Author’s response to reviews

Title: The association of circulating irisin with metabolic risk factors in Chinese adults: a crosssectional community-based study

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Author’s response to reviews:

Dear editor and reviewers,

Thank you very much your time and comments from the reviewers. Please find enclosed our point-by-point responses that are shown in red text. All changes made in the original manuscript have been tracked in the revised manuscript.

Reviewer reports:

Hongting Zheng, M.D. (Reviewer 1): Tang et al. conducted a cross-sectional study to find the association between serum irisin levels and obesity in an elderly Chinese population. They found a significant lower irisin level in obese subjects compared with normal weight participants. Further correlation analysis showed that the serum irisin levels were negatively correlated with some obesity and insulin resistance-related indicators such as waist circumference, fasting insulin and HOMA-IR. Moreover, the authors also conducted linear and logistic regression to further confirmed the correlation between irisin and obesity. The study is interesting and designed in an appropriate fashion. Still, there are some major points which have to be addressed.

Major revision:
1. Table 2, please show data on Pearson's correlation after adjustment for age and sex.

Thank you for the reviewer’s comment. The data of Pearson's correlation was adjusted by age and sex, we didn’t clearly describe it. We have added this description in the statistical section (line 7, page 5)

2. Table 3, multiple linear regression analysis should better look for determinants of a decreased irisin concentrations, not for a "correlation" with HOMA-IR. It is better to set the irisin levels as the dependent variable, and other parameters which might be the explanatory variable(s) for irisin should be set as the independent variable(s). Note: it does not make sense to add potential determinants that are tightly associated with HOMA-IR (like parameters indicating fasting insulin and fasting glucose) in the same analysis, because that may cancel the association with HOMA-IR. Thus, such pathophysiological factors should be analyzed in a separate analysis.

Thank you for the reviewer’s comment. We agree that the importance of looking at the determinants for irisin, however, the main purpose of this analysis is to show if there is any association of irisin with insulin resistance. Previous study investigated the association between irisin and insulin resistance also used HOMA-IR as dependent variables (Xiulin Shi et al BMC Endocr Disord. 2016; 16: 44;). We have included a table below for the reviewer to see regarding to irisin as dependent variable, we will go further about this subject in order to uncover the determinants for irisin from future studies. In our regression model, we included BMI (which was tightly associated with HOMA-IR) because we want to see even after adjustment of BMI, irisin was still associated with HOMA-IR, which explained the contribution of irisin on insulin resistance.

The explanatory variables associated with irisin.

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>Standard Error</th>
<th>t-Value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Error</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>-0.00528</td>
<td>0.00378</td>
<td>-1.4</td>
<td>0.1648</td>
</tr>
<tr>
<td>sex</td>
<td>-0.16124</td>
<td>0.068562</td>
<td>-2.35</td>
<td>0.0201</td>
</tr>
<tr>
<td>WC</td>
<td>-0.00752</td>
<td>0.004107</td>
<td>-1.83</td>
<td>0.0693</td>
</tr>
<tr>
<td>TG</td>
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<td>0.048042</td>
<td>1</td>
<td>0.3177</td>
</tr>
<tr>
<td>Scr</td>
<td>-0.00489</td>
<td>0.00224</td>
<td>-2.18</td>
<td>0.0309</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-0.03876</td>
<td>0.052431</td>
<td>-0.74</td>
<td>0.461</td>
</tr>
</tbody>
</table>

3. Further, the approach to multi-factorial regression analysis is questionable: It is not common to include parameters in a multiple regression analysis that have not been nearly
(p < 0.10) significant in univariate linear regression analyses. I recommend that this be redone with the present data set.

Thank you for the reviewer’s comment. Table 3 was multiple linear regression and Table 4 was logistic regression. As sex and age are usually been included in order to exclude all the confounding factors which might affect the results in regression model except other parameters (smoking, alcohol and medication use…).

Minor revision:
1. Spaces should be inserted before and after a mathematical symbol.

We have revised the manuscript according to the reviewer’s suggestion.

2. Some statistical symbols should be italic, please refer to the author's instruction of this journal.

We have revised the manuscript according to the reviewer’s suggestion.

3. Page 5 line 10 "coded as 1" is redundant.

We used logistic regression to determine the association of irisin with odds of overweight. Therefore, in SAS analysis, we processed BMI and coded controls=0 (defined as 18.5≤BMI<25 kg/m2), overweight=1 (defined as BMI≥25 kg/m2) by using the PROC logistic syntax.

4. Table 1, P-value, some "0" before the decimal point were omitted, please unify the format or refer to the author's instruction.

We have unified the format according the reviewer’s suggestion.

5. The manuscript should be revised by a native English speaker familiar with medical terminology.

We have consulted a native English speaker to make further improvements in order to meet the high standards required by the journal.

Gangyi Yang (Reviewer 2): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.
This is a very interesting large study on 524 nondiabetic subjects to investigate the association of serum irisin levels with metabolic parameters in middle aged Chinese population. The authors found that serum irisin levels were lower in overweight subjects. Moreover, serum irisin levels were inversely correlated with adverse metabolic parameters including WC, WHR, creatinine, HOMA-IR and fasting insulin, suggesting that irisin may play a role in obesity related insulin resistance. Thus, modification of circulating irisin level may help in the management of obesity and related metabolic diseases.

Overall, the study was well designed and conducted and the results are interesting and important. They systematically analyzed the relationship of serum irisin with full panel of traditional anthropometric, metabolic and cardiovascular risk measures which represents a prominent strength of the study. The paper is well written.

I have two minor suggestion.

In the Introduction section in the 2ed paragraph authors write: "Irisin is a recently discovered myokine, it is a cleaved membrane protein encoded by the fibronectin type III domain containing 5 (FNDC5) gene. Recent studies showed irisin can stimulate the expression uncoupling protein-1 (UCP-1), result in browning of white adipose tissue, thereby stimulating energy expenditure." Please cite appropriate references.

The references have been added according to the reviewer’s suggestion.

In the Results section, the authors wrote "Sex, age smoking, alcohol and medication use were adjusted for model", I suggest the authors added it in the statistical section and would you please explain why did you adjust for all these factors?

Thank you for the reviewer’s comments, we have added it in the statistical section (line 12, page 5). Those factors might be confounding factors and according to “enter” method of statistics and all confounding factors should be included in regression model and most studies adjusted those factors in their multivariate regression model.

Yours sincerely,

Nanwei Tong