Author's response to reviews

Title: Insights into the clinical management of the syndrome of supine hypertension - orthostatic hypotension (SH-OH): The Irish Longitudinal Study on Ageing (TILDA)

Authors:

Roman ROMERO-ORTUNO (romeror@tcd.ie)
Matthew DL O'CONNELL (OCONNEM8@tcd.ie)
Ciaran FINUCANE (cfinuc@tcd.ie)
Christopher SORAGHAN (csoraghan@stjames.ie)
Chie Wei FAN (cfan@mater.ie)
Rose Anne KENNY (rkenny@tcd.ie)

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Author's response to reviews: see over
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Dear Prof. Mitnitski

Insights into the clinical management of the syndrome of supine hypertension - orthostatic hypotension (SH-OH): The Irish Longitudinal Study on Ageing (TILDA).

MS: 8945419719442233 (Revision 1)

Please find below a point-by-point response to the reviewers.

We look forward to hearing from you,

The Authors.
Reviewer: Joshua Armstrong

Major Compulsory Revisions

Methods Section: K-means analyses

• It is not clear on how the authors determined the number of clusters (k). Was there a process to arrive at k=3? This information should be included in the methods section.

Response: the number of clusters k=3 was determined based on previous physiological theory outlining three patterns of orthostatic blood pressure behaviour (references 26-28 in the text). There was no statistical process to arrive at k=3. This has been clarified in the manuscript (page 12, penultimate paragraph).

• For any cluster analyses, the variables that are selected to be included in the analysis greatly influence the clusters that are formed. What was process for determining which variables were included in the k-means analyses?

Response: the variables included in the k-means analysis were key morphological descriptors of the beat-to-beat orthostatic blood pressure response we intended to model. This is explained in the methods section (page 12, last paragraph).

• Outliers can impact k-means analyses. What steps were taken to avoid the influence of outliers?

Response: thanks to all the steps outlined in the active stand data pre-processing section, there were no significant outliers for the purpose of the K-means cluster analysis. This is explained in page 12, last paragraph.
Standardization of variables was reported to not have occurred in preparing the data for analysis. How does this impact the results? Change in SBP is not in a similar range as the other variables…this may cause some variables to be more influential than others in the analyses. Some discussion of the choice not to standardize variables should be included in the methods. Furthermore, discussion of this problem should also be discussion in the limitations section.

Response: The issue of standardisation of variables in K-means cluster analysis is not free of controversy, with some arguing that variable standardisation (z-scores specifically) can result in misleading conclusions when true group structure is present (explained in page 13, first paragraph, see new reference number 36). Thus, the variables were entered unstandardised. However, we acknowledge in the limitations of the study that the K-means cluster analysis is exploratory in nature and the scale and variability of the clustering variables may affect the clustering results in unstandardised analyses (page 22, second paragraph, see new reference number 67).

Methods Section: Logistic Regression Models

For the multivariate logistic regression models, how were the predictor variables chosen? Why they all were included in the model? What approaches to model selection were considered? It seems as if every potential was placed into a model. It may have been more appropriate to look at the predictor variables independently, or controlling for a minimum number of confounders, prior to developing a final model. Alternatively, automatic model selection techniques or other variable selection techniques may have been employed to determine the most powerful predictors of the outcomes of interest.
Response: We thank the reviewer for this suggestion. As suggested, we explored several backward/forward stepwise selection techniques, and we now provide abbreviated tables based on SPSS forward conditional procedure. The automatic model selection techniques resulted in essentially the same predictors identified from the previous ‘full’ models. However, some effects are clearer in the reduced models, which has given us an opportunity to further discuss findings in the light of previous literature (for example, the previously unidentified protective effect of peripheral calcium channel blockers).

- With the large number of variables, is multicollinearity an issue? Were any model diagnostics checked? While little interpretation of the results were found within the manuscript, models containing such a large number of predictor variables are very difficult to interpret. How does this impact the findings of the paper?

Response: multicollinearity statistics (tolerance and variance inflation factors, VIF) were checked for the models and, even in the ‘full’ models, all VIFs were less than 2. This has been explained in the results section (page 16, last paragraph). We have acknowledged general limitations of the multivariable models in the discussion section (page 22, last paragraph).

- It is not clear what the elevated number of variables used in the models has to do with the cut off levels for p-values? Please elaborate.

Response: we thank the reviewer for this observation. We have clarified that given the elevated number of characterisation variables, we focused on the most statistically significant associations (i.e. \( P < 0.01 \)) (page 13, last paragraph).
Discussion Section

- *The limitations section should include some points related to the statistical approaches utilized within the study.*

  Response: the last two paragraphs of page 22 are now entirely devoted to the discussion of the limitations of the statistical approaches.

- *Some of the results from the logistic regression models should be interpreted with more caution due to the nature of how the multivariate logistic models were developed. The presence of the large number of covariates in the regression models should be mentioned when discussing the results.*

  Response: this limitation has also been incorporated. The last two paragraphs of page 22 are now entirely devoted to the discussion of the limitations of the statistical approaches.
Reviewer: Ruth Peters

1. *The question is well defined in that it is clearly based on previous work generating a morphological classification of Orthostatic Hypotension (OH). What is less clear is how the classification was generated, how it compares to this population and more generally the characteristics of the population under study in these analyses.*

Reply: the classification via K-means cluster analysis is now explained in greater detail in the Methods section (page 12, last 2 paragraphs; page 13, first paragraph). The advantage of the present study is that it is based on a population-based survey, as opposed to the previous study which was based on a convenience sample (this has been added to the first paragraph of the discussion). The characteristics of the population under study are explained in more detail in the methods section, with especial attention to the different characteristics of those who were able to attend the Heath Assessment Centre (reference 31), and the differences in those who attended the Health Assessment Centre but had no MOH data. The first paragraph of page 22 has comments on all those limitations.

2. *Much more explanation needs to be provided with regard to the K-means cluster analysis used, how it is used etc. For example, are cut-off values used to generate the groups or does the method separate out the groups? If the latter, how can you be sure that you truly are finding the same three categories? How will this translate clinically into a way to potentially identify those in each category?*

Reply: as per reviewer 1, the K-means cluster analysis methodology is explained in further detail (see page 12, last 2 paragraphs; page 13, first paragraph). The K-means clustering
technique is a classification technique that automatically separates out the groups, and the finding of three groups with similar clinical characteristics as previously investigated with a smaller, convenience sample (as per Table 1) makes it plausible that these three groups are groups that one can clinically recognize in clinical practice (this reflection is now on the second paragraph of page 22). In terms of the clinical translation of the findings, the Conclusion section incorporates some clinical guidance based on our results. As a rule of thumb, MOH-3 should be recognised in practice by the presence of baseline hypertension (>140 mmHg), initial orthostatic blood pressure drop greater than 40 mmHg, and failure to recover to reach 90% of the baseline blood pressure after 2 minutes of standing.

3. With regard to the population, it seems that those who were unable to attend the clinic were excluded? Is this the case and did they differ from those who did attend? Also were partners included in these analyses and if so were they different in age as they were allowed to be lower than the minimum age at entry.

Reply: partners were sampled but we excluded in the analyses everyone under the age of 50 (as explained in the methods section). As explained in the methods section, active stand with Finometer was only available in the Health Assessment Centre. The first paragraph of page 22 discusses the differences between those who did and did not attend the Health Centre, and the differences between those attending the Health Centre who did and did not have MOH information. The former differences are emphasized in relation to our previously published study (reference 31). The latter differences are illustrated with new results in Table 1.
4. Would it be possible to add a flow chart showing the inclusion and exclusion of participants at the different time points, the reasons for exclusion and the numbers included in the analyses? There were 8175 participants >50 and 4467 were analysed so this would be very helpful.

Reply: the flow chart has been added as requested (new Figure 1).

5. Would it be possible to have the baseline characteristics for those who were not included in these analyses – it would be interesting to see whether these people were older/had higher blood pressure etc.

Reply: The first paragraph of page 22 discusses the differences between those who did and did not attend the Health Centre, and the differences between those attending the Health Centre who did and did not have MOH information. The former differences are emphasized in relation to our previously published study (reference 31). The latter differences are illustrated with new results in Table 1. Overall, we are concluding that due to those design issues, the frailest in the population may have been underrepresented in the analytic sample.

6. Would it be possible to add ranges to the existing table – particularly for age?

Reply: age ranges have been added to Table 2.
7. Given the numbers involved would there be any gain in combining the cardiovascular medications?

Reply: we decided against combining medication groups as the medications are already grouped in pharmacological groups according to the WHO-ATC classification. However, we acknowledge that only few participants were on medications potentially associated to MOH-3 such as peripheral vasodilators and antiarrhythmics, so the results for the latter classes may have been underpowered (page 22, last paragraph).

8. The average age is quite young at 61-64. Given that this may be something that is more relevant in older adults is it possible to rerun the analyses in those >80 versus those >=80, or 75, or even 70? The younger adults may be diluting an age related effect.

Reply: as suggested, the stepwise models were repeated in those aged 70 or more. The predictors of MOH-3 did not significantly change in the older subgroup. The Results and the Discussion sections have been updated as necessary with the results of these subgroup analyses.

9. It seems odd the OI was less likely to be reported by females and at advancing age – can this be explored further?

Reply: the second paragraph of page 19 discusses this finding in some more detail. However, we emphasise that non-modifiable risk factors such as age and sex were not the main focus of our study.
10. Please discuss the limitations of this study in greater depth, particularly the population characteristics. Given the age of participants conclusions about older patients should be drawn with care, see in particular the conclusions given in the abstract.

Reply: limitations of the sample have been added in the discussion (page 22, paragraph 1). We have reiterated at the beginning of the Discussion that in view of the observational and cross-sectional nature of the study, results need to be interpreted with caution and represent ‘insights’ rather than confirmed signals.

11. In addition as these analyses are cross sectional they are subject to usual issues of extrapolation of association and this should at least be stated in the discussion.

Reply: this has been emphasized throughout the manuscript (see for example last paragraph of page 21).

12. With regard to the antihypertensive trials, is there a reason for selecting Syst-Eur, CONVINCE and VALUE? There may be better references for this also, if not to the trial results themselves then to systematic reviews. For example there is a Cochrane review looking at antihypertensive treatment in the elderly.

Reply: Syst-Eur, CONVINCE and VALUE are quoted as examples only. We have added the suggested Cochrane review (reference 66). We echo that the Cochrane review was limited in that it could not collect information of patient risk factors, pre-existing cardiovascular disease and competing co-morbidities.
13. In the conclusion paragraph you mention the potential for the development of guidelines in this area – it would be useful if the clinical application could be further explored earlier. How might clinicians identify such patients in a typical clinic setting?

Reply: based on our results, some practical clinical guidance is now offered in the Conclusion paragraph.
Reviewer: Michael R Rockwood

1. Clearly this paper has associated many individual factors with orthostatic hypotension. Given that this is a complex disorder involving a number of body systems, it seems prudent to include an analysis of the impact of frailty. If this cannot be done analytically in TILDA, then further consideration should at least be given to this in the Discussion. For example, older adults without measured hypertension, who are not on an anti-hypertensive medication, appear to have high physiological reserve in general. [Rockwood MR, Howlett SE. Blood pressure in relation to age and frailty. Can Geriatr J 2011;14(1):2-7.] Unsurprisingly then, many of the people with OH have other many health deficits as well (some of which are remediable, as the authors note). Together, these deficits can combine to make the person frail and when frailty is taken into account, the specific influence of OH on risk is greatly attenuated, even becoming no longer statistically significant. [Rockwood MR, Howlett SE, Rockwood K. Orthostatic hypotension (OH) and mortality in relation to age, blood pressure and frailty. Arch Gerontol Geriatr 2012;54(3):e255-260.]

Reply: We thank the reviewer for these valuable comments. The impact of frailty on the outcomes of this study is an area of ongoing research in TILDA and we felt it merits individual consideration in a longitudinal dimension. We have incorporated these reflections and the suggested references.

2. There will be a lot of interest in understanding how a clinically derived analysis of OH translates in a population setting, and whether the fact of the OH coming to clinical attention is incidental to its risk or essential to it. As the authors point out, only a longitudinal study would allow the clinical importance of OH and OI to be better understood. It is striking, however, that the most clinically relevant features (blackouts and fainting) are not
significantly related to the MOH state in this setting. This would seem to merit further acknowledgment in the Discussion.

Reply: We thank the reviewer very much for his inspiring comments. The second paragraph on page 20 discusses the observation that MOH-3 was not associated with the high-level clinical endpoints of our study. We make a theoretical case that OI is the mediator between MOH-3 and those high-level outcomes.

3. Usefully, the authors present a lot of information (Tables 1-4) to show the MOH cluster analysis and the influence of many potential confounders on MOH-3 and OI. Many of the items listed, however, appear not to be significant, and go without (or with very little) comment in the paper. Perhaps these tables might be reduced in the body of the paper to focus on a few specific effects, while the remainder might be better presented in an appendix for the reader with a specific interest in the topic.

Reply: we now present the results of the stepwise models, so the tables have been simplified.

5. The dotted line used in the figure to represent MOH-3 is difficult to differentiate from the one used to represent MOH-1.

Reply: the Figure has been updated for clarity. Different colours for the MOH patterns are now shown.