

April 23th, 2019

Dear Editor and Reviewers,

Thank you for your thoughtful review of our manuscript NO: 46613, entitled " Relationship between circulating irisin levels and overweight/obesity: a meta-analysis".

We have carefully considered each of the comments, and revised the manuscript accordingly. All revisions are indicated in red fonts in the revised version of our manuscript.

An itemized response to each of the critiques follows:

Editor:

Comments to the Author:

1. We checked the paper by crosscheck, there are similar sentences (highlighted in the report) with other articles, please see details on the crosscheck report and rewrote these sentences.

Response: Thank you for your reminder, we have rewritten these sentences.

2. A short running title of less than 6 words should be provided.

Response: According your request, we have added a short running title at page 1.

3. The approved grant application form(s) will be released online together with the manuscript in order for readers to obtain more information about the study and to increase the likelihood of subsequent citation.

Response: We have submitted relevant certificates about the approved grant application forms as requested.

4. Please offer the audio core tip.

Response: We have submitted the audio core tip file according to the requirements .

5. The guidelines for writing and formatting Article Highlights.

Response: According to your advice, we wrote an article highlight in page 14 to 15.

6. Repeat with ref 12, please revise.

Response: Thank you so much for this reminder, we have revised the references.

7. Please add ref number for all cited references.

Response: We have added reference number for all cited references according your requirements.

8. Please provide the decomposable figure, whose separate parts are movable and words can be edited. Thank you.

Response: We change the format of the figure for future editing and submitted relevant files online. We also added titles to each figure.

Reviewer: 1

Introduction Definition of obesity in first line should be complete. The reference for prevalence for obesity should be update (ref 2). Previous meta-analysis or systematic review regarding to irisin should be given .Description of irisin, this cytokines secrete by muscle tissue?? And related to obesity? The reference for the sentences after “... That have been reported”. The Scopus should be search for this meta-analysis. Number of Prospero. Why this study only limit for English articles. Inclusion and exclusion criteria did not acceptable. It is not clear that this meta-analysis was conducted for adults or children. It should better that subgroup analysis done according to age. Why both random and fixed effect was use?????????????

1.Introduction Definition of obesity in first line should be complete.

Response: Thank you for your suggestion, we have completed the definition of overweight/obesity. (page 4)

2.The reference for prevalence for obesity should be update (ref 2).

Response: Thank you for your advice, we have updated the prevalence of overweight/obesity. (page 4,5)

3.Previous meta-analysis or systematic review regarding to irisin should be given .Description of irisin, this cytokines secrete by muscle tissue?? And related to obesity?

Response: According to your comment, we have added some systematic reviews about irisin in the introduction, and we also described the link between irisin and overweight/obesity in the introduction. Irisin was secreted by muscle tissue induced by exercise, and liver and adipose tissue could secret a small amount. Some clinical studies reported that irisin levels are different in normal and overweight/obese people. (page 5-6)

4.The reference for the sentences after “... That have been reported”

Response: According to your advice, we have relabeled the number of the references. (page 6)

5. The Scopus should be search for this meta-analysis.

Response: Thank you for your comment, we re-searched the SCOPUS database and identified a total 376 potential relevant articles, 264 were duplicates, please see Table 1 for details.

6. Number of Prospero.

Response: Thank you for your advice, we have tried to registered in the PROSPERO, unfortunately, they did not accept our registration for that data extraction, risk of bias assessment and data analysis have been completed. And in the future, we will register first if we do some other systematic reviews.

7. Why this study only limit for English articles.

Response: English is the most widely used language in the world, and it is conducive to the extraction of data.

8. Inclusion and exclusion criteria did not acceptable.

Response: Thank you for your advice, we have improved the inclusion and exclusion.(page 7)

9. It is not clear that this meta-analysis was conducted for adults or children. It should better that subgroup analysis done according to age.

Response: Thank you for your advice, we have considered doing subgroup analysis according to age, however, we can not extract exactly data of different age groups, and we sent e-mails to the authors for help but got no replies. Thus, we did subgroup analysis in adults and children respectively, and it needs more studies in the future in this aspect.

10. Why both random and fixed effect was use?????????????

Response: Thank you for your suggestion. The appropriate model should be chosen according to the heterogeneity and in the statistics of this study, we adopted random model according to heterogeneity.

Reviewer: 2

Proposed manuscript by Jia and co-authors is a meta-analysis investigating the relationship between circulating irisin levels and overweight/obesity based on 18 published studies (1,005 cases and 1,242 controls). Results from the meta-analysis showed that in African (but not European, Asian or American) population, the circulating levels of irisin in overweight or obese population were significantly higher compared to those in normal-weight controls. Also, higher circulating irisin levels are observed in obese, compared to normal-weight children (from all racial groups). The topic of this analysis is interesting, since the data and the general knowledge on the functions of irisin is very scarce. Current analysis is based on small amount of data, not enough to make firm conclusions (4 studies demonstrated lower irisin levels in overweight/obese individuals compared to normal-weight controls, 9 publications found the opposite, 5 showed no statistically significant effect). Still, in my opinion as a peer reviewer, such a summarization is useful. This study uses different racial groups using the same BMI criteria but it needs to be noted that weight stratification in the Asian population is based on different BMI values.

1. This study uses different racial groups using the same BMI criteria but it needs to be noted that weight stratification in the Asian population is based on different BMI values.

Response: Thank you for your good advice, standards of overweight/obesity according to BMI values in Asian is different from global criteria, we add this part in the article. (page 12)