nature portfolio

Peer Review File

# The Impact of Gender-Affirming Interventions on Eating Disorder Diagnosis Risk among Transgender and Gender-Diverse Individuals

Corresponding Author: Mr Matthew Loria

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
This paper aims to investigate the relationship between gender affirming interventions and eating disorder. This is an interesting study with the advantage of a big sample size. Overall the paper is well presented. The authors have made considerations to the statistical analysis, with the use of IPTW to account for observed confounding. However some clarifications on the analysis approach is needed. Further comments are given below:
- It appears that the Cox proportional hazards model was performed separately for HT and SX groups (vs NI). Were the propensity scores obtained separately for the two groups?
- Were the models checked for proportional hazards assumption?
- What is the average (or median) time since GID diagnosis for each of the groups?
- What are the p-values Table 1 comparing? It was stated that these were from univariate analyses, however the groups Any GAMT, HT, and SX are not mutually exclusive.
- Figure 1: please show x-axis in a logarithmic scale for visualisation of HR (95% CI).

Reviewer #2

(Remarks to the Author)
The study utilized the TriNetX database to evaluate the likelihood of being diagnosed with an eating disorder (AN, BN, or BED) and effect of GAMT (both hormone therapy and gender-affirming surgeries) on diagnosis among TGD populations (transfeminine and transmasculine).

Introduction

1. The authors can consolidate the writing throughout, e.g. (lines 88-89): "…prevalence increasing from 3.5% during 2000-2006 to 7.8% during 2013-2018."
2.In line 98, may remove comma after i.e.
3.The authors reference several key studies related to eating disorders in TGD populations in lines 99-117. However, multiple systematic reviews and meta-analyses have been published in this area that would be a better fit for an introduction rather than reporting the statistical findings of single studies (e.g. lines 103-105). Consider the following reviews to provide a broader and more robust introduction:
a.Rasmussen, S. M., Dalgaard, M. K., Roloff, M., Pinholt, M., Skrubbeltrang, C., Clausen, L., & Kjaersdam Telléus, G. (2023). Eating disorder symptomatology among transgender individuals: a systematic review and meta-analysis. Journal of eating disorders, 11(1), 84. https://doi.org/10.1186/s40337-023-00806-y
b.Campbell, L., Viswanadhan, K., Lois, B., & Dundas, M. (2024). Emerging Evidence: A Systematic Literature Review of Disordered Eating Among Transgender and Nonbinary Youth. The Journal of adolescent health : official publication of the Society for Adolescent Medicine, 74(1), 18–27. https://doi.org/10.1016/j.jadohealth.2023.07.027
c.Jones, B. A., Haycraft, E., Murjan, S., & Arcelus, J. (2016). Body dissatisfaction and disordered eating in trans people: A systematic review of the literature. International review of psychiatry (Abingdon, England), 28(1), 81–94. https://doi.org/10.3109/09540261.2015.1089217
d.Heiden-Rootes, K., Linsenmeyer, W., Levine, S., Oliveras, M., & Joseph, M. (2023). A scoping review of the research literature on eating and body image for transgender and nonbinary adults. Journal of eating disorders, 11(1), 111. https://doi.org/10.1186/s40337-023-00828-6
e.Heiden-Rootes, K., Linsenmeyer, W., Levine, S., Oliveras, M., & Joseph, M. (2023). A scoping review of research literature on eating and body image for transgender and nonbinary youth. Journal of eating disorders, 11(1), 168.

https://doi.org/10.1186/s40337-023-00853-5
f.Coehlo (already in your reference list)
4.Lines 106-108 (prevalence of ED symptoms) would be a better fit after lines 109-111 (broader introduction to symptomology vs. diagnosis).
5.In addition to body shape concerns and body dysmorphia (line 112), the authors can elaborate on the theorized causes of higher eating disorder diagnoses and symptomology in this population.
6.Given that this study looks at the intersection of GAMT, the authors may wish to further elaborate on the related studies, their findings, and the research gaps (lines 113-117).
7.The authors present a sound flow in the introduction. However, a description of the gap in the current research is missing —why is this study warranted?
8.Lines 118-128 read as a purpose/objectives section. If that is the intent, please label this subsection accordingly and utilize the relevant language, e.g. “The purpose of this study was to evaluate the risk of…”

Methods

9.Please identify the study design.
10.The supplemental file specifies that the pull was from 2000-2023; consider adding this to the main text as this is key information.
11.Since the data pull precedes ICD-10 codes, please clarify why ICD-9 codes were not used as well (lines 146-147).
12.I appreciate the authors explanation that the approach of using ICD codes is justified based on the existing studies; a note regarding the pathologization of one’s transgender identity into a medical diagnosis would be helpful here as well.
13.It appears the authors grouped hormone therapy and gender-affirming surgeries together into “gender-affirming care.” In the results section, it is evident that these are divided into those on HT, those who received surgeries, or either HT/surgeries. Please clarify in the methods section.
14.Please clarify the demographic data reported (line 154).
15.Please clarify why gender was not reported as demographic data.
16.How was “unknown” data handled, especially for sex at birth?
17.Though AN, BN, and BED are included, please clarify why OSFED or EDNOS were not included.
18.In lines 157-158, the authors explain that the primary outcome was a new ED diagnosis after the index event/GID diagnosis. It is unclear to me why the authors required the GID diagnosis to come before the ED diagnosis. It seems a patient could first present with the ED, then receive the GID diagnosis, unless the authors feel the order of those events is critical to the design, in which case this may require further clarification.
19.I appreciate the authors note regarding non-binary identities (lines 160-169).

Results

20.Please add percentages to better conceptualize these findings (lines 190-195).
21.Line 194 makes it seems as though there are 2 groups for those receiving GAMT, though the methods makes it seem as though these are grouped into 1; please clarify. Please consider defining these groups/subgroups in the methods rather than introducing them in the results section.
22.Lines 208-212: please revise writing for clarity. Consider breaking this into shorter sentences.
23.Line 208: recommend language of “…TF on* HT”
24.Table 2: given that the authors do drill down to the type of eating disorder (AN, BN, BED), please consider revising the purpose/aims and statistical analysis subsection to reflect that this will be reported.

Discussion

25.Consider dividing the discussion into subsections to guide the reader’s expectations for each section.
26.Line 254: Please consider revising tone, e.g. “Evidence supports that eating disorder risk is greater among TGD populations relative to cisgender counterparts.”
27.Line 258: Food *insecurity
28.Line 260: please incorporate research that has looked at both EDs and food insecurity, e.g.:
a.Linsenmeyer, W. R., Katz, I. M., Reed, J. L., Giedinghagen, A. M., Lewis, C. B., & Garwood, S. K. (2021). Disordered Eating, Food Insecurity, and Weight Status Among Transgender and Gender Nonbinary Youth and Young Adults: A Cross-Sectional Study Using a Nutrition Screening Protocol. LGBT health, 8(5), 359–366. https://doi.org/10.1089/lgbt.2020.0308
29.Line 274: Recommend revising to, “…increase *the risk…”
30. Lines 304-311: Are the authors suggesting there is any reason why this reality would impact AMAB and AFAB people differently?
31. Lines 336-351: May wish to recommend what disciplines should be included in a care team.
32.Lines 344-346: The barriers to accessing gender-affirming care are quite broad; consider either elaborating on what is meant here, or removing this statement so as not to distract from this section.
33.Please expand on areas for future research.
34.The authors did a good job of offering several founded explanations for the study findings.

Conclusion
35.Lines 376-380 requires revision for sentence flow.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The authors have addressed all my concerns and I have no further comments.

Reviewer #2

(Remarks to the Author)
The authors adequately addressed the reviewer comments. A few final notes:

1) The authors state in the rebuttal file that unknown data were excluded from the analysis. Please include this information in the methods section of the manuscript.

2) The authors state in the rebuttal file how OSFED/EDNOS may have been captured. Please explain this in the manuscript as well, both in the methods and limitations.

3) In the rebuttal file, the authors explain why the GID diagnosis precedes the ED diagnosis due to the statistical model. But, the order of diagnoses may vary in the real world; please explain this as a limitation in the manuscript.

4) Line 208: Recommend revising to, "Among transfeminine individuals (TF), those on HT had an increase in risk of being diagnosed with any new eating disorder compared to TF not* receiving any gender-affirming medical interventions (NI)..."

5) Line 149: second *objective rather than purpose

6) Line 404: Please revise to, "This care team should consist of gender affirming health care providers, including physicians, psychologists, social workers, registered dietitians, and clinical researchers with expertise in ED."

7) Link 437: Please revise to, "Future studies may stratify findings by to race and ethnicity to further understand the intersections with gender identity, how this may influence access to care, and the importance of financial/economic resources."

8) Line 453: Please revise to, "...the risk of being diagnosed with* AN was the most significant..."

**Response to Reviewers**

Reviewer #1 (Remarks to the Author):

This paper aims to investigate the relationship between gender affirming interventions and eating disorder. This is an interesting study with the advantage of a big sample size. Overall the paper is well presented. The authors have made considerations to the statistical analysis, with the use of IPTW to account for observed confounding. However some clarifications on the analysis approach is needed. Further comments are given below:

1. It appears that the Cox proportional hazards model was performed separately for HT and SX groups (vs NI). Were the propensity scores obtained separately for the two groups?
    a. **Yes, we obtained propensity scores separately for each grouped analysis, as each makes up a subset of the larger dataset.**
2. Were the models checked for proportional hazards assumption?
    a. **We tested the proportional hazards assumption using Schoenfeld individual test (cox.zph function in R), which resulted in non-significant p-value. This indicates no violation of the hazards assumption**
3. What is the average (or median) time since GID diagnosis for each of the groups?
    a. **All patients: Mean = 993.6 days, Median = 675.0 days**
    b. **Any GAMT: Mean = 1201.9 days, Median = 908.0 days**
    c. **HRT: Mean = 1236.9, Median = 952.0 days**
    d. **SX: Mean = 823.3 days , Median = 510.0 days**
    e. **NI: Mean = 653.7, Median = 370,**
    f. **We added this information into Table 1**
4. What are the p-values Table 1 comparing? It was stated that these were from univariate analyses, however the groups Any GAMT, HT, and SX are not mutually exclusive.
    a. **The p-values in table 1 are comparing characteristics between patients receiving any GAMT to patients that have no record of receiving GAMT (No GAMT). Therefore the compared groups are mutually exclusive and statistically appropriate. The column labeled as "Overall" is not being compared, and only represents the total count/percentage of each characteristic, across both groups. To alleviate confusion, we have adjusted the table caption as follows:**
        i. **Table 1. Baseline demographics and characteristics between patients with gender dysphoria (GD) and no documented gender-affirming medical therapy (no GAMT) versus patients with GD and with any documented GAMT.**
5. Figure 1: please show x-axis in a logarithmic scale for visualisation of HR (95% CI).
    a. **We thank the reviewer for this suggestion and have adjusted the x-axis to logarithmic scale.Please see the updated figures**

Reviewer #2 (Remarks to the Author):

The study utilized the TriNetX database to evaluate the likelihood of being diagnosed with an eating disorder (AN, BN, or BED) and effect of GAMT (both hormone therapy and gender-affirming surgeries) on diagnosis among TGD populations (transfeminine and transmasculine).

Introduction

1. The authors can consolidate the writing throughout, e.g. (lines 88-89): "…prevalence increasing from 3.5% during 2000-2006 to 7.8% during 2013-2018."

- **Thank you for this comment. We have done our best to consolidate writing.**

2.In line 98, may remove comma after i.e.

- **We have made this correction**

3.The authors reference several key studies related to eating disorders in TGD populations in lines 99-117. However, multiple systematic reviews and meta-analyses have been published in this area that would be a better fit for an introduction rather than reporting the statistical findings of single studies (e.g. lines 103-105). Consider the following reviews to provide a broader and more robust introduction:

a.Rasmussen, S. M., Dalgaard, M. K., Roloff, M., Pinholt, M., Skrubbeltrang, C., Clausen, L., & Kjaersdam Telléus, G. (2023). Eating disorder symptomatology among transgender individuals: a systematic review and meta-analysis. Journal of eating disorders, 11(1), 84. https://doi.org/10.1186/s40337-023-00806-y

b.Campbell, L., Viswanadhan, K., Lois, B., & Dundas, M. (2024). Emerging Evidence: A Systematic Literature Review of Disordered Eating Among Transgender and Nonbinary Youth. The Journal of adolescent health : official publication of the Society for Adolescent Medicine, 74(1), 18–27. https://doi.org/10.1016/j.jadohealth.2023.07.027

c.Jones, B. A., Haycraft, E., Murjan, S., & Arcelus, J. (2016). Body dissatisfaction and disordered eating in trans people: A systematic review of the literature. International review of psychiatry (Abingdon, England), 28(1), 81–94. https://doi.org/10.3109/09540261.2015.1089217

d.Heiden-Rootes, K., Linsenmeyer, W., Levine, S., Oliveras, M., & Joseph, M. (2023). A scoping review of the research literature on eating and body image for transgender and nonbinary adults. Journal of eating disorders, 11(1), 111. https://doi.org/10.1186/s40337-023-00828-6

e. Coehlo (already in your reference list)

- **Thank you for providing these wonderful references. We have worked most of them into the introduction at some point. We also have expanded the literature we reviewed to include more explanation about the difference in ED risk and symptomatology.**

4.Lines 106-108 (prevalence of ED symptoms) would be a better fit after lines 109-111 (broader introduction to symptomology vs. diagnosis).

- **We have rearranged this paragraph to address concerns of flow**

5.In addition to body shape concerns and body dysmorphia (line 112), the authors can elaborate on the theorized causes of higher eating disorder diagnoses and symptomology in this population.

- **We have expanded both the risk and protective factors associated with ED symptomatology in lines 109-112 and 117-119.**

6.Given that this study looks at the intersection of GAMT, the authors may wish to further elaborate on the related studies, their findings, and the research gaps (lines 113-117).

- **We have added information about GAMT and how current research explore this intersection with ED (Line 117-125)**

7.The authors present a sound flow in the introduction. However, a description of the gap in the current research is missing—why is this study warranted?

- **We have added in lines 126-132 discussing the gap in the literature.**

8.Lines 118-128 read as a purpose/objectives section. If that is the intent, please label this subsection accordingly and utilize the relevant language, e.g. “The purpose of this study was to evaluate the risk of…”

- **We have updated the manuscript to reflect this language (135-149)**

Methods

9.Please identify the study design.

- **We have updated the manuscript to include the study design**

10.The supplemental file specifies that the pull was from 2000-2023; consider adding this to the main text as this is key information.

- **We have moved this information to the main manuscript.**

11.Since the data pull precedes ICD-10 codes, please clarify why ICD-9 codes were not used as well (lines 146-147).

- **The TriNetX database converts all old ICD-9 codes to their ICD-10 counterparts. This platform does not allow for querying via the ICD-9 code system.**

12.I appreciate the authors explanation that the approach of using ICD codes is justified based on the existing studies; a note regarding the pathologization of one’s transgender identity into a medical diagnosis would be helpful here as well.

- **Thank you for this insightful comment. We strongly agree that this clarification was necessary and have updated our manuscript accordingly.**

13.It appears the authors grouped hormone therapy and gender-affirming surgeries together into “gender-affirming care.” In the results section, it is evident that these are divided into those on HT, those who received surgeries, or either HT/surgeries. Please clarify in the methods section.

- **We have updated the manuscript to ensure that the methods section clearly explains what we showed in our results.**

14.Please clarify the demographic data reported (line 154).

- **We have added those specifics into the methods section.**

15.Please clarify why gender was not reported as demographic data.

- **TriNetX only contains data according to sex assigned at birth. Gender is not included anywhere in their demographic data.**

16.How was “unknown” data handled, especially for sex at birth?

- **Any individual with unknown data, including sex assigned at birth, is excluded from the analysis. The missing data was only reported in the baseline characteristics.**

17.Though AN, BN, and BED are included, please clarify why OSFED or EDNOS were not included.

- **We included a category of being diagnosed with any eating disorder which would capture those diagnosed with OSFED and EDNOS. However, we chose to pursue specific analysis of AN, BN, and BED as these were the three most prevalent diagnoses. However, if the reviewers would like to see this information we would be able to add this data to the manuscript.**

18.In lines 157-158, the authors explain that the primary outcome was a new ED diagnosis after the index event/GID diagnosis. It is unclear to me why the authors required the GID diagnosis to come before the ED diagnosis. It seems a patient could first present with the ED, then receive the GID diagnosis, unless the authors feel the order of those events is critical to the design, in which case this may require further clarification.

- **The goal of this paper was to understand how the risk of being diagnosed with an eating disorder changes according to GID diagnosis, start of HT or gender affirming surgery. In order to use the Cox proportional hazard model with a time varying analysis, we are required to have a uniform index event for all cohorts, this must be the GID diagnosis as this is the only common diagnosis amongst all cohorts. By setting this as the uniform index event, we were then able to analyze the risk of being diagnosed with a new eating disorder among each cohort. If a GID diagnosis did not precede a new ED diagnosis, this model would not be able to function.**

19.I appreciate the author's note regarding non-binary identities (lines 160-169).

- **Thank you for this remark.**

Results

20.Please add percentages to better conceptualize these findings (lines 190-195).

- **We have added this in.**

21.Line 194 makes it seems as though there are 2 groups for those receiving GAMT, though the methods makes it seem as though these are grouped into 1; please clarify. Please consider defining these groups/subgroups in the methods rather than introducing them in the results section.

- **We updated the methodology to reflect the appropriate groups and subgroups.**

22.Lines 208-212: please revise writing for clarity. Consider breaking this into shorter sentences.

- **We have updated the clarity of this paragraph to increase the readability.**

23.Line 208: recommend language of “…TF on* HT”

- **We have made this change.**

24.Table 2: given that the authors do drill down to the type of eating disorder (AN, BN, BED), please consider revising the purpose/aims and statistical analysis subsection to reflect that this will be reported.

- **We have included this note into the aims and statistical analysis sections. (124-126) and (189-190)**

Discussion

25.Consider dividing the discussion into subsections to guide the reader's expectations for each section.

- **We have added in subsections**

26.Line 254: Please consider revising tone, e.g. "Evidence supports that eating disorder risk is greater among TGD populations relative to cisgender counterparts."

- **We have revised the tone of this sentence.**

27.Line 258: Food *insecurity

- **We have fixed this.**

28.Line 260: please incorporate research that has looked at both EDs and food insecurity, e.g.:
a.Linsenmeyer, W. R., Katz, I. M., Reed, J. L., Giedinghagen, A. M., Lewis, C. B., & Garwood, S. K. (2021). Disordered Eating, Food Insecurity, and Weight Status Among Transgender and Gender Nonbinary Youth and Young Adults: A Cross-Sectional Study Using a Nutrition Screening Protocol. LGBT health, 8(5), 359–366. https://doi.org/10.1089/lgbt.2020.0308

- **Thank you for pointing out this article. We have incorporated it into the discussion.**

29.Line 274: Recommend revising to, "…increase *the risk…"

- **We have made this change**

30. Lines 304-311: Are the authors suggesting there is any reason why this reality would impact AMAB and AFAB people differently?

- **After reviewing this paragraph, we wanted to state that this pressure would uniformly impact all TGD individuals. But, we expanded this point with literature about obesity rates among AFAB and AMAB and how this explanation is less plausible to account for our findings. Thank you for helping point out this unclear area.**

31. Lines 336-351: May wish to recommend what disciplines should be included in a care team.

- **We have delineated the individuals we believe should be included in this team.**

32.Lines 344-346: The barriers to accessing gender-affirming care are quite broad; consider either elaborating on what is meant here, or removing this statement so as not to distract from this section.

- **We have removed this statement**

33.Please expand on areas for future research.

- **We have added in areas of future research**

34.The authors did a good job of offering several founded explanations for the study findings.

- **We appreciate this remark. We worked hard to offer many explanations for these intriguing findings.**

Conclusion

35.Lines 376-380 requires revision for sentence flow.

- **We have updated these lines to improve sentence flow.**

1) The authors state in the rebuttal file that unknown data were excluded from the analysis. Please include this information in the methods section of the manuscript.

- **Thank you for this comment. We have included this information in the methods section. Please see lines 200-202**

2) The authors state in the rebuttal file how OSFED/EDNOS may have been captured. Please explain this in the manuscript as well, both in the methods and limitations.

- **Thank you for this comment. We made sure to add this in. Please see lines 193-197 and lines 443-446.**

3) In the rebuttal file, the authors explain why the GID diagnosis precedes the ED diagnosis due to the statistical model. But, the order of diagnoses may vary in the real world; please explain this as a limitation in the manuscript.

- **We have added this in as a limitation. Please see lines 439-443.**

4) Line 208: Recommend revising to, "Among transfeminine individuals (TF), those on HT had an increase in risk of being diagnosed with any new eating disorder compared to TF not* receiving any gender-affirming medical interventions (NI)..."

- **Thank you for this clarification. We have made this change to improve clarity.**

5) Line 149: second *objective rather than purpose

- **We have made this change.**

6) Line 404: Please revise to, "This care team should consist of gender affirming health care providers, including physicians, psychologists, social workers, registered dietitians, and clinical researchers with expertise in ED."

- **Thank you for this revision, we have made this change.**

7) Link 437: Please revise to, "Future studies may stratify findings by to race and ethnicity to further understand the intersections with gender identity, how this may influence access to care, and the importance of financial/economic resources."

- **We have incorporated this change. Thank you.**

8) Line 453: Please revise to, "...the risk of being diagnosed with* AN was the most significant..."

- **We have incorporated this change. Thank you.**