Author’s response to reviews

Title: Prevalence, Determinants and Association of Unawareness of Diabetes, Hypertension and Hypercholesterolemia with Poor Disease Control in a Multi-ethnic Asian Population Without Cardiovascular Disease

Authors:

Ryan E.K. Man (man.eyn.kidd.ryan@seri.com.sg)
Alvin Hong Wei Gan (alvingan91@gmail.com)
Eva K Fenwick (eva.fenwick@seri.com.sg)
Alfred Tau Liang Gan (alfred.gan.t.l@seri.com.sg)
Preeti Gupta (preeti.gupta@seri.com.sg)
Charumathi Sabanayagam (charumathi.sabanayagam@seri.com.sg)
Nicholas Tan (nicholas.tan2@mohh.com.sg)
Kah Hie Wong (kahhie.wong@mohh.com.sg)
Tien Yin Wong (wong.tien.yin@singhealth.com.sg)
Ching-Yu Cheng (cheng.ching.yu@seri.com.sg)
Ecosse Lamoureux (ecosse.lamoureux@duke-nus.edu.sg)

Version: 1 Date: 09 Aug 2019

Author’s response to reviews:

8th August 2019

To the Editorial Board

Population Health Metrics

RE: Manuscript POHM-D-18-00067
We appreciate the reviewers’ supportive comments of our paper. We have addressed their queries in this revised draft and the changes are tracked. Specific responses to all comments raised are provided below. It also appears that Reviewer 2 was unable to access the supplementary tables, although Reviewer 1 could do so. We are unsure if this is technical matter. Can you please look into this?

Kind regards

Ecosse

Professor Ecosse L. Lamoureux
Singapore Eye Research Institute
Mobile (+65) 9641-3010
DID: (+65) 6576 7382
Email: ecosse.lamoureux@seri.com.sg

REVIEWER 1

1. It is unclear what are the test characteristics (sensitivity and specificity) and the test performance (predictive values of positive and negative tests) of the authors' questions on unawareness of diabetes mellitus, hypertension, and hypercholesterolemia. For example, it is difficult to believe that participants who reported taking medications for diabetes mellitus, hypertension, or hypercholesterolemia were classified in this study as being unaware that they had those conditions. In the Discussion section (lines 342-346), the authors admit that participants who took medications for hypertension and hypercholesterolemia were more aware of their conditions than those who did not take such medications. Perhaps the authors should recast their conclusions about unawareness by emphasizing that specific medication use implies awareness even if the participant cannot articulate that awareness (cf., make Supplemental Table 3 more prominent in the Results).

Author response: Based on this reviewer’s comments, we have relooked at our data and it appears there was an error: we indeed over-reported the number of individuals who were unaware of their condition(s), but were on medication for them. However, there were still a number of individuals who fell into the above category (i.e. were on medication, but were not aware of their condition;
4.7% for diabetes, 9.5% for hypertension and 10.3% for hypercholesterolemia). These figures are unlikely to be the result of interviewer error or recall bias, as participants’ medical regimen was cross-checked based on actual medication labels where possible. We have noted this detail within the appropriate methodology sections in this modified submission.

While it seems improbable that an individual can be prescribed medication for a particular disease without being aware of the condition, it is an unfortunate reality in Asian populations, particularly in the elderly who are entirely dependent on their caregivers (their children or maids) for their care. These individuals usually have very little, if any education, and can only communicate in their native dialect, making doctor-patient communication extremely difficult. Hence any interactions with their doctors are done through their caregivers. In turn, they are not apprised of their condition (due to their poor grasp of medical jargon) and are simply told that they need to take their medication for their continued good health. In our sample, we found that over 50% of individuals who professed non-awareness of their condition, but were actually on medication for that particular disease, had primary or below education (64.7%, 57.3% and 70.2% for diabetes, hypertension and hypercholesterolemia, respectively). Of these, over 65% were aged ≥ 60 years (80.0%, 65.7% and 78.9% for diabetes, hypertension and hypercholesterolemia, respectively). Hence, it is likely that their caregivers have indeed communicated with their doctors on the elderly participant’s behalf. Previous work has confirmed the existence of this phenomenon, e.g. Pirasath and colleagues found that approximately 14% of patients attending a hypertension clinic in Northern Sri Lanka were unaware that they had hypertension.1 In light of this reviewer’s comment, we have also added an additional paragraph to the discussion about this issue.

Page 15: “Interestingly, when we looked more closely at the data, we found that there was a small proportion of individuals who professed a lack of awareness of their condition, in spite of reporting using medications to control the disease (Supplementary Table 2). This phenomenon appears to be common in Asian societies, where elderly individuals depend heavily on their caregivers to guide them in their activities of daily living. These individuals usually have little to no education, and can only communicate in their native dialect, making day-to-day communication with others who do not speak the dialect difficult. As such, these individuals are often not apprised of their condition (since their poor grasp of medical jargon makes understanding difficult) and are simply told that they had to take the medication for their continued good health. We found within this sample of persons who were on medication, yet lacked awareness of their condition, that over 50% of them (73.5%, 63.6% and 59.6% for diabetes, hypertension and hypercholesterolemia, respectively) had primary and below education. Of these, over 65% were aged ≥ 60 years (80.0%, 65.7% and 78.9% for diabetes, hypertension and hypercholesterolemia, respectively). Hence, it is likely that their caregivers have indeed communicated with their doctors on the elderly participant’s behalf. Previous work has confirmed the presence of this phenomenon, for example, Pirasath and colleagues found that ≈14% of individuals in Sri Lanka attending a hypertensive clinic were unaware of having the disease.1 Our results indicate a need for awareness campaigns to
utilize simplified language and descriptions about these three CVD risk factors in order to improve awareness in this group of individuals.”

With regards to the reviewer’s comment on the sensitivity, specificity, positive and negative predictive value of the awareness questions, we have provided a table detailing the diagnostic statistics below. Specifically, we compared self-reported awareness with medication use. As can be seen, sensitivity (i.e. persons who were on medication and reported being aware that they had the condition) was quite high (≥90% for all three diseases). However, these results would be affected by the phenomenon described in the previous paragraph (i.e. patients on medication for the 3 CVD risk factors under investigation not necessarily being aware that they had these conditions due to communication barriers). Combined with the fact that the diagnostic statistics are not the main focus of this article (which was to access the rates, determinants and impact of a lack of awareness of key CVD risk factors) we have therefore decided not to include these results within the main article.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>97.6 (96.6, 98.3)</td>
<td>71.0 (68.1, 73.7)</td>
<td>82.7 (80.8, 84.5)</td>
<td>95.3 (93.6, 96.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>91.8 (90.7, 92.8)</td>
<td>77.4 (75.8, 79.0)</td>
<td>80 (78.6, 81.4)</td>
<td>90.5 (89.3, 91.6)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>91.5 (90.2, 92.8)</td>
<td>72.8 (70.7, 74.8)</td>
<td>76.9 (75.1, 78.6)</td>
<td>89.7 (88.0, 91.2)</td>
</tr>
</tbody>
</table>

2. The authors' explanation about why awareness of diabetes mellitus was associated with worse control of their diabetes mellitus (lines 315-326) is unconvincing. The difference in HbA1c levels between participants who were unaware of their diabetes and those who were aware of their diabetes is small, and nowhere near the levels when diabetes symptoms get "dangerously high".

Author response: We agree that the mean HbA1c values of participants we presented in the original submission may not be a convincing indicator of possible symptomatic disease. As a result of this comment, we took a closer look at the data and found that the number of individuals with HbA1c ≥ 9% was similar between the group that was aware of their diabetes versus those who were unaware (19.7% vs 17.6%). As such, we have modified our explanation to reflect that further qualitative work is warranted to understand the mechanism(s) underpinning the better apparent diabetes control of individuals unaware of their diabetes, compared to individuals who are aware of their condition.
Page 18: “However, when we explored the data in greater detail, we found that the proportion of individuals with HbA1c ≥ 9% was similar between the aware and unaware groups (19.7% vs 17.6%). As such, the results do not appear to support our theory; hence future qualitative work to elicit possible reasons underpinning the better disease control observed in individuals unaware of having diabetes may be warranted.”

REVIEWER 2

1. First, I have no access to the supplementary tables.

Author response: This is unfortunate as we have attached the supplementary tables as instructed in the submission, and Reviewer 1 has apparently been able to access them. Perhaps the Editors in charge of this submission could check and get back to this reviewer?

2. There are two approaches for selecting probable confounding covariates in such studies to be included in the multivariable analysis for adjustment. The one is what the esteemed authors chose that is selecting those variables based on their association via chi-square or t-test and the other one is based on univariable logistic regression (in this case) and then selecting those significant variables to include them in the multivariable logistic regression which is the main and ultimate model of the current study. Yet, regardless of the which model is selected, the level of significance should be considered higher than 0.05 in the univariable models as we are not sure whether a specific variable with a little p-value higher than that of 0.05 (namely 0.07) would be significant in multivariable along with other variables or not. In this case, the common level of significance in the univariable analyses considered as 0.2 or 0.25. However, it is not mentioned that whether the authors chose higher p-value in their univariable analyses or not? If this has not been done the whole results is questionable and needs reanalysis. Please clarify this issue explicitly. I don't know, maybe you have done and be in the supplementary tables that I did not have access. Anyway, this issue should be clarified in the statistical analysis section. Besides, the second approach for selecting covariates is suggested though the one you chose is not incorrect.

Author response: This reviewer is partly correct in saying that we included variables that were significantly different in t-/chi-square tests (P<0.05) between aware and unaware groups for multivariable analyses. This significance value has been added in the statistical analysis section for additional clarity in response to comment (7) by this reviewer. However, to counter potentially missing out on other variables that might not be significant in univariable analyses, but could have turned out to be a significant determinant of unawareness, we included variables that were found
to be significant in previous reports on unawareness in other populations, whether or not they were significant in our univariable analyses. Our methodology has been noted clearly in our original submission under the “Statistical Analysis” section on page 10: “Variables that were significantly associated with the outcomes in univariable analyses (see Supplementary Table 1) or those that were found to be associated with unawareness of the condition(s) in previous studies were then assessed for an independent association with unawareness of each disease by simultaneous inclusion as covariables in a multivariable logistic regression model.”

To additionally address this reviewer’s concern, the only variables from the initial list of participant socio-demographic and clinical characteristics that were excluded from our multivariable analyses were “lives alone” and “works outdoors”. We excluded “works outdoors” in our models to prevent potential over-adjustments, as “occupation” was already included as a determinant. The inclusion of “lives alone” in the model showed no significant associations with the lack of awareness of any of the three CVD risk factor outcomes. As such, we will not modify our list of potential determinants. The results of the independent associations between “lives alone” and lack of awareness of the CVD risk factor outcomes are presented below for the reviewer’s information:

Lack of Awareness    Multivariable-adjusted OR for lives alone

**DM**     1.04 (0.64, 1.70), P: 0.869

**Hypertension**  1.01 (0.74, 1.37), P:0.968

**Hyperlipidemia**   0.93 (0.63 to 1.36), P:0.698

3. Please provide the list of all covariates (those included and not included in the final model) in this section.

Author response: We have done so as requested.

Page 11: “These variables include age, gender, ethnicity, BMI (continuously and categorically), income, occupation, marital status, housing, number of non-CVD related comorbidity and mutually for each other.”

And page 11: “These variables include age, gender, ethnicity, body mass index, self-reported non-cardiovascular co-morbidity, income, education, smoking, occupation, marital status, housing, duration of diabetes (for lack of awareness of diabetes only), and mutually for each other.”
4. In the Results section, I didn't find any tables displaying descriptive statistics. Please prepare and add.

Author response: This was listed in Supplementary Table 1 of the original submission. Based on this reviewer’s comment, we have moved this table out of the supplementary materials and renamed it as Table 1 instead.

5. Please display only those p-values less than 0.0001 as <0.0001 and for other p-values please mention the exact ones (e.g. in line 214).

Author response: We respectfully disagree with this reviewer. The convention in the literature is to report P-values of less than 0.001 as <0.001, as this value already implies a strong statistical association. There would be little point to report P values in gradations beyond 3 decimal places as it adds very little to the interpretation of statistical significance.

6. About age and BMI, it is suggested to consider them as categorical; for age like those categories in table 1; 40-49, 50-59, 60-69, and \( \geq \)70 yrs and for BMI as normal, overweight and Obese. Specifically, about BMI the results will be more understandable and interpret easily.

Author response: We agree and have updated Table 3, as well as the abstract, relevant results and discussion sections, with this information.

7. In line 222, please mention the p-values.

Author response: The P-value for significant associations have been added as requested.

8. About what modeled in table 2, please provide details concerning the ORs of other covariables in supplementary tables.

Author response: We are unsure what this reviewer is referring to in this comment, as Table 2 of the original submission showed the rates of disease unawareness across the three main Singaporean ethnicities. No adjustments were made for confounders in that particular table.
9. Line 289: if the BMI considered as normal, overweight and obese, the results will be more understandable by readers.

Author response: As noted in the response to comment (6), this has now been incorporated into the manuscript.

10. In line 326, it is suggested to provide this information in supplementary tables based on age and ethnicity groups like table 1 and 2.

Author response: Line 326 references the mean HbA1c level of those aware and unaware of their diabetes. As noted in the 2nd response to reviewer 1, we have reworked the explanation to compare the proportion of individuals with HbA1c ≥ 9% between the 2 groups. Given that there were no appreciable overall differences between the groups, the results do not support our theory that those who were unaware were less likely to have poor glycemic control. As such, we have elected not to evaluate the results further. This has been reflected in the updated discussion on page 18.

11. None of supplementary tables were available to me for further assessment.

Author response: As mentioned earlier, it is unfortunate that this reviewer was unable to access the supplementary tables and they were duly uploaded and retrieved by the other reviewer. We have asked the Editor to look into this matter.

REFERENCES