Author’s response to reviews

Title: Association of 25-hydroxyvitamin D with cardiometabolic risk factors and metabolic syndrome: a mendelian randomization study

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Author’s response to reviews:

Reviewer #1: Interesting study but needs more improvement. (Please find reviewer #1's comments in the attachment.)

Response: Thank you for your interest in our study. We have addressed concerns according to your suggestions in the attachment, except that two points we should explain in detail here.

Current smoking was defined as having smoked at least 100 cigarettes in one’s lifetime and currently smoking cigarettes. Actually, this definition was widely used in epidemiological studies including NHANES (https://www.cdc.gov/nchs/nhanes/) and China Noncommunicable Disease Surveillance study [JAMA 2013, 310:948-959].

When it comes to whether there is a middle class. Each of the 23 study sites was allocated to high or low economic status in comparison with the GDP per capita of the whole nation (6807 US dollars from World Bank) in 2013. Hence there is no middle class. Thank you!
Reviewer #2: Adequate enough (Reviewer #2 did not have comments.)

Response: Thank you for your interest in our study. It is an honor to get such comments from you.

Reviewer #3: Generally, I found the research well done but I do have few minor issues that could help for improvement of the research.

1. The result under abstract should focus on the significant factors. E.g. The MR-derived estimates for MS traits were also not significant; it would be good to replace them with significant factors or other findings.

Response: Thank you for your suggestion. We have replaced them with significant findings. “The MR-derived estimates for raised fasting plasma glucose was 0.578 (95% CI 0.321, 0.980) per 10nmol/L GRSsynthesis determined increase of 25(OH)D levels.” Thanks.

2. In the conclusion of the abstract, you suggest that efforts to increase vitamin D may not be a clinically relevant intervention in cardio-metabolic disease prevention. But I would suggest exploring and stating the limitations of your study that can result to the finding (no risk) rather than stating not clinically relevant interventions and of course it is possible to suggest further different studies.

Response: Thank you for your wonderful suggestion. We have added limitations of our study and suggested further studies instead of stating not clinically relevant interventions in the conclusion of the abstract in the revised manuscript.

“Conclusions We found no evidence that genetically determined reduction in 25(OH)D conferred an increased risk of MS and its metabolic traits. However, we created our GRS only on the basis of common variants, which represent limited amount of variance in 25(OH)D. MR studies using rare variants, and large-scale well-designed RCTs about the effect of vitamin D supplementation on MS are warranted to further validate the findings.”
3. The information in page-4 line 90-91 which stated "genetic variants associated with lower 25(OH) D should be associated with a higher risk of MS and its metabolic traits" please give reference/s.

Response: Thank you for your suggestion. We have added a reference in this place.

4. The conclusion has to focus on your findings. The findings from other studies (MR studies, RCTs) are already discussed in the discussion part so as to me no need to include in the conclusion part.

Response: Thank you for your good suggestion. We have deleted the findings from other studies in the conclusion section in the revised manuscript. Thank you!

Reviewer #4: The influence of vitamin D on several pathophysiological conditions and diseases has been extensively discussed in recent years. The present work deals with the effect of genetically lowering vitamin D levels on risk factors of metabolic syndrome or its metabolic traits using mendelian randomization methodology. The results of the work are significant and bring benefits, despite the undetected association between the genetically determined reduction of 25 (OH) D and an increased risk of metabolic syndrome. However, the manuscript requires little refinement: The authors report that there were 60% women in the study population and 40% men in Table 1. Authors should define the data collection questionnaire more precisely. Has the questionnaire been standardized and validated? (lines 129-131)

Response: Thank you for your good question. We begin questionnaire development by defining the construct. The definition explains not only what the construct is, but also what it is not. The exact topic of knowledge and the relevant sub-sections are specified. After the items have been developed and the appropriate response formats determined, the questions are reviewed by a panel of experts specialized in epidemiology, statistics and endocrinology. In addition to having the items reviewed by a panel of experts, a small sample of the target audience (ten participants) also completes the questionnaire before recruiting the final sample. In each study site, the same staff performed all data collection. They were trained according to a standard protocol that made them familiar with the specific tools and methods used. The same trained staff used the standardized and validated questionnaire to collect information on the demographic characteristics, medical history, and lifestyle risk factors. Thanks.
2. In Table 1, the number of men and women, their age and other parameters should be added separately, as the gender dependent level of vit. D is known. For women, it should be reported how many women (%) were of the hormone active age.

Response: We have separated men and women and reported the proportion of premenopausal women in Table 1 in the revised manuscript. Thanks.

3. Figure 2 was not found in the manuscript ((lines 231-232)).

Response: Thank you for your question. We are very sorry for the careless mistake that we forgot to submit figure 2 in the original paper. We make sure that figure 2 is included in the revised manuscript. Thank you!

4. All abbreviations and symbols used in Figure 1 should be explained in the legend to the figure. The discussion is well and comprehensible. The conclusion is adequate to the presented result.

Response: OK, we have explained abbreviations and symbols used in the legend to figure 1. Thank you.