Author's response to reviews

Title: A genetic variant of the atrial natriuretic peptide gene is associated with left ventricular hypertrophy in a non-diabetic population - The Malmo Preventive Project Study

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Author's response to reviews: see over
Response letter

The authors would like to thank the reviewers for their time and their valuable comments, which will help us improve the manuscript. We revised our manuscript, and changes have taken place. So, hereby we send the revised manuscript, and a version containing all the changes to be visible.

REVIEWER 1:
Reviewer’s report
Title: A genetic variant of the atrial natriuretic peptide gene is associated with left ventricular hypertrophy in a non-diabetic population - The Malmo Preventive Project Study
Version: 4
Date: 1 March 2013
Reviewer: Carolina Medina-Gomez

Major Compulsory Revision

Comment 1. The numbers in table 2 are not explained in the document and is surprised the elevated sample size. As far as I understand the reported analysis of association is based in are based in 968 individuals, so it is not clear what reference population the authors are using which has a frequency of 16,931 subjects. I think it is important the comparison of subjects with diabetes and non diabetes, although I think it is more interesting if the analyzed sample (n=968) is divided based on the outcome of interest. Moreover, how can the total sample represents only 92.8%?. Why the total numbers are not the sum of diabetic and non diabetic individuals?

Response: We agree. The data previously presented regarded the total population, and not the subpopulation that is analysed in our study, which is wrong. Data on relevant variables for the 968 individuals included in analysis for the population based on outcome of interest (a population with left ventricular hypertrophy and a population without left ventricular hypertrophy) are now presented in table 2 in accordance with referees wishes.

Comment 2. Based on the discussion of the authors perhaps LVH indexed for height should be used as “gold standard” although under that model the effect of the SNP is even less significant, this is never discussed by the authors.

Response: Regarding the discussion, we mean that LVM indexed for height raised to the 2.7 power of (p-value 0.041 in a model adjusted for age and sex, p=0.165 in a fully adjusted model) is a better model than LVM indexed solely for height, and should be used as the golden standard. Height-based adjustment has been proposed to correct for obesity, and the most accurate estimation of LVH appears to be derived from indexing for height raised to the power of 2.7, where 51g/m raised to the power of 2.7 appears to be a reliable cut off value to define LVH, as used in our study (p-value adjusted for age and sex = 0.021, p-value in fully adjusted model 0.061).

Minor Essential Revisions
Comment 1. In tables 7 and 8 do not need to report the “Full equation” line. Nonetheless the information of the explained variance is important and should be discussed both in results and discussion sections. In these tables what do the authors refer as B and what as Beta it should be clearly stated for the readers to follow
Response: We agree. Regarding the full equation line, we were asked to report it by another reviewer. The information on the explained variance is added to the results section (page 8, line 4) and also mentioned in the discussion section (page 8, line 18-21). Explanations on SE, B and Beta values are now added to the table text in accordance with referees wishes.

Comment 2. The table regarding multicollinearity is based on the model LVM Indexed for Height and not in the LVM, I do not think results are different is just strange to me since it seems for the authors the main interest is in this model.
Response: Thank you for your comment. The reason why the multicollinearity table is based on LVM indexed for height raised to the 2.7 power of and not LVH is that we were asked by another reviewer to explain the variance specifically for LVM indexed for height raised to the 2.7 power.

Comment 3. In page 8, regarding the p-value you can report less significant figures for the p-value.
Response: We agree. The p-value for the Hardy Weinberg equilibrium significance analysis is now adjusted and is reported with 3 decimals instead (p-value = 0.117).

Comment 4. In page 9 what do the authors mean by “Our sample size was relatively small and despite significant associations, the results warrant replication in a larger cohort”. The success of the replication is uncertain until the replication of the findings is done. This lack of replication is by far the weakest point in this article.
Response: We agree that the lack of replication in a larger cohort is definitely the weakest point of our study. The line “Our sample size was relatively small and despite significant associations, the results warrant replication in a larger cohort” is now modified to “As our sample size was relatively small, the results warrant replication in a larger cohort” (page 9, line 23) in order to make it clearer for the reader that the sample size is a limitation to this study.

Comment 5. In the conclusion “However, our findings suggest that rs5068 or genetic variant in linkage disequilibrium might affect susceptibility for LVH and support the possible protective role of NP.” The word variant should be changed to variants.
Response: We agree. The word “variant” is now changed to “variants”.

REVIEWER 2:
Reviewers report
Title: A genetic variant of the atrial natriuretic peptide gene is associated with left ventricular hypertrophy in a non-diabetic population - The Malmo Preventive Project Study
Version: 4
Date: 3 March 2013
Reviewer: Jose-Luis Perez-Castrillon

Reviewer’s report:
The authors have answered the comments of review.
Level of interest:
An article of importance in its field
Quality of written English:
Acceptable
Statistical review:
No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests

Response
We thank the referee for these comments.

REVIEWER 3:
Reviewer's report
Title:
A genetic variant of the atrial natriuretic peptide gene is associated with left ventricular hypertrophy in a non-diabetic population - The Malmo Preventive Project Study
Version: 4
Date: 18 March 2013
Reviewer: Maria Hurle
Reviewer's report: the authors have answered your points sufficiently well to allow their manuscript to be published
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.

Response
We thank the referee for these comments.