Author's response to reviews

Title: The influence of family history of Hypertension on disease prevalence and associated metabolic risk factors among Sri Lankan adults

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Author's response to reviews: see over
RE: MS: 1789274285163427 “The influence of family history of Hypertension on disease prevalence and associated metabolic risk factors among Sri Lankan adults”

Thank you for your letter and the opportunity for resubmission. The constructive feedback from the journal was invaluable and we are now submitting the revised manuscript.

We have attached our responses to your comments made on a point by point basis and have indicated explicitly the ways in which we have changed the manuscript in line with the reviewer comments. We have made necessary changes in the manuscript based on the suggestions.

Thank you for considering the paper for publication.

Yours Sincerely,

Dr. Priyanga Ranasinghe
Corresponding author
**Editorial comments**

The topic of this paper is important in the area of hypertension and the sample size is reasonably large. It is essential to respond to comments from the Reviewers, particularly to major comments, point by point. Please also respond to the following comments.

1. Because a family history of hypertension was investigated using questionnaires, accuracy of the information may be somewhat limited. The authors should discuss this limitation.

   **Author response:** This was included as a limitation, together with an appropriate reference.

2. The authors should also conduct an analysis of covariance (ANCOVA) using BP as a continuous outcome.

   **Author response:** The above test (ANCOVA) was done for all the analyses in Tables 2 and 3 using BP as covariate. Although the means were adjusted accounting for baseline variations in the covariate, all values that were significant at present remained significant even after the ANCOVA (i.e results remains the same). Please clarify what exactly needs to be done? It is not clear to us.

3. Abstract: Please add the number of subjects with a family history of hypertension in the Results of the Abstract.

   **Author response:** Suggested change was done.

4. Abstract: Please clarify that the odds ratios in the Results of the Abstract are adjusted for other confounding factors.

   **Author response:** They are indeed adjusted OR. A clarification was included in the abstract.
5. Tables 2 and 3: Please add gender, smoking status, alcohol intake and physical activity to Tables 2 and 3.

**Author response:** Table 2 and 3 present means and SDs of data (i.e continuous variables). All above mentioned variables are %s and including them in the same table would confuse the readers. Details on gender and physical activity are discussed in the text separately. We do not have complete data on smoking and alcohol intake, to be included in this analysis.

6. Table 3: Headings are confusing. For example, the top heading says "Patients with hypertension (n=1188)" while the 2nd heading says "(n=508)" for the same columns. Lines in the heading section should be separated like Table 2.

**Author response:** The ambiguity has been clarified. The main 2 columns should actually be named as follows; patients with hypertension & a family history of hypertension (n=508) (column 1) and Patients without hypertension, with a family history of hypertension (n=1325) (column 2)

7. Table 4: Multivariable analysis should also include diabetes, lipids and smoking status as covariates.

**Author response:** We do not have complete data on smoking and alcohol intake, to be included in this analysis. Other variables were included and regression analysis was re-done.
Reviewer comments

Reviewer: alfonso otero gonzalez1 (Version: 2, Date: 31 March 2015)

The work done by Ranasinghe P et al is very interesting and very useful clinically.

Two considerations:

1. In the pathogenesis of hypertension, I think you should include the role of Uric Acid and oxidative stress as an important element in the genesis of hereditary hypertension

   Author response: We have included/mentioned these factors, with appropriate references in the introduction section where pathogenesis is briefly discussed. However, we feel that a detailed discussion regarding these two factors is not relevant in the context of the present study.

2. The HTA was more prevalent in rural or urban environment

   Author response: Urban adults (26.5%) had a significantly higher prevalence of hypertension than their rural counterparts (22.9%). This detail was included in the revised results sections.

The work seems very appropriate for publication
The authors examine data on hypertension and its family history from a population-based survey (n=5,000) among adults from Sri Lanka. They found that among those with a positive family history of hypertension the prevalence of the disease was higher than among those without such family history. They also found that the strength of this association grew with the presence of hypertension across generations and that family history of hypertension increased the risk for associated conditions (obesity and metabolic syndrome). These are my comments:

**Minor:**

1. The definitions of hypertension and obesity (page 7, lines 18–25) need references.

   **Author response:** References were added

2. The authors have an opportunity to test for recall bias (controlling for or stratifying by age, is a positive family history of hypertension more common among previously diagnosed than among newly diagnosed cases of the disease?).

   **Author response:** We have discussed recall bias as potential limitation and also in order to minimize recall bias we have carried out a separate analysis on patients with newly diagnosed diabetes, which is presented as a supplementary file (Supplementary file 1).

3. Tables 1, 2, and 4 need the sample size for each column.

   **Author response:** Table 2 and 4 sample sizes were included. Table 1, its not possible to give a sample size for each column as different levels of family history (parent, grandparent, etc) have different responses (yes, no, don’t know). But each row adds up to the total sample size given in the first and second large columns (those with hypertension and those without).
4. The number of subjects with family history information on grandparents is small. Not enough for the strong conclusion about the graded nature of the association between family history and hypertension and other conditions.

**Author response:** We acknowledge this limitation and have changed the conclusions of the study accordingly.

**Major:**

5. The ranking of familial risk by generations may not be the best option. This risk is better expressed by degree of relationship (first or second degree relatives) and the age at onset of the disease (early onset signs a higher risk). Probably the authors don’t have age at onset of hypertension among relatives but early onset in their subjects may be related to a strong familial risk. I would like to encourage the authors to use a risk stratification based on degree of relationship. There are several score systems, which are actually better to show the graded relationship between family history and risk of disease. For example, see the following website and check the reference if possible.


**Author response:** Unfortunately we lack the data to do this kind of analysis. We predominately have family history for First degree relatives (parent, child, sibling) only. We have only one second degree relative (grandparent), however majority (over 1/3rd) were unaware, and only a very few knew correctly about family history in grandparent (as you also have observed in a previous comment). Furthermore, we also lack the data on age of onset of hypertension in the index case. Hence although we have initially also given thought to this kind of analysis, we were not able to proceed due to lack of data. Thank you, for your observation and comment.
6. The tables are confusing in the sense that they present the data by hypertension status (subdivided by family history status). Patients with hypertension should be excluded from some or all of these tables. By definition, family history of a disease is no longer a risk factor when the person already has the disease. Yes, the authors can use the cases of hypertension to examine the influence of family history on the prevalence of the disease; but when they examine how the other risk factors (metabolic, anthropometric, clinical) relate to family history of hypertension, they must exclude the cases of previously diagnosed hypertension and simply examine among the rest the differences between those with a positive and those with a negative family history of hypertension.

**Author response:** It seems that the confusion is with table 1, 2 and 3. In the first table (as suggested by the reviewer as well), we have used the cases of hypertension to examine the influence of family history on the prevalence of the disease. In the second and third tables, to do the change recommended we have to just delete the major column on those with hypertension (and associated 2-3 sub-columns). However, we feel that inclusion of this data helps to convey a complete message/picture to the reader. In the third table we have changed the title of the columns to make it clearer. We would like editors/reviewer discretion, whether such a major omission of data is necessary.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:** I declare that I have no competing interests