Author's response to reviews

Title: MTNR1B rs10830963 is associated with fasting plasma glucose, HbA1C and impaired beta-cell function in Chinese Hans from Shanghai

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Author's response to reviews: see over
Dear editors of *BMC Medical Genetics,*

We appreciate the reviewer’s and associated editor’s comments on the manuscript titled “*MTNR1B* rs10830963 is associated with fasting plasma glucose, HbA1c and impaired beta-cell function in Chinese Hans from Shanghai”. The response to review’s critique is attached with this letter, and our manuscript has been revised accordingly. Revised portion is highlighted in red. Hopefully, the revised manuscript will be eligible for being published in The BioMed Central.

Thank you very much for your attention and consideration.

Best regards,

Yours sincerely,

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For your guidance, itemized response to each reviewer’s comments is appended below.

Reviewer's report (Dr. Ehm Astrid A Andersson):

I think that the authors have responded adequately to all questions raised and have thereby improved their manuscript substantially. The results are of interest and especially the meta-analysis gives a nice overview of previous studies. I have only one additional comment:

The authors should comment upon the heterogeneity observed among the European studies in the meta-analysis. This heterogeneity may introduce bias to the comparison among Chinese and European overall effects and the result should therefore be interpreted with caution.

We highly appreciate and agree with the reviewer's comment. To be more discreet, we removed the sentence “Combing all data available shows that the effect size in Asians tends to be smaller than in white Europeans (P=0.06).” in the abstract section (page 1, line 18-19). We also described the heterogeneity among Europeans according to the reviewer's comment by replacing “Meta-analyses of our data in Chinese and the published data, including all studies in White Europeans [5, 7, 9-11] and Asians [12, 13], showed no heterogeneity in effect size of MTNRI B rs10830963 on fasting glucose levels among Asian populations, including the current Beijing and Shanghai Chinese Hans (P for heterogeneity =0.37).” with “Meta-analyses of our data in Chinese and the published data, including all studies in White Europeans [5, 7, 9-11] and Asians [12, 13], showed significant heterogeneity in effect size on fasting glucose levels among white Europeans (P for heterogeneity = 7.7 × 10^-4) but not among Asian populations (P for heterogeneity = 0.37).” in the result section (page 7, line 100-104).

In the discussion section, we changed “Meta-analyses of the MTNRI B rs10830963 effect size on fasting glucose showed no evidence for heterogeneity among Asian populations. The overall effect size among Asians tended to be smaller than in white Europeans.” with “Significant heterogeneity in effect size on fasting glucose was observed only among White Europeans, but not among Asians in meta-analyses with data from our study and the previously reported. The overall effect size on fasting glucose among Asians tended to be smaller than that in white Europeans. However, this result should be interpreted with caution since the heterogeneity observed in White Europeans may introduce bias to the comparison among Chinese and European overall effects. More studies are required to draw a firm conclusion.” (page 8, line 123-129).
The associate editor commented:

The authors have meticulously dealt with all comments and questions. They provided thorough, detailed responses to all issues previously raised and their many changes to the manuscript have greatly improved it.

One minor additional comment by the reviewer, advising the addition of a cautionary note on the interpretation of the meta-analysis results could simply be rectified with an additional sentence or two. This relates to differences in heterogeneity between the Asian and European studies, such that the greater heterogeneity seen among the European results could affect the comparison between these two ethnic groups. This heterogeneity is evident from visual inspection of the newly added meta-analysis figure and may relate, in part, to the larger number of European studies. The reviewer raises a very minor point which I consider optional, but which is worth the authors attention.

This comment is highly appreciated. Since the heterogeneity observed among Europeans may introduce bias to the comparison between Asians and Europeans, we preferred not report it as a major finding in the abstract. We removed the sentence “Combing all data available shows that the effect size in Asians tends to be smaller than in white Europeans (P=0.06).” in the abstract section (page 1, line 18-19). The heterogeneity observed among Europeans is unexpected, and may be attributed to the large number of studies in Europeans and the differences in study exclusion criteria and participants characteristics. However, when we excluded some studies which were conducted mainly in women (TwinsUK) and in young peoples (NFBC86 and Haguenau), the diversity still existed. Therefore, the real reason for the heterogeneity is largely unknown, and we preferred not explain it. We added more information on the heterogeneity among Europeans by replacing “Meta-analyses of our data in Chinese and the published data, including all studies in White Europeans [5, 7, 9-11] and Asians [12, 13], showed no heterogeneity in effect size of MTNR1B-rs10830963 on fasting glucose levels among Asian populations, including the current Beijing and Shanghai Chinese Hans (P for heterogeneity =0.37).” with “Meta-analyses of our data in Chinese and the published data, including all studies in White Europeans [5, 7, 9-11] and Asians [12, 13], showed significant heterogeneity in effect size on fasting glucose levels among white Europeans (P for heterogeneity = 7.7 × 10^{-4}) but not among Asian populations (P for heterogeneity = 0.37).” in the result section (page 7, line 100-104). We also changed “Meta-analyses of the MTNR1B rs10830963 effect size on fasting glucose showed no evidence for heterogeneity among Asian populations. The overall effect size among Asians tended to be smaller than in white Europeans.” with
“Significant heterogeneity in effect size on fasting glucose was observed only among White Europeans, but not among Asians in meta-analyses with data from our study and the previously reported. The overall effect size on fasting glucose among Asians tended to be smaller than that in white Europeans. However, this result should be interpreted with caution since the heterogeneity observed in White Europeans may introduce bias to the comparison among Chinese and European overall effects. More studies are required to draw a firm conclusion.” in discussion section (page 8, line 123-129).