Author’s response to reviews

Title: Estrogen Receptor 1 Gene Polymorphisms Are Associated with Metabolic Syndrome in Postmenopausal Women in China

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Title: Estrogen Receptor 1 and 2 Gene Polymorphisms associated with the metabolic syndrome in Postmenopausal Chinese Women

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Response to Reviewers' comments

Dear Dr. Pradeepa,
Thanks for your careful consideration of our manuscript. We appreciate your response and overall positive initial feedback. According to the comments made by the reviewers, we have modified the manuscript to improve the presentation of our results. Now we provide a more complete context for the research that may be of interest to your readers.

We hope that the revised paper suitable for the publication of BMC Endocrine Disorders, and we look forward to contributing to your journal. Please do not hesitate to contact us if there are other questions or concerns in the manuscript.

Best regards,

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Technical Comments:

1. Please note that the order of authors in your manuscript file differ from those entered in the submission system - please correct so they are consistent with each other.
Response: Thanks for your good advice. We have modified the sequence of the authors in the submission system.

2. Please move the 'Declarations' section after the 'Abbreviations'

Response: Thanks for your suggestion. 'Declarations' section has been moved after the 'Abbreviations' section. (Page 19-20)

Editor Comments:

1. The following Power calculation mentioned by the authors is not satisfactory.

"BMI was used to calculate the power, as in a previous study [1]. The mean difference of BMI between the two groups was 25.6-24.4=1.2, that is, the allowable error of BMI between the two groups was 1.2. The total standard deviation σ was 2.9. The formula of power calculation is: (Sorry Reviewer #3, there is a statistical formula that can't be uploaded, if you need, I can send it to you by email.) Hence, power was calculated as 1-β=94.5."

This calculation has been added in the manuscript as well. It has to be removed from the manuscript. It is not known why BMI was used for power calculation. The major conclusion of the study is that "The ESR1 gene XbaI polymorphism was associated with MetS in Chinese postmenopausal women". Is the study powered enough to arrive at this conclusion is the question. Hence, power calculation needs to be based on the allele/genotype frequency of the XbaI polymorphism and not based on BMI.

Since, power calculation has been raised by all three Reviewers, it is expected that the authors calculate the power and present it.

Response: We agree with the Reviewer. It was corrected (METHODS section Line7-8 Page10). XbaI gene polymorphism in case group and control group was used as an example to calculate the power and test efficacy. The frequency of genotypes AA, AG and GG in the case group was 14.67%, 55.33% and 30.0%, while that in the control group was 26.67%, 55.33% and 18.00%,
respectively, as described in a previous study [1]. Chi-square test of the genotypes’ frequency in case and control group can be used to calculate the power.

The function of pwr.chisq.test() in pwr of R package can be used to calculate power. The function can be set as the following formula:

```r
data <- matrix(c(0.1467, 0.5533, 0.3, 0.2667, 0.5533, 0.18), byrow=TRUE, nrow=2)
es <- ES.w2(data)
pwr.chisq.test(w=es, df=2, sig.level = 0.05, N=304)
```

At last, the test power was calculated (power=1) which indicated that the conclusion in the paper was credible. (RESULTS section Line6-9 Page11).

2. Supplementary Figures S1, S2, S3 need not be included for publication. The authors have now mentioned in the manuscript that the genotyping was confirmed by sequencing. That statement is sufficient, figures are not needed.

Response: That is a good advice. We have deleted the relative content in the paper. (METHODS Genomic DNA extraction and genotyping section the last line Page9)

3. Supplementary Table 1 is also not needed for publication. Moreover, It has been wrongly mentioned in Results section (page 12, line 23) that Supplementary Table 1 shows hardy-Weinberg values. Please correct it.

Response: We thank the Reviewer for the comment. We are very sorry for the mistake. It was corrected. Supplementary Table 1 describes the linkage disequilibrium test results. We described the linkage disequilibrium results (RESULTS section Line 9-13 Page 11). Otherwise, 'Supplementary Table 1' was also deleted from the publication. (RESULTS Allele frequencies and genotype distribution section, The last line of the second paragraph)
4. Comment 4 of Reviewer 3 regarding Table 2 has not been addressed properly. The authors have mentioned that it has been checked and corrected but it has not been done. The subjects with AluI AA, AG and GG genotypes in controls counts to 156 (10+50+96=156) as against the total number of control subjects which is 154. And the frequency of A allele and G allele is also wrong in the control group. It needs to be corrected.

Response: We are very sorry for the mistake. We have checked the original data and modified them in Table 2 (page27). Moreover, we found some OR value haven’t been rectified, so we modified them together and added a note at the bottom of (Line 4 below Table 2). Because the OR value changed after correction, part of the description of Table 2 in the result needs to be deleted (ABSTRACT Results section Line 2-5 Page 3; RESULTS Allele frequencies and genotype distribution section the last eight lines of the third paragraph). In addition, a sentence in the result was also modified (RESULTS section Line 9-13 Page 11).

We also found some minor mirrors existed in the paper and listed them in the following.

Minor mirrors:

1. The typeface in the manuscript was not consistent. Therefore, we have changed the typeface Cambria to Times New Roman.

2. There is a redundant null string which has been deleted. (RESULTS Demographic and clinical variables section Between the first and second paragraphs)

3. Supplementary Table S1 was changed to Supplementary Table S2 (Results section Line 9-13 Page 11).

4. There was a repeating content has been deleted. (RESULTS Relationship between genotypes and clinical characteristics section Lines 7-10)

5. The format of references is not standard, we have adjusted the format of all documents.

6. There is a spelling error in Supplementary Table 1. Therefore, we have corrected the error. (B5b to B5)