PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Epidemiology of depressive disorders in people living with hypertension in Africa: a systematic review and meta-analysis
AUTHORS	Endomba Angong, Francky Teddy; Mazou, Temgoua Ngou; Bigna, Jean Joel

VERSION 1 – REVIEW

REVIEWER	Handan Ankaralı Istanbul Medeniyet University Istanbul – Turkey Biostatistics, Data science, Machine learning, Big Data, Bioinformatics
REVIEW RETURNED	08-Mar-2020

GENERAL COMMENTS	It was planned and analyzed according to the aim. It is also well written. Its contribution level to the literature is good.

REVIEWER	Professor Hania Salah Zayed Rheumatology and Rehabilitation Department Faculty of Medicine Cairo University Egypt
REVIEW RETURNED	27-Mar-2020

GENERAL COMMENTS	Please take the following comments into consideration: Registration number in PROSPERO has not been mentioned. “We searched PubMed, Excerpta Medica Database (EMBASE),…….. with any language restriction.” Comment:……without any language restriction. Discussion: The discussion needs to be revised to avoid repetitions and modify some statements. “..meta-analysis on the prevalence of depression in patients with hypertension and which included 41 studies (most of them from China) found higher rates of depression with a summarized prevalence of 26.9% (95%CI: 21.7% - 32.3%).The same meta-analysis found that 28.5% (95% CI: 22.2% - 35.3%) of Chinese patients with hypertension had depression.”

	Comment: Unclear statement. Was the prevalence of depression 26.9% or 28.5%? “This could be link to patients’ confusion about depression and hypertension symptoms such as poor appetite, fatigue and sleep disturbances.” Comment: This could be linked to…. “Mahmood and colleagues while assessing depression among 411 hypertensive outpatients in a Pakistan hospital by using PHQ-9 with a score of 10 or above as cut-off point found a prevalence of 40.1%” Comment: Please refer to the 4 studies included in your meta-analysis. Did they use different cut-off values to define depression? “However, some characteristics that may further explain heterogeneity were not reported or there was no enough study to conduct..” Comment: ….there were not enough studies … “Second, the various geographic regions and countries were variably represented and some countries were represented” Comment: ……and some countries were not represented. References: Some of the cited journals are written in their full name. Kindly use the journal abbreviation for all references in the reference list. Reference 21: The city where this book has been published and the pages of the chapter have not been mentioned.

REVIEWER	Elizabeth Dean PhD University of British Columbia Canada
REVIEW RETURNED	23-Jun-2020

GENERAL COMMENTS	Review of ‘Epidemiology of depressive disorders in people living with hypertension in Africa: a systematic review and metaanalysis’ (BMJ Open bmjopen-2-2—037975) The investigators argue that improved understanding of the epidemiology of depressive disorders in people with hypertension will augment strategies to address the problem comprehensively. The aim of the study was to estimate the prevalence of depressive disorders and symptoms in people living with hypertension in Africa. They conducted a systematic review and meta-analysis. Based on conventional methods for conducting systematic reviews and meta-analyses, 11 studies were included in the study. Several African countries were included in these studies. Diagnostic tools differed across studies, however the prevalence of depressive disorders was 17.9%; the prevalence of depressive symptoms and major depressive symptoms was 33,3% and 7.8%, respectively. The investigators concluded that ‘Depressive disorders and symptoms are prevalent in people living with hypertension in Africa’ with implications for clinicians, researchers and public health policy makers. Substantive Comments The aim of the study ‘….was to estimate the prevalence of depressive disorders and symptoms in people living with hypertension in Africa’. If this was the aim, I think another type of study would have been designed either as a primary investigation or secondary analysis of existing statistics. Thus, lines 88-89 are very

	important as the sentence alludes to why a review was a first step. I suggest contextualizing the aim so that the design (systematic review and meta-analysis) has justification. Perhaps something like 'Given that continent-wide valid statistics are unavailable, the goal of this study was to explore the prevalence of depressive disorders, depressive symptoms, and major depression in individuals with hypertension concurrently with these mental health conditions.' Having had links to African colleagues and working collaboratively with them over the years, I fully appreciate the challenges of conducting original research such as establishing the prevalence of hypertension and mental ill health across Africa. This systematic review is a starting point for understanding the epidemiology and relationship between mental health and hypertension in African countries. Having said that, I have some recommendations to strengthen its contribution. The aim can be tightened, the methods are established and strong, the results are balanced, and the discussion can be expanded to address some of the broader methodological points I raise below. In addition, to knowing how the levels of mental health were defined and assessed, we do not really know the criteria for the diagnosis of hypertension. This could be a limitation. A section could be added in the discussion related to 'Implications for Conducting Primary Research on Hypertension and Mental Health in Africa'. Reference could be made as to the need for registries across the continent (not unlike other health statistics) so that secondary analyses can be conducted. I appreciate the variability of sophistication across the African countries when it comes to data collection and record keeping, but it is always beneficial to keep reinforcing the need, rather than been reconciled to the challenges of doing so. I encourage the investigators in their work. When Africa does well, we all do well. Regarding mental health assessment, the tools reported in the 11 source articles come from English speaking western countries. No mention is made of their appropriateness and how they were administered (In English? Translated? Verbally by interview or written? What about individuals who may have been illiterate?). These queries are not a criticism of the work, but how we need to ensure the tools we use in contexts where the tools were not developed or validated in, need to be studied and perhaps modified to the cultural context. This in fact could be distinct in the regions or countries of Africa. Much work needs to be done. The conclusion would better read 'Depressive disorders and symptoms appear prevalent in people living with hypertension in select African countries. Including an assessment of mental health in patients with hypertension seems prudent, with the potential for intervention. Future studies are needed to establish the true prevalence for African countries, which may differ across them.' Editorial Comments The Ms. would benefit from being copy edited. There is variability in the quality of the English scientific writing throughout. I have great respect for my international colleagues whose first language may not be English and write for scientific journals in English. I can hardly write a shopping list in another language. I appreciate they have worked hard to get the English to the highest level possible. Copy editing would take it to a higher level yet.

	You will need to check the journal’s policies regarding person first language (i.e., people with hypertension vs. hypertensive patients; and reference to the individuals as ‘patients’. The term patients is now used more selectively. The source studies used the term ‘patients’ so probably best to stay with this. Examples of edits needed: Line 60. ‘continent’ rather than ‘region’ Line 61 Replace with ‘The deleterious effects of hypertension’ Line 63. What are ‘invalidating’ complications exactly? Word choice issue. Line 70. Replace with ‘on the African continent..’ Line 73. Replace with ‘have been interested in the interaction…’ Line 75. Delete ‘to the fact’ Line 77. Replace ‘inversely’ with ‘conversely’ Line 85. Replace with ‘…one hypertensive patient in tent has…’ Line 87. Replace sentence with ‘In western contexts, depression in hypertensive patients is common.’ These are just examples above, to show the careful line by line copyediting that is required. The refencing format and style needs to be tidied up. A host of errors.

REVIEWER	Hae-Young Kim NYMC, USA
REVIEW RETURNED	07-Jul-2020

GENERAL COMMENTS	The authors conducted a systematic review and meta-analysis to determine the prevalence of depressive disorders/symptoms in people living with hypertension in Africa. * Comments 1) The main concern is the number of studies used. Only 5 studies were used for the depressive disorders, 6 data from 5 studies were used for the depressive symptoms, and only 2 studies were used for the major depressive symptoms. What are the differences in these outcomes? This was not clearly stated. Without sufficient numbers of studies, there will have a problem estimating the between-studies variance, which has important implications for many aspects of the analysis. 2) In order to know the prevalence of different category, the prevalence and heterogeneity by subgroup (gender, study type, setting, etc.) are needed to be reported. This study did not report any subgroup analysis results. 3) The author stated that they included 3 types of studies (cross-sectional, case-control, and cohort studies), but the study type for each study was not reported in the Table 1. 4) More specific information is needed for the inclusion criteria. For example, the author did not state whether only adults were also included or not. 5) The author stated that 8 of 11 studies used the probabilistic sampling and 3 of 11 studies used non-probabilistic sampling.

	However, based on the Supp Table 2, only 3 used the probabilistic sampling and other 8 studies used the non-probabilistic sampling (such as Convenience, etc.). This can be also the limitation, since it would be difficult to generalize the results to the population as a whole and it can have the biased results using this type of sampling method. 6) Please clarify why two different results for Ademola 2019 were added in "B. Depressive symptoms" in Supplementary Figure 1.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Handan Ankaralı
Institution and Country: Istanbul Medeniyet University, Istanbul - Turkey
Please state any competing interests or state 'None declared': Biostatistics, Data science, Machine learning, Big Data, Bioinformatics

It was planned and analyzed according to the aim. It is also well written. Its contribution level to the literature is good.

Authors: We thank the reviewer for this comment.

Reviewer: 2
Reviewer Name: Professor Hania Salah Zayed
Institution and Country: Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University, Egypt
Please state any competing interests or state 'None declared': None declared

Please take the following comments into consideration:

1) **Registration number in PROSPERO has not been mentioned.**
Authors: The PROSPERO registration number has been now provided: CRD42020168979

2) "We searched PubMed, Excerpta Medica Database (EMBASE),…….. with any language restriction."
Comment:……without any language restriction.
Authors: Thanks for the comment. We corrected it.

3) Discussion:
The discussion needs to be revised to avoid repetitions and modify some statements.

"..meta-analysis on the prevalence of depression in patients with hypertension and which included 41 studies (most of them from China) found higher rates of depression with a summarized prevalence of 26.9% (95%CI: 21.7% - 32.3%).The same meta-analysis found that 28.5% (95% CI: 22.2% - 35.3%) of Chinese patients with hypertension had depression."
Comment: Unclear statement. Was the prevalence of depression 26.9% or 28.5%?

Authors: Thanks for the comment. As noticed in our discussion, the cited meta-analysis included many countries but most of studies originated from China. The overall prevalence was 26.9% but

while taking specifically studies on Chinese settings, the prevalence was 28.5%. We have revised this sentence to present only the overall prevalence from this meta-analysis.

4) **“This could be link to patients’ confusion about depression and hypertension symptoms such as poor appetite, fatigue and sleep disturbances.”**
Comment: This could be linked to….

Authors: Thanks for the comment. We have corrected as suggested.

5) **“Mahmood and colleagues while assessing depression among 411 hypertensive outpatients in a Pakistan hospital by using PHQ-9 with a score of 10 or above as cut-off point found a prevalence of 40.1%”**
Comment: Please refer to the 4 studies included in your meta-analysis. Did they use different cut-off values to define depression?

Authors: The 4 studies that used the PHQ-9 in our review used different cut-off and also studied diverse degrees of depression. Some of these studies focused on severe depression (the one of Hamer and colleagues) with of cut-off set at 15, while others considered also mild (more than 5 and above) or moderate depression.

6) **“However, some characteristics that may further explain heterogeneity were not reported or there was no enough study to conduct..”**
Comment: ….there were not enough studies …

Authors: Thanks for the comment. We have corrected as suggested.

7) **“Second, the various geographic regions and countries were variably represented and some countries were represented”**
Comment: ……and some countries were not represented.

Authors: Thanks for the comment. We have corrected as suggested.

8) **References:**
Some of the cited journals are written in their full name. Kindly use the journal abbreviation for all references in the reference list.
Reference 21: The city where this book has been published and the pages of the chapter have not been mentioned.

Authors: Thanks for the comment. We have corrected as suggested.

Reviewer: 3
Reviewer Name: Elizabeth Dean PhD
Institution and Country: University of British Columbia, Canada
Please state any competing interests or state ‘None declared’: None declared.

The investigators argue that improved understanding of the epidemiology of depressive disorders in people with hypertension will augment strategies to address the problem comprehensively. The aim of the study was to estimate the prevalence of depressive disorders and symptoms in people living with hypertension in Africa. They conducted a systematic review and meta-analysis. Based on

conventional methods for conducting systematic reviews and meta-analyses, 11 studies were included in the study. Several African countries were included in these studies. Diagnostic tools differed across studies, however the prevalence of depressive disorders was 17.9%; the prevalence of depressive symptoms and major depressive symptoms was 33,3% and 7.8%, respectively. The investigators concluded that 'Depressive disorders and symptoms are prevalent in people living with hypertension in Africa' with implications for clinicians, researchers and public health policy makers.

Substantive Comments

1) **The aim of the study '….was to estimate the prevalence of depressive disorders and symptoms in people living with hypertension in Africa'. If this was the aim, I think another type of study would have been designed either as a primary investigation or secondary analysis of existing statistics. Thus, lines 88-89 are very important as the sentence alludes to why a review was a first step. I suggest contextualizing the aim so that the design (systematic review and meta-analysis) has justification. Perhaps something like 'Given that continent-wide valid statistics are unavailable, the goal of this study was to explore the prevalence of depressive disorders, depressive symptoms, and major depression in individuals with hypertension concurrently with these mental health conditions.'**

Authors: Thanks for this valuable comment. We have revised as suggested.

2) **Having had links to African colleagues and working collaboratively with them over the years, I fully appreciate the challenges of conducting original research such as establishing the prevalence of hypertension and mental ill health across Africa. This systematic review is a starting point for understanding the epidemiology and relationship between mental health and hypertension in African countries. Having said that, I have some recommendations to strengthen its contribution. The aim can be tightened, the methods are established and strong, the results are balanced, and the discussion can be expanded to address some of the broader methodological points I raise below.**

Authors: Thanks for the comment. We have considered all your comments and improved all manuscript sections when needed. We highlighted this idea in the Discussion section.

3) **In addition, to knowing how the levels of mental health were defined and assessed, we do not really know the criteria for the diagnosis of hypertension. This could be a limitation. A section could be added in the discussion related to 'Implications for Conducting Primary Research on Hypertension and Mental Health in Africa'. Reference could be made as to the need for registries across the continent (not unlike other health statistics) so that secondary analyses can be conducted. I appreciate the variability of sophistication across the African countries when it comes to data collection and record keeping, but it is always beneficial to keep reinforcing the need, rather than been reconciled to the challenges of doing so. I encourage the investigators in their work. When Africa does well, we all do well.**

Authors: Thanks for the comment. We have added words on the implication you highlighted. We have added references to support this.

4) **Regarding mental health assessment, the tools reported in the 11 source articles come from English speaking western countries. No mention is made of their appropriateness and how they were administered (In English? Translated? Verbally by interview or written? What about individuals who may have been illiterate?). These queries are not a criticism of the work, but how we need to ensure the tools we use in contexts where the tools were not developed or validated in, need to be studied and**

perhaps modified to the cultural context. This in fact could be distinct in the regions or countries of Africa. Much work needs to be done.

Authors: Thanks for this valuable comment. Indeed, in their method sections, some studies indicated that they worked with a native/local speaker (depending on the study setting) or used back translations (the study of Bhana and colleagues, and the one of Umer and colleagues). We add a sentence on this aspect in the Methods section. We have also revised the Table to specify the Language of the administration and who administer the questionnaire (hetero or auto-administration).

5) **The conclusion would better read 'Depressive disorders and symptoms appear prevalent in people living with hypertension in select African countries. Including an assessment of mental health in patients with hypertension seems prudent, with the potential for intervention. Future studies are needed to establish the true prevalence for African countries, which may differ across them.'**

Authors: Thanks for the comment. We have revised as suggested.

Editorial Comments

The Ms. would benefit from being copy edited. There is variability in the quality of the English scientific writing throughout. I have great respect for my international colleagues whose first language may not be English and write for scientific journals in English. I can hardly write a shopping list in another language. I appreciate they have worked hard to get the English to the highest level possible. Copy editing would take it to a higher level yet.

You will need to check the journal's policies regarding person first language (i.e., people with hypertension vs. hypertensive patients; and reference to the individuals as 'patients'. The term patients is now used more selectively. The source studies used the term 'patients' so probably best to stay with this.

Examples of edits needed:
Line 60. 'continent' rather than 'region'
Line 61 Replace with 'The deleterious effects of hypertension'
Line 63. What are 'invalidating' complications exactly? Word choice issue.
Line 70. Replace with 'on the African continent..'
Line 73. Replace with 'have been interested in the interaction…'
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Line 87. Replace sentence with 'In western contexts, depression in hypertensive patients is common.'

These are just examples above, to show the careful line by line copyediting that is required.

The refencing format and style needs to be tidied up. A host of errors.

Authors: Thanks for the comments. The manuscript has been proofread.

Reviewer: 4
Reviewer Name: Hae-Young Kim
Institution and Country: NYMC, USA

Please state any competing interests or state ‘None declared’: None declared

The authors conducted a systematic review and meta-analysis to determine the prevalence of depressive disorders/symptoms in people living with hypertension in Africa.

* Comments

1) The main concern is the number of studies used. Only 5 studies were used for the depressive disorders, 6 data from 5 studies were used for the depressive symptoms, and only 2 studies were used for the major depressive symptoms. What are the differences in these outcomes? This was not clearly stated. Without sufficient numbers of studies, there will have a problem estimating the between-studies variance, which has important implications for many aspects of the analysis.

Authors: In this study, depressive symptoms were all manifestations of depressive disorders, especially on the cognitive, affective and behavioural domains. The major symptoms were depressive mood and anhedonia. While selecting our studies, for the diagnosis of clinical depression (depressive disorders) we considered the Diagnostic and Statistical Manual of Mental Health Disorders IV or V, or International Statistical Classification of Diseases and Related Health Problems-10. In studies were depressive disorders were not defined using the aforementioned criteria, we considered the definition used by authors, including especially diagnostic scores such as the Patient Health Questionnaire-9. Indeed, the small number of studies and the variability of outcomes and used tools, are limitations of our analysis. Sentences have been added in the Methods section to clarify.

2) In order to know the prevalence of different category, the prevalence and heterogeneity by subgroup (gender, study type, setting, etc.) are needed to be reported. This study did not report any subgroup analysis results.

Authors: Dear reviewer, all study were cross-sectional. Therefore, it was not possible to perform subgroup analysis according to this characteristic. Although there was limited number of studies to perform subgroup analysis, we have explored analysis by setting and sex. These findings were discussed. Thank you for this valuable suggestion that helped to improve our manuscript.

3) The author stated that they included 3 types of studies (cross-sectional, case-control, and cohort studies), but the study type for each study was not reported in the Table 1.

Authors: Dear Reviewer, when we have designed the protocol, the aim was to include cross-sectional, case-control, and cohort studies where it will be possible to extract prevalence data. However, of the 11 included studies, all were cross-sectional as we have already mentioned in the Methods section. We have not mentioned this information in the Table 1 to avoid having a large (more than one page) Table 1. In the revised version of the manuscript, we have added this information.

4) More specific information is needed for the inclusion criteria. For example, the author did not state whether only adults were also included or not.

Authors: Thanks for the comment. We included studies among adults.

5) The author stated that 8 of 11 studies used the probabilistic sampling and 3 of 11 studies used non-probabilistic sampling. However, based on the Supp Table 2, only 3 used the probabilistic sampling and other 8 studies used the non-probabilistic sampling (such as Convenience, etc.). This can be also the limitation, since it would be difficult to generalize the results to the population as a whole and it can have the biased results using this type of sampling method.

Authors: Thanks for this comment. We have revised and highlighted this limitation in the Discussion section.

6) Please clarify why two different results for Ademola 2019 were added in “B. Depressive symptoms” in Supplementary Figure 1.

Authors: Concerning this comment, in Figure 1, Ademola and colleagues worked in two different samples for the same publication. One sample of Ghanaians individuals and the other one of Nigerian people; and they sampled differently.

VERSION 2 – REVIEW

REVIEWER	Elizabeth Dean PhD University of British Columbia Canada
REVIEW RETURNED	22-Sep-2020

GENERAL COMMENTS	Review of 'Epidemiology of depressive disorders in people living with hypertension in Africa: a systematic review and metaanalysis' (BMJ Open bmjopen-2-2—037975.R1) The investigators have done a satisfactory job of addressing reviewers' comments and suggested edits. My only remaining concern that warrants being addressed is the directionality of the association of depressive disorders and hypertension. The prevailing directionality is that people with hypertension may have depressive disorders. However, some mention is needed about people with depressive disorders may have a higher prevalence of hypertension. This would suggest that controlling depression may help reduce prevalence of hypertension, as well as potentially vice versa. Minimally, mention of this point needs to be raised in the Discussion. Finally, there is reference to tailored pharmacologic treatment, ostensibly for both conditions. However, there is much evidence supporting non-pharmacologic interventions and lifestyle approaches to improving mental health as well as physical health. The manuscript would benefit from this balanced perspective being reflected in the Discussion. Much of the literature on exploiting lifestyle behavior change is based on western literature. I appreciate what would be effective in African countries with respect to lifestyle change may be distinct, however this warrants mention. Non-pharmacologic approaches need to be consistently prioritized over pharmacologic interventions whenever possible. Established clinical practice guidelines for hypertension include lifestyle modification as the priority across all levels of hypertension and across levels of concurrent conditions.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Reviewer Name: Elizabeth Dean PhD
Institution and Country: University of British Columbia, Canada

Review of 'Epidemiology of depressive disorders in people living with hypertension in Africa: a systematic review and metaanalysis' (BMJ Open bmjopen-2-2—037975.R1)

The investigators have done a satisfactory job of addressing reviewers' comments and suggested

edits.

My only remaining concern that warrants being addressed is the directionality of the association of depressive disorders and hypertension. The prevailing directionality is that people with hypertension may have depressive disorders. However, some mention is needed about people with depressive disorders may have a higher prevalence of hypertension. This would suggest that controlling depression may help reduce prevalence of hypertension, as well as potentially vice versa. Minimally, mention of this point needs to be raised in the Discussion.
Authors: We thank the reviewer for this valuable comment. We have added a sentence to mention the relationship between the risk of hypertension and exposure to depressive disorders. Please read in the Discussion section: *"A meta-analysis of prospective cohort studies suggested that people with depressive disorders had higher risk of hypertension. Therefore, implementing strategies to reduce the burden of depressive disorders could help to reduce the prevalence of hypertension."*

Finally, there is reference to tailored pharmacologic treatment, ostensibly for both conditions. However, there is much evidence supporting non-pharmacologic interventions and lifestyle approaches to improving mental health as well as physical health. The manuscript would benefit from this balanced perspective being reflected in the Discussion. Much of the literature on exploiting lifestyle behavior change is based on western literature. I appreciate what would be effective in African countries with respect to lifestyle change may be distinct, however this warrants mention. Non-pharmacologicapproaches need to be consistently prioritized over pharmacologic interventions whenever possible. Established clinical practice guidelines for hypertension include lifestyle modification as the priority across all levels of hypertension and across levels of concurrent conditions.

Authors: Thank you for this valuable comment. We have added this sentence in the Discussion section: *"Although pharmacological interventions can help to reduce the burden of depressive disorders, cost-effective non-pharmacological interventions should be explored first in a context of resources limited setting like most of countries in Africa."*