Author's response to reviews

Title: Heritability of Cardiovascular Risk Factors in a Brazilian Population: Baependi Heart Study

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Author's response to reviews: see over
Dear Melissa Norton
Editor-in-Chief,
BMC Medical Genetics

Please find attached a copy of the revised version of the manuscript entitled “Heritability of Cardiovascular Risk Factors in a Brazilian Population: Baependi Heart Study” that we would like to re-submit for publication as an original article in *BMC Medical Genetics*.

This manuscript is the first manuscript of a research project aimed at the mapping of genetic risk factors for cardiovascular traits in the Brazilian population. We appreciate the suggestions made by reviewers and have carefully considered each one of them in this new version of our manuscript. In particular, we would like to thank Dr. MacCluer for the revised draft with grammar and stylistic corrections of the submitted version.

We realize that English was a major point for all reviewers. Therefore, we have copyedited the entire manuscript and several grammar and spelling corrections were made. In addition, there is a point-by-point description of the changes made and commentaries on reviewers' suggestions.

We are confident on the improved status of this new version.

We hope this information will be interesting to *BMC Medical Genetics* readers.

Thank you very much in advance for your kind attention,

Best regards,

Alexandre Pereira
Heart Institute, University of São Paulo Medical School, Brazil
Reviewer 1:

Reviewer #1 has suggested the incorporation of further analysis to the manuscript. In particular, the suggestion of incorporating MSX heritability datum has been considered. Nevertheless, we feel the analysis of metabolic syndrome may deserve a manuscript on her own since it is our opinion that the utilization of other analytical tools (e.g. data reduction methods) may indeed need to be used for these particular analyses. The main objective of the present manuscript is to provide a detailed description of the study and heritabilities estimative for the classical cardiovascular risk factors. We do not disagree with this reviewer on the interesting aspect of the suggested analysis, but we have decided to describe them in a separate manuscript.

An extremely important point was raised by this reviewer regarding the cut offs used in this study and the dependence of the obtained results with the chosen parameters. We have provided detailed description on the cut offs used, all derived from the ATPIII criteria, in the methods section. In addition, we have extended the discussion on this issue in the Discussion section of the manuscript. We understand that this parametrization may indeed bias our results and have added further warning of this fact in the discussion section.
Reviewer 2:

We would like to thank this reviewer for providing a document containing suggestions on many stylistic/grammatical errors. We have carefully considered all suggestion made by this reviewer and have incorporated all the points raised.

Used cut offs were revised and definition of smoking status was added in the methods section. We have revised Table 1 title and subtitle.

In tables 1 and 2 we have corrected: “distolic blood pressure” for “diastolic blood pressure”.

We have included an explanation on why weren´t all 1,712 individuals included in the analyses.
Reviewer 3:

1. We agree with this reviewer with her explanation on the observed effect of model 3 of our adjustment. Indeed, after carefully considering the issue we also agree that the observed behavior may be due to an indirect effect of unusual values of the trait and hence this could explain some of the genetic variation. We have added this alternative in the discussion section, stating that it may be the most probable one.

2. We have corrected Table 4. Indeed, Baependi Heart Study estimatives were not derived from one single model and we have corrected this. All estimatives for the Baependi Heart Study cited are from model 2. Of particular importance, based on reviewer 3 suggestion we have expanded Table 4 with information on the population studied in each study, the number of individuals, and families. Information regarding the different adjustment models used in each particular study was also added. Finally, we have included a paragraph in the discussion section on the issue of different adjustment models on heritability studies comparison.

3. We have corrected this and substituted the term controversial for inconsistent in the description of the results of previous studies.

4. We have clarified the information regarding the use of fewer individuals in the current analysis (methods and results section). The field work of the present project was carried out with the participation of a group of more than 100 individuals and the important help of the community of the studied city. Thanks to this special intersection of factors it was possible to conduct the whole ascertainment part of the project in just 2 months.

5. We have corrected information regarding the use of covariates for model adjustment. We have deleted the sentence stating that covariates were
considered significant if the p-value was <0.05, as this was not the case. We have used covariate adjustment in the framework of two different models (described in the methods section): “(…) two sets of covariate effects on each traits were considered: under Model 2 the covariates were sex, age, age², and sex x age interaction; under Model 3, besides the covariates from Model 2, current medication use was also considered.”. We have included information on the use of tdist procedure in the methods section.

6. We have corrected our definition of heritability on page 7.

7. We have corrected the information on the higher prevalence of hypertension among males.

8. We have carefully revised and corrected English throughout the entire manuscript.

9. All presentation changes suggested by the reviewer were taken into account and changes were made accordingly.
Reviewer 4:

1. We have corrected citations according to reviewer 4 suggestion.
2. We have conducted this study in a rural city in Brazil (small city in a rural area) mainly because of logistic issues. Because of migration issues associated with the economic history of Brazil it would be very difficult to conduct such study in a large city. We do not think this issue should be brought into discussion in the manuscript since it does not relate to the main objective of the manuscript.
3. The questionnaire administered was based on the WHO-MONICA questionnaire for cardiovascular risk factors prevalence studies. We have added this information on the methods section of the manuscript. In addition, information on the administration of the questionnaire was also included in the new version of the manuscript.
4. We agree that the issue of model adjustment for different covariates is a sensitive issue surrounding this entire literature. We have carefully described our adjustment models and the limitations of this process. We are providing in the results section the number of individuals in use of medications for the studied traits.
5. We agree that shared environmental variance is confounded with genetic factors in the current design. We have added this limitation in the discussion section.
6. We have corrected the provided definition of heritability.
7. We have provided references and information on the cut-off values used.
8. As noted by this reviewer a number of families were excluded because of the small sample size (less than 3 individuals). We have added this information in this new version of the manuscript.
9. We have corrected the information regarding hypertension prevalence.
10. We have corrected the explanation provided to justify the use of the tdist procedure.
11. We have discussed the use of non-fasting samples in the FHS in the discussion section and added a note in Table 4 remembering the reader to this particular fact.

12. As pointed out by this reviewer we were reporting estimatives for waist circumference instead of truncal obesity in the Northern Manhattan Study. We have corrected this information in the current version of the manuscript.

13. We have added a new interpretation of the findings observed in model 3 based on the comments of this and reviewer 3.

14. We agree that the use of quantitative traits is more informative than the use of qualitative traits for gene mapping effort. This is certainly a limitation in the interpretation of our and others data. We do believe, however, that obtaining heritability estimates for clinically used dichotomized traits is important for study comparison and future mapping efforts and algorithm construction. As such, we have maintained these calculated estimatives and discussed this issue in the discussion section of the manuscript.

15. We have corrected names in Table 3.

16. We have considered and corrected all minor points raised by this reviewer.