

Peer Review File

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Reviewer A

This paper would be significantly improved with more focus. What is your goal in writing this review article? What is novel about what you found? What are the specific gaps you think future studies should address?

Reply: The goal of writing this review article is to expand the readers' knowledge on updates in gender medicine, allowing for better understanding and clinical recognition that will pave the way for improved health care outcomes.

There is still a gap in understanding the biological basis of gender diversity and gender dysphoria. Potentially understanding the role of neuroanatomic differences and neuroendocrine influences would hopefully elicit not just improvement in medical and mental health management for transgender and gender diverse individuals with or without gender dysphoria, but also policy changes that will bring about long-term benefits.

The authors use some outdated terminology and imprecise definitions that could use rewording. For example, most experts in this field no longer use gender non-conforming. Additionally, "transgenders" or "transgendered" should never be used - instead, you should say "a person who identifies as transgender" or "a person of transgender experience" or simply "transgender man or transgender woman." Gender identity can be more broadly defined as the personal sense of one's gender instead of including the binary terms "male or female" in the definition. Gender dysphoria is a very specific DSM-V diagnosis, as you included, but not all transgender youth experience dysphoria. This should be clarified in the paper.

Reply: Terminologies updated within the manuscript.

Introduction: It's important to include more citations in your introduction. While the statistics may be changing, it is unlikely that the actual numbers of gender diverse youth are increasing.

Reply: Citations added to introduction.

Methods: The methods section needs significant elaboration. What were your inclusion and exclusion criteria?

Reply: Inclusion and exclusion criteria expanded.

Results/Discussion: The rest of the paper should be organized better. Your results should highlight what you found in the literature. The first section about biological basis of gender is cited well; however, the evaluation section has minimal literature support. Much of this section is already thoroughly written about in the WPATH guidelines or from the American Academy of Pediatrics. While you list a lot of the findings in various papers, you don't have a substantial discussion section that considers how these results impact patient care.

Reply: Discussion section revised, adding citations that support importance of early recognition and proper evaluation of children and adolescents with gender-related concerns presenting to health care providers.

Conclusion: The conclusion focuses on a gap in knowledge and research about long-term effects of gender-affirming therapy, but this is not really addressed throughout the article. There are many publications regarding risks and benefits of these therapies, the types of therapies that may be included in a gender affirming care model, and the importance of counseling (e.g. fertility risks, bone health, etc.) but none of these seem to be included in this manuscript. The conclusion should better align with what is written. Additionally, I don't know that many experts would agree that "much is known about the benefits" - there have been studies that have shown benefits (and of course I agree, as someone who provides gender affirming care), but I do believe that this is still controversial and the reason why many anti-trans laws keep being written.

Reply: Conclusion revised to be more aligned with revisions in the discussion. As gender-affirming therapy will be discussed in a different review article, we focused on etiology, epidemiology and clinical recognition.

I do believe this is a very important topic and should be better represented in the literature; however, I think this specific paper needs to be significantly reorganized and focused to be accepted for print.

Reviewer B

This is a well-written, authoritative review. It is timely given the increasing need for information in the area of gender dysphoria, as prevalence rises, among trans girls in particular. A few minor comments

Should ICD 11 criteria also be considered in Table 1, and a discussion with DSM V made?

Reply: ICD-11 revisions added to the manuscript, reflecting ongoing changes to definitions and terms related to gender identity-related health.

Some possible future areas of research could be suggested to close the gaps in knowledge.

Line 86: There have been more recent studies that might be good to cite here; Fernandez 2018 and 2020, Theisen 2019

Reply: Thank you for these suggested studies, which have been incorporated to the manuscript.

Line 99: Individual studies looking at digit ratio in trans populations have found conflicting results. Might be better to cite the recent meta-analysis (Siegmann et al. 2020)

Reply: Thank you for this suggested article, which has been incorporated to the manuscript.

Line 108: Perhaps should qualify here that differences were seen in adulthood, after symptoms of GD occur. Also, if participants were receiving hormone treatment in these studies, differences in brain structures might be the result of hormone treatment and not the cause of seeking it.

Line 146: Also evidence that ADHD and autism co-occur in transgender youth at higher rates than in the general population, which can't necessarily be accounted for by social stigma like depression and anxiety likely can be

Reply: Brief discussion related to this topic was added to manuscript.

Line 162: Evidence that transgender populations also receive worse health care – another reason why recognition is important (see Riggs et al. 2014)

Reply: Thank you for this suggested article, which has been incorporated to the manuscript.

Line 200: Is 'pronounce' meant to say 'pronouns'?

Reply: Word 'pronounce' changed to 'pronouns'.