PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and factors associated with medication adherence among hypertensive patients in sub-Saharan Africa: protocol for a systematic review and meta-analysis
AUTHORS	Agbor, Ndip; Takah, Noah; Aminde, Leopold

VERSION 1 – REVIEW

REVIEWER	Tim Mathes University Witten/Herdecke
REVIEW RETURNED	27-Nov-2017

GENERAL COMMENTS	This is an interesting manuscript on an important topic. However, before publication the methods require some revision. Methods In general I think the work actually addresses two different topics, namely prevalence and risk factors for non-adherence. The two topics require different methodological approaches (e.g., study designs, data extraction items). Therefore I suggest, that the manuscript should be separated into two parts, or the different approaches for the different topics should be more clearly distinct in another way. Eligibility criteria For a consistent study selection a clear definition of all eligible study designs is necessary. It seems as the mentioned study types are only examples. Moreover, it is necessary to describe the eligible study designs for evaluating the prevalence (cross-sectional study designs) and the risk factors (cohort type studies) separately because very different study designs are relevant. Please, justify why the eligibility is limited to 1997. Otherwise, to not apply publication date limits. The heading seems to be wrong. I think you do not mean “study duration” but publication date. Please specify, what is meant by “poorly definite methodologies”. I think, if this is not operationalized crystal clear, study selection can be very subjective. The type of adherence measure should be clearer. Will initiation, implementation and discontinuation be considered? A clear definition for adherence should be used (e.g.: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3403197/)

	Also, relevant measures should be specified (e.g., mean/median doses taken, % adherent patients). In the section “data items” only “adherent cases” are mentioned. Will other measures (e.g. mean doses) not be extracted? Data source It is claimed that MESH-terms will be used. However, the search strategy in table 1 do not encompass MESHs. Please, use validated geographic search filters: https://guides.library.ualberta.ca/c.php?g=342568&p=4521604 Will full-text screening also performed by two reviewers independently? Data items The studies risk factors will be adjusted for very different factors. To ensure interpretability, the factors for that the analysis is adjusted for should be extracted. I would suggest extracting data on univariate as well as multivariate analysis. Especially, because pooling of adjusted measures might not be straight forward. Risk of bias The risk of bias of “risk factor” studies should be also assessed. A suitable tool would be QUIPS. How many reviewers will perform risk of bias assessment? Two independently? Data synthesis and analysis The decision to perform a meta-analysis should be rather informed by clinical heterogeneity than by methodological heterogeneity. Please, specify the role of clinical heterogeneity for the decision to perform a meta-analysis in addition to the different adherence measures.

REVIEWER	Andrew E Moran Columbia University, USA
REVIEW RETURNED	01-Dec-2017

GENERAL COMMENTS	Hypertension is an important cause of noncommunicable disease burden in sub-Saharan Africa. Efforts to control high blood pressure world-wide are complicated by low awareness, treatment, and control rates. Control is in turn confounded by poor medication adherence. Adherence is particularly low in sub-Saharan African countries, but exact quantificaiton of the problem and its drivers is lacking. In this light, the proposed systematic review of the evidence on antihypertensive medication adherence studies in sub-Saharan Africa proposed in this study protocol paper by Agbor et al. is timely. Generally the paper presents a very sound and well planned systematic review that will be registered on the PROSPERO database and following PRISMA-P protocol for systematic reviews. To this reviewer, the protocol does not seem in any way novel or

	complex (for example, no individual participant datasets will be used), so it is not clear to me why a stand-alone study protocol had to be published. I feel that these methods could be presented along with the results of the review, even if some of the methods were reported in an online supplement. Nonetheless, I found some aspects of the protocol lacked sufficient detail: 1) the authors mention "different measures of adherence" but they do not elaborate on which measures of adherence they expect to encounter. Will all be self-report (e.g. Morisky scale)? Will there be any that are based on pharmacy report or pill counts? How will the quality of the information on adherence be rated and/or weighted? 2) A key objective of the study is identify the drivers or predictors of adherence. But the investigators do not present a strategy for synthesizing evidence on adherence drivers. Rather than pooling odds ratios for predictors of adherence, the authors might consider a meta-regression approach that would allow them to stratify on predictors and make estimates of adherence that are adjusted for predictors.

REVIEWER	Alberto Morales-Salinas Cardiocentro "Ernesto Che Guevara", Santa Clara, Cuba
REVIEW RETURNED	05-Dec-2017

GENERAL COMMENTS	'No' answers 4. Please see comments on attached document 8. I suggest include the following references: a) J Am Coll Cardiol 2017;69:437–51 and b) Morrissey et al. Systematic Reviews (2016) 5:96 12. Please see comments on attached document - The author also provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 1 – AUTHOR RESPONSE

To the Editor-in-Chief,
BMJ Open

Re: Submission of revised protocol (Manuscript ID: bmjopen-2017-020715).
"Prevalence and factors associated with medication adherence among hypertensive patients in sub-Saharan Africa: protocol for a systematic review and meta-analysis"

Sir/Madam,
We are pleased to submit our revised protocol referenced above for publication in your journal.
We appreciate the reviewers' comments, which we note have greatly improved the quality of our planned work. We have provided a point-by-point response below and all changes in the manuscript are highlighted in yellow. Thank you for considering our manuscript.

Sincerely,

Leopold N. Aminde, M.D.
Faculty of Medicine, The University of Queensland, Australia

Response to reviewers' comment

Reviewer # 1

Reviewer's comment 1: Methods: In general I think the work actually addresses two different topics, namely prevalence and risk factors for non-adherence. The two topics require different methodological approaches (e.g., study designs, data extraction items). Therefore I suggest, that the manuscript should be separated into two parts, or the different approaches for the different topics should be more clearly distinct in another way.

Authors' response 1: Thank you for your suggestion. The methods, subsections "data items and extraction" and "data synthesis and analysis" have been detailed separately according to the outcomes of interest, i.e. prevalence and factors associated with adherence to antihypertensive pharmacotherapy.

Action: This section now reads, "Data will be extracted according to the outcome of interest: i) prevalence and ii) factors associated with adherence to antihypertensive pharmacotherapy.

a. Prevalence of adherence to antihypertensive pharmacotherapy

The following items shall be extracted: the last name of the first author and year of publication, year (s) the study was conducted, the country and region (Southern, Eastern, Western, and Central Africa) where the study was conducted, study design, study setting (rural versus urban) and study type (community-based versus hospital-based). Data on method used to assess medication adherence including self-report (using tools like Brief Medication Questionnaire, Eight-Item Morisky Medication Adherence scale and Medication Adherence Report Scale), or pill count, electronic monitoring, pharmacy records and prescription claims, biological assay will be collected. The approach to data collection (face-to-face interview versus self-administered), sample size, total number of cases adherent to antihypertensive medication, mean or median doses taken, mean or median age and age range in years and the male proportion in the respective studies will also be obtained.

The three different components of adherence: initiation (the time interval from prescription of antihypertensive medication until when the patient took the first dose of his medication), implementation (the time from initiation to when the patient took the last dose of his antihypertensive medications) and discontinuation (the point when the patient misses the next dose to his treatment and no further dose is taken; this marks the end of therapy) will be considered when defining adherence to antihypertensive pharmacotherapy [14].

b. Factors associated with adherence to antihypertensive pharmacotherapy

In addition to general data items obtained in the previous section, the measure of association (odds ratio (OR) or relative risk (RR) with their respective confidence intervals) for each associated factor will be extracted and specification made if obtained from a univariate or multivariate analysis. In case of multivariate analysis, the variables adjusted for will also be obtained.

Overall, for multinational studies, the prevalence of adherence to hypertensive medication as well as the associated factors will be disaggregated and reported separately for individual studies. In case it is impossible to separate individual country data for a multinational study, we will present as a single study, and the individual countries in which the study was conducted in will be highlighted."

Reviewer's comment 2: Eligibility criteria: For a consistent study selection a clear definition of all eligible study designs is necessary. It seems as the mentioned study types are only examples. Moreover, it is necessary to describe the eligible study designs for evaluating the prevalence (cross sectional study designs) and the risk factors (cohort type studies) separately because very different study designs are relevant.

Authors' response 2: Thank you for highlighting this. The eligible study designs have been differentiated according to the outcome of interest. The first inclusion criteria now reads, "Observational studies with available data on the prevalence (cross-sectional, case series with at least 30 participants and cohort studies), and factors associated with adherence to antihypertensive pharmacotherapy (cross sectional, case-control, cohort and randomised control trials) among hypertensive patients residing in SSA."

Reviewer's comment 3: Eligibility criteria: Please, justify why the eligibility is limited to 1997. Otherwise, to not apply publication date limits.

Authors' response 3: Thank you for your suggestion. The lower publication date limit has been taken off.

Reviewer's comment 4: The heading seems to be wrong. I think you do not mean "study duration" but publication date.

Authors' response 4: Thank you. We have corrected.

Reviewer's comment 5: Please specify, what is meant by "poorly definite methodologies". I think, if this is not operationalized crystal clear, study selection can be very subjective.

Authors' response 5: Thank you. To avoid ambiguity and subjectivity of our study selection/inclusion process, we have deleted the above exclusion criteria.

Reviewer's comment 6: The type of adherence measure should be clearer. Will initiation, implementation and discontinuation be considered? A clear definition for adherence should be used (e.g.: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3403197/)

Authors' response 6: Thank you for this important remark and suggestion. Initiation, implementation and discontinuation will be considered when defining adherence. This has been clarified in section Methods/data item and extraction/ a. Prevalence of adherence to antihypertensive pharmacotherapy/paragraph 2, which now reads:

"The three different components of adherence: initiation (the time interval from prescription of antihypertensive medication until when the patient took the first dose of his medication), implementation (the time from initiation to when the patient took the last dose of his antihypertensive medications) and discontinuation (the point when the patient misses the next dose to his treatment and no further dose is taken; this marks the end of therapy) will be considered when defining adherence to antihypertensive pharmacotherapy [13]."

Reviewer's comment 7: Also, relevant measures should be specified (e.g., mean/median doses taken, % adherent patients). In the section "data items" only "adherent cases" are mentioned. Will other measures (e.g. mean doses) not be extracted?

Authors' response 7: Thank you for the question. We shall also extract data on the mean or median doses taken. We have updated the data item section accordingly. However, instead of percentage of adherent patients, we plan to extract the actual number of patients' adherent to antihypertensive pharmacotherapy, alongside the respective study sample sizes, as those are the parameters required during the meta-analysis process.

Reviewer's comment 8: It is claimed that MESH-terms will be used. However, the search strategy in table 1 do not encompass MESHs.

Authors' response 8: The search strategy has been updated to include MeSH terms. Please, see table 1.

Reviewer's comment 9: Please, use validated geographic search filters: https://guides.library.ualberta.ca/c.php?g=342568&p=4521604

Authors' response 9: Thank you very much for sharing the link. We have included this search filter in our search strategy.

Action: Line 8 of the data sources and search strategy of the method section now reads, "To improve the sensitivity and precision of our search geographically, we shall use a validated search filter proposed for Africa [12]"

Reviewer's comment 10: Will full-text screening also performed by two reviewers independently?

Authors' response 10: Yes, two authors will do screening of full-text independently.

Action: The Method/study records/screening has been updated. This section now reads,

“The titles and abstracts of papers retrieved from the search will be carefully screened, and the full-text of potentially eligible articles retrieved as earlier discussed. This exercise will be conducted independently by two authors (VNA and NFT), who will further review the full-texts of potential articles for final inclusion. The authors will compare their results at every step of the selection process, and discrepancies will be resolved through discussion and consensus. A third author (LNA) will be consulted in case of any disagreement. In the event of unclear or ambiguous information, the corresponding author of the said study shall be contacted for clarification.”

Reviewer’s comment 11: The studies risk factors will be adjusted for very different factors. To ensure interpretability, the factors for that the analysis is adjusted for should be extracted. I would suggest extracting data on univariate as well as multivariate analysis. Especially, because pooling of adjusted measures might not be straight forward.

Authors’ response 11: Thank you for this suggestion. We intend to narratively discuss the factors associated with adherence to antihypertensive pharmacotherapy. Nonetheless, we shall extract data on associated factors based on whether or not a multivariate analysis was done. The section Method/data synthesis and analysis/ b. Factors associated with adherence to antihypertensive pharmacotherapy/ of the manuscript now reads,

“It is anticipated that there will be significant variation in factors associated with adherence to antihypertensive medication that have been investigated either clinically or methodologically/statistically. As such, pooling such data may put to question the reliability of the final summary estimate. Available data on these identified factors will thus be summarized in tabular form, accompanied by a narrative discussion.”

Reviewer’s comment 12: The risk of bias of “risk factor” studies should be also assessed. A suitable tool would be QUIPS.

Authors’ response 12: Thank you for the suggestion. The QUIPS tool will be used to assess the risk of bias for studies reporting on factors associated with adherence to antihypertensive pharmacotherapy.

Action: The methods section, subsection ‘Assessment of methodological quality and risk of bias’ now reads: “The risk of bias tool for prevalence studies developed by Hoy and colleagues [14] will be used to assess the quality and risk of bias among included studies reporting the prevalence of adherence to antihypertensive pharmacotherapy (See supplementary file 1 for Hoy et al. tool). On the other hand, the QUIPS tool will be used to assess the risk of bias for cohort/prognostic studies reporting the factors associated with medication adherence [15]. The risk of bias for included studies will be presented in a tabular form.”

Reviewer’s comment 13: How many reviewers will perform risk of bias assessment? Two independently?

Authors’ response 13: Yes. Two authors (VNA and NFT) will independently assess the risk of bias of the included studies. This has been specified in the manuscript.

Reviewer’s comment 14: The decision to perform a meta-analysis should be rather informed by clinical heterogeneity than by methodological heterogeneity. Please, specify the role of clinical heterogeneity for the decision to perform a meta-analysis in addition to the different adherence measures.

Authors’ response 14: Thank you for this important point. We agree with the reviewer that clinical heterogeneity has a major role to play when pooling effect estimates across studies and its presence can have far-reaching consequences, sometimes leading up to inaccurate summary measures and conclusions. In this planned review, we intend to perform a meta-analysis only for prevalence of adherence and report on the associated factors in a narrative fashion. As such, to account for clinical heterogeneity and in addition to other subgroup analyses, we shall perform further stratified analysis of the prevalence of adherence to antihypertensive medication by age, sex, comorbidities and duration of treatment.

Action: We have updated the section on ‘data synthesis and analysis’, which now reads, “In case of substantial clinical and/ or methodological heterogeneity, we will perform a subgroup analysis. The following variables will be investigated: age (below versus at or above the median), sex (male versus female), comorbidities (presence versus absence) and duration of treatment (below versus at or

above the median). Other variables that will be considered include: study design (cross-sectional versus cohort studies), study setting (rural versus urban), study type (hospital-based versus community-based), tool used to evaluate adherence, method used to assess medication adherence, method of data collection (face-to-face interview versus self-administered), geographical region (Southern, Eastern, Western, and Central Africa) and study quality."

Reviewer 2
Reviewer's comment 1: the authors mention "different measures of adherence" but they do not elaborate on which measures of adherence they expect to encounter. Will all be self-report (e.g. Morisky scale)? Will there be any that are based on pharmacy report or pill counts?
Authors' response 1: Thank you. The possible tools and methods used to evaluate adherence, which we expect to encounter, have been detailed in the manuscript.
Action: The method section, subsection presentation and reporting of results now reads: "The prevalence of adherence to antihypertensive pharmacotherapy will be reported according to the study setting (hospital-based versus community-based study), tool (e.g. Brief Medication Questionnaire, Eight-Item Morisky Medication Adherence scale and Medication Adherence Report Scale) and method used to evaluate medication adherence."

Reviewer's comment 2: How will the quality of the information on adherence be rated and/or weighted?
Authors' response 2: Thank you the question. Quality of adherence data for included studies will be rated using the risk of bias tools proposed by Hoy et al for prevalence studies and the QUIPS tool for cohort/prognostic studies. We have revised the corresponding section on methodological quality and risk of bias, which now reads,
"The risk of bias tool for prevalence studies developed by Hoy and colleagues [15] will be used to assess the quality and risk of bias among included studies reporting on the prevalence of adherence to antihypertensive pharmacotherapy (See supplementary file 1 for Hoy et al. tool). On the other hand, the Quality In Prognosis Studies (QUIPS) tool will be used to assess the risk of bias for cohort and prognostic studies reporting the factors associated with medication adherence [16]."
Reviewer's comment 3: A key objective of the study is identify the drivers or predictors of adherence. But the investigators do not present a strategy for synthesizing evidence on adherence drivers. Rather than pooling odds ratios for predictors of adherence, the authors might consider a meta-regression approach that would allow them to stratify on predictors and make estimates of adherence that are adjusted for predictors.
Authors' response 3: Thank you for your comment. However, we do not plan to do a meta-analysis for factors associated with adherence to antihypertensive pharmacotherapy. We will rather report the results of our findings narratively for this section. This has been highlighted in the manuscript.
Action: The data extraction and analysis section, subsection, now reads,
"It is anticipated that there will be significant variation in factors associated with adherence to antihypertensive medication that have been investigated either clinically or methodologically/statistically. As such, pooling such data may put to question the reliability of the final summary estimate. Available data on these identified factors will thus be summarized in tabular form accompanied with a narrative discussion."

Reviewer 3
Reviewer's comment 1: Authors forgot the main limitation of this type of study "Adherence was measured (e.g. self-report, pill counts, direct questioning, electronic, monitoring, drug blood levels) and calculated in different ways (e.g. using arbitrary cut-off points to define adherence such as 80%), and in addition was usually assessed unblinded to allocation status, which made the comparison of RCTs difficult. Levels of adherence in the control groups of the trials studied ranged from 12% to 94%, which is indicative of the heterogeneity in both criteria for defining adherence and the participants studied. With no agreed definitions on how adherence should be measured and defined,

it is not surprising that formost interventions the impact on adherence and blood pressure appears to be variable. Because of the different definitions for adherence that have been adopted in individual RCTs, it has not been possible to examine the relationship between adherence to medication and subsequent blood pressure control"(1). Reference: 1 Schroeder K, Fahey T, EbrahimS. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings.CochraneDatabase of SystematicReviews 2004, Issue 3.Art.No.:CD004804.DOI: 10.1002/14651858.CD004804.

Authors' response 1: Thank you for carefully pointing this to us. The fourth point under the strength and limitation section has been modified accordingly and now reads,
"There is currently no universally agreed method and/or tool used to evaluate medication adherence. Additionally, the use of arbitrary cut-off values to sometimes define adherence remain potential sources of substantial heterogeneity we anticipate while assessing the prevalence of adherence to antihypertensive pharmacotherapy reported across studies done on the subject in SSA."
Reviewer's comment 2: The aim should be "...prevalence of non-adherence to .... and factors associated with medication non-adherence...."
Authors' response 2: Thank you for this suggestion. However, we intend to evaluate the prevalence of adherence and associated factors, which we believe by default will reflect the situation of non-adherence.
Reviewer's comment 3: I would like to know about the following condition: non-African origin but residing in Africa.
Authors' response 3: Thank you for the question. Our first exclusion criteria states: "Studies conducted among participants of non-African origin, or of African origin but residing outside Africa". This implies we will exclude;
1. Studies that recruited participants who do not originate from Africa (Caucasians, Asians etc.)
2. In addition, if these studies recruited participants originating from Africa, but who are living out of the African continent (e.g. North America, Europe etc.) they shall automatically be excluded.
However, since our review is concerned with sub-Saharan Africa, we have modified this criterion for clarity. It now reads,
"Studies conducted among participants of non-SSA origin, or of African SSA origin but residing outside the region."
This means only studies reporting on individuals originating from sub-Saharan Africa and currently residing in the region at the time of the study will be considered. Consequently, studies recruiting participants from North Africa and other settings will be excluded.
Reviewer's comment 4: Why did the authors select this "threshold" (less than 30)?
Authors' response 4: One of the worries with case-series is their inability to provide reliable epidemiological data due to their small sample sizes. Even though, to be best of our knowledge, there is no recognized threshold for the minimum number of participants a case-series must have for it to be included in a systematic review, most authors choose a threshold of 20 participants as it is assumed that no reliable epidemiological data can be generated below this cut-off. Our cut-off of 30 participants is conservative, admittedly subjective; we however intend to enhance the reliability of data included in our systematic review and meta-analysis by raising the threshold.
Reviewer's comment 5: 4 item is included at 3 item and viceversa I suggest to combine those items.
Authors' response 5: Thank you for the suggestion. On a second thought, and as suggested by another reviewer, the criterion dealing with exclusion of studies with "poorly defined methodologies" has been deleted as it is likely to make our study selection/inclusion process somewhat subjective.
Reviewer's comment 6: I would like to hightlight that authors most not combine community-based with hospital-based datas because there are great differences bewteen these setting in term of prevalence of adherence and factors associated with adherence.
Authors' response 6: Thank you for this key remark. We do not intend to combine data from community- and hospital-based studies. As stated, this data shall be extracted and analyzed

separately. The prevalence of adherence will be reported separately for community-based and hospital-based studies.
The method section, subsection 'presentation and reporting of results' now reads,
"The prevalence of adherence to antihypertensive pharmacotherapy will be reported according to the study setting (hospital-based versus community-based study), tool (e.g. Brief Medication Questionnaire, Eight-Item Morisky Medication Adherence scale and Medication Adherence Report Scale) and method used to evaluate medication adherence."
Reviewer's comment 7: It is the key element of the Methods and analysis. So, authors should give more details about "type of tool/method used to assess medication adherence" in their protocol
Authors' response 7: Thank you for your suggestion. Due to the great disparity in currently used tools (e.g. Brief Medication Questionnaire, Eight-Item Morisky Medication Adherence scale and Medication Adherence Report Scale) and methods (e.g. pill count, electronic monitoring, Pharmacy Records and Prescription Claims, Biological Assay, Patient interview, etc.) used to assess for medication adherence, we intend to extract data on all these tools/ methods used to comprehensively evaluate adherence to antihypertensive medication in Africa. We shall report the prevalence of adherence according to the type of tool and method used in a sub-analysis.
The method section, subsection 'presentation and reporting of results' now reads,
"The prevalence of adherence to antihypertensive pharmacotherapy will be reported according to the study setting (hospital-based versus community-based study), tool (e.g. Brief Medication Questionnaire, Eight-Item Morisky Medication Adherence scale and Medication Adherence Report Scale) and method used to evaluate medication adherence."
Reviewer's comment 8: Hoy is not the 1rst reference. Please, Authors most check references item. It should be eliminated because Hoy was already cited as the "13" references,
Authors' response 8: Thank you for the remark. This reference has been deleted and all references crosschecked for correctness and consistency with the citations within the text.
Reviewer's comment 9: I suggest include the following references: a) J Am Coll Cardiol 2017;69:437–51 and b) Morrissey et al. Systematic Reviews (2016) 5:96
Authors' response 9: Thank you. We have added the study by Ferdinand et al, 2017 has been included. Please, see reference 7 (7. Ferdinand K, Senatore F, Clayton-Jeter H, Cryer D, Lewin J, Nasser S, et al. Improving Medication Adherence in Cardiometabolic Disease. JACC. 2017;69:437–51.)

VERSION 2 – REVIEW

REVIEWER	Tim Mathes Institute for Research in Operative Medicine (University Witten/Herdecke), Germany
REVIEW RETURNED	02-Jan-2018

GENERAL COMMENTS	The protocol is very well revised. The search date is not updated In the abstract.

REVIEWER	Alberto Morales-Salinas Cardiocentro "Ernesto Che Guevara", Villa Clara, Cuba
REVIEW RETURNED	08-Jan-2018

GENERAL COMMENTS	The authors included the reviewerss suggestion.

VERSION 2 – AUTHOR RESPONSE

Dear Editor,

Thank you for the opportunity to submit a revision of our manuscript. The reviewers comments have been addressed and we are pleased to present an updated copy of the manuscript and a point-by-point response to the comment raised. Changes in the manuscript are highlighted in yellow colour.

Reviewer 1
Remark: The protocol is very well revised.
Response: Thank you.

Comment: The search date is not updated in the abstract
Response: We have now updated the abstract.

Reviewer 2
Remark: The authors included the reviewers suggestion.
Response: Thank you, we found them very useful and improved the quality of the manuscript.

Thank you for publishing our work.

Regards,
Leopold N. Aminde, M.D.