PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The highly neglected burden of resistant hypertension in Africa: a systematic review and meta-analysis
AUTHORS	Nansseu, Jobert Richie; Noubiap, Jean Jacques; Mengnjo, Michel; Aminde, Leopold; Essouma, Mickael; Jingi, Ahmadou; Bigna, Jean Joel

VERSION 1 - REVIEW

REVIEWER	Giuseppe Biondi-Zoccai Sapienza University of Rome, Italy I have consulted/lectured for several companies manufacturing anti-hypertensive agents or devices.
REVIEW RETURNED	22-Feb-2016

GENERAL COMMENTS	This review is an interesting effort, despite the few retrieved studies. I have the following recommendations: 1. Throughout: The article might benefit from some language polishing. 2. Methods: PRISMA are reporting guidelines, and they don't explicitly guide the conduct of a review. 3. It would benefit reporting that at least 1 African registry of studies was searched as well, at least to prove that you maintained an African focus as well. 4. Methods: Pooling cannot be performed using standard statistical approaches for observational studies (eg Fisher exact test). I recommend to pool risk estimates with the metaprop package in R, providing point estimates and 95% confidence intervals (from both random and fixed effect models). Inconsistency/heterogeneity analysis is also needed, as is providing a forest plot and a funnel plot. Even if you included only three studies, you need to follow good practice rules.

REVIEWER	Jeff Bakal University of Alberta, Canada
REVIEW RETURNED	02-Mar-2016

GENERAL COMMENTS	Overall this seems to be a well presented, honest review of the available studies. I would ask that the authors be clear on their use of +/- as SD at least at least at first presentation. I think that the readers would be better served with confidence intervals on these. Many of the results on page 10/11 could be tabled, and should include counts along with percentages.

REVIEWER	Paul Ronksley University of Calgary, Alberta, Canada
REVIEW RETURNED	14-Mar-2016

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. The purpose of this systematic review was to determine the prevalence of resistant hypertension in Africa and to identify patient-level risk factors that are associated with this outcome. The authors identified 3 studies that report on the prevalence of resistant hypertension in Africa, with each study using a different definition to define the condition of interest. Overall they conclude that the prevalence may be in keeping with estimates observed in European and America countries but additional research is required to truly inform this area. This is a very interesting topic, however, I do have concerns around the methodology used to report the overall prevalence estimate as well as some concerns with the overall reporting/interpretation of the findings. The majority of my comments focus on methodological considerations and ways of improving the overall clarity of the paper. 1. The author may consider highlighting that to the best of their knowledge, this is the first and only systematic review that has focused on resistant hypertension in Africa. While this is mentioned near the end of the discussion, it may be nice to put this in the introduction to bolster its importance. 2. Did the authors follow a pre-specified study protocol? Though there are statements within the manuscript that suggest a pre-conceived screening guide and collection form were used throughout the review, the PRISMA checklist suggests otherwise. Please clarify. 3. The search strategy performed was not as “comprehensive” as it could have been. While the authors address this as a limitation in the abstract and discussion, I would argue that this is a modifiable limitation that could easily be addressed by including other relevant and important databases (e.g. EMBASE). I would encourage the authors to include this database in a revised search strategy. 4. The authors may consider including additional terms within their PubMed/Medline search related to the theme of “prevalence” or “risk factors”. 5. Additional detail is required to understand the Google Scholar search, especially if researchers want to replicate research findings. How were these terms combined and how did you systematically search the web results obtained? A simple search on Google scholar using the 3 terms listed yields thousands of citations. Did you scroll through each internet page to review these? 6. Did the authors consider calculating a measure of agreement (kappa statistic) between reviewers during the initial screening and full-text phases of the review? 7. Additional detail is required for the study inclusion/exclusion criteria within the search strategy. A modified PICOD statement for systematic reviews of observational studies would be appropriate. For example, the study (P)opulation of interest was adults (defined as). The (O)utcome of interest was resistant hypertension (defined as). The study (D)esigns of interest included observational studies

	(cross-sectional, prospective/retrospective cohort studies, case-control studies, etc). 8. The use of the Newcastle-Ottawa scale to assess quality of observational studies is appropriate. However, the use of a scoring method is not as informative to readers as a component-based approach when describing quality. For example, a moderate score (4-6) based on the proposed categorization doesn't tell the reader where potential biases may lie in these individual studies. I would suggest including the individual quality components within Table 2 and having a check mark or label (Y/N) next to each. You could always keep the scoring method as a column within this table if the authors prefer. 9. Within the data analysis paragraph, please include a statement about the reporting of proportions, as this is the primary outcome measure of interest. 10. The authors state that meta-analysis was inappropriate based on different thresholds used to define RH, yet they report an overall prevalence of the condition (10.7%). If this is based on the Fisher Exact test, this method is incorrect in my opinion. If the authors feel the need to present an overall or "pooled" prevalence for Africa – then appropriate random effects models that are weighted by within study and between study error is required. Based on a quick calculation, this would result in a 10.3 (95% CI: 4.2-16.4%) pooled estimate (see attached document with analysis). It is important to note the much wider confidence intervals that accompany this overall estimate than those proposed from the test currently performed by the authors. This has implications for the interpretation of the study findings given this level of imprecision and the ability to make comparative statements about prevalence to other continents. Given the I squared value obtained from this pooled estimate (suggesting very high heterogeneity) and the fact that operational definitions were different for each study, I would discourage the reporting of an overall estimate but rather a range from the 3 identified studies. 11. I would recommend using the country name (as opposed to a combination of city and country to identify the 3 key papers throughout the manuscript). This consistency will improve the overall clarity of the results and discussion section. 12. With the results section, it might be worthwhile adding additional information about how studies identified risk factors. Though there is mention that no regression analyses were performed, it appears that most findings are based on stratified analysis. I would highlight this basic analysis of risk factor identification as more important limitation than the current limitation statement related to the number of databases searched (as the former is not modifiable and severely limits your ability to identify key patient-level factors associated with the outcome). 13. Please provide more detail in the paragraph related to study quality. Specifically, where were most of the biases identified? (This relates to the comment #8 above) This is helpful for readers to understand the overall quality of the 3 key papers in this area. 14. Given the incorrect analysis performed for the overall prevalence of RH, it may be worth reworking the discussion paragraph around

	prevalence (to be more conservative in your interpretation). I thought the wording used in the conclusion was more appropriate (where you talk about ranges of prevalence) as opposed to a prevalence of 10%. . metan prev lowci highci, random Study | ES [95% Conf. Interval] % Weight 1 | 14.600 12.100 17.500 32.96 2 | 4.900 3.300 7.100 34.08 3 | 11.700 9.200 14.600 32.96 D+L pooled ES | 10.339 4.244 16.434 100.00 Heterogeneity calculated by formula Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 } where variance_i = ((upper limit - lower limit)/(2*z))^2 Heterogeneity chi-squared = 38.25 (d.f. = 2) p = 0.000 I-squared (variation in ES attributable to heterogeneity) = 94.8% Estimate of between-study variance Tau-squared = 27.4407 Test of ES=0 : z= 3.32 p = 0.001

REVIEWER	Adrisn Doroszko Wroclaw Medical Unniversity, Department of Internal Medicine and Hypertension, Poland
REVIEW RETURNED	03-May-2016

GENERAL COMMENTS	This is an interesting manuscript, which reveals a lack of data regarding the burden of RH in Africa. This review is based mostly on the three eligible studies included to the analysis, which is an important limitation of the study. Furthermore the criteria for RH are inconsistent in these papers, which is another limitation for interpretation the statistical data. However, these limitations cannot be solved by the Authors and are already mentioned in the manuscript The appropriate diagnosis of RH needs to eliminate the secondary causes of resistant hypertension e.g. obstructive sleep apnea, atherosclerosis and renal or hormonal disorders, as well as to exclude pseudo-hypertension, inappropriate blood pressure measurement and control as well as the white coat effect. This paper briefly summarizes the data presented in the studies. In my opinion some more data regarding the diagnostics performed in order to exclude the secondary forms of hypertension in particular studies cited in this manuscript (presented in one simple table or diagram) would significantly improve the analyses and allow to draw more balanced and reliable conclusions.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1: Giuseppe Biondi-Zoccai, Sapienza University of Rome, Italy
Reviewer's Comment 1
This review is an interesting effort, despite the few retrieved studies. I have the following

recommendations:
1. Throughout: The article might benefit from some language polishing.
Authors' Response 1
We are most grateful for your appreciation. Following your suggestion, the manuscript has benefited from a thorough language editing.
Reviewer's Comment 2
2. Methods: PRISMA are reporting guidelines, and they don't explicitly guide the conduct of a review.
Authors' Response 2
Thank you for this remark. We reworded the related sentence as one can read on page 6: "We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines as the template for reporting the present review".
Reviewer's Comment 3
3. It would benefit reporting that at least 1 African registry of studies was searched as well, at least to prove that you maintained an African focus as well.
Authors' Response 3
We thank you very much for this suggestion in the respect of which two African registries were screened in the revised literature search, notably Africa Wide Information and Africa Index Medicus.
Reviewer's Comment 4
4. Methods: Pooling cannot be performed using standard statistical approaches for observational studies (eg Fisher exact test). I recommend to pool risk estimates with the metaprop package in R, providing point estimates and 95% confidence intervals (from both random and fixed effect models). Inconsistency/heterogeneity analysis is also needed, as is providing a forest plot and a funnel plot. Even if you included only three studies, you need to follow good practice rules.
Authors' Response 4
Thank you for raising this point. Accordingly, statistical heterogeneity between studies was measured. Besides, we conducted a random effects meta-analysis using Comprehensive Meta-Analysis software, Version 2 (Biosta, Inc. USA). These precisions have been made in the revised manuscript under the "Data analysis and presentation of results" section as it reads on page 9: "Data analysis used the Comprehensive Meta-Analysis software, Version 2 (Biosta, Inc. USA). Data were summarized using ranges, means ± standard deviations (SD), and frequencies (percentages) where appropriate Forest plots were drawn to visualize the combined prevalence of RH and extent of statistical heterogeneity between studies. Statistical heterogeneity was assessed using the $\chi 2$ test on Cochrane's Q statistic, and quantified by calculating the I2 (with values of 25 %, 50 % and 75 % being representative of low, medium and high heterogeneity respectively). When I2 statistic was less than 50% and the p-value for the test of heterogeneity ≥ 0.1, studies were considered homogenous and a fixed effects meta-analysis was used to estimate the overall prevalence; otherwise, a random effects meta-analysis was used".

REVIEWER 2: Jeff Bakal, University of Alberta, Canada
Reviewer's Comment 1
Overall this seems to be a well presented, honest review of the available studies. I would ask that the authors be clear on their use of +/- as SD at least at first presentation. I think that the readers would be better served with confidence intervals on these.
Authors' Response 1
We thank you very much for your appreciation. Besides, your suggestion was taken into consideration in the revised manuscript as it reads on page 9: "Data were summarized using ranges, means ± standard deviations (SD), and frequencies (percentages) where appropriate".
Reviewer's Comment 2
Many of the results on page 10/11 could be tabled, and should include counts along with percentages.
Authors' Response 2

Thank you for these suggestions. Counts were indeed added along with percentages. Moreover, the majority of results on page 10-11 were already figuring in Table 1; precision has been made in the revised manuscript. But some few results like duration of hypertension since diagnosis, signs and symptoms, and complications were available in only one of the studies. Therefore, we found it unsuitable to summarize them in a table.

REVIEWER 3: Paul Ronksley, University of Calgary, Alberta, Canada
Reviewer's Comment 1
Thank you for the opportunity to review this manuscript. The purpose of this systematic review was to determine the prevalence of resistant hypertension in Africa and to identify patient-level risk factors that are associated with this outcome. The authors identified 3 studies that report on the prevalence of resistant hypertension in Africa, with each study using a different definition to define the condition of interest. Overall they conclude that the prevalence may be in keeping with estimates observed in European and America countries but additional research is required to truly inform this area. This is a very interesting topic, however, I do have concerns around the methodology used to report the overall prevalence estimate as well as some concerns with the overall reporting/interpretation of the findings. The majority of my comments focus on methodological considerations and ways of improving the overall clarity of the paper.
Authors' Response 1
We are most grateful for your appreciation. We thank you also for your comments and suggestions which have greatly improved the clarity and quality of our manuscript.
Reviewer's Comment 2
The author may consider highlighting that to the best of their knowledge, this is the first and only systematic review that has focused on resistant hypertension in Africa. While this is mentioned near the end of the discussion, it may be nice to put this in the introduction to bolster its importance.
Authors' Response 2
We thank you for this suggestion which we have taken into account in the revised manuscript as it reads at the end of the introduction section (page 6): "To the best of our knowledge, this is the first and only systematic review that has focused on resistant hypertension in Africa".
Reviewer's Comment 3
Did the authors follow a pre-specified study protocol? Though there are statements within the manuscript that suggest a pre-conceived screening guide and collection form were used throughout the review, the PRISMA checklist suggests otherwise. Please clarify.
Authors' Response 3
We thank you very much for having raised this point. No, we did not follow a pre-specified study protocol. Nonetheless, as stated in the document, before starting reviewing the databases to search for eligible papers, all review authors developed and piloted a screening guide to make sure that the inclusion criteria were adhered to and consistently applied by them all. Also, the authors in charge of data abstraction first developed the abstraction form before independently pulling out the data. Clarifications have been made in the revised manuscript as one can read on page 8: "Although no complete study protocol was written before starting this review, we developed and piloted a screening guide to make sure that the inclusion criteria were adhered to and consistently applied by all review authors". Additionally, it has been indicated in the PRISMA checklist.
Reviewer's Comment 4
The search strategy performed was not as "comprehensive" as it could have been. While the authors address this as a limitation in the abstract and discussion, I would argue that this is a modifiable limitation that could easily be addressed by including other relevant and important databases (e.g. EMBASE). I would encourage the authors to include this database in a revised search strategy.
Authors' Response 4
Thank you for this proposition in the regard of which EMBASE was added in our revised search strategy, as well as two other registries: Africa Wide Information and Africa Index Medicus. By the way, Google Scholar was cancelled from the list.

Reviewer's Comment 5
The authors may consider including additional terms within their PubMed/Medline search related to the theme of "prevalence" or "risk factors".
Authors' Response 5
Many thanks for this suggestion. However, the addition of these terms to our initial search strategy yielded only four propositions on the whole, which were even clearly irrelevant. We preferred thus to remain as much inclusive as possible, maintaining thereby the initial search strategy.
Reviewer's Comment 6
Additional detail is required to understand the Google Scholar search, especially if researchers want to replicate research findings. How were these terms combined and how did you systematically search the web results obtained? A simple search on Google scholar using the 3 terms listed yields thousands of citations. Did you scroll through each internet page to review these?
Authors' Response 6
We thank you very much for raising this issue. We have tried to screen the majority of these pages, and did not find relevant publications. But clearly agreeing with your comment, we preferred to remove Google Scholar from our list of electronic databases searched, considering these difficulties, and considering that it did not help to catch up more potentially eligible papers.
Reviewer's Comment 7
Did the authors consider calculating a measure of agreement (kappa statistic) between reviewers during the initial screening and full-text phases of the review?
Authors' Response 7
We thank you for this remark. In our revisions, we considered calculating the kappa statistic assessing agreement between review authors. Precisions in this respect have been made as it reads on page 10: "Agreement between review authors was high (Kappa = 0.88, $p < 0.001$)".
Reviewer's Comment 8
Additional detail is required for the study inclusion/exclusion criteria within the search strategy. A modified PICOD statement for systematic reviews of observational studies would be appropriate. For example, the study (P)opulation of interest was adults (defined as). The (O)utcome of interest was resistant hypertension (defined as). The study (D)esigns of interest included observational studies (cross-sectional, prospective/retrospective cohort studies, case-control studies, etc).
Authors' Response 8
Thank you for this remark. We have introduced a new section entitled "eligibility criteria" which reads on page 7: "We systematically identified and appraised reports of original peer-reviewed publications conducted among African populations living inside the continent, including hypertensive patients aged 18 years and above, and published from inception to May 19, 2016. They must have reported the incidence, prevalence and/or risk factors for RH. RH must have been clearly defined in the study, as a systolic (and/or diastolic) blood pressure (BP) >140 (90) mmHg while being on at least three antihypertensive drugs at optimal dosages including a diuretic 8 9. Studies with higher cut-offs could be included as well, considering that the definition might have changed over time. Other subsets of uncontrolled hypertension were not considered in this review. The study design of interest included observational studies (cross-sectional, prospective/retrospective cohort studies, or case-control studies). Experimental studies, letters, reviews, commentaries, editorials, case reports or case series were not included. In case of duplicate reports, the most comprehensive and up-to-date version was taken into account".
Reviewer's Comment 9
The use of the Newcastle-Ottawa scale to assess quality of observational studies is appropriate. However, the use of a scoring method is not as informative to readers as a component-based approach when describing quality. For example, a moderate score (4-6) based on the proposed categorization doesn't tell the reader where potential biases may lie in these individual studies. I would suggest including the individual quality components within Table 2 and having a check mark or label (Y/N) next to each. You could always keep the scoring method as a column within this table if the authors prefer.

Authors' Response 9
We thank you very much for having raised this point. Table 2 has been revised, including the individual quality components of the NOS to assess the methodological quality of studies retained for this review.
Reviewer's Comment 10
Within the data analysis paragraph, please include a statement about the reporting of proportions, as this is the primary outcome measure of interest.
Authors' Response 10
We thank you for this suggestion. Indeed, this statement was included in our revised manuscript as it reads on page 9: "Data were summarized using ranges, means ± standard deviations (SD), and frequencies (percentages) where appropriate".
Reviewer's Comment 11
The authors state that meta-analysis was inappropriate based on different thresholds used to define RH, yet they report an overall prevalence of the condition (10.7%). If this is based on the Fisher Exact test, this method is incorrect in my opinion. If the authors feel the need to present an overall or "pooled" prevalence for Africa – then appropriate random effects models that are weighted by within study and between study error is required. Based on a quick calculation, this would result in a 10.3 (95% CI: 4.2-16.4%) pooled estimate (see attached document with analysis). It is important to note the much wider confidence intervals that accompany this overall estimate than those proposed from the test currently performed by the authors. This has implications for the interpretation of the study findings given this level of imprecision and the ability to make comparative statements about prevalence to other continents. Given the I squared value obtained from this pooled estimate (suggesting very high heterogeneity) and the fact that operational definitions were different for each study, I would discourage the reporting of an overall estimate but rather a range from the 3 identified studies.
Authors' Response 11
We thank you very much for having raised this concern. Statistical heterogeneity between studies was measured. Besides, we conducted a random effects meta-analysis using Comprehensive Meta-Analysis software, Version 2 (Biosta, Inc. USA). These precisions have been made in the revised manuscript under the "Data analysis and presentation of results" section as it reads on page 9: "Data analysis used the Comprehensive Meta-Analysis software, Version 2 (Biosta, Inc. USA). Data were summarized using ranges, means ± standard deviations (SD), and frequencies (percentages) where appropriate Forest plots were drawn to visualize the combined prevalence of RH and extent of statistical heterogeneity between studies. Statistical heterogeneity was assessed using the $\chi 2$ test on Cochrane's Q statistic, and quantified by calculating the I2 (with values of 25 %, 50 % and 75 % being representative of low, medium and high heterogeneity respectively). When I2 statistic was less than 50% and the p-value for the test of heterogeneity ≥ 0.1, studies were considered homogenous and a fixed effects meta-analysis was used to estimate the overall prevalence; otherwise, a random effects meta-analysis was used".
Reviewer's Comment 12
I would recommend using the country name (as opposed to a combination of city and country to identify the 3 key papers throughout the manuscript). This consistency will improve the overall clarity of the results and discussion section.
Authors' Response 12
Many thanks for this remark. Corrections have been made accordingly.
Reviewer's Comment 13
With the results section, it might be worthwhile adding additional information about how studies identified risk factors. Though there is mention that no regression analyses were performed, it appears that most findings are based on stratified analysis. I would highlight this basic analysis of risk factor identification as more important limitation than the current limitation statement related to the number of databases searched (as the former is not modifiable and severely limits your ability to identify key patient-level factors associated with the outcome).

Authors' Response 13
We thank you very much for these suggestions. Information about how studies identified potential risk factors for RH have been added as it reads on page 11: "No study undertook logistic regression analyses to investigate the independent factors impacting RH. The Chi-square test was used in two studies to identify potential risk factors for RH (Table 1)". Additionally, the limitation section of the manuscript was reworded as one can read on page 16: "Unfortunately, we identified just a few studies to have a clear estimate of the prevalence of RH across Africa. No study was recorded from Eastern and Northern Africa. This could perhaps jeopardize generalization of our results to the entire African continent. Furthermore, definition of RH was not homogeneous across studies, and no regression analyses were undertaken to assess risk factors for RH. This lack of adequate statistical methods critically limited our ability to identify key factors against which intervention measures can be developed to curtail the burden of RH in Africa. Nonetheless, we conducted this review following the rigor and standards of the art. Besides, and to the best of our knowledge, this is the first systematic review drawing a clear picture of the prevalence and risk factors for RH in Africa".
Reviewer's Comment 14
Please provide more detail in the paragraph related to study quality. Specifically, where were most of the biases identified? (This relates to the comment #8 above) This is helpful for readers to understand the overall quality of the 3 key papers in this area.
Authors' Response 14
We thank you for raising this issue. This paragraph has been refined, as it reads on page 12: "The risk of bias assessment using the Newcastle-Ottawa Scale quality score is depicted by Table 2. All studies failed to provide the response rate and characterize the non-respondents in comparison to the respondents; likewise comparability between RH and non-RH patients was unsatisfactory. In studies from Cameroon and Lesotho, no statistical tests were used to compare RH and non-RH patients. On the whole, two studies (Cameroon and Lesotho) presented a moderate risk of bias (6 stars each), while the two others (Nigeria and Burkina Faso) exhibited a low risk of bias (7 stars each; Table 2)".
Reviewer's Comment 15
Given the incorrect analysis performed for the overall prevalence of RH, it may be worth reworking the discussion paragraph around prevalence (to be more conservative in your interpretation). I thought the wording used in the conclusion was more appropriate (where you talk about ranges of prevalence) as opposed to a prevalence of 10%.
Authors' Response 15
Thank you for having raised this concern. Given that we have undertaken a random effect meta-analysis, we found as mentioned on page 10 that: "The overall prevalence was 10.5% (95%CI 6.6-16.3%)", which is more highlighted by figure 2.

REVIEWER 4: Adrisn Doroszko, Wroclaw Medical University, Department of Internal Medicine and Hypertension, Poland
Reviewer's Comment 1
This is an interesting manuscript, which reveals a lack of data regarding the burden of RH in Africa.
Authors' Response 1
We thank you very much for appreciating this piece of work.
Reviewer's Comment 2
This review is based mostly on the three eligible studies included to the analysis, which is an important limitation of the study. Furthermore the criteria for RH are inconsistent in these papers, which is another limitation for interpretation the statistical data. However, these limitations cannot be solved by the Authors and are already mentioned in the manuscript
Authors' Response 2
Thank you for this comment.
Reviewer's Comment 3
The appropriate diagnosis of RH needs to eliminate the secondary causes of resistant hypertension e.g. obstructive sleep apnea, atherosclerosis and renal or hormonal disorders, as well as to exclude

pseudo-hypertension, inappropriate blood pressure measurement and control as well as the white coat effect. This paper briefly summarizes the data presented in the studies. In my opinion some more data regarding the diagnostics performed in order to exclude the secondary forms of hypertension in particular studies cited in this manuscript (presented in one simple table or diagram) would significantly improve the analyses and allow to draw more balanced and reliable conclusions.

Authors' Response 3

We thank you for raising this point. Unfortunately, no study carried-out diagnostic tests to exclude secondary forms of resistant hypertension. We notified nonetheless that in Burkina Faso, AMBP was undertaken to exclude pseudo-hypertension due to the white coat effect. Furthermore, pseudo-resistant hypertension was extensively discussed in this paper.

VERSION 2 – REVIEW

REVIEWER	Giuseppe Biondi-Zoccai Sapienza University of Rome, Latina, Italy I have consulted for several companies manufacturing anti-hypertensive drugs
REVIEW RETURNED	03-Jun-2016

GENERAL COMMENTS	All my comments have been satisfactorily addressed.

REVIEWER	Paul Ronksley University of Calgary, Alberta, Canada
REVIEW RETURNED	12-Jun-2016

GENERAL COMMENTS	Thank you for the opportunity to review a revised version of this interesting manuscript. I believe the quality and overall message of the paper has improved - however, I still feel there are some minor points that need to be addressed. I have listed these below: 1. There is no need to use an acronym for risk fact (RF) and Newcastle Ottawa Scale (NOS) - the terms are not used enough to justify an abbreviation. Further the use of RF and RH in the abstract will make it difficult for readers to understand. 2. Mention that this is a systematic review and meta-analysis in the last paragraph of the introduction - not just a systematic review 3. The order of the text in the methods section should be modified. It is better to start with a section titled "Data sources and Search strategy" before getting into description about the eligibility criteria (which would be the following paragraph which could be titled "Study selection criteria") 4. I disagree with the idea of using a fixed effect model in light of low heterogeneity. Usually it is better to have decided a-priori if you believe there is one true effect (i.e. a single population measure of RH in Africa and the only variability in this measure will be through within study variability). If you believe there is true - then a fixed effect model is appropriate. However, this is not the case - we would expect there to be variability in measures used to define RH and more importantly differences in RH prevalence across all countries in Africa given patient and provider level differences that are known to exist across countries. Therefore - you would expect there to be "between" study variability as well as "within" study variability - making the random effects model the appropriate choice overall. Please remove mention of the consideration of using fixed effect

	models in light of low heterogeneity in the methods and results sections. 5. It is better to call it an overall “pooled” prevalence (as opposed to just overall prevalence) (bottom of page 10) 6. Bottom of page 11 (unless this is just a typographical error - there is no need to report p values <0.0001 (if it is this significant - usually just report <0.001) 7. I felt there was still a bit too many results presented in text within the “results section” - this became a bit repetitive and didn’t add much to what could be found within the respective tables. 8. Overall - I believe some minor editing for grammar and sentence structure would help improve the clarity of the paper - particularly the discussion section.

REVIEWER	Adrian Doroszko Wroclaw Medical University Poland
REVIEW RETURNED	01-Jun-2016

GENERAL COMMENTS	The authors have addressed all the reviewer's comments.

VERSION 2 – AUTHOR RESPONSE

REVIEWER 1: Giuseppe Biondi-Zoccai, Sapienza University of Rome, Latina, Italy
Reviewer’s Comment 1
All my comments have been satisfactorily addressed.
Authors’ Response 1
We are most grateful for your appreciation.

REVIEWER 3: Paul Ronksley, University of Calgary, Alberta, Canada
Reviewer’s Comment 1
Thank you for the opportunity to review a revised version of this interesting manuscript. I believe the quality and overall message of the paper has improved - however, I still feel there are some minor points that need to be addressed. I have listed these below.
Authors’ Response 1
We thank you for your appreciation and for these new comments that have obviously contributed to improve once gain the clarity and quality of the paper.
Reviewer’s Comment 2
There is no need to use an acronym for risk fact (RF) and Newcastle Ottawa Scale (NOS) - the terms are not used enough to justify an abbreviation. Further the use of RF and RH in the abstract will make it difficult for readers to understand.
Authors’ Response 2
We thank you for raising these points. These acronyms have been cancelled throughout the manuscript.
Reviewer’s Comment 3
Mention that this is a systematic review and meta-analysis in the last paragraph of the introduction - not just a systematic review.
Authors’ Response 3
Thank you for this suggestion in the regard of which changes were made in the revised manuscript as it reads on page 6: “To the best of our knowledge, this is the first and only systematic review and meta-analysis that has focused on resistant hypertension in Africa”.

Reviewer's Comment 4
The order of the text in the methods section should be modified. It is better to start with a section titled "Data sources and Search strategy" before getting into description about the eligibility criteria (which would be the following paragraph which could be titled "Study selection criteria")
Authors' Response 4
Thanks a bundle for this proposition. Accordingly, the methods section of the manuscript was re-formatted/re-arranged.
Reviewer's Comment 5
I disagree with the idea of using a fixed effect model in light of low heterogeneity. Usually it is better to have decided a-priori if you believe there is one true effect (i.e. a single population measure of RH in Africa and the only variability in this measure will be through within study variability). If you believe there is true - then a fixed effect model is appropriate. However, this is not the case - we would expect there to be variability in measures used to define RH and more importantly differences in RH prevalence across all countries in Africa given patient and provider level differences that are known to exist across countries. Therefore - you would expect there to be "between" study variability as well as "within" study variability - making the random effects model the appropriate choice overall. Please remove mention of the consideration of using fixed effect models in light of low heterogeneity in the methods and results sections.
Authors' Response 5
Many thanks for raising this issue. We totally agree with this comment and viewpoint. Indeed, a random-effects model was used for the meta-analysis; we removed the mention of the consideration of using fixed effect models.
Reviewer's Comment 6
It is better to call it an overall "pooled" prevalence (as opposed to just overall prevalence) (bottom of page 10).
Authors' Response 6
We thank you very much for this suggestion which we took into consideration in the revised document.
Reviewer's Comment 7
Bottom of page 11 (unless this is just a typographical error - there is no need to report p values <0.0001 (if it is this significant - usually just report <0.001).
Authors' Response 7
We thank you for this remark. Corrections were made accordingly.
Reviewer's Comment 8
I felt there was still a bit too many results presented in text within the "results section" - this became a bit repetitive and didn't add much to what could be found within the respective tables.
Authors' Response 8
Thank you for this remark. We erased some of the results that were extensively presented in the table. However, we refined our literature search and identified an additional study presented as a conference abstract, which modified some of the results.
Reviewer's Comment 9
Overall - I believe some minor editing for grammar and sentence structure would help improve the clarity of the paper - particularly the discussion section.
Authors' Response 9
Thank you for this comment. The manuscript was thoroughly revised for language edition.

REVIEWER 4: Adrian Doroszko, Wroclaw Medical University, Department of Internal Medicine and Hypertension, Poland

Reviewer's Comment 1
The authors have addressed all the reviewer's comments.

Authors' Response 1
We thank you very much.

VERSION 3 - REVIEW

REVIEWER	Paul Ronksley University of Calgary, Canada
REVIEW RETURNED	05-Jul-2016

GENERAL COMMENTS	Thank you for the opportunity to review a second revision of this important manuscript. All of my previous comments have been addressed.

VERSION 3 – AUTHOR RESPONSE

REVIEWER 1: Paul Ronksley, University of Calgary, Alberta, Canada
Reviewer's Comment
Thank you for the opportunity to review a second revision of this important manuscript. All of my previous comments have been addressed.
Authors' Response
We are most grateful for your appreciation.