PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Hypertension incidence among middle-aged and older adults: Findings from a 5-year prospective study in rural South Africa, 2010-2015
AUTHORS	Houle , Brian; Gaziano, Thomas A.; Angotti, Nicole; Mojola, Sanyu A; Kabudula, Chodziwadziwa; Tollman, Stephen; Gómez-Olivé, F. Xavier

VERSION 1 – REVIEW

REVIEWER	Dereje, Nebiyu MyungSung Medical College, Public Health
REVIEW RETURNED	31-Mar-2021

GENERAL COMMENTS	Thank you for providing me the opportunity to review a research paper entitled "Hypertension incidence among middle-aged and older adults: Findings from a 5-year prospective study in rural South Africa, 2010-2015". The study determined the incidence of hypertension and identified the socio-demographic, health and behavioral risk factors among the adult population in rural South Africa. The study is relevant and adds to the efforts to prevent and control the burden of hypertension, particularly in SSA. The paper is well-written and comprehensive. However, there are some points need to be addressed or clarified. My comments are given as follows. General comment • The study was conducted among normotensive individuals recruited in 2010 and followed through 2015. Why the paper did not get published until now, given that several things including the risk factors are changing rapidly? Abstract • "In multivariable analyses, those that became hypertensive were more likely to have a high waist circumference (incidence rate ratio (IRR): 1.557 95% CI: 1.074-2.259) and be employed (IRR: 1.579 95% CI 1.071-2.329) at baseline". Older age is missing. HIV status was not significantly associated with incidence of HTN. But, the interpretation given here is misleading. • Conclusions seems too broad and not specific to the scope of this study. …" As the burden of hypertension continues to increase in sub-Saharan Africa, this study provides evidence of modifiable risk factors in a poor, rural South African setting to inform public health prevention strategies and programs. I think the words "continues to increase" seems to be comparative (showing a trend) which is not the scope of this study and not supported by your data. Moreover, this study did not show associations of modifiable risk factors (smoking, alcohol, physical activity, dietary pattern). I think the conclusions need to be re-written based on the findings of the study.

Strengths and limitations

• "In response to the urgent call for longitudinal sub-Saharan African studies…" I don't think this is a methodological strength of the study. Also, please consider the timing of publication of this study and the urgent call.

Introduction

• The background of the study is well-described. However, the references used to state the scarcity of researches on determining incidence and risk factors of hypertension in South Africa are studies conducted among HIV positive individuals, which might not be generalizable to all the population. This has to be clearly mentioned as a limitation of the prior studies and should be used as a justification for the current study.

• The last paragraph of the Introduction is better if taken to the methods section.

Methods

• Were both of the studies (2010 and 2015) conducted in the same individuals (Was it repeated measurement)?

• Adequacy of the sample size should be determined and the power of the study should be given.

• Blood pressure measurement: Were there time intervals between the measurements? ….better if hypertensive medication changed into antihypertensive medications.

• How was physical activity measured and categorized? How was alcohol use and smoking status defined and categorized? This information should be provided in the methods section than simply putting as a footnote of Tables.

• Detailed descriptions of the data analysis considerations are provided. However, there is no clear information with regard to whether the authors check assumptions for Poisson regression or not (e.g. independence of observations, equidispersion…). If this is done, please include in the description.

• Reference citations are missing on the Anthropometry and high waist circumference and Random blood glucose and diabetes measurements (definition).

• Do you think Poisson regression will account for the longitudinal nature of the data (repeated measurements of BP)?

Results

• Better if the interval estimate (95% CI) of the incidence rate is given to show the precision of the estimate and also can be used for comparison with others' findings.

• Table 2: Exposure variables were measured at baseline. Don't you think some of the variables might have been changed in between the study interval (For e.g., physical activity, dietary factors, smoking status, alcohol…)?

• The description provided for findings of Table 2 might be misleading as they are not adjusted estimates (The 3rd paragraph of Results section).

• "The results for high waist circumference were in the same direction but the 95% CI overlapped with the null value of 1, likely due to the reduced sample size." The explanation "likely due to the reduced sample size" better be placed in Discussion section.

• "Older ages, being employed (IRR: 1.579 95% CI: 1.071-2.329),….." Please include the IRR and the 95% CI also for Older ages. It is also better if you mention that the IRR is adjusted (Better if use aIRR).

Discussion

• Limitations: You acknowledged that migration history was not assessed as a risk factor in this study. Is this the only variable you acknowledge? What about nutritional variables such as

	consumption of fruits and vegetables, type of oil consumed, salt consumption… • Social desirability bias and recall bias might also affect this study.

REVIEWER	Sen, Indrani Mayo Clinic
REVIEW RETURNED	09-Jun-2021

GENERAL COMMENTS	Dear authors Overall interesting and well written, congratulations on your work. Regards

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author:

Thank you for providing me the opportunity to review a research paper entitled "Hypertension incidence among middle-aged and older adults: Findings from a 5-year prospective study in rural South Africa, 2010-2015". The study determined the incidence of hypertension and identified the socio-demographic, health and behavioral risk factors among the adult population in rural South Africa. The study is relevant and adds to the efforts to prevent and control the burden of hypertension, particularly in SSA.

The paper is well-written and comprehensive. However, there are some points need to be addressed or clarified. My comments are given as follows.

General comment

•   The study was conducted among normotensive individuals recruited in 2010 and followed through 2015. Why the paper did not get published until now, given that several things including the risk factors are changing rapidly?

Given the lack of longitudinal studies on these issues, we were able to build a cohort of individuals from two studies that were conducted separately of each other. Linking together these separate studies to make them comparable, along with linking to the census data for follow-up information for those who were eligible but were not measured in 2015 involved a substantial effort.

Abstract

•   "In multivariable analyses, those that became hypertensive were more likely to have a high waist circumference (incidence rate ratio (IRR): 1.557 95% CI: 1.074-2.259) and be employed (IRR: 1.579 95% CI 1.071-2.329) at baseline". Older age is missing. HIV status was not significantly associated with incidence of HTN. But, the interpretation given here is misleading.

We agree and have added older age to the abstract. We have also clarified the wording of the association of HIV status with hypertension incidence.

"In multivariable analyses, those that became hypertensive were more likely to be older, have a high waist circumference (incidence rate ratio (IRR): 1.557 95% CI: 1.074-2.259) and be employed (IRR: 1.579 95% CI 1.071-2.329) at baseline. Being HIV-positive and not on antiretroviral therapy at baseline was associated with lower risk of incident hypertension" (p2)

•   Conclusions seems too broad and not specific to the scope of this study. ..." As the burden of hypertension continues to increase in sub-Saharan Africa, this study provides evidence of modifiable risk factors in a poor, rural South African setting to inform public health prevention strategies and programs. I think the words "continues to increase" seems to be comparative (showing a trend) which is not the scope of this study and not supported by your data. Moreover, this study did not show associations of modifiable risk factors (smoking, alcohol, physical activity, dietary pattern). I think the conclusions need to be re-written based on the findings of the study.

We agree and have adjusted the conclusions to align with the study findings. We now write:

"Over a 5-year period, 29% of respondents developed hypertension. Given the high burden of hypertension in South Africa, continued longitudinal follow-up is needed to understand the complex interplay of noncommunicable and infectious diseases and their underlying and modifiable risk factors to inform public health prevention strategies and programs." (p2)

Strengths and limitations

•   "In response to the urgent call for longitudinal sub-Saharan African studies…" I don't think this is a methodological strength of the study. Also, please consider the timing of publication of this study and the urgent call.

We agree and have adjusted this bullet point to also include the point just below on the importance of the study including both HIV positive and negative individuals. We have also omitted a mention of urgent in the discussion and abstract.

"We provide longitudinal evidence on hypertension incidence from a population-based cohort in rural South Africa including both HIV positive and HIV negative individuals." (p3)

Introduction

•   The background of the study is well-described. However, the references used to state the scarcity of researches on determining incidence and risk factors of hypertension in South Africa are studies conducted among HIV positive individuals, which might not be generalizable to all the population. This has to be clearly mentioned as a limitation of the prior studies and should be used as a justification for the current study.

We have added this important point to the introduction.

"However, there are currently a limited number of longitudinal studies examining risk factors for incident hypertension in the region, with most of these restricted to HIV positive individuals.[24–27]" (p5)

•   The last paragraph of the Introduction is better if taken to the methods section.

We have moved this paragraph to the beginning of the methods section as suggested.

Methods

•   Were both of the studies (2010 and 2015) conducted in the same individuals (Was it repeated measurement)?

These were two separate studies. The 2015 study, however, included participants from the first study who were aged 40-plus at the time of sampling. Our study is restricted to those individuals.

•   Adequacy of the sample size should be determined and the power of the study should be given.

As we note above, these were two separate studies with different designs and goals. Thus, while we were able to form a cohort from those individuals who were eligible for both studies, the relevant power calculations were done for those studies separately and thus would not apply to this study.

•   Blood pressure measurement: Were there time intervals between the measurements? ….better if hypertensive medication changed into antihypertensive medications.

We have added the timing of the measurement intervals and adjusted the text on the medication as suggested.

"BP was measured three times using a Boso BP instrument two minutes apart in 2010 and an Omron M6W automated cuff two minutes apart in 2015. Validation studies of similar blood pressure monitoring devices indicate that they can provide accurate measurements.[31–33] Consistent with national surveillance guidance, we used the average of the second and third measurements.[34] Hypertension was defined as a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or if the respondent self-reported taking antihypertensive medication. (p6)

•   How was physical activity measured and categorized? How was alcohol use and smoking status defined and categorized? This information should be provided in the methods section than simply putting as a footnote of Tables.

We have added details on these measures to the methods section.

"Respondents were asked about smoking (never, prior, current) and alcohol history (not in past 30 days, less than weekly, weekly), physical activity (using the International Physical Activity Questionnaire (IPAQ)), and if they were using ART." (p7)

•   Detailed descriptions of the data analysis considerations are provided. However, there is no clear information with regard to whether the authors check assumptions for Poisson regression or not (e.g. independence of observations, equidispersion…). If this is done, please include in the description.

We thank the reviewer for noting this. All of our estimates use robust standard errors and we have now included this detail in the methods section.

"We used Poisson regression with robust standard errors to examine the association of hypertension status with socio-demographic, health and behavioural factors from the baseline study." (p7)

Each study was based on a random sample of individuals (p5) which satisfies the independence assumption.

•   Reference citations are missing on the Anthropometry and high waist circumference and Random blood glucose and diabetes measurements (definition).

We thank the reviewer for pointing this out and have included these references.

"High waist circumference was defined as >102cm for men and >88cm for women.[35] Obesity was classified as a body mass index (BMI; kg/m^2) ≥30.[35]" (p6)

"Diabetes was defined as a random blood glucose level of ≥11.1 mmol/L or if the respondent self-reported medication use for diabetes.[36]" (p6)

• Do you think Poisson regression will account for the longitudinal nature of the data (repeated measurements of BP)?

A Poisson model is commonly used in these circumstances. Since the study is on hypertension incidence, we only include those who were normotensive at baseline to examine incidence of hypertension over the follow-up period. Since hypertension can only occur once for these individuals, the modelling approach is appropriate for this situation.

Results

• Better if the interval estimate (95% CI) of the incidence rate is given to show the precision of the estimate and also can be used for comparison with others' findings.\

We thank the reviewer for this suggestion and have included the 95% CI for the incidence rates in the text.

"There were 193 incident cases of hypertension since baseline. The overall hypertension incidence rate was 8.374 per 100 person-years (95% CI: 7.242-9.721) for those completing both studies (men 9.097 (95% CI: 7.266-11.496); women 8.159 (95% CI: 6.832-9.804); Table 2)." (p9)

• Table 2: Exposure variables were measured at baseline. Don't you think some of the variables might have been changed in between the study interval (For e.g., physical activity, dietary factors, smoking status, alcohol…)?

We agree that this is an important point. We use baseline variables since they are temporally prior. Since the exact time of incident hypertension is unknown, we do not know how this timing would relate to changes in exposures between 2010 and 2015. More detailed examination of changes in risk factors will be possible with ongoing additional waves of data collection as part of the second study. We have noted this potential in the discussion:

"A longer period of follow-up, which will be possible as future waves of the study are completed, will permit a greater understanding of the interplay between hypertension, HIV, and treatment of both and related conditions." (p14)

• The description provided for findings of Table 2 might be misleading as they are not adjusted estimates (The 3rd paragraph of Results section).

While we note the reviewer's concern, we think that presenting the bivariate results is useful as a point of comparison to the adjusted results. For clarity for the reader, we have added that the IRRs presented in this paragraph are unadjusted.

"Table 2 shows incident rates and ratios (unadjusted) for those completing both studies by baseline socio-demographic, health, and behavioural risk factors." (p10)

• "The results for high waist circumference were in the same direction but the 95% CI overlapped with the null value of 1, likely due to the reduced sample size." The explanation "likely due to the reduced sample size" better be placed in Discussion section.

As suggested by the reviewer, we have removed this from the results.

• "Older ages, being employed (IRR: 1.579 95% CI: 1.071-2.329),....." Please include the IRR and the 95% CI also for Older ages. It is also better if you mention that the IRR is adjusted (Better if use aIRR).

Given the 4 different coefficients for age groups, we have included one as an example for the reader. We have also adjusted IRR to aIRR throughout as suggested, including the table headers and supplementary materials.

"Older ages (e.g., ages 60-69 aIRR: 2.4 95% CI: 1.463-3.938), being employed (aIRR: 1.579 95% CI: 1.071-2.329), and having a high waist circumference (aIRR: 1.557 95% CI: 1.074-2.259) were associated with higher risk of incident hypertension in 2015." (p10)

Discussion

• Limitations: You acknowledged that migration history was not assessed as a risk factor in this study. Is this the only variable you acknowledge? What about nutritional variables such as consumption of fruits and vegetables, type of oil consumed, salt consumption…

We thank the reviewer for this suggestion and have included the importance of nutritional factors as another set of variables to consider in the limitations.

"Other important factors to consider include nutritional factors such as consumption of fruits and vegetables and salt intake." (p14)

We have also included additional detail on the study setting in the method related to this point:

"The area is a low rainfall setting with limited subsistence farming." (p5)

•   Social desirability bias and recall bias might also affect this study.

We agree and have included this as an additional limitation.

"Our self-reported measures may also be subject to social desirability and recall bias." (p14)

Reviewer: 2

Comments to the Author:

Dear authors

Overall interesting and well written, congratulations on your work.

Regards

We thank the reviewer for their careful review and positive comments.

VERSION 2 – REVIEW

REVIEWER	Dereje, Nebiyu MyungSung Medical College, Public Health
REVIEW RETURNED	01-Oct-2021

GENERAL COMMENTS	The authors have satisfactorily addressed my comments and the article is improved.