

## Peer Review File

Article Information: <https://dx.doi.org/10.21037/tau-24-153>

### Reviewer A

**Comment 1:** The topic to be discussed is very interesting, and there is truly little published about it. However, since it is a review work, it has to be exhaustive, and clearer in its conclusions.

**Reply 1:** Thank you for your comment. We will do our best to make this review exhaustive and to make the conclusions clear.

**Changes in the text:** None.

**Comment 2:** There is a lack of bibliographical references, especially in the introduction (they are indicated in the attached pdf text). For a review article there are few references (only 30).

**Reply 2:** We have modified our text as advised.

**Changes in the text:** see Page 4, line 60-61. Page 5, line 60-61,76,82. Page 9, line 126-127.

**Comment 3:** Language needs to be corrected.

**Reply 3:** Corrected language based on Editorial Comments.

**Changes in the text:** see Page 2, line 24,32,34,38. Page 3, line 40,42,43. Page 5, line 63,66,67,82. Page 8, line 116. Page 9, line 129,140,144. Page 11, line 179,204,205. Page 12, line 209,210. Page 14, line 288. Delete line 293-295.

**Comment 4:** Including "discussion" as a heading does not make sense when nothing has been previously discussed.

**Reply 4:** We have modified our text as advised.

**Changes in the text:** see Page 8, line 101.

**Comment 5:** The summaries after each topic: MTHFR gene polymorphism and male infertility and erectile dysfunction, do not reflect the summary of the literature.

**Reply 5:** We have modified our text as advised.

**Changes in the text:** see Page 10, line 168. Page 12, line 236.

**Comment 6:** The heading: "The correlation between MTHFR gene polymorphism and male infertility" after "MTHFR gene polymorphism and male infertility" is meaningless.

**Reply 6:** We have modified our text as advised.

**Changes in the text:** see Page 8, line 103. Page 11, line 195.

**Comment 7:** The conclusions are not clear. It seems more like a discussion.

**Reply 7:** We have modified our text as advised.

**Changes in the text:** see Page 13, line 246. Page 15, line 297-305.

**Comment 8:** Table 1 does not appear in the text.

**Reply 8:** We have modified our text as advised.

**Changes in the text:** see Page 6, line 94-96.

## **Reviewer B**

**Comment 9:** The review is described as non-systematic, which may limit the comprehensiveness of the literature surveyed. A systematic approach can provide a more robust analysis and reduce potential bias in selecting studies.

**Reply 9:** Thank you for your comment. This manuscript is written as a narrative review. The systematic review does provide more robust analysis and potential bias in selecting studies. But we believe that the conclusions and discussions of this narrative review manuscript are sufficiently accurate.

**Changes in the text:** see Page 1, line 2-3.

**Comment 10:** Although this review discusses a variety of studies, less attention is paid to the methodological quality of these studies. A more rigorous assessment of study design and quality of evidence could strengthen the conclusions drawn.

**Reply 10:** Thank you for your comment. This manuscript is written as a narrative review. Given the limited research on this topic in recent years, the methodological quality, research design, and evidence quality of the references have been reviewed by all authors.

**Changes in the text:** None.

**Comment 11:** Please list relevant important references in a table.

**Reply 11:** We have modified our text as advised.

**Changes in the text:** see Page 6-8, line 97-98.

**Comment 12:** Suggest a diagram to illustrate the biochemical pathways affected by MTHFR polymorphisms.

**Reply 12:** We have modified our text as advised.

**Changes in the text:** see Page 4, line 55-57.