

Peer Review File

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Reviewer A

In the following study, the authors (to which this reviewer is blinded) present a retrospective review of erectile dysfunction (ED) as it relates to smoking status and spicy food consumption. They conclude that a higher intake of “spicy foods,” as reported through questionnaires, is associated with higher rates of ED in non-smoking men. Overall, this reviewer feels that the authors’ study design (i.e. a retrospective review of questionnaires) is not the appropriate design to answer this question, let alone publish conclusions drawn from the data presented.

Reply: We understand the reviewer’s concerns about the study design. We chose a retrospective study based on the following considerations: on one hand, such studies can quickly obtain a certain number of sample sizes, on the other hand, the purpose of the study is to preliminarily explore the relationship between the intake of spicy foods and erectile dysfunction (ED). Despite certain limitations, prospective randomized controlled trials are difficult to implement due to the private nature of the ED disease.

We used the internationally recognized IIEF-5 scale to assess the severity of ED and controlled for other confounding factors. Additionally, we conducted sensitivity analyses to eliminate the possible impact of recall bias.

Although the sample was limited to one hospital, considering the habit of local residents to consume a large amount of spicy food, the sample is representative of the local population. At the same time, we also took into account the issue of a small sample size.

We agree with the reviewer’s opinion that the relationship between spicy food and ED needs to be verified by more rigorous prospective studies. We plan to conduct related randomized controlled trials in the future to further determine the causal relationship of this association.

We did not absolutize the research conclusions, but rather viewed them as a preliminary exploratory finding. In the discussion section, we mentioned the limitations of the study and the issues that need further validation.

We will carefully consider the reviewer’s suggestions and make further revisions and improvements to the paper to make the research more rigorous and reliable. We thank the reviewer for their valuable comments, which are of great significance for us to improve our research.

Change in the text: None

Reviewer B

This study is notable because it prompts curiosity regarding whether diet can decrease the risk of erectile dysfunction. Based on previous research, we are aware of several significant risk factors for the development of ED, including age, physical activity, obesity, smoking, and co-morbidities. Various diets have been explored to mitigate the risk of ED and other lifestyle diseases, with the Mediterranean diet showing the most favorable outcomes. Additionally, certain spices originating from Asia have exhibited promising potential in modifying the risk of developing and advancing ED. In this study, the authors investigated the role of smoking and spices on the prevalence of ED, reporting that a high intake of spices can negatively impact erectile function, particularly in non-smokers.

Here are my comments in the order they appear in the manuscript.

The abstract is confusing. It does not provide a rationale for why the examination of fasting blood was performed. Methods should rather include tools with which data on food intake and smoking were collected and how ED was diagnosed/verified. Please provide the names of the questionnaires.

Reply: Thank you for your valuable advice. Our study included a detailed questionnaire and blood draw indicators. We have revised the methods section of the abstract as per your suggestions. We delineate the titles of questionnaires utilized for diagnosing erectile dysfunction (ED), the SIEDY questionnaire for assessing etiological aspects of ED, and associated data pertaining to dietary habits and smoking status.

Change in the text: Lines 58-63.

Line 39. I would remove 'association' and use something more correct for the research.

Reply: Thank you for your helpful advice. In the revised version, we replaced the term 'association' with 'Structured Interview on Erectile Dysfunction (SIEDY)' in the keywords section to reflect the specific assessment tool used in our study.

Change in the text: Lines 80-81.

Line 61. Please formulate the goal of the study clearly. Add information about diet habits, explain what does patient's state means, and introduce smoking as it is mentioned in the title and the abstract.

Reply: Thank you for your helpful advice. We have rewritten the last paragraph of the background section. We have made the purpose of the study clearer and explained the habits of eating and the state of the patients.

Change in the text: Lines 117-130.

Line 65. Move the description of questionnaires to the Methods.

Reply: We appreciate this helpful comment. We moved the description of questionnaires to the methods.

Change in the text: Lines 148-158.

Line 75. The aim of the work should be moved to the objective section.

Reply: Thank you for your helpful advice. The sentence has been rewritten.

Change in the text: Lines 133-134.

Line 73. How did you determine that they had ED?

Reply: Thank you for your valuable question. Currently, there is no gold standard for the diagnosis of Erectile Dysfunction (ED). The method used in our study to diagnose ED is a commonly used diagnostic tool, the International Index of Erectile Function-5 (IIEF-5) questionnaire, with a score of less than 22 indicating EDⁱ. The use of questionnaires for diagnosis introduces subjective factors. Therefore, our research aims to identify more influencing factors of ED and to judge the presence of ED from multiple perspectives.

Change in the text: None.

Line 81. Please kindly provide a reference for the SIEDY questionnaire.

Reply: We appreciate this helpful comment. We have added references of the SIEDY questionnaireⁱⁱ. Our team is the first to apply the SIEDY questionnaire to a Chinese male population.

Change in the text: Line 148.

Line 88. IIEF-5 questionnaire is only on ED. It is not related to CVD. Please correct and provide a reference for this questionnaire.

Reply: Thank you for your helpful advice. We have previously studied the relationship between ED and CVD, and there is literature suggesting a relationship between the IIEF-5 scale and CVD^{iiiiv}. However, the relationship between the IIEF-5 scale and CVD is not indicated by any guidelines. Therefore, thank you for your correction, and we have removed CVD. Additionally, we have provided relevant references.

Change in the text: Lines 161-162.

Line 92. What questionnaires were used for the assessment of dietary and lifestyle habits? Provide names, descriptions and references.

Reply: Thank you for your helpful question. This questionnaire, which our team has compiled and contains over a hundred questions, analyzes various aspects of patients' working environment, dietary habits, and psychological state. Previously, we have published multiple SCI papers based on this research^{vivii}.

Change in the text: None.

What type of spices did you include in the analysis?

Reply: Thank you for your helpful advice. Our focus was on spicy foods, particularly those with capsaicin such as chili peppers. Chili peppers are a commonly consumed spicy food in China, especially in Hunan province, where excessive consumption of

spicy foods is noted. However, further research is needed to determine which components in spicy foods affect ED and to explore their mechanisms of action.

Change in the text: None.

Line 100. Provide a brief description of GAD-7 and PHQ-9 questionnaires.

Reply: Thank you for your valuable advice. We have provided a detailed description of the PHQ-9 and GAD-7 questionnaires and included relevant references^{viiiix}.

Change in the text: Lines 176-182.

Line 106. How was daily sedentary time measured and classified? How was the presence of diabetes, hypertension, and hyperlipidemia determined? Medical records or patient declarations?

Reply: Thank you for your helpful question. “Daily sedentary time” refers to the average number of hours per day participants spend continuously sitting, which was specifically inquired. The methods used to confirm the presence of diabetes, hypertension, and hyperlipidemia include: 1. A detailed inquiry into the participants’ medical history to determine if they have previously had these conditions. 2. Laboratory examinations were conducted to measure the patients’ blood pressure, fasting blood glucose, and related lipid markers. By combining these two aspects, we can confirm the presence and severity of diabetes, hypertension, and hyperlipidemia in the participants.

Change in the text: None.

Line 130. A description of the questionnaires should be placed in the methods.

Reply: We appreciate this helpful comment. Our methods section has already described the SIEDY scale, so we have deleted the relevant descriptions in the results section.

Change in the text: Lines 148-158.

Line 188. Can you please explain how you measure cardiovascular risk? I mean with which questionnaire? It looks as if it is mistaken with the risk of ED. Please carefully review your manuscript.

Reply: Thank you for your helpful advice. This should refer to ED risk, which we have corrected in the manuscript. This was an elementary error, and we apologize for the oversight.

Change in the text: Line 277.

Line 204. There is no analysis shown on cigarettes per day in the results. No new data should be introduced in the discussion. Please such an analysis of the results.

Reply: Thank you for your helpful advice. We have moved this sentence to the results section.

Change in the text: Lines 226-228.

Line 244. Please add a reference.

Reply: Thank you for your valuable advice. We have added relevant references in the manuscript^x.

Change in the text: Line 347.

Line 257. Can you add a reference confirming the relationship between eating spicy foods and irritable character?

Reply: Thank you for your valuable advice. We added a reference that confirms the relationship between eating spicy food and an anxious disposition^{xi}.

Change in the text: Lines 374-376.

Line 278. Add references to the consumption of Chili peppers in China.

Reply: Thank you for your valuable advice. Chili pepper has been one of the most popular spice consumed nationwide by Asian, especially Chinese, populations. Hunan Province is the province that consumes the most chili in China, with a staggering 99.7% of participants in Hunan consumed spicy food weekly. We added the relevant reference.

Change in the text: Lines 404-407.

In each table, please add the number of patients per analyzed group.

Reply: We appreciate this helpful comment. We have added the number of patients per analyzed group.

Change in the text: Table 2-Table 4.

I also would like to draw your attention to testosterone. As you measured and discussed a testosterone level and its association with the consumption of spicy food. Can you please add a short description of testosterone's role in the development of ED? I recommend a reading on this – a paper by Kałka et al. Diagnosis of hypogonadism... *Transl Androl Urol.* 2020 Dec;9(6):2786-2796. Another study showed that testosterone can be linked to spicy food as well. Please see the paper by Bègue et al. Some like it hot: testosterone predicts....*Physiol Behav.* 2015 Feb;139:375-7.

Reply: We appreciate this helpful comment. We have read the two articles you recommended and have briefly summarized the role of testosterone in the development of ED and its relationship with spicy food intake in the discussion section of the paper. Further research is needed to fully understand the complex relationship between testosterone, spicy food intake, and ED risk.

Change in the text: Lines 357-365.

Conclusions – how did you determine that the increase in ED risk is particularly high in non-smoking men? I don't see a comparison between smoking and non-smoking consumers of spicy foods that would be significant. OR is calculated for the total sample and all other analyses are conducted separately for smokers and non-smokers.

Reply: We appreciate this helpful comment. In the study, we drew conclusions regarding the heightened risk of erectile dysfunction (ED) in non-smoking men based

on a comparative analysis of the association between spicy food consumption and ED among smokers and non-smokers. The data was separated into two groups: smokers and non-smokers. Among the non-smokers, there was a clear positive correlation between the frequency of eating spicy food and the severity of ED, as indicated by the IIEF-5 scores ($P=0.017$). However, no significant relationship was observed between the frequency of spicy food consumption and ED in the group of smokers ($P=0.554$). These findings led to conclude that a high intake of spicy food is particularly associated with an increased risk of ED in non-smoking men. This conclusion is also supported by the odds ratio (OR) calculation specifically for non-smokers, which revealed a 158% higher risk of ED with frequent spicy food consumption (OR 2.58, 95% CI 1.27–5.26, $p=0.008$). Therefore, the increased ED risk observed in non-smokers was determined through the differential analysis comparing the effects of spicy food consumption on ED between smokers and non-smokers.

Change in the text: None.

Finally, language needs to be improved. Please check typos, abbreviations, grammar, and clarity.

Reply: Thank you for your valuable advice. We have reviewed the document and made several improvements to the language, checking for typos, abbreviations, grammar, and clarity.

Change in the text: Full text.

Reviewer C

This is an interesting work. Anyway I have comments and suggestions-

Abstract

none

Background

- clarify better the literature behind your topic, using PMID: 18331273, PMID: 34922653

Reply: Thank you for your valuable advice. We have read the two articles you provided, which explain the specific mechanisms of cigarette smoking leading to ED and the relationship between e-cigarettes and ED. We have also introduced the connection between ED and smoking more clearly in the literature background.

Change in the text: Lines 98-104.

Materials and methods

- have you calculated the sample size?

Reply: Thank you for your valuable advice. We used G-power software to calculate the sample size we needed^{xiii}. Our parameters were: Tail: two, effect size:0.5, α err prob:0.05, power:0.95. The final calculation results showed that at least 42 samples were needed per group.

Change in the text: Lines 200-202.

- please, insert ethical committee number approval

Reply: Thank you for your helpful advice. We have included the ethical approval number in the Materials and Methods section.

Change in the text: Lines 142-143.

- please, clarify better your inclusion/exclusion criteria,

Reply: Thank you for your helpful advice. We have better clarified our inclusion/exclusion criteria. We described the enrollment criteria for the healthy control group and also rewrote the exclusion criteria to be clearer.

Change in the text: Lines 135-140.

Results:

- have you data on subjects with diabetes, duration and antihyperglycemic drugs used? (using PMID: 36823962, PMID: 36297044).

Reply: Thank you for your valuable advice. Regarding the issue you raised about diabetic patients, I regret to inform you that our study did not conduct specific analyses on diabetic patients, nor did we collect detailed information about their disease duration and use of hypoglycemic medications. We only measured blood glucose levels for all participants in the study, but did not conduct further subgroup analyses. However, we have read the two articles you recommended, which we find very helpful, and have discussed the relationship between diabetes and ED in the discussion section. In the future, we will consider collecting more relevant information in subsequent studies to further explore the impact of chronic diseases such as diabetes on the study results.

Change in the text: Lines 318-320.

Discussion

- clarify better the strenghts and limitations of you study

Reply: Thank you for your valuable advice. In the last section of the discussion, we have thoroughly discussed the strengths and limitations of this study.

Change in the text: Lines 412-417.

Conclusions

- insert conclusion of this study, separated by discussion

Reply: Thank you for your helpful advice. We have inserted the conclusions of this study, separate from the discussion section.

Change in the text: Line 419.

References

- ⁱ Rob A A Van Kollenburg, Daniel Martijn De Bruin, and Hessel Wijkstra, 'Validation of the Electronic Version of the International Index of Erectile Function (IIEF-5 and IIEF-15): A Crossover Study', *Journal of Medical Internet Research*, 21.7 (2019), e13490 <<https://doi.org/10.2196/13490>>.
- ⁱⁱ L Petrone and others, 'Structured Interview on Erectile Dysfunction (SIEDY©): A New, Multidimensional Instrument for Quantification of Pathogenetic Issues on Erectile Dysfunction', *International Journal of Impotence Research*, 15.3 (2003), 210–20 <<https://doi.org/10.1038/sj.ijir.3901006>>.
- ⁱⁱⁱ Yuxiang Dai and others, 'Sexual Dysfunction and the Impact of Beta-Blockers in Young Males With Coronary Artery Disease', *Frontiers in Cardiovascular Medicine*, 8 (2021), 708200 <<https://doi.org/10.3389/fcvm.2021.708200>>.
- ^{iv} Shakeel Ahmed Memon and others, 'Association between Erectile Dysfunction, Cardiovascular Risk Factors, and Coronary Artery Disease: Role of Exercise Stress Testing and International Index of Erectile Function (IIEF-5) Questionnaire', *IJC Heart & Vasculature*, 40 (2022), 101033 <<https://doi.org/10.1016/j.ijcha.2022.101033>>.
- ^v Xiucheng Li and Dongjie Li, 'The Suggestive Effect of Apo A, Apo B, and Apo A/Apo B on Erectile Dysfunction', *The Journal of Sexual Medicine*, 18.3 (2021), 448–56 <<https://doi.org/10.1016/j.jsxm.2020.12.004>>.
- ^{vi} Xiu-Cheng Li and others, 'Is Mild Erectile Dysfunction Associated with Severe Psychological Symptoms in Chinese Patients with Moderate-to-Severe Chronic Prostatitis/Chronic Pelvic Pain Syndrome?', *Asian Journal of Andrology*, 23.3 (2021), 319 <https://doi.org/10.4103/aja.aja_71_20>.
- ^{vii} Zhang - Cheng Liao and others, 'Is Milder Psychological Stress Responsible for More Severe Erectile Dysfunction?', *Andrologia*, 52.4 (2020) <<https://doi.org/10.1111/and.13550>>.
- ^{viii} 'Accuracy of Patient Health Questionnaire-9 (PHQ-9) for Screening to Detect Major Depression: Individual Participant Data Meta-Analysis', *BMJ*, 2019, 11781 <<https://doi.org/10.1136/bmj.11781>>.
- ^{ix} Andreas Hinz and others, 'Psychometric Evaluation of the Generalized Anxiety Disorder Screener GAD-7, Based on a Large German General Population Sample', *Journal of Affective Disorders*, 210 (2017), 338–44 <<https://doi.org/10.1016/j.jad.2016.12.012>>.
- ^x Meng Zhang and others, 'Identification of Novel Susceptibility Factors Related to CP/CPPS - like Symptoms: Evidence from a Multicenter Case - control Study', *The Prostate*, 82.7 (2022), 772–82 <<https://doi.org/10.1002/pros.24319>>.
- ^{xi} Chunchao Zhang and others, 'The Association between Spicy Food Consumption and Psychological Health in Chinese College Students: A Cross-Sectional Study', *Nutrients*, 14.21 (2022), 4508 <<https://doi.org/10.3390/nu14214508>>.
- ^{xii} Hyun Kang, 'Sample Size Determination and Power Analysis Using the G*Power Software', *Journal of Educational Evaluation for Health Professions*, 18 (2021), 17 <<https://doi.org/10.3352/jeehp.2021.18.17>>.