Author's response to reviews

Title: Prevalence, awareness, and associated risk factors of hypertension in older adults in Africa: a systematic review and meta-analysis protocol

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Author’s response to reviews:

Reviewer #1: Introduction

1. A paragraph on systematic reviews (lines 75-81, page 5) should be moved towards the end of introduction section at line 115 (page 7).

Paragraph moved as suggested.

Revised: Lines 114-122

There are several reasons why a systematic review on the prevalence of hypertension in older adults in Africa is needed. While a number of systematic reviews of hypertension have been undertaken at country level [39-42], sub-regional [19] and continental levels [17, 43, 44] and recently among children and adolescents [45] there is little information among the older adult population in Africa. To date, only one systematic review with meta-analysis of the prevalence of hypertension in older adults in Africa has been published [46]. Unlike our proposed review which defines older age as 50 years and older in line with other studies [23, 31, 47], the Kaze et al study used a threshold of 55 years [46] and reported a pooled prevalence of hypertension of 55.2% among persons aged 55 years and older.

2. Please, delete the last paragraph (lines 115-119).

This paragraph deleted as recommended and so no longer appears in the revised manuscript.

3. It is not very convincing what new evidence adds your review when there is a very recent systematic review by Kaze 2017. You state that the age threshold for being old used in the
Kaze 2017 review was 55 years as opposed to 50 years defined in your review. Would the difference of 5 years lead to appreciable differences in the effect estimates of prevalence of hypertension and risk factors between the two reviews?

4. I think you need stronger rationale to justify novelty of your review findings. Perhaps you need to highlight methodological or generalizability limitations of the previous review that your review is going to address? One of them being quality appraisal of included studies which was not done in the Kaze review. You may capitalize that you will appraise the study quality and risk of bias unlike the previous review. I found that you cover some of this in Discussion section (1st and 2nd paragraphs on lines 267-281 and 283-290).

5. So why don't you bring up these paragraphs and integrate them with the paragraph starting at line 115, thereby covering the limitations of previous reviews at the end of Introduction section (right before Review Questions)? This would reinforce the differences in your and Kaze's reviews. Moreover, these paragraphs (lines 267-281 and 283-290) are out of place in the Discussion section.

In line with the reviewer’s comments 3-5, we have restructured the manuscript and presented our justification for the present protocol upfront in the introduction section rather than in the discussion, as was the case in the original manuscript.

We argue that the study selection method in the Kaze et al 2017 publication may have contributed to the marked heterogeneity in their review. We expect that the number and profile of the subject in our included studies will be significantly different from that of Kaze et al 2017. We clearly present the differences in the age groups, time period and inclusion criteria between the two studies. It would therefore be erroneous to assume that the two reviews differ mainly on a five-year age gap.

Contrary to the observation in comment 4, we note that the Kaze et al 2017 paper did a study quality assessment.

Revised: Lines 114-149

There are several reasons why a systematic review on the prevalence of hypertension in older adults in Africa is needed. While a number of systematic reviews of hypertension have been undertaken at country level [39-42], sub-regional [19] and continental levels [17, 43, 44] and recently among children and adolescents [45] there is little information among the older adult population in Africa. To date, only one systematic review with meta-analysis of the prevalence of hypertension in older adults in Africa has been published [46]. Unlike our proposed review which defines older age as 50 years and older in line with other studies [23, 31, 47], the Kaze et al study used a threshold of 55 years [46] and reported a pooled prevalence of hypertension of 55.2% among persons aged 55 years and older. There was substantial heterogeneity (I² = 95.5%) across the studies analysed, due probably in part to their method of study selection. Our review will analyse studies primarily targeting older persons, whereas their review extracted data
pertaining to older persons as a subset from any study of the general population. These differences in study selection could lead to substantial differences in the number and sample sizes in the final set of studies that are analysed. For example, two papers by Addo et al [48, 49] conducted respectively in rural subjects aged 18-99 years and urban civil servants aged 25-68 years would not be eligible in our study whereas they contributed three data points from the age groups 55-64 years, ≥55 years and ≥65 years in the Kaze et al [46] study.

Besides the differences in the set of studies to be analysed, we expect the different study selection methods to yield different study sample sizes, both of which affect heterogeneity across studies. In household surveys in Africa, the older age groups tend to be under-represented. Consistent with this observation, the 55+ years age group constituted only about 21% of the total sample size in the Kaze et al [46] review. As an example of the differences in the sample size to be evaluated, whereas our review on the prevalence of hypertension will include all (100%) the 3,840 South Africans aged 50 years and older in an eligible study [50], the Kaze et al [46] review included only the age group 60 years and older which represented 55.9% of the total sample. Further, we expect that the inclusion of studies published prior to the year 2000 will yield additional relevant studies.

Restricting our studies to those that were conducted specifically in older persons will provide a better basis to make policy proposals relating to this age group than the Kaze et al review in which the included studies covered a mix of age groups. A study conducted with the aim to assess the difference in the prevalence of hypertension between formal and informal urban areas in an African city [51] or one that aimed to estimate the prevalence of hypertension and associated risk factors in civil servants [49] would hardly be expected to yield findings that are directly relevant to older persons. Thus, we expect the profile of subjects in the included studies between our review and the published review [46] to be significantly different owing to the differences in the age groups, time period and inclusion criteria.

Review questions

6. I would delete the 3rd question (i.e., on level of awareness, detection, treatment, etc.). This is another construct, which merits separate searches and a systematic review of its own. The set of studies on prevalence and risk factors that will be included in your review will not allow you to review this evidence systematically. You did not cover these issues (awareness, control, treatment) in the methodology of protocol either. I suggest to drop them.

Answer: There several reviews on the awareness, detection, treatment of hypertension have not been included as specifically search terms. They include systematic reviews of hypertension of the African Region or sub-region by Adeloye & Basquill 2015; Atalklte 2015 or Bosu 2915 and reviews outside the region by Tailakh et al 2014; Diaz & Ferrant 2015; and Naing et al 2014.

The point is that you can hardly do a review of population-based studies on awareness or treatment of hypertension without going through the hypertension /blood pressure prevalence layer. Hence, if investigators accomplish a comprehensive review of all population-based studies within the region, they can be confident that their findings on awareness, treatment and
control are similarly comprehensive. At worst, the authors can caution interpretation within the bounds of the inclusion criteria.

Revised (lines 158-159): no change

7. Since you are going to include studies from 1980, one could analyse the temporal trend/change in the prevalence and risk factors of hypertension over time. This would be a valuable information (would serve as question #3 and additional contribution to the field). If you decide to add this question, please also cover it in other sections such as data extraction and data analysis.

Thank you for this suggestion. We have included the analysis of trends in the review questions as well as in the data analysis. The data extraction form already collects data on publication and study years.

Revised: Lines 155-156

What is the prevalence and trends in hypertension in adults aged 50 years and older living in Africa?

Revised: Lines 293-295

We will report the crude and pooled estimates of the prevalence of hypertension in 10-year time periods over the period 1980-2017 in order to provide trends [19, 61]. In addition, we will analyse the temporal trends in the prevalence of hypertension using cumulative meta-analysis [46, 62].

Methods - Inclusion criteria

8. Lines 143-145: if you are going to systematically review the prevalence and risk factors of hypertension in elderly in Africa, you may need to divide them by study design. For example, the prevalence will be reviewed in population-based cross-sectional studies. You cannot assess the prevalence of hypertension in [non-population based] follow-up cohort or case-control studies. The risk factors can be reviewed in observational follow-up cohort, case-control, as well as cross-sectional studies (population-based or not). It should be noted that the cross-sectional design is not optimal for assessing risk factors, because it does not allow to determine the temporal relationship between the risk factor and the occurrence of hypertension. Although the use of cross-sectional studies for risk factors will be acknowledged as a limitation, they are still informative.

In the sub-group analyses in the meta-analyses, we will summarize the prevalence estimate by the study design.

Revised: Lines 300-302
Separate sub-group analyses will be performed to assess the causes of any heterogeneity and, if appropriate, to estimate the pooled prevalence of hypertension by sex, age group, geographic locality, study design and year of publication (by decades)

9. Is there any rationale why 1980 was chosen for eligibility to include?

The year 1980 was chosen to allow sufficient period of time (almost 40 years) for trends and patterns to be observed. The down-side however is that most of the earlier studies use the higher threshold of 160/95 mmHg to define hypertension. To put this in context, another systematic review of hypertension in Africa (Adeloye & Basquill 2015) used the same 1980 as an inclusion criterion. On the other hand, other studies have include studies dating from 1946 (Defo et al 2017) or much later from 2000 (Ataklte et al 2015).

Revised: Lines 320-321

Further, the four-decade period covered by the review is sufficiently long to establish patterns and relationships with the outcome.

10. P (population). Will the authors specify if the eligible population should be healthy, with one or more chronic disease, and/or mixed?

Revised: Line 180

Apparently healthy adults aged 50 years and older living in Africa

11. Next after P (population), the authors may need to add a new entry called I/E (intervention/exposure): any risk factor

The ‘I’ in PICOS approach is not applicable in this review

12. C (comparator): no exposure/no risk factor/reference group

The ‘C’ in PICOS approach is not applicable in this review as there is no comparison group

13. Outcome: please add 'the association between a risk factor and hypertension'

Since risk factors are not outcomes, we have defined our outcome as the occurrence of hypertension (incidence or prevalence)

Methods - study selection
14. At title/abstract screen, who will screen the studies, one or more reviewers? Will they be independent in their assessments? How the conflicts between the two reviewers will be solved? Consensus will be reached between the two reviewers or using a third adjudicator?

Two reviewers will independently screen the studies. Discordance will be resolved by mutual consensus.

Revised: Lines 229-233

The titles and abstracts of the articles of results that emerge from the search strategy will be screened independently by two reviewers to exclude obviously non-relevant papers (Figure 1). Then the full-text versions of the remaining potentially eligible articles will be retrieved and further assessed independently by two reviewers to determine if they satisfy the inclusion criteria. Any discrepancies will be resolved through consensus.

15. Lines 203-204 (extracted data from multiple publications): this sentence should be in data extraction section.

This sentence (Lines 203-204) has now been shifted to the data extraction section as suggested.

Revised: Lines 252-255

Where multiple papers pertaining to the same study population and site are encountered, we will extract data from the most informative paper(s) but they will be linked together as one unique study paper.

16. Lines 204-205 (bibliographies of selected papers): this sentence should be in the Literature Search section.

This sentence (Lines 204-205) has now been shifted to the literature search section as recommended.

Revised: Lines 222-224

The bibliographies of the selected papers that the selected databases yield will also be hand-searched to locate further articles of interest.

17. Will the authors mention the PRISMA study flow diagram to describe the screening process and reasons for exclusion at full text screen level?

In addition to the section “Protocol and registration”, PRISMA framework is now included in the “Selection of studies” section
Revised: lines 235-236

In line with the PRISMA framework, the reasons for exclusion at full text screen level will be documented

Methods - data extraction

18. Lines 240-242 (sensitivity analysis): this sentence should be moved to the 'Data analysis and synthesis section'

Lines 240-242 has now been moved to the 'Data analysis and synthesis section’ as recommended

Revised: Lines 286-287

We will perform a sensitivity analysis to examine the effect of excluding studies with high-risk of bias on the overall prevalence and relationships

19. Lines 242-244 (GRADE): this sentence should read as follows: "The overall quality of evidence will be assessed using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)."

Correction has been effected, replacing “systematic review” with “evidence”

20. Please, move this sentence to the end of the Data analysis section or create a new section (should follow the data analysis section) titled Overall strength of evidence (or Grading the evidence).

Sentence has been moved to the end of the Data analysis section

21. GRADE system is used to assess the overall strength of evidence across intervention and diagnostic studies. I am unaware if it can be applied to prevalence studies. The authors are asked to provide any relevant reference or if not, describe in the data analysis section on how this system will be adapted to prevalence studies.

Responses to Comments 19-21

The application of the GRADE criteria for the evaluation of evidence is explained below.

Revised: Lines 307-313

The overall quality of evidence will be based on an adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [66]. The
GRADE criteria for the evaluation of evidence are risk of bias, consistency (heterogeneity), directness (generalizability), precision (statistical significance of effect measures) and publication bias. The quality of evidence is graded as high, moderate, low or very low. For observational studies, the quality of evidence starts of as low [67]. The risk of bias will be derived from the Hoy et al tool designed for prevalence studies [59].

Methods - data analysis and synthesis

22. Please specify what summary measure will be used for prevalence, will it be a proportion prevalence (%)? What summary measure will be used for risk factor-hypertension association, RR, OR?

The prevalence will be summarised as a proportion. The strength of association between risk factors will be pooled as a summary odds ratio, in the absence of substantial heterogeneity.

Revised: Lines 289-291

The prevalence will be summarised using as a proportion prevalence and summary measures of risk factor-hypertension association presented as odds ratios.

23. The authors will try to pool the ORs/RRs for prevalence. Will they try to pool the ORs/RRs for risk factors as well?

See comment 22 above

24. Will the authors perform any subgroup analysis (e.g., separate meta-analyses by sex, time period, age group, and geographic locality) or a meta-regression to explain any potential heterogeneity in the prevalence of hypertension, if such exists?

We will perform sub-group analysis as explained below.

Revised: Lines 300-302

Separate sub-group analyses will be performed to assess the causes of any heterogeneity and, if statistically appropriate, to estimate the pooled prevalence of hypertension by sex, age group, geographic locality, study design and year of publication (by decades).

Discussion

25. Will the authors discuss the policy implications of this research and future research plans outlined by their systematic review findings? This section will also cover limitations and strength of the review as well as evidence itself.
The discussion section already includes the strengths and limitations of the review and potential policy implications. To make this clearer, an introductory sentence on the strengths and an additional limitation have now been inserted.

Revised: Lines 319

Furthermore, our review has several other strengths.

Revised: Lines 327-329

Another limitation is that most of the studies will be cross-sectional and so will not be best suited to assess temporal sequence between a risk factor and the outcome.

Reviewer #2: General comments

This manuscript is a protocol for a systematic review on the prevalence, awareness, treatment and risk factors for hypertension in older adults in Africa.

The authors think the study is warranted because: (i) the features (prevalence, awareness, complications, treatment and control) of hypertension in older adults in Africa are unknown (or not well-known) (ii) existing attempts were not sufficiently comprehensive (iii) because of multi-morbidity in this age group, hypertension poses different health related problems as compared to younger age groups and (iv) the fast-growing proportion of older adults in the population of Africa due to demographic transition. The authors will be conducting a systematic review of both cross sectional and follow up studies from 1980 to present. They planned to search major electronic databases and the grey literature for unpublished data. The data extraction and assessment of the quality of publications will be conducted independently by two reviewers. A meta-Analysis is planned if the included studies meet criteria, else a narrative synthesis will be presented.

I would like to congratulate the authors for identifying a relevant research topic and presenting a protocol that rigorously adheres to good standards for conducting a systematic review. Hypertension as a common risk factors for NCDs is warrant of attention in Africa with the rising burden of NCDs along with persistent communicable diseases and data among older adults are even more needed. The protocol presented adheres to the core quality principles for systematic review. I therefore found it warrant of publication if the authors can accept to revise/clarify some minor points.

We thank the Reviewer for these kind comments

26. My major concern pertains to the time span of the intended review: from 1980 to present (37 years). I would find this "too wide" particularly if one intends to present pooled estimates of the burden of hypertension as we agree on the fast-changing pattern of hypertension due to epidemiologic transition. Going back to 1986 can prove interesting in depicting trends, but if
meta-analysis was to be carried out we suggest pooled prevalence are presented per segment of relevant periods that can reasonably be held for homogenous as it was proposed for age groups, sex and locality.

The year 1980 was chosen to allow sufficient period of time (almost 40 years) for trends and patterns to be observed. The down-side however is that most of the earlier studies use the higher threshold of 160/95 mmHg to define hypertension. To put this in context, another systematic review of hypertension in Africa (Adeloye & Basquill 2015) used the same 1980 as an inclusion criterion. On the other hand, other studies have included studies dating from 1946 or 1950 (Defo et al 2017) or much later from 2000 (Ataklte et al 2015).

As suggested, we would report the pooled estimates of the prevalence in 10-year time periods over the period 1980-2017 in order to provide trends. The longer time period from 1980 instead of 1986 may allow a sufficient number of eligible studies to be analysed.

Revision: Lines 293-295

We will report the crude and pooled estimates of the prevalence of hypertension in 10-year time periods over the period 1980-2017 in order to provide trends [19, 61]. In addition, we will analyse the temporal trends in the prevalence of hypertension using cumulative meta-analysis [46, 62].

27. I understand Africa as a whole is the scope of this review, but some sections in the rationale tend to suggest SSA is the target…

The statistics on SSA have now been replaced by those on Africa wherever possible such as the UN data of population and the Global Burden of Disease Study. In other publications, continent-wide information is unable as it is often divided into that of Sub-Saharan Africa on one hand and North Africa combined with Middle East (and Central Asia) on the other hand (NCD Risk Factor Collaboration 2016; Sarki et al 2015).

Revisions: Lines 78-80

An epidemiological model showed that the pooled prevalence of hypertension in Africa in the elderly ranges from two to four times that in those 40 years or younger [21].

Revisions: Lines 91-92

The population of Africa is ageing with the proportion aged 60 years and above (60 +) projected to increase from 5.2% in 2000 to 8.9% in 2050 and 19.6% in 2100 [32].

Revisions: Lines 94-97

The Institute of Health Metrics and Evaluation estimates that the proportion of total deaths due to NCDs in Africa that occurred among persons aged 50+ years increased from 67.3% in 1990 to
71.1% in 2015 [33]. The share of all NCD deaths among those aged 50+ years also increased from 66.5% to 71.6% over the same period.

Revisions: Lines 99-104

Among persons aged 50-69 years in Africa, the leading risk factors for disease burden, measured in disability-adjusted life years (DALYs) lost, are high systolic blood pressure (SBP), high body mass index and high fasting plasma glucose. The proportion of deaths attributable to cardiovascular diseases in Africa remained stable at 29.1% in 1990 and 28.9% in 2015. The proportion of DALYs attributable to cardiovascular diseases decreased slightly over the same period was from 23.1% to 22.1%.

Specific comments

28. Title: I suggest adding the treatment and awareness to the title to fully reflect the content. So the title could reads as following: prevalence, awareness, treatment and risk factors for hypertension in older adults in Africa: a systematic review and meta-Analysis protocol

Thanks for the suggestion, although another reviewer has suggested that this aspect be deleted from the systematic review as the specific search terms do not cover awareness, treatment and control. There are several examples of studies with similar titles as recommended:

• Hypertension awareness, treatment and control in Africa: a systematic review (Kayima et al 2013)

• The prevalence, awareness, and control of hypertension among workers in West Africa: a systematic review (Bosu 2015)

• Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension (Anchala et al 2014)

Revision: Lines 1-2

The prevalence, awareness, treatment and control of hypertension in older adults in Africa: a systematic review and meta-analysis protocol

Introduction

29. Line 76: I suggest you replace imperative with needed or warranted

Correction has been made – “imperative” has been replaced with “needed”

Revision: Lines 114-115
There are several reasons why a systematic review on the prevalence of hypertension in older adults in Africa is needed.

Exclusion criteria

30. Line 161: since older adults are here defined as 50 years and above, that is beyond the reproductive span (15-49) and so pregnant women are unlikely to be eligible for the study.

Although pregnancy beyond 50 years does occur (Carolan 2013), we have now deleted this point from the exclusion criteria.

Revision: Line 192

Studies involving older adults in a restricted population such as those who are unwell …

31. Line 163: Is there any rationale for excluding population based studies among refugees? I would tend to think this is making it too restrictive. It's likely that other studies in the general population will fail to capture data on refugees.

The characteristics of refugees, being forced migrants who have survived catastrophic events, likely differ in ways from the similar-aged persons in the general population of their host country (Jacobsen & Landau 2003). These differences may be related to hypertension. They are therefore excluded to reduce selection bias.

Selection of studies

32. Line 203-204: The criterion for selection of the paper to be included in the review from a set of multiple papers pertaining to the same study population and site needs to be further explained and clarified. There are many concerns: what if the papers are reported data from sufficiently different periods in time? What of the quality of the study (validity?) which does not always equate to "informative"?

Data on hypertension and its correlates on the same sample may be published as multiple papers with different themes although they may contain overlapping data. We will extract data from across the different papers to obtain maximum information. If the papers are published over widely different periods, the earliest year of publication will be extracted. It is worth noting that the data on the population itself at a particular point in time will be the same regardless of the findings are published. The study quality will be assessed based on the study methods gleaned from the multiple papers.

Revision: Lines 254-255
The earliest year of publication will be reckoned if multiple papers of the same study are published at different times.

33. "The bibliographies of selected papers will be hand-searched to locate further articles of interest"…I would have moved this to the literature search section.

Thank you for the suggestion. This sentence has now been moved this to the literature search section.

Revised: Lines 222-224

The bibliographies of the selected papers that the selected databases yield will also be hand-searched to locate further articles of interest.

Data analysis

34. Line 262: Because Asymmetry of funnel plot can stem from various reasons, funnel plots are generally considered relevant for assessment of “small study effects” (the tendency for smaller studies in meta-analysis to show larger treatment effects).

Thank you for the comment which will be taken into account in the assessment of publication bias.