## PEER REVIEW HISTORY



## ARTICLE DETAILS

| | |
|---|---|
| **TITLE (PROVISIONAL)** | Non-pharmacological interventions to achieve blood pressure control in African patients: a systematic review |
| **AUTHORS** | Cernota, Monique; Kroeber, Eric; Demeke, Tamiru; Frese, T; Getachew, Sefonias; Kantelhardt, Eva; Ngeh, Etienne; Unverzagt, Susanne |

## VERSION 1 – REVIEW

| | |
|---|---|
| **REVIEWER** | Jones, Janet<br>Southeastern Louisiana University |
| **REVIEW RETURNED** | 15-Mar-2021 |

| | |
|---|---|
| **GENERAL COMMENTS** | The abstract does not contain a description of the study appraisal and synthesis methods.<br>The research question is not stated as such; however the objective is clear.<br>Mention is made that the effect sizes were calculated and in RevMan as a forest plot. I think the review would benefit from inclusion of the forest plot, especially since there is no meta-analysis. The rationale for not conducting a meta-analysis was clear.<br>Limitations were laid out in detail and quite clear.<br>Overall this systematic review was well done and reported in an organized concise manner. |

| | |
|---|---|
| **REVIEWER** | Mizuno, Tomohiro<br>Fujita Health University School of Medicine |
| **REVIEW RETURNED** | 20-Mar-2021 |

| | |
|---|---|
| **GENERAL COMMENTS** | Title: Non-pharmacological interventions to achieve blood pressure control in African patients: a systematic review<br><br>Comments:<br><br>The authors reviewed the studies regarding non-pharmacological interventions to add the evidence for effective blood pressure control. To improve the outcome of patients with hypertension in Africa, The current study is necessary. However, the authors should reconsider the strategy of study.<br><br>The authors mentioned the deviations from the protocol. However, this limitation cannot be ignored. In this systematic review, the authors handled with the studies with interventions from different medical stuff. In addition, some studies conducted pharmacological interventions (e.g. use of diuretics and a beta blocker, authorization to prescribe an expanded range of drugs on |

| | |
|---|---|
| | NCDs). The current methods is not sufficient for supporting the conclusion of the study. Since this review might take wrong information to readers, the authors should reconsider the protocol of this review. |

| | |
|---|---|
| **REVIEWER** | Okpechi, Ikechi G<br>University of Cape Town, Division of Nephrology and Hypertension |
| **REVIEW RETURNED** | 14-Aug-2021 |

| | |
|---|---|
| **GENERAL COMMENTS** | 1. Although a meta-analysis was not conducted, it is possible to still identify which interventions were associated with greater BP reductions from the studies.<br><br>2. I will suggest that since the authors didn't report NYHA, hospitalizations, and mortality as outcomes, these should be removed from outcomes assessed and limit the study outcome to BP.<br><br>3. There are discrepancies with labelling of Tables and Figures. For instance, there are two Table 1 labelled and Figures 3 and 4 were not provided, even though these were referenced in text. This made reading and following the paper very difficult.<br><br>4. Please include a full search strategy used for identifying studies in the different databases - even if as a supplementary Table.<br><br>5. Please include the non-pharmacological interventions sought for in the methods section on "Interventions".<br><br>6. The number of articles screened in Figure 1 don't add up: 5079 - 4742 = 337. Please clarify<br><br>7. You used a different referencing format in the results section (page 12 lines 43 – 47 and so on):<br>"Nearly all studies stated improved medication adherence (Adeyemo 2013, Bobrow 2016, Bolarinwa 2019, Labhardt 2011, Saunders 1991, Stewart 2005), implementation of lifestyle recommendations (Ayodapo 2019, Mendis 2010), linkage to care (Labhardt 2011, Mendis 2010, Vedanthan 2019)"<br>I think you should follow the same referencing format throughout the paper. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Janet Jones, Southeastern Louisiana University Comments to the Author:

The abstract does not contain a description of the study appraisal and synthesis methods.
Answer of the authors:
Thank you for the comment. We made a small change in the Design part. The synthesis method is now described as narrative synthesis in the abstract. The narrative synthesis was planned in the protocol to give a comprehensive overview on this area of research. In the main manuscript the narrative synthesis is supported by Forest Plots to visualize the treatment effects on hypertension. Due to the heterogeneity of the studies, we refrained from doing a meta-analysis.

In the abstract's results section, we added two sentences describing study quality based on the results of our Cochrane risk of bias tool study quality assessment.

In the abstract:
We assessed the study quality using the Cochrane risk of bias tool and narratively synthesized studies on non-pharmacological hypertension interventions.

Due to the type of interventions studied, risk of bias in domain blinding of staff/ participants was frequent (83%). Though incomplete outcome data in 61% of the studies is critical, the general study quality was reasonable.

The research question is not stated as such; however the objective is clear.
Answer of the authors:
We agree, we did not state the phrase research question. We rather used the term main aim of the study.

In the manuscript it is stated at the end of the introduction:
The main aim of this systematic review is to summarize the best available evidence on the effectiveness of non-pharmacological strategies on blood pressure control in African patients with hypertension.

In the abstract it is summarized as follows:
Objectives: This systematic review aims to evaluate the evidence of non-pharmacological strategies to improve blood pressure (BP) control in hypertensive patients from African countries.

Mention is made that the effect sizes were calculated and in RevMan as a forest plot. I think the review would benefit from inclusion of the forest plot, especially since there is no meta-analysis. The rationale for not conducting a meta-analysis was clear.

Answer of the authors:

Thank you for the comment. We indeed calculated effect sizes and depicted them in a forest plot using RevMan. We agree that these forest plots (figure 3 and figure 4) shall be included in the paper. For reasons we were not able to trace back, these two figures appeared in the proofread but disappeared from the original submission files. The manuscript contained information on where to insert these figures. The figures are now uploaded accordingly.

Figure 3: Treatment effects on blood pressure of educational strategies to improve adherence

Figure 4: Treatment effects on blood pressure of individualized treatment strategies

Limitations were laid out in detail and quite clear.
Overall this systematic review was well done and reported in an organized concise manner.

Reviewer: 2
Dr. Tomohiro Mizuno, Fujita Health University School of Medicine Comments to the Author:
Title: Non-pharmacological interventions to achieve blood pressure control in African patients: a systematic review

Comments:

The authors reviewed the studies regarding non-pharmacological interventions to add the evidence for effective blood pressure control. To improve the outcome of patients with hypertension in Africa, The current study is necessary. However, the authors should reconsider the strategy of study.

The authors mentioned the deviations from the protocol. However, this limitation cannot be ignored.

Answer of the authors:
We completely agree with you. This systematic review is the first of four reviews to summarize evidence from randomized controlled trials on non-communicable diseases and we have learnt a lot and improved the protocols for the next systematic reviews with narrower indications (diabetes, stroke and chronic obstructive pulmonary diseases).
For this review, we basicaly planned to give a comprehensive summary of all RCTs to prevent, diagnose, and treat patients with cardiovascular diseases in African countries. Due to the unexpected high number and heterogeneity of eligible studies in the first systematic search, we decided to focus on studies on patients with hypertension. Due to the recently published systematic review by Seeley et al. 2020 (Seeley A, Prynn J, Perera R, Street R, Davis D, Etyang AO. Pharmacotherapy for hypertension in Sub-Saharan Africa: a systematic review and network meta-analysis. BMC Medicine. 2020;18:1-11) this publication concentrates on non-pharmacological strategies. To increase traceability of the deviations from the protocol, we changed figure 1 and added a list of all excluded studies due to changes in the protocol in the appendix. We reported and explained all deviations from the protocol in detail under strengths and limitations of this study and in the discussion.
On the other hand, this systematic review gives a comprehensive overview on non-pharmacological interventions for hypertension in African countries and adds important effective and affordable interventions to improve treatment, adherence and outcome of patients with hypertension in African countries.

2. In this systematic review, the authors handled with the studies with interventions from different medical stuff. In addition, some studies conducted pharmacological interventions (e.g. use of diuretics and a beta blocker, authorization to prescribe an expanded range of drugs on NCDs).

Answer of the authors:
Thank you for the comment. In this regard we argue that the inclusion of the mentioned studies may remain. We included studies that studied interventions that are carried out by different medical professional groups (e.g. physicians, nurses) as providers of non-pharmacological treatment strategies. We suppose the comment that we included studies that included studies on pharmacological interventions (use of diuretics and a beta blocker) relates to the randomized controlled trial by Adeyemo, 2013. This trial assessed treatment adherence to the same pharmacological intervention in intervention and control group.
The trial was designed to evaluate the effect of a nurse-led intervention and home visits compared with nurse-led intervention alone. Therefore, we judged the intervention as non-pharmacological and included it in the review. Furthermore, we judged expansion of authorization of drug prescription to non-physician staff as a non-pharmacological intervention. The difference in the treatment does not primarily on the pharmacological side but rather the shift of responsibilities for the same medication, thus being non-pharmacological.

The current methods is not sufficient for supporting the conclusion of the study. Since this review might take wrong information to readers, the authors should reconsider the protocol of this review.

Answer of the authors:
Thank you for the comment. We critically reexamined the conclusions drawn in the abstract as well as the main text. We generally stand by the conclusions drawn in abstract and main text but made small changes. Main aim of our systematic review is to give a comprehensive overview on the evidence from randomized controlled trials to improve prevention, diagnosis and treatment in patients with hypertension to guide recommendations in African countries.
Our conclusion contains a description of the available evidence with their limitations. We conclude that the studies included in the review offer diverse approaches to support hypertensive patients as tested in African settings. As can be seen in figures 3 and 4, several studies show promising results. Especially the interventions using physical activities show clinically relevant blood pressure reduction. Educational interventions show mixed, oftentimes non-significant, result. Nevertheless, these are valuable to inform future research as well as local African guidelines since they draw on trials performed in settings that may be more comparable to other African settings than for example European/ American studies. Our summary does support but does not free the reader from critically assessing individual interventions and the related results.

From the abstract:
Conclusions: The identified studies offer diverse low-cost interventions including educative and task shifting strategies, individualized treatment, and lifestyle modifications to improve BP control. Especially trialed physical activity interventions show clinically relevant BP changes. All strategies were trialed in African countries and may be used for recommendations in evidence-based guidelines on hypertension in African settings.

From the main text:
Conclusion
This systematic review shows that even though hypertension is a critical health problem, there are still few randomized studies on non-pharmacological treatment of hypertension conducted on the African continent. Available studies do not represent all Africans since they were conducted in only six countries, many in urban settings only. It is advisable to plan and implement studies on patients with hypertension and health-care professionals in rural areas as well as Northern and Central African countries.
An improvement in the prognosis of patients with high BP in Africa requires the implementation of practical and effective solutions to diagnose, treat and control hypertension in specific settings (9). The identified studies describe diverse approaches tested in African countries that may be used to generate local African evidence-based guidelines on hypertension treatment. Especially trialed physical activity interventions and individualized treatment strategies show clinically relevant BP changes. Educational strategies for patients and medical personnel show mixed results and offer a comprehensive insight into trialed approaches as well as a basis for future research opportunities. This review summarizes miscellaneous low-cost interventions including task shifting, education, individualized treatment and lifestyle modifications to improve BP control.

Reviewer: 3
Dr. Ikechi G Okpechi, University of Cape Town Comments to the Author:

1. Although a meta-analysis was not conducted, it is possible to still identify which interventions were associated with greater BP reductions from the studies.

Answer of the authors:
Thank you for the comment. We did not perform a meta-analysis. Nevertheless, we indeed calculated effect sizes and depicted them in a forest plot using RevMan (figures 3 and 4). For reasons we were not able to trace back, these two figures disappeared from the original submission while the

manuscript contained information on where to insert these figures. The figures are now uploaded accordingly.

Figure 3: Treatment effects on blood pressure of educational strategies to improve adherence

Figure 4: Treatment effects on blood pressure of individualized treatment strategies

2. I will suggest that since the authors didn't report NYHA, hospitalizations, and mortality as outcomes, these should be removed from outcomes assessed and limit the study outcome to BP.

Answer of the authors:
We changed the abstract, the methods section and table 1 and deleted NYHA, hospitalizations, mortality and costs as outcomes. The change of pre-planned outcomes (mortality, NYHA, and hospital admission) is explained under Strength and limitations of the review.

3. There are discrepancies with labelling of Tables and Figures. For instance, there are two Table 1 labelled and Figures 3 and 4 were not provided, even though these were referenced in text. This made reading and following the paper very difficult.

Answer of the authors:
We are very sorry for the inconvenience. For reasons we were not able to trace back, these two figures disappeared from the original submission while the manuscript contained information on where to insert these figures. The figures are now uploaded accordingly.

Figure 3: Treatment effects on blood pressure of educational strategies to improve adherence
Figure 4: Treatment effects on blood pressure of individualized treatment strategies

We prepared three different tables, labelled accordingly. Table 2: Study characteristics was wrongly labelled Table 1. Again, we are sorry for the inconvenience.

Table 1: Inclusion and exclusion criteria
Table 2: Study characteristics
Table 3: Risk of bias assessment

4. Please include a full search strategy used for identifying studies in the different databases - even if as a supplementary Table.

Answer of the authors:
We've included a full search strategy detailing searches in databases: Medline (Ovid) (cardiovascular diseases (CVD) and hypertension update); CENTRAL (CVDs and hypertension update); CINAHL (hypertension); International Clinical Trials Registry Platform (hypertension). The document is uploaded as a supplementary PDF file and is consistent with the search strategy description in the methods section of the manuscript:

Two electronic databases (Medline Ovid, Central) and registers of ongoing and completed studies (International Clinical Trials Registry Platform) were searched to identify all relevant studies (see Additional file 1). We added a search in CINAHL to cover nursing interventions. The main keywords of the search strategy included hypertension, high blood pressure, blood pressure control, Africa, a list of all African countries, and randomized controlled trials. The first searches in 2017 included all CVDs,

while updated strategies were limited to hypertension. The last search was conducted in June 2020. All searches were done without time frame constrictions.

5. Please include the non-pharmacological interventions sought for in the methods section on "Interventions".

Answer of the authors:
Thank you for the comment. We've added a sentence describing non-pharmacological interventions, as suggested.

In the manuscript:
Non-pharmacological interventions are considered non-medication treatment strategies such as educational programs for patients or health professionals, individualized treatment, physical activity or nutrition modification strategies (18).

6. The number of articles screened in Figure 1 don't add up: 5079 - 4742 = 337. Please clarify

Answer of the authors:
Thank you very much. We apologize for the mistake. We screened a total of 5079 and checked 340 potentially relevant full-text articles. This means, we excluded a total of 4739 records as a result of the title and abstract screening. We corrected figure 1.

7. You used a different referencing format in the results section (page 12 lines 43 – 47 and so on):
"Nearly all studies stated improved medication adherence (Adeyemo 2013, Bobrow 2016, Bolarinwa 2019, Labhardt 2011, Saunders 1991, Stewart 2005), implementation of lifestyle recommendations (Ayodapo 2019, Mendis 2010), linkage to care (Labhardt 2011, Mendis 2010, Vedanthan 2019)"
I think you should follow the same referencing format throughout the paper.

Answer of the authors:
Thank you for the comment. We agree with the reviewer We've checked the results and discussion sections for referencing consistency using the following rules:

When speaking about results from the included studies, we reference in the usual numerical system. E.g., (66) will be the 66th reference at the bottom of the manuscript.

In order to connect the text to table two and make it more readable we've added a second referencing point. It consists of the studies' first author and the publishing year. E.g., (Wahab 2017) can be found table 2 under the same name.

Both references will appear like this: e.g., (Wahab 2017) (66)

In order to keep readability, we use both references if one sentences references one or two studies only. We solely use the numerical reference if a sentence references three or more studies.

To link table 2 to the full references, the numerical reference is now added to the short name within tables 2 and 3.