Author’s response to reviews

Title: C-reactive protein mediates the association between leisure-time physical activity and lung function in middle-aged and older adults

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Author’s response to reviews:

Dear Reviewer 1:

Thank you for your nice comments. Following your suggestions, we have made careful modifications on the manuscript. We hope that the revision could be satisfactory to you.

Below you will find our point-by-point responses to your comments.

Yours sincerely,

Yili Wu

Abstract: Well done and concise.

Reply: Thank you.

Background: A note differentiating mediation vs moderating effect of CRP would be good.

Reply: Following you suggestion, we have added some statements related to the difference between mediating effect and moderating effect in Background section. (Line 87-97)
Methods: Well described. Happy to see the use of Directed Acyclic Graph (DAG). I noted that those with lung and or cardiovascular disease were included and adjusted for. I wonder if separating the groups would provide different results. For instance participants with lung disease or who smoke, they have a different biochemistry to those who do not; and are likely to have more CRP and other inflammatory markers in their serum. Are these measures truly accounted for just by adjusting for them? Those with such illnesses are also more likely to have reduced PA. Later you mention that you excluded those who have lung disease as a strength. Were they excluded or they were adjusted for?

Reply: Sorry for the confusion. In the primary analysis, lung and cardiovascular disease were adjusted for. Following your suggestion, we conducted the sensitivity analysis by excluding participants who had chronic lung diseases and cardiovascular diseases such as angina, congestive heart failure and stroke. And the results are robust. We added the results of sensitivity analysis as an Additional File in the revision (Methods Line 170-171, Results Line 216-217, Additional File 1). Meanwhile, we re-wrote the strength in the Discussion section. (Line 274-276)

Results: Presented well and clearly.

Reply: Thank you.

Discussion: Solid argument put forward and limitations well discussed.

Reply: Thank you.

Dear Reviewer 2,

We are very grateful of your very constructive comments. Following your suggestions, we have made careful modifications on the manuscript. The new version looks better than before.

Below you will find our point-by-point responses to your comments.

Yours sincerely,

Yili Wu

1. Line 26 - change 'were' to 'are' - biological mechanisms 'are' unclear.

Reply: It has been modified. (Line 26)
2. Line 78-79 - change to read 'Regular PA produces anti-inflammatory ...'
Reply: It has been modified. (Line 78-79)

3. Line 79 - change to read 'suppress serum levels of C-reactive ...'
Reply: It has been modified (Line 79-80)

4. Line 88-89 - change to read '... between PA and lung function. The extent to which inflammation mediates this association is unclear.'
Reply: This sentence has been deleted because we modified the Background section according to Reviewer 1’s suggestion.

5. Line 111. I assume that the ONLY 2 tests are FVC and FEV1? If so, 'including' FVC and FEV1 is misleading as it implies that there were others. A minor re-write may be required here.
Reply: The lung function tests in ELSA including forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and peak expiratory flow (PEF). Only data of FEV1 and FVC were used in this study. Following your suggestion, we rewrote the sentence. (Line 116-117)

6. Section on LTPA. I understand that this particular categorisation (of PA to high/moderate/low) appears to have been used serially back to ~2007. However, this categorisation does not substantively address issues of volume (i.e. the overall amount of PA that is reported). Thus, independent of reporting bias, this classification could introduce error regarding PA levels (i.e. some individuals may perform a large volume of low intensity activity and be classified 'less' active than someone who performs 2 very short bouts of moderate level activity). The authors might like to address this as a limitation.
Reply: Following your suggestion, we have discussed this as a limitation in the Discussion section. (Line 280-285)

7. Line 262. I think that the statement 'Based on this epidemiological data, we proved the role of inflammation as a mediator ...' is too strong a comment / conclusion to draw. 'Prove' is an awfully strong term to be throwing around.
Reply: We have changed the ‘proved’ into ‘found’ (Line 268).
8. Line 288. Please re-write - 'This study profound a far-reaching public health ...' is very poor English.

Reply: It now reads:

‘In the view of public health, these findings are potentially significant in the planning of preventive intervention strategies and physical activity-based programs, which aimed at reducing the systemic inflammation and promoting health.’ (Line 297-299)

9. Line 325. Can the authors provide a specific Ethics approval reference # for the approval for ELSA?

Reply: We have added this in the revision. (Line 335-339)

10. Line 340 (reference 1) - this is a poor source - surely there is an authoritative source that underlies the contents of this web-page that could be cited?

Reply: Reference 1 is one of a web-page of the World Health Organization. We have modified the source of Reference 1 in accordance with the Submission Guidelines for References. (Line 363-364)

11. Line 339 References: there is inconsistent captialisation across reference titles

Reply: Thank you very much. All of the References have been checked. The forms for titles are consistent now.