

Peer Review File

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Reviewer A

In their article, Gender Differences in Congenital Heart Defects: A Narrative Review, Pugnaroni et al. performed a well-structured literature review in a narrative style. The topic of gender differences is indeed important in daily patient's care and the authors are right, that a gender-based management of CHD should become an established medical approach. Unfortunately, I am quite unsure whether the novelty content justifies a full publication. The content is more or less known and e.g. already published as a book chapter in 2018 by Yoo BW (DOI: 10.1007/978-3-319-77932-4_3). A systematic review approach or meta-analysis using tables would be preferable, due to all epidemiological parameters.

Some comments have to be made:

Overall

Comment1:

1. I have problems with the use of the term "gender" in this article, as most literature and findings refer to biological sex. In my opinion, the difference between biological sex and sociocultural gender needs to be pointed out in several places in the article. In my understanding, the term biological "sex" refers to all biological, anatomical, and physiological differences between men and women that are determined by genetic factors and hormones. A counterpart to biological sex, referred to as "gender", is the social or cultural role of male/female identity. This has to be stated in the Introduction-Section, as well as a limitation. It also should be emphasized in the Conclusion.

Reply1: We really thank the reviewer for this valuable comment. We have, accordingly, revised the text to emphasize this point. A detailed definition about biological sex is provided in the Introduction session and in the Discussion paragraph. Changes in the text: Page 3, Lines 79-81.

Comment 2: Please delete the numbering before the headings.

Reply 2: We thank the reviewer for this suggestion and we have deleted numbering before headings

Comment 3: Introduction

1. The Introduction is well written. Nevertheless, as stated above the difference between sex and gender has to be explained here. 'Rationale' and 'Objective' can be streamlined and shortened.

2. Line 90f is no objective and should be deleted.

Reply3: We agree. We added a statement about how gender was considered for this review (Written in green, Page 3, Lines 79-81). Additionally, we shortened the Rationale and Objective paragraph and we deleted Line 90f, as suggested. Changes are marked in yellow.

Changes in the text: Page 4, Lines 92-98

Comment 4: Results

1. To the best of my knowledge a narrative review doesn't have a results section. Please delete line 112. Lines 113 to 120 belong to the Methods Section.

Reply 4: We thank the reviewer for pointing this out. In the guidelines for authors by Translational Pediatrics the main body of the text can be arranged with subheadings based on the authors' preferences. We therefore believe that including a Results paragraph highlighting the key findings of the review, despite not being a systematic review, would be beneficial for the reader. (<https://tp.amegroups.com/pages/view/guidelines-for-authors> “Main text: Arranged as Introduction, Methods, main body (the word “main body” should not be used as a subheading and authors are free to decide on the subheadings for content of the main body) and Conclusions.)

We also believe that lines 113-120 belong to the Result Section.

Comment 5 Discussion

1. Shorten Lines 123 to 136, as this is only an introduction to the subject and not a result of the review.

2. As no single study really assessed gender differences, replace "gender" with "sex".

3. The whole Discussion can be streamlined. Especially statements like in line 249f can be deleted as such things count for almost all of Europe and the statements should be kept rather general in the context of a review.

4. Why does the review only address differential prevalence/preponderances between heart defects based on biological sex, even though the authors state in the introduction that the "morbidity burden" is so high in CHD? In particular, papers such as DOI: 10.1007/978-3-319-77932-4_3 or DOI: 10.1016/j.ijcchd.2021.100185 are much more progressive and holistic in this regard. Please adapt or rewrite the background.

Reply 5

1. We shortened the paragraph. Changes are highlighted in green. Changes in the text (Page 5, Lines 130-136)

2. Several studies that are reported in our narrative review described gender differences in prevalence of different CHDs. As the reviewer suggested before, we are considering biological gender through the text and we prefer to keep this definition rather than “sex”

3. We agree with the reviewer and we reorganized both the “Prevalence of specific

CHD among genders “and the discussion paragraph. Changes in the text: Pages 5-12.
4. We thank the reviewer for this suggestion. The cited articles are indeed excellent examples of the influence of biological gender on various comorbidities associated with CHD. However, the focus of our narrative review is specifically analyzing gender differences in the epidemiological aspects of CHD, while other aspects fall outside the scope of this study. Nevertheless, we appreciate the reviewer's comment, and it would be interesting to explore these aspects in a future, broader investigation.

Comment 6: Strength and Limitations

1. Pure knowledge of epidemiological numbers on prevalence won't change management or therapy, as even current guidelines propose therapies that were based on data from men and simply extrapolated to women. Despite this, women continue to be underrepresented in cardiovascular clinical trials. Please adapt your limitations accordingly

2. Please also add “differences in race, and ethnicity” to the limitations section, e.g. line 305f.

Reply 6

1. We appreciate the reviewer's comment and accordingly, we have incorporated your suggestion in the text. Modified text is written in red. Changes in the text: Page 12, Lines 352-356

2. We added a sentence about this topic, written in blue. Changes in the text: Page 12, Lines 342-343

Comment 7. Conclusion

1. Given that a narrative review is very long to read, I would recommend summarizing the main findings in a more concise manner at the beginning of the conclusion.

2. Delete "significantly" in line 317, as this is a narrative review.

3. Line 319 is a filler sentence - please be more specific.

4. The implications for practice (lines 325ff) should be more specific. An outlook on how a sex-/gender-specific approach could be implemented would greatly enhance the Conclusion.

Reply 7:

1. As recommended by the reviewer, we have included a summarizing sentence (marked in pink). changes in the text: Page 13, Lines 361-363

2. We deleted “significantly”. Changes in the text: Page 13, Line 361

3. We changed this sentence. Changes in the text: Page 13, Lines 364-367

4. We added some consideration about this topic, highlighted in red. Changes in the text: Page 13, Lines 368-374

Comment 8. Tables

1. Please add thousands of separators in Table 2 for better readability.

Reply 8. We changed the Table as suggested.

Reviewer B

I had a great honor to review the manuscript titled “Gender differences in Congenital Heart Defects: a Narrative Review Authors” by Flaminia Pugnali et al.

The patient’s gender is an important information for every clinician in case of congenital defects, especially in syndromic cases. I would like to congratulate the Authors their effort and the idea of review.

Comment 1: The Authors wrote, “The identification of gender differences in CHD prevalence and distribution may affect treatment strategies and prognostic stratification to improve the entire management of people born with CHD.” That sentence needs clarification. How gender may affect and improve management? Why may it affect detection? That should be discussed for isolated congenital heart defects (CHD) and for CHD that are part of genetic syndromes.

Reply 1: We thank the reviewer for this suggestion. We added a consideration about that in the conclusion paragraph suggesting how a gender-specific approach could be implemented in clinical practice, changes are highlighted in red. Changes in the text: Page 13, Lines 368-374

Additionally, we completely agree that it would be really interesting focusing on the differences among isolated and syndromic cases and this could represent a valuable aspect for further studies.

Comment 2 “[...] wrong study design/conference abstracts and irrelevant papers for the topic, seventeen full-text studies were considered potentially eligible for inclusion.”

What does it mean “wrong study design”? The clarification is strongly needed. It is quite unbelievable that only 17 studies are eligible and included in the review regarding this subject.

Reply 2: We thank the reviewer for this comment. We used the generic definition of “wrong study design” to identify all the studies that had a study setting different from the inclusion criteria (observational, prospective, population based and retrospective studies). A clearer and more descriptive explanation of the term is provided in the description of the exclusion criteria, highlighted in gray. Changes in the text: Page 4, Lines 109-110.

Comment 3. The title of the study may suggest that the Authors describe congenital heart defects (CHD) generally. CHD are the defects that develop during the prenatal period of life. Some of the fetuses with CHD would not reach delivery and die in utero. The Authors do not consider fetuses at all.

Reply3. We thank the reviewer for this valuable comment. We totally agree with this issue but unfortunately studies focusing on gender-specific distribution of CHD in fetal life are extremely scarce. Moreover, as discussed in the “Changing Incidence and Prevalence of CHD” paragraph, the greater availability of prenatal diagnosis services

and increased voluntary abortion rates could lead to conflicting data regarding the actual prevalence of CHD in the fetal period, and therefore, we chose to focus on the gender distribution in the postnatal age.

Comment 4. What is more, the manuscript is unstructured. The information are provided as a plain, continuous text. There is no summary, for example table presenting selected CHD and their distribution regarding specific CHD. It is rather a presentation of really poor number of scientific papers.

Reply 4: You raised an important point here. As a narrative review, the studies were selected and presented uniformly following the author guidelines provided by the journal (<https://tp.amegroups.com/pages/view/guidelines-for-authors#content-3-6>). These guidelines include specific instructions regarding the structure to be followed and emphasize that narrative reviews are descriptive in nature. We selected the more interesting papers on this issue and we summarized the results in Table 2. To enhance clarity, Table 2 has been made more concise, and a summarizing sentence has been added in the conclusion paragraph (highlighted in pink). Changes in the text: Page 13, Lines 361-363

Moreover, we restructured the paragraph “Prevalence of specific CHD among genders” to make the message clearer. Changes in the text: Page 5-10, Lines 147-281

Comment 5. The discussion should be more profound with more precise conclusions. I can agree that included papers are really important and present great numbers of included cases, but the review must contain more data.

Reply 5. We thank the reviewer for this suggestion. We have, accordingly, changed the structure of the discussion paragraph and “Prevalence of specific CHD among genders” paragraph in order to clarify the main findings.

Changes in the text: Page 5- 12; Lines 147-332

Reviewer C

Thank you for submitting an interesting narrative review on sex differences in CHD. It is informative data and might provide more insight in future treatment and follow-up strategies.

Comment 1. I would however like you to change the structure of the paper. At this moment, it reads like a sum up of information, and the context and conclusions are spread throughout the article. I would suggest re-writing it while acknowledging all the subjects. For example, the paragraph 3.2 prevalence of specific CHD among genders should be structured on the different subjects: start with the information about mortality and sex-differences and maybe discuss that (see below), sex differences on the structural defects (preferably per defect all information in 1 piece TGA, ASD etc.), the sex difference in relation to genetics and syndromes, the influence of maternal

information.

Reply 1. We thank the reviewer for this valuable feedback. We shortened and rearranged the discussion paragraph and, as suggested, we reorganized the “prevalence of specific CHD among genders” paragraph focusing on type of defect instead of listing all the studies reviewed. Changes in the text: Page 5-10, Lines 147-281.

Comment 2. One major point up for discussion is gender versus sex. Both are used in this paper and I think that is incorrect.

Reply 2. We thank the reviewer for pointing this out. We added a clear definition of how gender is considered throughout the text in the Introduction paragraph (written in green). In the text we considered biological gender, also referred as Sex, as the classification of individuals as males or females based on a combination of genetic, hormonal, and anatomical factors. Changes in the text: Page 3, Lines 79-81.

Comment 3. 3.2 prevalence of specific CHD among genders

It is a nice and accurate overview of the data. For me it would be helpful if the diseases were clustered with the conclusions; instead of the authors or time periods. For example, TGA is mentioned in several paragraphs, maybe it is possible to align all the evidence concerning TGA (and following all other heart defects).

It would be helpful to start this line with the introduction of all studies about to be discussed as an introduction.

The line on BAV was subdivided into several lines, this should be one.

Reply 3. Based on this comment, we have modified the structure of the paragraph. Changes in the text: Page 5-10, Lines 147-281

Comment 4 Please take a close look at the following sentence: Furthermore, large population-based studies conducted on adult patients (26) confirmed that the gender 221 distribution of CHD in adulthood resembles that at birth and in childhood.

It was not clear for me where this leads to. I think it needs an introduction (or even be moved to the start of the line or the end). Because it is a quite important message. "In the adult population based studies no differences in sex distribution across ages are observed, therefore it supports the fact that mortality is not influenced by sex. This is an interesting conclusion since the most complex CHD was seen in males.

Reply 4: We completely agree with this point. This observation, which has been reported before (Somerville J. The Denolin lecture: the woman with congenital heart disease. *Eur Heart J.* 1998;19:1766–1775; Moodie DS. Adult congenital heart disease. *Curr Opin Cardiol.* 1994;9: 137–142) supports the hypothesis that overall mortality during childhood is not influenced by gender. However, it should be considered that overall mortality during childhood and adolescence is influenced by multiple factors such as sudden cardiac events, complications associated with cardiac surgery, and acquired heart diseases in adolescents and/or adults with congenital heart diseases.

These factors require specific attention, which impacts the definition of mortality, indicating that it is not solely dependent on gender.

Comment 5 Change the style of this sentence In addition, when analyzed by anatomical type of CHD, large population-based studies have shown that gender preponderance may also be influenced by race/ethnicity as well as geographic distribution.

Reply 5: We thank the reviewer; having corrected the paragraph concerning the subtypes of CHD, the sentence has been deleted. However, we added a comment on the role of race/ethnicity in the paragraph “ strength and limitation”, marked in blue. Changes in the text: Page 12, Lines 342-343

Comment 6 I do not understand this part. In univariate analysis, severe CHD were significantly associated with male sex, younger age, higher NYHA class, absence of systemic hypertension and hematocrit >50%. Moreover, male sex remained significantly associated with the presence of a severe CHD when multivariate logistic regression was performed. (37)

Some parts are commonsense: severe CHD are more likely to be diagnosed at young age. But how is the hematocrit related?

Could you incorporate more context about these statements?

Reply 6: We thank the author for this comment. In more severe CHDs, the heart's ability to pump blood effectively may be compromised. As a compensatory mechanism, when the heart is unable to deliver sufficient oxygen to peripheral tissues the body tries to maintain adequate tissue oxygenation by increasing the production of red blood cells, which carry oxygen to the tissues, leading to an elevation in hematocrit levels.

In more severe CHDs, therefore, the body's compensatory response may drive the hematocrit levels above the typical range.

Comment 7 I would like to see the conclusion more to the point, right now it reads like a summary of the article.

Reply 7: We have changed the conclusion paragraph according to this suggestion. Furthermore, based on the valuable comments from all the reviewers, we have incorporated a paragraph of recommendations in the conclusion section regarding the clinical applicability of the knowledge about gender differences in the prevalence of CHD, changes are highlighted in pink and red.

Changes in the text: Page 13-14, Lines 359-376