PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of uncontrolled hypertension in people with comorbidities in sub-Saharan Africa: a systematic review and meta-analysis
AUTHORS	Mohamed, Shukri; Uthman, Olalekan; Mutua, Martin; Asiki, G; Abba, Mustapha; Gill, Paramjit

VERSION 1 – REVIEW

REVIEWER	Antignac, Marie Assistance Publique - Hôpitaux de Paris, pharmacy St Antoine Hospital
REVIEW RETURNED	31-Jan-2021

GENERAL COMMENTS	Manuscript Number: bmjopen-2020-045880 “Prevalence of uncontrolled hypertension in people with comorbidities in sub-Saharan Africa: a systematic review and meta-analysis” by Mohamed SHUKRI et al The authors review the published data on the Prevalence of uncontrolled hypertension in people with comorbidities in Africa, focuse ont patients with diabetes and discuss their results. I commend the authors on taking on this important topic, adequate control of hypertension is critical to prevent cardiovascular events. Premature cardiovascular mortality could reach 25 to 50% of all-cause mortality in low and middle income countries by 2025, if the prevalence of risk factors continues to rise, with hypertension and diabetes being major risk factor. Major comments: Major studies were excluded from the systematic review, without explanations (PURE study, MAY Measurement study …), those studies have a higher level of confidence, with better methodologies than studies included in the systematic review. Authors didn’t explain exclusion criteria. Independently of the work of the authors, poor quality of studies included in the systematic review could be detrimental to the results and conclusion of the review. Furthermore, knowing lack of data in sub-Saharan Africa, authors should present general results and may be analysis by comorbidity, region, …. should be limited, and they should discuss results with more caution. In introduction, Authors didn’t enough explain why they performed this analysis, because they present results in the introduction, where they tell that uncontrolled BP is already known in SSA and

	is “reported a (93%) high prevalence of uncontrolled hypertension”. Methodology : Antihypertensive treatment is not included in the description of the studies included in the systematic review, then how explain the uncontrolled HTA (due to lack of access to treatment, lack of prescription …), there are probably a large heterogeneity between population of studies. Results : - In table 2 and 3, P values from should be explained , For example : authors concluded to a difference between prevalence of uncontrolled BP according to size of the study and detail one p value for small size and one for large size, what is the p value of the difference of prevalence. This comment is appropriate to all criteria associated to uncontrolled BP by the authors. - Fig 2 and 4 - - Please explained the dispersion of points because it is probably unclear for the readers of BMJ OPEN - could be moved as supplemental figures, Discussion : In the discussion, Authors tell that this is the first systematic review but they cited ATAKLTE F (2015) who published a systematic review in the same field. Minor comments P 4 line 44-47 : unclear sentence P7 line 55 “proportionmean” P15 line 45 “coormodities”

REVIEWER	Monyeki, Kotsedi University of Limpopo, Physiology and Environmetal Health
REVIEW RETURNED	04-Apr-2021

GENERAL COMMENTS	One wonders if cohort studies were not available for selection as they could provide good evidence under study. Community studies could also provide better evidence if available for selection

REVIEWER	Dzudie, Anastase University of the Witwatersrand
REVIEW RETURNED	19-Apr-2021

GENERAL COMMENTS	Title: Could be Prevalence of uncontrolled hypertension in people with "treated" comorbidities in sub-Saharan Africa: a systematic review Se method section Abstract : No comment Introduction Page 4, line 26, In the lastest systematic...How this will this read in 20 years? Authors are advised to just say "In a systematic (not the latest)", and correct this kind of sentences in the writing style. Strength and limitation section: See comments on discussion section Method section

	Definition of terms and especially the outcome of interest. 1. How did authors defined "uncontrolled hypertension? Was there a variation in the definition regarding medications used? If defined as "systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg in patients taking anti-hypertensive treatment", then the method section would be understandable. However, if define as Is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg irrespective of treatment, then one would expect many studies to be included. Although my understanding is that the first definition applies, a clarification of this aspect is necessary. If the definition of Uncontrolled HTN is as all cases of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg irrespective of treatment, then authors might consider limiting the study to a hospital setting and that would solve this misunderstanding. 2. Page 5, Search strategy, line 12-13. Eligibility criteria: The sentence "studies that included hypertension prevalence but did not report on the prevalence of hypertension among those on antihypertensive medication" is unclear. A patient on antihypertensive medication is consider as hypertensive. Please clarify. Also, So what was the rationale of excluding these patients? A number of studies on hypertension in people with diabetes/HIV are left out, and I guest it related to this exclusion criteria. Discussion Strengths and limitation section: Page 17, Line 27, 28: "Two independent reviewers were used in data extraction and the assessment of the risk of bias". This is a common methodological requirement for systematic reviews (PRISMA), I do not foresee this as a particular strength following a usual requirement. Authors should remove this. Line 41, 42: It is good to say precisely the number or proportion of hospital based studies that used non-random sampling procedures. Line 45: "Therefore, the prevalence of UHTN in these populations needs to be confirmed by further". This sentence is irrelevant in this section, authors may want to indicate that population studies are warranted. A weakness of this study is that while the authors are focussing on uncontrolled hypertension as inclusion criteria for studies, hypertension is generally uncontrolled, this is particularly true in LMICs and especially Sub Saharan Africa. More than 90% of hypertension is uncontrolled, so even when the term uncontrolled does not appear in the study, hypertension is definitely uncontrolled in that study. Therefore a number of population studies do not appear here because they reported on hypertension without the term uncontrolled and including them but could yield different results. Some examples are: 1. Katte JC, Dzudie A, Sobngwi E, Mbong EN, Fetse GT, Kouam CK, Kengne AP. Coincidence of diabetes mellitus and hypertension in a semi-urban Cameroonian population: a cross-sectional study. BMC Public Health. 2014 Jul 8;14:696. doi: 10.1186/1471-2458-14-696. PMID: 25000848; PMCID: PMC4107975.

	2. Mutemwa M, Peer N, de Villiers A, Mukasa B, Matsha TE, Mills EJ, Kengne AP. Prevalence, detection, treatment, and control of hypertension in human immunodeficiency virus (HIV)-infected patients attending HIV clinics in the Western Cape Province, South Africa. Medicine (Baltimore). 2018 Aug;97(35):e12121. doi: 10.1097/MD.0000000000012121. PMID: 30170445; PMCID: PMC6392528. But again, the definition of uncontrolled HTN needs to be clear here. Authors are advised to discuss this or to simply indicate in the method section clearly that they limit the scope of their study to a hospital/health falcility setting, which actually makes sense because it is generally in the hospitals that comorbid conditions would be diagnosed and also, a hypertensive patient without comorbidity in the community has very little chances to be treated. Also, factors related to non adherence to antihypertensive medications in SSA. Access to care and medications shall be discussed as this appear in several studies as being a major barrier to hypertension control. It is important to raise accessibility when discussing adherence in SSA References Introduction, Page 4, line 22, 23: Sub- Saharan African (SSA) countries have the highest (30%) prevalence of hypertension in the world (5). The statement is valid but Reference 5 does not compare prevalence of hypertension across different regions of the world, this citation is not appropriate. Please cite a different paper

REVIEWER	Chen, Lingxiao The University of Sydney Institute of Bone and Joint Research
REVIEW RETURNED	29-May-2021

GENERAL COMMENTS	It is a well-done study. I only have two minor concerns. 1. For the search strategy section, the authors should update the search. 2. For the eligibility criteria section, the term sub-Saharan should be clarified. I suggest the authors list names of all countries so that readers could understand the term easily.

VERSION 1 – AUTHOR RESPONSE

Response to reviewers:
Reviewer: 1

I commend the authors on taking on this important topic, adequate control of hypertension is critical to prevent cardiovascular events. Premature cardiovascular mortality could reach 25 to 50% of all-cause mortality in low and middle income countries by 2025, if the prevalence of risk factors continues to rise, with hypertension and diabetes being major risk factor.

Our response: We thank the reviewer for taking the time to review this manuscript and to highlight the importance of this topic.

Major comments:
Major studies were excluded from the systematic review, without explanations (PURE study, MAY Measurement study …), those studies have a higher level of confidence, with better methodologies than studies included in the systematic review. Authors didn't explain exclusion criteria.
Independently of the work of the authors, poor quality of studies included in the systematic review could be detrimental to the results and conclusion of the review. Furthermore, knowing lack of data in sub-Saharan Africa, authors should present general results and may be analysis by comorbidity, region, …. should be limited, and they should discuss results with more caution.
Our response: The target population of this study were people on treatment for hypertension and continue to have uncontrolled hypertension (BP>140/90). Hence, we excluded those who were not on treatment or were not aware of their condition as this was not the focus of this paper. The exclusion criteria are under the eligibility criteria on page 5-6.

In introduction, Authors didn't enough explain why they performed this analysis, because they present results in the introduction, where they tell that uncontrolled BP is already known in SSA and is "reported a (93%) high prevalence of uncontrolled hypertension".
Our response: Thank you for this comment. In the introduction, we provide the current state of hypertension control to be low in SSA and its association with comorbidities. The aim (page 5) of this review was to estimate the burden of uncontrolled hypertension among patients with comorbidities in SSA.

Methodology: Antihypertensive treatment is not included in the description of the studies included in the systematic review, then how explain the uncontrolled HTA (due to lack of access to treatment, lack of prescription …), there are probably a large heterogeneity between population of studies.
Our response: Thank you for this comment. Our inclusion criteria is (under the eligibility criteria section - see page 5-6) was all people on treatment for hypertension and had a comorbidity of interest.

Results:
- In table 2 and 3, P values from should be explained ,

For example : authors concluded to a difference between prevalence of uncontrolled BP according to size of the study and detail one p value for small size and one for large size, what is the p value of the difference of prevalence. This comment is appropriate to all criteria associated to uncontrolled BP by the authors.
Our response: In this section we only highlight the differences noted and we have also provided the confidence intervals that show whether the differences are significant or not. Please note that since the review has been updated, the difference for study size is reduced.

- Fig 2 and 4
- - Please explained the dispersion of points because it is probably unclear for the readers of BMJ OPEN
- could be moved as supplemental figures,

Response: Thank you and these comment we have chosen to keep the figures in the main document.

Discussion: In the discussion, Authors tell that this is the first systematic review but they cited ATAKLTE F (2015) who published a systematic review in the same field.
Our response: Thank you for this comment. Our review is different from Ataklte's review as we looked at uncontrolled hypertension among people with comorbidities whereas the later didn't do that. Ataklte's systematic review focussed on providing the pooled prevalence of hypertension, awareness,

treatment and control in general.

Minor comments
P 4 line 44-47 : unclear sentence
P7 line 55 “proportionmean”
P15 line 45 “coormodities”
Our response: These have been addressed.

Reviewer: 2
One wonders if cohort studies were not available for selection as they could provide good evidence under study.
Community studies could also provide better evidence if available for selection
Our response: Thank you for your comment. Our inclusion criteria for studies to be included were all study designs that included people on treatment and have comorbidities except for case studies, commentaries, editorials, letters, qualitative studies, and systematic reviews.

Reviewer: 3
Title:
Could be Prevalence of uncontrolled hypertension in people with "treated" comorbidities in sub-Saharan Africa: a systematic review
Se method section
Our response: Thank you very much for the suggestion by we feel our title conveys our aim. We did not assess whether the study participants were on treatment for their comorbidities rather our main inclusion criteria was that they were on treatment for hypertension and that they are not controlled while on treatment.

Introduction
Page 4, line 26, In the lastest systematic...How this will this read in 20 years? Authors are advised to just say "In a systematic (not the latest)", and correct this kind of sentences in the writing style.
Our response: This is noted and has been addressed.

Strength and limitation section: See comments on discussion section
Our response: Noted and addressed below.

Method section
Definition of terms and especially the outcome of interest.
1. How did authors defined "uncontrolled hypertension? Was there a variation in the definition regarding medications used? If defined as "systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg in patients taking anti-hypertensive treatment", then the method section would be understandable.

However, if define as Is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg irrespective of treatment, then one would expect many studies to be included. Although my understanding is that the first definition applies, a clarification of this aspect is necessary. If the definition of Uncontrolled HTN is as all cases of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg irrespective of treatment, then authors might consider limiting the study to a hospital setting and that would solve this misunderstanding.
Our response: Thank you for this comment. The outcome of interest (Uncontrolled hypertension) was defined as "systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg in patients taking anti-hypertensive treatment".

2. Page 5, Search strategy, line 12-13. Eligibility criteria: The sentence "studies that included hypertension prevalence but did not report on the prevalence of hypertension among those on antihypertensive medication" is unclear. A patient on antihypertensive medication is consider as hypertensive. Please clarify. Also, So what was the rationale of excluding these patients? A number of studies on hypertension in people with diabetes/HIV are left out, and I guest it related to this exclusion criteria.
Our response: Please see our inclusion criteria (under the eligibility criteria section - see page 5-6). The main inclusion criteria was that the patient needed to be on treatment for hypertension and have one of the comorbidities of interest.

Discussion
Strengths and limitation section:
Page 17,
Line 27, 28: "Two independent reviewers were used in data extraction and the assessment of the risk of bias". This is a common methodological requirement for systematic reviews (PRISMA), I do not foresee this as a particular strength following a usual requirement. Authors should remove this.
Response: Noted and removed.

Line 41, 42: It is good to say precisely the number or proportion of hospital based studies that used non-random sampling procedures.
Response: This is noted and revised (see last paragraph before conclusion).

Line 45: "Therefore, the prevalence of UHTN in these populations needs to be confirmed by further". This sentence is irrelevant in this section, authors may want to indicate that population studies are warranted.
Response: Thank you for this comment. We have revised this sentence to reflect the need for population based studies (see last paragraph before conclusion).

A weakness of this study is that while the authors are focussing on uncontrolled hypertension as inclusion criteria for studies, hypertension is generally uncontrolled, this is particularly true in LMICs and especially Sub Saharan Africa. More than 90% of hypertension is uncontrolled, so even when the term uncontrolled does not appear in the study, hypertension is definitely uncontrolled in that study. Therefore a number of population studies do not appear here because they reported on hypertension without the term uncontrolled and including them but could yield different results. Some examples are:
1. Katte JC, Dzudie A, Sobngwi E, Mbong EN, Fetse GT, Kouam CK, Kengne AP. Coincidence of diabetes mellitus and hypertension in a semi-urban Cameroonian population: a cross-sectional study. BMC Public Health. 2014 Jul 8;14:696. doi: 10.1186/1471-2458-14-696. PMID: 25000848; PMCID: PMC4107975.
2. Mutemwa M, Peer N, de Villiers A, Mukasa B, Matsha TE, Mills EJ, Kengne AP. Prevalence, detection, treatment, and control of hypertension in human immunodeficiency virus (HIV)-infected patients attending HIV clinics in the Western Cape Province, South Africa. Medicine (Baltimore). 2018 Aug;97(35):e12121. doi: 10.1097/MD.0000000000012121. PMID: 30170445; PMCID: PMC6392528.

But again, the definition of uncontrolled HTN needs to be clear here.
Authors are advised to discuss this or to simply indicate in the method section clearly that they limit the scope of their study to a hospital/health falcility setting, which actually makes sense because it is generally in the hospitals that comorbid conditions would be diagnosed and also, a hypertensive patient without comorbidity in the community has very little chances to be treated.
Response: We thank the reviewers for bringing these to our attention. Please note that our inclusion criteria were explicit (under the eligibility criteria section - see page 5-6) hence these studies were not included. I hope this clarifies why many of these studies were not included in the current review.

Also, factors related to non-adherence to antihypertensive medications in SSA. Access to care and medications shall be discussed as this appear in several studies as being a major barrier to hypertension control. It is important to raise accessibility when discussing adherence in SSA
Response: Thank you for this comment. We have added limited accessibility to medications as a barrier to adherence in the discussion section.

References
Introduction,
Page 4, line 22, 23: Sub-
Saharan African (SSA) countries have the highest (30%) prevalence of hypertension in the world (5).
The statement is valid but Reference 5 does not compare prevalence of hypertension across different regions of the world, this citation is not appropriate. Please cite a different paper
Response: This is noted and revised.

Reviewer: 4
Dr. Lingxiao Chen, The University of Sydney Institute of Bone and Joint Research
Comments to the Author:
It is a well-done study. I only have two minor concerns.
1. For the search strategy section, the authors should update the search.
2. For the eligibility criteria section, the term sub-Saharan should be clarified. I suggest the authors list names of all countries so that readers could understand the term easily.
Response: Thank you for your comment. We have now updated the search as of June 2021. In regards to the term sub-Saharan Africa, all countries in SSA were listed in the search – see supplement file S1. [Medline (line 34), Embase (line 33) and Web of Science (line 34)].

VERSION 2 – REVIEW

REVIEWER	Dzudie, Anastase University of the Witwatersrand
REVIEW RETURNED	03-Oct-2021

GENERAL COMMENTS	Unfortunately reference 5 is no longer correct. Please see the most recent paper by NCD-risk group, DOI:https://doi.org/10.1016/S0140-6736(21)01330-1. The paper shows that Africa is one of the region of the world with highest rates of uncontrolled BP. I find this more suitable for your work. Please replace the current ref 5 with this . Kind regards,

VERSION 2 – AUTHOR RESPONSE

Response to reviewers:

Reviewer: 3

Comments to the Author:

Unfortunately reference 5 is no longer correct. Please see the most recent paper by NCD-risk group, DOI:https://doi.org/10.1016/S0140-6736(21)01330-1. The paper shows that Africa is one of the

region of the world with highest rates of uncontrolled BP. I find this more suitable for your work. Please replace the current ref 5 with this.

Our response: We thank the reviewer for taking the time to review the revised manuscript and also for bringing to our attention the most recent article which was published after this manuscript was submitted for review. We have read the suggested article and we have updated the text and reference 5 with the suggested article by Zhou et.al.