions regarding puberty suppression and hormone therapy, for example, and by systematically reviewing the same evidence came to more positive conclusions regarding their usefulness for gender diverse children and young people.[43–45] Next, we consider the new evidence that was generated for the Cass Report.

2. The Primary Research

The Cass Report commissioned primary research consisting of (i) a retrospective cohort study using electronic primary care records, (ii) an international survey of gender services for children and young people, and (iii) a qualitative study. Despite the methodological flaws in the cohort study and the qualitative study, which we demonstrate below, these studies were cited in the Cass Report, without due attention to its limitations, to support several of its claims (see for example 10.70 and 10.71, p. 146).

In the study of electronic health records, the authors aimed "to estimate for people aged 18 and under with GD: changes in incidence and prevalence over time". They did not account for changing acceptance, stigma, diagnostic criteria and clinical coding available to GPs (i.e. from DSM-IV to DSM-V and ICD-10 to ICD-11),[46,47] or clinical guidelines, which may alter sampling over time and bias GD prevalence estimates (see "chronology bias" or "surveillance bias").[48,49] The authors fail to demonstrate that the observed increase is either unexpected or of concern, yet the assumption of both underpins the Cass Review and its commissioning. Regarding the co-occurrence of ASD and GD, the authors conclude that this has increased, without appropriate statistical tests (e.g., time trend analysis)[50] or consideration of changes in the visibility and diagnosis of ASD, despite also warning of large confidence intervals. The authors also claim there was a two-phase growth in referrals for GAC, with an "acceleration" in 2015, without justifying this by statistically modelling the claim and comparing it to alternative models of the data. In the Cass Report, a discussion of statistical significance, bias, type I errors, and power is included (p. 51), as well as description of statistical significance (and lack thereof) in cited studies (p. 187). Given this evidence of statistical understanding, the failure to apply the same critical thought to the results of the primary research suggests a potential double standard.

The qualitative research summary links to a study protocol submitted before the research began. Critically, there is a lack of appropriate information about the overall methods, especially recruitment methods, and no discussion of selection biases (also lacking in Hall et al., 2024[7]). Additionally, there is no mention of reflexivity or positionality (where the researcher stands in relationship to those they are interviewing), which has consequences for the data interpretation and is an important indicator of rigour in qualitative research of healthcare.[51] The lack of consideration for how rigorous qualitative studies are designed, combined with the aforementioned exclusion of qualitative research from the systematic reviews, and the use of single (and sometimes misrepresented; see below) quotes from participants to support much broader conclusions demonstrates a misunderstanding of qualitative evidence in the Cass Report and the valuable insights about GAC that have been generated through qualitative research (see Horton, 2023[52]).

As outlined above, the results from these studies carried out for the Cass Report were used to produce conclusions and recommendations about GAC without sufficient warning of their methodological limitations, in stark contrast to the exclusion of research with far fewer limitations from the systematic reviews. This seeming double standard calls into question the Cass Review's claims that it has been "*[s]ystematically* reviewing and evaluating the evidence" (p. 65, our emphasis).

3. How the Cass Report frames GAC

These flaws have not prevented proponents of the Cass Report from praising its application of EBM whilst criticising existing literature on GAC as "substandard".[53] This view is based upon an inappropriate use of a paternalistic lens which views GAC as quasi-psychiatric care, and upon an inappropriate methodological lens which centres randomised controlled trials and downplays the value of high-quality observational data, issues that we turn to next as they are also apparent in the Cass Report.

3.1. Use of a paternalistic lens

Recognising and supporting the authenticity and competence of transgender young people is an important aspect of the provision of high-quality care.[54] However, the Cass Report emphasises their distress, rather than their treatment wishes: the report describes them as "children with gender dysphoria and/or gender-related distress" (p.52) and then emphasises the resolution of this distress as the main goal of interventions. Framed in this way, GAC becomes one of several treatment options for a quasi-psychiatric condition, rather than the authentic preference of competent individuals (note that Gillick competence is still applicable, without special limits, to under-16s seeking GAC, after the Court of Appeal quashed the High Court judgement that set restrictions specifically for GAC).[55] The reviewers' approach allows them to consider alternatives which they allege are in equipoise with GAC due to a lack of evidence, but which run contrary to patient wishes.[56] Given that transgender people have a care need rather than a disease and seek actualisation of their identities as opposed to a cure, this paternalistic lens is inappropriate.[57] Moreover, such a lens is also generally inappropriate in psychiatric care, where patient autonomy should be supported wherever possible.[58]

GAC should instead be considered through a similar lens as reproductive healthcare, akin to how healthcare providers and the public think about contraception, hormone replacement therapy, or fertility treatment.[57] Reproductive care requires not just the absence of illness, but "a state of physical, emotional, mental, and social well-being in relation to all aspects of sexuality and reproduction".[59] All individuals have the right to make decisions regarding their own reproductive care and must have access to services that support that right. Having a young person with GD undergo their natal puberty is not a neutral or desirable act just because it is a natural occurrence, in the same way that continuing an unwanted pregnancy or having intrusive menopausal symptoms should not be considered the default option. By failing to use a reproductive healthcare lens, the review risks creating an environment where non-affirming alternatives can be undertaken contrary to competent patients' wishes, where unethical controlled studies can be performed (see below), and in which the role of observational and cohort studies is downplayed.[56]

3.2. Use of an inappropriate methodological standard

The Cass Report sets out that randomised controlled trials (RCTs) are the gold standard to assess the efficacy of gender-affirming care (GAC), leading to the implication that the "research protocol" which will be the only method of accessing puberty blockers will be an RCT (e.g., p. 177). Indeed, the benefit of RCTs lies in their high internal validity, achieved through the randomisation process which reduces biases related to confounding factors.[60] However, their external validity is often criticized,[61] both regarding study population representation and extrapolating experimental conditions to real-life settings.[62] In transgender medicine, youths willing to subject themselves to a RCT are likely not representative of the broader population, and the homogeneous treatments in an RCT do not easily translate to individualized care in clinical practice.[56] Perhaps of most concern is the unethical and coercive nature of access to puberty blockers being contingent on consenting to participation in research.

Moreover, the causal agent in an RCT comes from the contrast between treatment and control groups to determine a treatment's effect.[62] In GAC, belonging to the control group, rather than the absence of treatment, can affect the outcome, threatening internal validity. Blinding is impossible due to the obvious effects of puberty blockers or hormone treatments, likely causing control group participants to feel resentful demoralization.[56] This resentment can bias responses of the controls or lead them to self-destructive behaviours,[56] shifting the causal link from the treatment effect to the knowledge of group assignment. Differential attrition is also likely, as youths with supportive families, better socioeconomic status, or living in areas with a better availability of GAC may leave the study if in the control group or not participate at all.[56]

Additionally, hormone treatments take time to show effects,[63] and various interventions may be needed at different times based on individual needs. This requires long-term follow-up in RCTs. However, the benefits of randomization diminish over time, leading to biases similar to observational studies.[60] This is especially true in transgender medicine, where affirmed youths' life trajectories differ from those without access to GAC, due to the experience of living in their authentic gender and differential exposure to discrimination. Participants might also access other types of GAC at different rates, adding more confounding factors. Thus, over the necessary duration to assess hormone treatment efficacy on wellbeing, the groups would likely diverge enough to lose the benefits of randomization, reducing the RCT's internal validity to that of a well-conducted observational study, which would not present the same ethical issues.

Finally, and perhaps more fundamentally, evaluating the efficacy of GAC based on psychosocial well-being is misguided. The primary goal of GAC is to prevent or induce the appearance of certain physical characteristics, and their physiological efficacy is undisputed. Mental health benefits are a logical consequence of living authentically.[57] Advocating for RCTs with mental health outcomes frames transness as a quasi-psychiatric condition, a distress whose suffering must be alleviated by the most evidenced-based methods, which contradicts the depathologisation of transness and its recognition as an issue of bodily autonomy and human rights.[64,65] Improvement in well-being does not come from a physiological action of hormones, which could be adequately isolated by an RCT, but from a combination of factors contributing to increased congruence. Proposing RCTs with a mental health outcome thus shows, at best, a profound misunderstanding of transness.

In their response to criticisms following the Review, the Cass team attempted to justify their criticism of cohort studies: ”the same level of rigour should be expected when looking at the best treatment approaches for this population as for any other population so as not to perpetuate the disadvantaged position this group have been placed in when looking for information on treatment options”.[66] The Cass team fail to mention that the majority of strong treatment recommendations in healthcare are based upon low or very low-quality evidence[67] or that, as elaborated above, cohort studies may be best suited for producing evidence that can best inform claims about GAC.

4. Unsupported Claims

Despite its emphasis on being evidence-based, the Cass Report includes many insufficiently evidenced claims that are used to inform conclusions and recommendations. We briefly describe select examples here (but for more, see Grijseels, 2024[68]).

In an analysis of changes in patient profile, the authors stated that ”the exponential increase in numbers within a 5-year timeframe is very much faster than would be expected for the normal evolution of acceptance of a minority group” (p. 118) but provided neither references nor data to support this claim, nor proper consideration of the complex relationship between referrals and factors associated with social acceptance.[69] Further, the authors made use of several flawed datasets and analyses, including double counting in referral data (Fig 11., p. 85), referral trajectories that are over 7 years old (Fig 15., p. 88), personal communications without associated methodology (Fig 16., p. 89), and flawed original research (see section 2). The authors also claimed that ”the switch from birth-registered males to birth-registered females” is ”unlike trans presentations in any prior historical period” (p. 26), without evidence for this change occurring, and without considering studies that contradict this claim.[70] On detransition, the authors claimed that there is a ”suggestion that the numbers are increasing” (p. 33), again without demonstrating or citing evidence that this is happening while also failing to cite major studies on detransitioning (e.g., Turban et al., 2021[71]).

On social transition, the authors state that ”others consider that it makes it more likely that a child’s gender dysphoria, which might have resolved at puberty, has an altered trajectory potentially, culminating in life-long medical intervention” (p. 31). Despite their own review concluding that it is difficult to assess the impact of social transition due to the small volume and low quality of current research[7] and that young people report reduced gender dysphoria and feeling more comfortable in themselves after socially transitioning (p.159), recommendations centre around considering partial rather than full transitioning for prepubertal children to prevent an altered ”developmental trajectory”. In addition to this contradiction, these recommendations frame early social transitioning and detransitioning through a lens of pathologisation that leaves little room for the possibility that the formation of gender identity is non-linear. Such identity explorations during childhood may be experienced positively.[72]

Finally, it appears the Cass report may have misrepresented participant quotes from its primary research to support its claims. For example, one participant is quoted as saying "there's not only one route or one set way to transition or be trans. They might want just hormones, or just surgery, people are different with different experiences, presentations, and bodies. It's fine for that to be the case, it's okay to have different plans for your medical transition." (p.147). While it seems that this participant is advocating for increased availability of care options for trans people, this quote directly informs 10.81, which suggests "it is important to inform people that medical transition is not the only option and that choosing not to go down that route does not invalidate their identity" (p.147). The report then reframes this response as evidence for the need to reduce the number of medical transitions, whereas this misinterpretation of what the person has said may reflect a confirmation bias from the review team that may have violated their participants' informed consent for research participation.

5. Political Context of the Cass Report

A further area of the Cass Report that requires scrutiny is its failure to comprehensively consider the wider sociopolitical context surrounding transgender healthcare, in the UK and worldwide. Systematic reviews should consider the social, cultural, and political context in which interventions are being implemented, especially when the intervention can affect the health of disadvantaged groups.[73] These contexts can influence both the outcome of interventions included within systematic reviews, and the implementation by policymakers of recommendations from reviews.[73,74] However, in both the Cass Report itself and the systematic reviews upon which it is based, there are relatively few reflections on social and political context. Within the final report of the Review, the main contextual observation is that there are "polarised debates about a range of societal issues involving transgender people in the UK" (p. 67). The report, however, fails to adequately consider the evidence of significant increases in societal transphobia in recent years. For instance, the number of recorded hate crimes against transgender people reached a record high in 2023, while the British Social Attitudes survey shows a marked decline in attitudes towards transgender people: 36% of people now describe themselves as prejudiced against transgender people, twice as many as in 2019.[75,76] Recent comparative research has found anti-transgender sentiments being shared widely by media actors and politicians within UK, as well as in several other European countries.[77]

While striving for the best evidence-based interventions and practice across healthcare, it is crucial to consider how these sociopolitical trends might influence the implementation of health interventions aimed at transgender people and the evaluation of what constitutes evidence, expertise or best practice. For example, a recent study examined the presentation of expertise and evidence within state hearings about a ban on gender-affirming care for children and adolescents in Arkansas. The authors identified a clear trend of misrepresentation and disinformation by actors positioning themselves as clinical experts.[78] The specific themes of misrepresentation and disinformation in both Arkansas and other states throughout the U.S. include insinuations that being trans is, in and of itself, evidence of mental illness and can be ”cured” through talk therapy, outdated and misleading claims about the process of gender-affirming care in the U.S., misrepresenting the evidence regarding ”desistance” in transgender youth, and rejection of scientific and medical authority.[79] By making this point, we make no assessment or claim of political bias on the part of the authors of the Cass Report and associated systematic reviews. Rather, we suggest that it is not possible for these authors to separate their research from this social and political context, as they attempt to do. The quality of their recommendations and the weight given to them should be critically considered while taking this context into account.

6. The future application of EBM in Gender Affirming Healthcare

The Cass Report's editorial argues for the importance of EBM to support clinicians in working with the everyday concerns and unknowns of practice. Central to EBM are the three pillars of best available evidence, clinical expertise, and the values and preferences of those accessing care. It is helpful to consider what the best available evidence could look like, in an approach tailored to the context of GAC, the view and preferences of gender diverse children and young people, and those who support them, and the clinical expertise of healthcare providers who deliver GAC.

The consideration of values and preferences have been historically absent in trans care—with its continued exclusion rooted in a legacy of pathologisation. Even among other cohorts that remain pathologised, efforts are increasingly made to value ”experts by experience”, including in the development of clinical guidelines.[80] Effective co-production needs to involve the community at every stage, not just superficially, as is common in NHS England initiatives.[81] In a good example of this, Ziegler led two reviews of clinical practice guidelines for adults and for children in primary care for which the broader team included both members of the trans community and primary care GAC providers.[23,24]

As outlined above, the Cass Report does not consider all of the best available evidence regarding GAC for children and young people and applies generic standards of evidence rather than considering what is the best possible evidence in this context given methodological, practical, and ethical constraints. It is our view that the best possible evidence regarding GAC is produced when the engagement and trust of participants is maximised through community involvement and clear communication,[82,83] when these participants are diverse and followed longitudinally in rigorous observational designs,[56,84] and to measure outcomes that are considered important by gender diverse children and young people, and those who support them, including the clinical expertise of healthcare providers who deliver GAC, using culturally appropriate and valid measures.[85–87] These recommendations are consistent with the methodological standards for validity, generalisability, and patient-centredness set out by the Patient-Centred Outcomes Research Institute[88] and capture the three pillars of EBM.

7. Conclusion

We have demonstrated that the Cass Report's application of EBM to GAC for children and young people is deeply flawed. Our critical analysis reveals significant methodological problems in the commissioned systematic reviews and primary research that undermine the validity of the Cass Report's recommendations. In light of this, and the Cass Report's poor understanding of transgender identities and experiences, it is vital the academic community question the integrity and validity of the Review's recommendations.

To truly uphold the principles of EBM, future research on GAC must generate high-quality observational data, involve transgender communities, and prioritise patient-centred outcomes. This approach ensures the validity, generalisability, and cultural appropriateness of findings. Only by addressing these critical gaps can we ensure that the healthcare system provides the necessary support and recognition for gender-diverse youth, aligning with ethical standards and promoting their well-being and autonomy.

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Supplementary Table 1. Summary of ROBIS Evaluations.

Domain 1: study eligibility criteria

Systematic Review	Did the review adhere to pre-defined objectives and eligibility criteria?	Were the eligibility criteria appropriate for the review question?	Were eligibility criteria unambiguous?	Were any restrictions in eligibility criteria based on study characteristics appropriate?	Were any restrictions in eligibility criteria based on sources of information appropriate?	Concerns regarding specification of study eligibility criteria
1	N	PY	PN	N	N	High
2	N	N	N	N	N	High
3	N	Y	N	Y	PY	High
4	PN	PY	PY	N	N	High
5	PY	Y	N	PY	N	High
6	N	N	PN	Y	PN	High
7	N	PN	N	PN	PN	High

Domain 2: identification and selection of studies

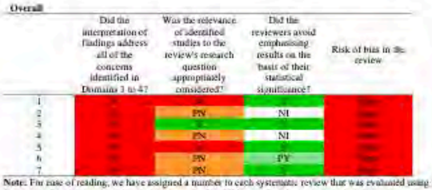
	Did the search include an appropriate range of databases /electronic sources for published and unpublished reports?	Were methods additional to database searching used to identify relevant reports?	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Were restrictions based on date, publication format, or language appropriate?	Were efforts made to minimise error in selection of studies?	Concerns regarding methods used to identify and/or select studies
1	N	Y	Y	N	Y	High
2	N	PY	PN	N	PY	High
3	Y	Y	Y	Y	Y	High
4	N	PY	PN	N	PY	High
5	N	N	Y	N	Y	High
6	PN	Y	PN	N	Y	High
7	PN	PY	PN	N	PN	High

Domain 3: data collection and study appraisal

	Were efforts made to minimise error in data collection?	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Were all relevant study results collected for use in the synthesis?	Was methodological quality formally assessed using appropriate criteria?	Were efforts made to minimise error in risk of quality assessment?	Concerns regarding methods used to collect data and appraise studies
1	NI	Y	Y	N	PY	High
2	PY	Y	PN	PN	Y	High
3	PY	Y	Y	PY	Y	Low
4	PY	PY	N	N	Y	High
5	PY	Y	PN	N	N	High
6	PY	Y	PN	N	Y	High
7	PY	Y	PY	N	N	High

Domain 4: synthesis and findings

	Did the synthesis include all studies that it should?	Were all pre-defined analyses reported or departures explained?	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Were biases in primary studies minimal or addressed in the synthesis?	Concerns regarding the synthesis and findings
1	Y	N	N	Y	N	N	High
2	Y	PN	N	Y	N	N	High
3	Y	N	Y	Y	PN	N	High
4	N	N	N	Y	N	N	High
5	NI	N	N	N	N	N	High
6	N	N	PY	Y	N	PN	High
7	PN	N	PY	PY	N	N	High



Overall

	Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Was the relevance of identified studies to the review's research question appropriately considered?	Did the reviewers avoid emphasising results on the basis of their statistical significance?	Risk of bias in the review
1	[illegible]	[illegible]	[illegible]	[illegible]
2	[illegible]	PN	NI	[illegible]
3	[illegible]	[illegible]	[illegible]	[illegible]
4	[illegible]	PN	NI	[illegible]
5	[illegible]	[illegible]	[illegible]	[illegible]
6	[illegible]	PN	PY	[illegible]
7	[illegible]	PN	[illegible]	[illegible]

Note: For ease of reading, we have assigned a number to each systematic review that was evaluated using the ROBIS as follows:
1: Impact of social transition in relation to gender for children and adolescents: a systematic review,
2: Psychosocial support interventions for children and adolescents experiencing gender dysphoria or incongruence: a systematic review,
3: Clinical guidelines for children and adolescents experiencing gender dysphoria or incongruence: a systematic review of guideline qualit
4: Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: a systematic review,
5: Characteristics of children and adolescents referred to specialist gender services: a systematic review,
6: Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: a systematic revie
7: Care pathways of children and adolescents referred to specialist gender services: a systematic review

Appendix C

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Biological and psychosocial evidence in the Cass Review: a critical commentary

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Biological and psychosocial evidence in the Cass Review: a critical commentary

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ABSTRACT

Background: In 2020, the UK's National Health Services (NHS) commissioned an independent review to provide recommendations for the appropriate treatment for trans children and young people in its children's gender services. This review, named the Cass Review, was published in 2024 and aimed to provide such recommendations based on, among other sources, the current available literature and an independent research program.

Aim: This commentary seeks to investigate the robustness of the biological and psychosocial evidence the Review—and the independent research programme through it—provides for its recommendations.

Results: Several issues with the scientific substantiation are highlighted, calling into question the robustness of the evidence the Review bases its claims on.

Discussion: As a result, this also calls into question whether the Review is able to provide the evidence to substantiate its recommendations to deviate from the international standard of care for trans children and young people.

KEYWORDS
gender identity; healthcare; policy; scientific rigor; transgender

Introduction

The Cass Review (2024) is an independent review, commissioned in 2020 by the UK's National Health Services (NHS) to provide recommendations on children's gender services. The Review was commissioned in the context of particular hostility in the UK toward trans individuals (Walters et al., 2020), and a high-profile legal case regarding trans children's ability to consent to puberty blockers (de Vries et al., 2021). The review was written independent of the NHS gender services, and itself commissioned further independent systematic reviews, performed by scholars at the University of York. After an interim report published in 2022, The Review released its final findings in April 2024. In this final report, it aims to provide recommendations for a new standard of care for trans youth in the UK.

One of the central aims of the Cass Review is the "best available collation of published evidence" (Cass, 2024, p. 52), and based on the collated evidence, provide scientifically substantiated recommendations. The Cass Review is based on 4 key sources, one of which, termed 'Evidence', forms the scientific basis of the Review. The evidence consists of a series of independent, peer-reviewed reviews, commissioned through the research programme, published in Archives of Disease in Childhood (Taylor et al., 2024a, 2024b, 2024c, 2024d), supplemented by additional qualitative and quantitative research throughout the Review. Among other topics, the Review discusses the biological and psychosocial evidence regarding the development of trans individuals and their brains, the effects of particular treatments, and how this may affect recommendations for healthcare for trans children and adolescents. Together, this evidence is used to substantiate the assertions which are used to support the key recommendations of the Review, notably several recommendations that deviate from the current international standard of care (SOC) as supported by the World Professional Association for Transgender Health (WPATH) (Coleman et al., 2022). As such, it is

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vital that the evidence is of high quality, and that its collection and collation follows standards of scientific rigor.

In this commentary, this scientific evidence is reviewed, particularly focusing on the biological and psychosocial claims reported in the Review. The scientific substantiation of assertions in the sections on understanding the patient cohort and clinical approaches is examined critically, resulting in the finding that the Review shows a number of issues that together point to a substandard level of scientific rigor in the Review. As such, it called in question whether the Review provides sufficient evidence to substantiate its recommendations to deviate from the international standard of care for trans children.

Changes in the patient profile

The Review first aims to understand the demographics of young people referred to gender services. To this end, a systematic review of the literature was commissioned. Taylor et al. (2024d) reviewed all English-language studies studying trans children and adolescents (<18yo) referred to gender or endocrinology services. The review includes data on referrals from 2000 until 2019, with varying coverage of this timeframe depending on the country. Based on this data, it notes both a sharp increase in overall referrals—in particular since 2014—and generally an increase in the percentage of individuals assigned female at birth. However, it is not clear whether these are statistically significant increases and what trend they follow over time. In addition, as the authors themselves points out, because of the low overall numbers in referrals, the ratio between those assigned female compared to male at birth tends to jump around for many countries included in the study (e.g. Scotland, Sweden, Germany). The authors conclude there is a "twofold to threefold increase in the number of referrals to specialist paediatric gender/endocrinology services over time across countries" (Taylor et al., 2024d, p. 6). However, it is unclear what timeframe this refers to specifically, and if this is based on the data corrected for population size, nor what the confidence interval is for the cited numbers.

The Cass Review further relies on a quantitative study of Clinical Practice Research Datalink (CPRD) data on gender dysphoria in the UK, which has not (yet) been published in a peer-reviewed journal, but is detailed in Appendix 5 of the Review (Cass, 2024). In this case, the authors claim a 100-fold increase, but do not include the precise numbers (prevalence in 2009 is cited as <0.1%) nor any statistics to support this claim. Although they provide 95% confidence intervals in their graphs, it is unclear what is used as the sample group to calculate these confidence intervals. The study does not discuss changes in confounds across the timeframe, such as changes in societal acceptance and diagnostic criteria across the measured timeframe (2009-2021), which may explain some of the increases in prevalence. Lastly, the study does not provide an introduction detailing previous studies on the topic, or a conclusion placing the results into the larger context of the current scientific literature. Overall the study as written provides too little information to draw any statistically sound quantitative conclusions.

In addition to data about the sex assigned at birth, Taylor et al. (2024d) also explore the prevalence of comorbidities, specifically mental health disorders. Notably, they wrongly report the incidence of autism spectrum condition (ASC) as reported by Morandini et al. (2022), writing "[o]ne study reported data separately for 2012 and 2015 and demonstrated an increase from 1.8% to 15.1%" (Taylor et al., 2024d, p. 5), when the reported numbers were a non-significant increase from 13.8% to 15.1% (p= .662) (Morandini et al., 2022). Besides this study, no consistent co-occurrence of ASC and gender dysphoria is reported. In addition, when assessing ASC, two studies were included that only reported the scores on Items 9 and 66 on the Teacher's Report Form (TRF) (Zucker et al., 2017) or on the CBCL (VanderLaan et al., 2015), which measure obsessions and compulsions. If participants scored higher than a 0 (scale 0-2) on either behavior, they were included in the sample of ASC by Taylor et al. (2024d), along with the studies using clinical diagnoses. Thus, the conclusions on co-occurrence between ASC and gender dysphoria are unreliable.

The review by Taylor et al. (2024d) is used as a key source in the Cass Review's discussion on the prevalence of psychiatric disorders in young people referred to gender services, noting that "rates of depression, anxiety and eating disorders were higher in the gender clinic referred population than in the general population" (Cass, 2024, p. 91). However, as Taylor et al. (2024d) discuss, this data is based on varying measures. For example, across studies depression is measured using the Child Behavior Checklist (CBCL), DASS-21 (Depression, Anxiety and Stress Scale), DSM-5, Youth Self Report (YSR), BDI II (Beck Depression Inventory) and prior clinical diagnoses. Similar conflation of psychometric scales and medical diagnoses is used across the other psychiatric disorders, as previously also demonstrated was the case for ASC. The vastly different criteria across these measures lead to a high variability across studies, and as such extreme caution should be taken when interpreting these results.

In further discussion of the prevalence of psychiatric disorders, the Cass Review claims in point 5.30 (p.91) that "[i]n Finland (Kaltiala-Heino et al., 2015; Karvonen et al., 2022) more than three-quarters of the referred adolescent population needed specialist child and adolescent psychiatric support due to problems other than gender dysphoria, many of which were severe, predated and were not considered to be secondary to the gender dysphoria." (Cass, 2024, p. 91). Kaltiala-Heino et al. (2015) reported 35/47 (74.5%) of the included participants had prior referrals for psychiatric treatment. They reported that 68% received these referrals prior to their first gender dysphoria treatment, however, no data is available about the referral time relative to gender dysphoria onset and the relative severity of these issues. Karvonen et al. (2022) report that 59.1% of adolescents received a psychiatric diagnosis. They also explicitly say that these disorders were not reported prior to gender dysphoria, and as such no causality can be inferred. Neither study supports the claim made in the Cass Report that more than three-quarters were referred for psychiatric issues other than gender dysphoria, or that the majority of these were severe and preceded gender dysphoria onset.

This section leads to a number of key recommendations (30-42). Notably, recommendation 31 (Cass, 2024, p. 26) states that "[a]mong referrals there is a greater complexity of presentation with high levels of neurodiversity and/or co-occurring mental health issues and a higher prevalence than in the general population of adverse childhood experiences and looked after children. The increase in referrals and change in case-mix is also being seen internationally". As demonstrated above, this claim is based on weak trends at best, with no clear support for increase in case-mix or psychiatric disorders among the population (Karvonen et al., 2022). The Review further states in recommendation 35 (Cass, 2024, p.26): "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". It is not clear what the source is for the claim of an exponential change, as no trend analysis is performed on the data in Figure 15 of the Review (Cass, 2024). There is also no discussion on what the expected change based on evolution in acceptance would be, and how this is measured. In fact, in point 7.6 (Cass, 2024, p. 106), the Review reports an unprecedented evolution in acceptance of non-binary genders among generation Z, suggesting the trends around trans acceptance do not follow a normal evolution of acceptance of a minority group. Similar observations about an increase in overall numbers and a difference in the demographics of adolescents referred to gender services are also noted in the WPATH's SOC (Coleman et al., 2022). However, this document discusses a number of reasons for these changes, including underestimation of numbers in previous studies, and changes to the sociopolitical landscape. Although some of the reasons are discussed by Cass (2024) in a later chapter, the Review fails to engage critically with the literature on this topic, for example by failing to discuss some of the key publications cited in the SOC.

Overall, the Review makes claims about trends in terms of demographics that are weakly substantiated, with no clear statistical basis for its quantitative discussion about exponential or two-to threefold increases. In addition, several sources are cited that do not support certain assertions, most notably those reporting trends in Finland. Furthermore, the Review shows internal inconsistencies, with seemingly contradictory reports on expected compared to unprecedented increases in acceptance of trans individuals. Lastly, despite difference in the conclusions between the Cass Review and the current SOC, the Review fails to critically engage in discussion of causes for such discrepancies.

Developmental considerations

The Review aims to find a biological basis of gender dysphoria, starting this section by stating that "[b]iological sex is determined by sex chromosomes" (Cass, 2024, p. 98). This is an oversimplification, as in the scientific literature there is no clear consensus about the exact meaning of 'biological sex' (Velocci, 2024). The Review goes on to discuss three "important ways in which sex differences are expressed" (Cass, 2024, p. 98): gender role behaviors, gender identity and sexual orientation (Babu & Shah, 2021). These three domains are used by studies looking at the psychosocial development of intersex individuals specifically, and it is unclear to what extent these domains would also apply to endosex individuals, i.e. those whose sex characteristics fit into the medical criteria of either male or female.

A central discussion point in this section of the Review relates to brain development. A main reference for the claims about brain development is a non-peer-reviewed article (Giedd, 2015). In the academic literature, the definition of a 'mature brain' is less clear, as the brain continually develops, grows and shrinks (Somerville, 2016; Tamnes et al., 2010). To highlight the importance of puberty and adolescence, the Review discusses the hypothesis of this time as a 'critical period' (Cass, 2024, p. 104), a theory put forward by Larsen and Luna (2018). However, while it seems the Review uses this term in its more colloquial meaning, the authors refer to a specific neurobiological phenomenon: a critical period is a time of increased plasticity when the neuronal network and its individual parts are particularly sensitive to incoming stimuli (Dehorter & Del Pino, 2020). In this meaning, there's not necessarily a clear link between brain maturation and the occurrence of a critical period during adolescence, nor is there clear consensus on the effect of hormones on neural circuits during a critical period. The only clear conclusion is—as the Cass Review rightfully notes—that more work is needed to understand these complex neurobiological interactions.

In summary, although puberty and adolescence are key times for brain development, claims about brain maturation are not as black-and-white as the Review posits. Additionally, the question as to how brain maturation should advise legal policies is a far-reaching one, beyond the scope of both this commentary and arguably the Cass Review, and should be considered with extreme caution (Somerville, 2016; Steinberg, 2009a, 2009b). The Cass Review provides insufficient evidence to claim that brain maturation should be a reason to prohibit or restrict gender care for children and adolescents, especially in the face of these far-reaching legal consequences for such a claim.

Growing up in the 2000s

Next, the Review discusses the societal background against which the current generation of trans children are growing up. A set of key points (7.16-7.20) poses a possible link between increased availability of sexually explicit materials and gender dysphoria, based on an article by Nadrowski (2024).[1] This article does not contain any primary research, but rather poses a yet untested theory. Indeed, the article itself notes that "no studies have yet directly linked exposure to pornography with gender dysphoria" (Nadrowski, 2024, p. 294). The argument in the Nadrowski paper is not supported by data, and as the only source, is not sufficient to suggest a link between pornography and gender dysphoria.

In point 7.28, the Review states that "[t]he increase in presentations to gender clinics has to some degree paralleled this deterioration in child and adolescent mental health" (Cass, 2024, p. 111), based solely on the fact that both have gone up in recent years. The Review seems to imply causation here, but since the causes of these increases is poorly understood, it is highly possible either a confound is present that would explain both increases, or that an increased number of children with gender dysphoria is impacted by societal pressure and hostility, leading to the increase in mental health problems. Indeed, the WPATH SOC stresses the effects of this "minority stress" on trans individuals in particular (Testa et al., 2015), leading to mental health disparities (Coleman et al., 2022), which is dismissed by Cass (2024) in point 8.41 and 8.42 without clear reason. The Cass Review further state that "[m]any young people with gender dysphoria are presenting with combinations of the above conditions" (Cass, 2024, p.112). No source is given for this statement here, so it is unclear how this compares to the overall population, and whether and statistically significant trends are present.

Overall, although this section discusses a number of important societal developments that may increasingly impact young people, it fails to engage critical with established theories on causes of mental health issues in trans youth, in particular the effects of minority stress. In addition the Review fails to provide any concrete evidence of causal links between the societal factors affecting the younger generation they discuss and increases in gender dysphoria.

Possible factors influencing the change in patient profile

In exploring the factors causing changes in patient profiles, the Review asserts that "[f]or many centuries transgender people have been predominantly trans females" (Cass, 2024, p. 114). It is unclear what evidence supports this statement. Studying the prevalence of transgender people and their identity has been made difficult by the continued criminalization of trans identities and the destruction of historical materials, for example when the Institut für Sexualwissenschaft was destroyed in Nazi Germany (Aghi et al., 2024). Despite this, many accounts of 'women' living as men, who may call themselves transmasculine or trans men in today's world, have been reported across history (Hager, 2018; Skidmore, 2017). In addition, genders outside of the strict binary have historically exists, and still do, across the world, such the various gender identities within Indigenous nations in North America (Robinson, 2019). The assumption that trans history was dominated by trans women primes the idea of a shifting patient profile, but there is no evidence to support this assertion.

In its discussion of the effects of hormone exposure on brain structure, the Review cites Ristori et al. (2020), to support the statement that "[t]here is evidence that masculinizing/feminizing hormone treatments alter brain structure" (Cass, 2024, p. 116). Within the paper by Ristori et al. (2020), three primary sources are cited for this claim (Pol et al., 2006; Rametti et al., 2012; Zubiaurre-Elorza et al., 2014). These studies into the effect of cross-sex hormones on the brains of trans individuals—all performed on cohorts with an average age of 25-30, not during puberty—indeed show changes in volume, cortical thickness, and white matter structure after hormone treatment. However, one should consider that brain structure naturally changes over time, and may be affected by endogenous hormones as well. Therefore, a proper matched control—which matches both in overall hormone levels and demographics—would be needed to conclusively say that masculinizing or feminizing hormone treatments alter brain structure.

Two of the three studies (Rametti et al., 2012; Zubiaurre-Elorza et al., 2014) discussed by Ristori et al. (2020) report differences in brain structure in trans individuals prior to the onset of hormone treatment. Indeed, the review later (point 8.19) cites Mueller et al. (2021), who also find differences between (non-hormonally treated) trans and cis individuals. The Review dismisses this paper saying it claims the "equivalent to suggesting that all neurodiverse people had the same unique brain" (Cass, 2024, p. 116). However, this is a misinterpretation of the claims by Mueller et al. (2021), who argue that the overall patterns of anatomy are statistically different between the four different groups (trans and cis men and women), rather than falling into two categories of 'male' and 'female'. Having dismissed this study, the Review claims "research in this area has not reliably identified brain changes directly linked to gender incongruence" (Cass, 2024, p. 116). Although a thorough review is needed to determine how reliable these brain changes are, three independent studies, two of which are primary sources to support another statement, show evidence of changes linked to gender incongruence, suggesting there is evidence available that people with gender dysphoria show differences in their brain structure.

In point 8.14, the Review cites Karamanis et al. (2022) as a large register-based population study, to show that trans identity is mainly determined by environmental factors, rather than having a genetic basis. However, this study included only 67 twins, and as such is much smaller than the numerous other studies (Alanko et al., 2010; Bailey et al., 2000; Burri et al., 2011; Sasaki et al., 2016; Van Beijsterveldt et al., 2006) which did find support for heritability of trans identity. The Review does not discuss or cite any of these other studies, or explain why the Karamanis study was determined to be the most relevant. The Review argues that this study gives more credence to the idea of sex hormone exposure in the womb causing gender dysphoria. However, given the numerous contradictory findings in the literature, this single study does not provide sufficient evidence to give due credence.

Next, the Review poses that "ACEs [Adverse Childhood Events] are a predisposing factor" (8.40) for gender dysphoria (Cass, 2024, p.119). Although Taylor et al. (2024d) report incidences of ACEs in trans youth, they do not provide evidence of it being a predisposing factor. Similarly, Di Ceglie (2002) reports incidences, but fails to include a control group, thus making it unclear whether the prevalence in trans individuals is significantly increased. Neither study is able to prove causality, as by the time of the assessment, the individuals had already presented with gender dysphoria. It is therefore possible that the ACEs are a consequence of gender dysphoria (e.g. when a child starts presenting gender divergent behavior, this may cause the parent to start abusing the child). To assert that something is a predisposing factor, a causal relationship should be demonstrable, which is not the case with ACEs and gender dysphoria.

Overall, this section discussing possible factors which have influenced the patient profile shows several issues in providing evidence to substantiate its claims. For several key assertion, single studies are cited when a wealth of contradictory studies are available, showing a lack of balanced consideration of the literature. This calls into question the robustness of the listed conclusions of this section (8.52-8.62), and any recommendations the Review makes based on these.

Clinical approach & clinical management

The section on clinical approach and clinical management discusses current practices for the treatment of trans youth, which is outside of the scope of this commentary. However, two key recommendations depend on scientific evidence: administration of puberty blockers and hormone therapy. The Review recommends the provision of puberty blockers only under a research protocol, which contradicts the WPATH SOC, which recommends puberty blockers for any adolescent who meets the outlined criteria and who has reached Tanner stage 2. The Review argues not enough evidence is available to justify the use of puberty blockers, given the risks perceived by the writers. Cass (2024) further recommends a minimum age of 18 for the administration of hormone therapy, whereas the WPATH SOC does not indicate a minimum age, but argues providing hormone therapy prior to the previous recommended age of 16 may be beneficial. The recommendations in the Cass Review are largely based on two commissioned reviews (Taylor et al., 2024a; 2024b), discussed below, as well as supplemental literature cited throughout the Review.

Taylor et al. (2024a) identified 50 papers of the effects of puberty blockers on physiological, psychosocial, gender dysphoria and physical health outcomes. Only one cross-sectional study was marked as high-quality, and 25 as moderate-quality, the remaining studies were excluded from analysis. Although the authors argue no clear conclusions could be drawn about psychosocial outcomes, of the four studies included, none showed negative effects within the first year. The only study showing decreased cognitive functioning, was potentially confounded by other treatments (such as cross-sex hormones). However, despite finding mixed results for height outcome—with three out of seven studies seeing no decrease in growth—the authors do conclude based on this evidence that "gains in height may lag behind that seen in other adolescents" (Taylor et al., 2024a, p. 12). This conclusion is subsequently listed in the Review as a risk of puberty blockers (point 14.43). However, the Review contradicts this finding itself, reporting in point 14.32 that "[e]vidence to date suggests that puberty blockers [does not] lead to substantially reduced adult height in transgender females" (Cass, 2024, p. 177). It is unclear based on what standards of proof either claim is made, and why two contradictory assertions are made within the Review.

When further discussing the results reported by Taylor, Mitchell, Hall, Heathcote, et al., the Review notes that vaginoplasty may be more difficult in trans women treated earlier in puberty with puberty blockers (14.41), which was reported in at least two studies (Lee et al., 2023; van de Grift et al., 2020). However, both studies note that those assigned female at birth are less likely to require a mastectomy, and if they do the surgery is less invasive, when they receive puberty suppression earlier. This is not discussed in the Review, and not considered in its recommendations on when to start puberty blockers for these individuals.

In a second review by Taylor et al. (2024b) 53 studies on hormone treatment were analyzed, with again only one marked as high-quality. Overall, the review surmises that no conclusions can be drawn regarding the effects of hormone treatment, due to inconsistent evidence and lack of quality of the studies, which is reported in the Cass Review. However, in a prior point arguing against the use of puberty blockers in trans men (14.56), the Review argues that "transgender males masculinize well on testosterone" (Cass, 2024, p. 180), which is in direct contradiction with this previous conclusion. Taylor et al. (2024b) further concluded there was no clear effect of hormone treatment on suicidality in trans individuals, despite three out of four papers showing a reduction in suicidality after hormone treatment. In addition to the papers included in this review, which examined studies up to April 2022, the Cass Review discusses several papers showing a reduction in suicidality (15.36-15.43), but—like Taylor et al. (2024b)—concludes the results to be too inconsistent.

Overall, the Cass Review generally cautions against drawing any conclusions about the positive effects of puberty blockers and hormone treatments, for example regarding improvements in psychosocial outcomes and suicidality. However, based on the same studies and similar quality evidence, the Review cautions against the potential negative outcomes, such as the effect of puberty blockers on adult height or vaginoplasty outcomes. Across the topics of puberty blockers and hormone treatment, neither the Cass review, or the commissioned reviews, give a clear definition of when results are deemed too inconsistent. Indeed, it seems like varying thresholds are employed throughout the texts. Ultimately Cass (2024) provides the recommendations of prescribing puberty blockers only on a research protocol, and not providing hormone therapy before the age of 18, which both critically deviate from the current SOC. This difference in recommendation seems to stem from the risks perceived by Cass (2024), which, as shown, are poorly evidenced, and are not of sufficient quality to warrant deviation from the SOC.

Detransition

Within the context of hormone treatment, the Review discusses detransitioners, people who have transitioned previously, but reverted to the gender matching their sex assigned at birth. In discussing the reasons for detransitioning, a main source cited is a study by Littman (2021). Notably, Littman previously published a study on gender dysphoria in adolescents (Littman, 2018). This study was subsequently widely criticized for its flawed methodology (Ashley, 2020; Restar, 2020), leading to a substantial correction of the original manuscript (Littman, 2019). Littman's work should therefore be considered with increased scrutiny, in particular regarding whether the methodology used to obtain the results is robust. Indeed, the cited study (Littman, 2021), as well as the second study cited in the Review (Vandenbussche, 2022) while discussing reasons for detransitioning, has similar methodological issues to the previous study: potentially biased recruitment practices. In both studies, participants were particularly recruited from online detransition-related groups, potentially artificially inflating the number of people with negative views about transitioning and gender affirmative care. These studies found that realizing their gender dysphoria had other causes was the main reason for detransitioning. In contrast, Turban et al. (2021) recruited participants from a large cohort of people who had filled out the Transgender Survey, and found that the most prominent reasons of detransitioning was pressure from parents or societal pressures. This study may also include a recruitment bias, for example, detransitioners may no longer identify as transgender, and therefore not fill out the Transgender Survey. However, given the issues with the two referenced studies, it would be appropriate to additionally discuss this much larger study to provide a balanced overview of the literature. In failing to do so, the Cass Review presents a flawed and unbalanced view, leading to potentially misrepresenting the major causes of detransition, and as such the type of support this population benefits from most. In particular, the Review posits other issues causing the gender dysphoria as the main cause for detransitioning, priming the recommendation that treating other issues—such as mental health issues—prior to providing gender-affirming care may reduce detransition rates. However, this recommendation would not be appropriate based on the reasons reported by Turban et al. (2021), who find external factors to be the major cause for detransitioning. In this case, increasing support and acceptance, both clinical and societal, is likely more effective at reducing detransitioning rates, and focussing on other issues prior to gender-affirming care may ultimately lead to worse clinical outcomes.

Discussion

Overall, this commentary highlights numerous of issues with the scientific substantiation of the biological and psychosocial claims made by the Cass Review. Where quantitative data is referenced or included, statistical measures are missing for claims about trends and differences between groups. In addition, in several claims a balanced discussion of the available literature lacks, and varying standards for quality of evidence are used throughout the Review. In addition, the Review makes a number of contradictory assertions. These issues point toward poor scientific rigor in the evidence collation and dissemination, leading to potentially wrong conclusions and recommendations.

Although the current commentary focuses on the biological and psychosocial evidence presented in the Cass Review, other issues with the Review and its process have previously been raised (Horton, 2024). This article raises a number of similar concerns discussed here, in particular inconsistent standards of evidence. However, further concerns regarding prejudice and a cis-normative bias are also examined. Although science claims to be fully impartial, it never exists in a vacuum, and the confounding factors discussed by Horton should be considered carefully when interpreting the Review.

One of the central recommendations of the Review is the discontinuation of puberty blockers as standard practice for trans children within the NHS. As this is in direct conflict with long-standing international standards of care (Taylor et al., 2024c), it would be expected this recommendation is supported by substantial question about its positive effects of puberty blockers, and/or overwhelming evidence of their adverse effects. Such evidence is not presented in the Cass Review. Similarly, the Review argues there is insufficient evidence of long-term positive effects of hormone treatment in adolescents, recommending against early treatments, again directly contradicting international standards, and the large number of studies used to develop these standards.

All in all, this commentary raises numerous concerns regarding the biological and psychosocial evidence in the Cass Review. These concerns include inferring trends and causality about demographic trends and comorbidities within statistical substantiation, misrepresenting results from the literature, varying thresholds for the inclusion of studies and using unbalanced evidence or references to make one-sided claims. Together, these concerns call into question whether the Review is able to provide sufficient evidence to substantiate its recommendations to deviate from WPATH's international standard of care for trans children (Coleman et al., 2022).

Note

1. This study is cited in the Review as Nadrowski (2023).

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