Author's response to reviews

Title: Ethnic differences in the association between blood pressure components and chronic kidney disease in middle-aged and older Asian adults

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The Editor
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Dear Editor:

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Ethnic differences in the association between blood pressure components and chronic kidney disease

Revision 1

Thank you very much for the review of the above manuscript.

We are pleased to address the comments raised in the review and have included all the reviewers’ suggestions in the enclosed revised manuscript. Additions to the revised manuscript are highlighted in blue colour.

Reviewer #1

My main concern is with possible biases that are difficult if not impossible to eliminate in such a study but may have contributed to the observed differential racial effects and warrant mention in the discussion, namely

1. Selection bases: Subjects for parent cohort were identified by age stratified random samples from lists provided by the Ministry for Home Affairs. It would be useful to describe briefly how the Dept of Home Affairs created these lists and the
potential for differential selection biases across races (e.g. if lists were in part based on health care utilization or socio economic status. This is also important in understanding how representative these subjects were of the general population. Secondly while response rates of those invited to participate were excellent (73%-79%), not all subjects had the necessary data available for the current analysis. Given the differences in baseline characteristics such as education level between races either declining to participate or having missing data may additionally introduce differential selection biases.

Author response: To address the reviewer’s concern, we have now briefly explained how Ministry of Home Affairs created this list and its representativeness under “Methods”, page 5 as follows:

“All study participants were recruited from the southwestern part of Singapore. According to the 2000 Singapore census, the residents of southwestern part were a fair representation of the Singapore population in terms of age distribution and socioeconomic status. Details of the study population and methods of SiMES have been published elsewhere. In brief, in SiMES, 5600 individuals were selected by an age-stratified random sampling method from the computer generated random list of 16,069 Malay names based on unique identity card number of the residents provided by the Ministry of Home Affairs.”

We have also discussed non participation bias as a limitation under “Discussion” section, page 15 as follows:

“Finally, while response rates of those invited to participate in the three studies were excellent (73%-79%), not all subjects had the necessary data available for the current analysis. Given the differences in baseline characteristics such as education level between ethnic groups, it is possible for non-participation or missing data to introduce a selection bias. However, the consistency of our findings on risk factor profile of the three ethnic groups with previously published reports (mentioned under “Discussion” section, paragraph 2, page 11) suggests that this bias is less likely to influence our findings.”

2. Secular Trends: The 3 cohorts were recruited over 3 consecutive time periods, leading to possibility of secular trends influencing the results, especially if there was focused public health interventions applied during this period.

Author response: Although the 3 cohorts were recruited over 3 consecutive time periods, the possibility of secular trends influencing our results are negligible as there was no focused public health intervention introduced during this period.

3. Systematic misclassification of eGFR: The outcome is based on estimation of GFR using the CKD EPI formula, I am not sure of the extent to which this has been validated in the 3 populations studied, however, if there were differences in
the validity of this formula between different racial groups this may contribute to the observed racial differences.

Author response: We are happy to clarify this point. Validation studies conducted in Singapore suggested adopting the CKD-EPI equation without ethnic adjustment. We have now mentioned the validation studies conducted in Singapore to support our use of CKD-EPI equation under ‘Methods’, subheading, ‘Measurement of outcome’, page 7 as follows:

“Validation studies conducted in Singapore have shown CKD-EPI to be more accurate than MDRD in particular at higher eGFRs27 and the prevalence of CKD by both MDRD and CKD-EPI to be similar in all three ethnic groups28 suggesting the adoption of CKD-EPI equation without ethnic adjustment.27”

4. Reverse causation: The potential for reverse causation is mention in the limitations section, however its effect is potentially magnified in the analysis of JNC 7 associations by the decision to attribute all subjects on antihypertensive treatment to Stage 1 hypertension.

We have now clarified the attribution of staging of subjects on antihypertensive treatment under “Methods” section, subheading, “Exposure measurement”, page 6 as follows:

“All subjects on anti-hypertensive medication were classified as hypertensive irrespective of current BP. Thus those on antihypertensive medication but with ‘normal or prehypertensive range of BP’ were categorized under stage 1 hypertension and the rest were classified under stage 2 hypertension.”

Reviewer #2

Study Title

5. Suggest revision Major Revision of Title

Title perhaps might be worthwhile including that these associations are in Middle aged and older adults from Singapore (as the study does not look at the entire population or multiple other ethnic groups) I also would include that it describes the description of Hypertension and CKD in the different ethnic groups as some of the interpretation of the Odds ratio derived Associations will need a note of the prevalence of CKD and HT in the different ethnic groups.

Author response: As suggested by the reviewer, we have now included ‘Middle aged and older adults’ in the title. As the three ethnic groups studied are the major ethnic groups in Asia and ethnic differences were observed only in the association of BP components with CKD, we have now changed the title to ‘Ethnic differences in the association between blood pressure components and chronic kidney disease in middle aged and older Asian adults’.
Major Revision to add to Limitations in Discussion

6. As microalbuminuria is an important additional outcome measurement both in respect to estimates of CKD and potential consequences of hypertension and Diabetes, the absence of this measurement is a limitation of the study.

Author response: We have included this as a limitation under “Discussion”, page 15 as follows:

“Fourth, we did not have information on microalbuminuria, another indicator of CKD, which is also associated with diabetes and hypertension. Therefore, we were not able to study the impact of BP on microalbuminuria.”

7. From a confounding variable perspective in Singapore, is there a difference in Socio economic status across the 3 ethnic groups that might also explain less well treated blood pressure and more obesity and hypertension, there is a profound difference in Malays in the proportion receiving anti hypertensive medication so we could assume perhaps that they also are less likely to receive ACEi or ARB, this lesser availability of antihypertensives consequent of whatever reason may explain the findings irrespective of the ethnicity.

Author response: We have now included the following sentences speculating the reasons for the higher prevalence of hypertension among Malays under “Discussion”, page 14 as follows:

“In the current study, Malays had higher levels of systolic and diastolic BP at all age groups and higher prevalence of CKD than Chinese and Indians. While hypertension was positively associated with CKD in all three ethnic groups, BP components including systolic BP, diastolic BP and PP were positively associated with CKD only in Malays. In Chinese and Indians, while systolic BP and PP did not show a significant association, diastolic BP showed an inverse association with CKD that could possibly be explained by the higher proportion of antihypertensive medication use in Chinese and Indians. It is possible that a higher prevalence of underlying risk factors for both hypertension and CKD may have influenced the positive association of BP with CKD in Malays. Although Malays and Indians both had similar adverse metabolic risk profile (lipids, diabetes and obesity) compared to Chinese, Indians had lower prevalence of CKD. This is consistent with a previous study in Singapore that reported Malay ethnicity to be associated with a higher prevalence of proteinuria51 and also consistent with reports from India that showed a lower prevalence of diabetic retinopathy52 and nephropathy53 among Indians suggesting that Indians may be less susceptible to microvascular complications.52;53 In addition, socioeconomic differentials across the three ethnic groups contributing to poor BP control despite treatment,54 and obesity55 may have also influenced the association of BP with CKD.”
Minor Revision

8. Appropriately education is measured and there is a very significant difference with lower levels of education among the Malays, it would be interesting if there were any other measure of SE status to compare this effect.

Author response: We have now included income, another measure of SES that showed similar effect in Malays. We have also included the interpretation of this measure under “Results” section, page 8 as follows:

“Malays were more likely to be primary & below educated, to have income < SGD 1000, and current smokers, had higher prevalence of hypertension, and overweight/obesity, had higher levels of systolic BP, diastolic BP and BMI and lower levels of eGFR and less likely to use antihypertensive medication.”

9. Methods of measurement of Outcome

All creatinine measurements are calibrated appropriately and the use of the CKD Epi formula in this population is also correct in the presence of a normal population, I would like to confirm that the earlier study 2004-2006 applied the same calibration standards as the later studies, as there is a temporal difference across the 3 studies. From a population perspective, it is a slightly older group with the mean age marginally different across the 3 groups although most in later middle age.

Author response: Although there is a temporal difference across the 3 studies, all three studies applied the same calibration standards and same protocol.

10. Major Revision how Odds Ratios across the different ethnic groups are demonstrated and explained. To assist the reader in understanding any potential explanations for differences in the odds ratios across the ethnic groups a figure showing the difference in distribution of the blood pressures across the 3 ethnic groups might be a helpful summary of the data, with this additional figure the question as whether the average blood pressures are different in the 3 groups. I note that when looking at the quartiles of systolic and diastolic BPs, the selected study related quartiles measured seem to higher in one ethnic minority over the other 2, this results in some difficulty in comparing the resulting odds ratios across the 3 groups and perhaps the highest quartile needs to be set at a higher blood pressure level across all three groups to allow the same description of blood pressure.

Author response: As suggested by the reviewer, we have now added a figure showing distribution of BP across the three ethnic groups (Figure 1A and 1B) and interpreted the findings under “Results” page 8 as follows:

“The distribution of SBP and DBP by age categories in the three ethnic groups are shown in Figure 1A and 1B. Systolic BP increased with age in all three
populations; diastolic BP increased up to 60 years, plateau around 60 years and began to decline after 70 years in Chinese whereas diastolic BP increased up to 60 years and began to decline after 60 years in Malays and Indians. Systolic BP was consistently higher across all age groups in Malays as compared to Chinese and Indians. A similar higher trend for diastolic BP was also noted in Malays as compared to Chinese and Indians.”

We have also justified the use of ethnicity-specific quartiles of BP under “Methods” section, “Statistical analysis” subheading, page 8 as follows:

“Since there were large differences in the distribution of systolic and diastolic BP among the three ethnic groups (p<0.0001), ethnicity-specific quartiles were used for categorizing BP components.”

11. Regarding the reporting of results, do the odds ratios mean the same thing if the Hypertension is much higher and more prevalent in one group than the other? You could consider using a fractional polynomials spline curve to allow a demonstration of the rate of change of OR using separate curves for different ethnic groups. It is important to discuss in the discussion how the baseline parameters of Blood pressure and education differ particularly in one ethnic group and this will influence the associations with CKD.

Author response: As suggested by the reviewer, we have now discussed how the baseline BP parameters and education in one ethnic group influence the associations with CKD under “Discussion”, page 14 as follows:

“In the current study, Malays had higher levels of systolic and diastolic BP at all age groups and higher prevalence of CKD than Chinese and Indians. While hypertension was positively associated with CKD in all three ethnic groups, BP components including systolic BP, diastolic BP and PP were positively associated with CKD only in Malays. In Chinese and Indians, while systolic BP and PP did not show a significant association, diastolic BP showed an inverse association with CKD that could possibly be explained by the higher proportion of antihypertensive medication use in Chinese and Indians. It is possible that a higher prevalence of underlying risk factors for both hypertension and CKD may have influenced the positive association of BP with CKD in Malays. Although Malays and Indians both had similar adverse metabolic risk profile (lipids, diabetes and obesity) compared to Chinese, Indians had lower prevalence of CKD. This is consistent with a previous study in Singapore that reported Malay ethnicity to be associated with a higher prevalence of proteinuria51 and also consistent with reports from India that showed a lower prevalence of diabetic retinopathy52 and nephropathy53 among Indians suggesting that Indians may be less susceptible to microvascular complications.52;53 In addition, socioeconomic differentials across the three ethnic groups contributing to poor BP control despite treatment,54 and obesity55 may have also influenced the association of BP with CKD.”
Minor Revision Change

See Discussion Paragraph 4

12. While few cross sectional studies conducted among Chinese,20 and Japanese21;41 adults have reported no significant association between systolic BP and CKD, few studies have shown a strong association between systolic BP and ESRD.19;38 This sentence may need to be revised as it sounds a little contradictory and it is not clear what the message of the sentence is, ie avoid double negatives. Several cross sectional studies among Chinese and Japanese adults have shown significant association between BP and CKD, however few have shown a strong association between systolic BP and ESRD, or does it mean few cross sectional studies among Chinese and Japanese adults have shown significant association between systolic BP and CKD or ESKD.

Author response: Thanks. We have now clarified this sentence under “Discussion”, section, page 12, as follows:

“While studies involving Western populations have shown a consistent positive association between systolic BP and CKD, the pattern of association of systolic BP with CKD has not been consistent in Asian populations. Systolic BP was shown to be strong predictor of ESRD in a large cohort of Chinese adults who participated in the China National Hypertension Survey Epidemiology Follow-up Study (CHEFS)38 and in a large cohort of middle-aged Japanese men who participated in the Kansai Healthcare Study in Japan.19 However, three cross-sectional studies involving Chinese,20 and Japanese21;41 adults reported no significant association between systolic BP and CKD.”

13. As using three different tables, there may need to be an additional figure to summarise the important odds ratios including the 3 ethnic group including the full multivariate models 1 and 2.

Author response: As suggested by the reviewer, we have now included a new Table (Table 5) summarizing the odds ratios of CKD for systolic and diastolic BP quartiles by ethnic groups. We have also referred this Table in text under “Results” section, page 10.

Please do not hesitate to contact me if you have any concerns. We look forward to a favorable decision from you.

Sincerely,

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