PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The prevalence and associated factors of preterm birth in Ethiopia: Systematic review and meta-analysis protocol
AUTHORS	Muchie, Kindie Fentahun; Molla, Ayenew; Teshome, Destaw; Yenit, Melaku; Sisay, Malede; Mekonnen, Fantahun Ayenew; Habitu, Yohanes Ayanaw

VERSION 1 - REVIEW

REVIEWER	Dezhi Mu West China Second University Hospital, China
REVIEW RETURNED	26-Nov-2019

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. This protocol aims to evaluate the prevalence and associated factors of preterm birth in Ethiopia. The authors stated the importance of the review: preterm birth in Ethiopia is not remarkable reduced. However, I have some questions and concerns below, particularly as relates to the associated factors of preterm birth. Major concerns: The study will include all observational studies. As we know, the bias are very common in observational studies. Also, the risk factors for preterm birth are complicated. How the authors avoid the impact of the bias? Is there any statistical method to detect the bias? Minor concerns: On Page 5 line 38-52, the authors list some risk factors for preterm birth. Some factors are overlapped. For example, pregnancy induced hypertension belongs to obstetric complication. This sentence should be reordered.

REVIEWER	Paolo Cavoretto IRCCS San Raffaele Scientific Centre Milan, Italy
REVIEW RETURNED	17-Feb-2020

GENERAL COMMENTS	The present study protocol present a project aimed at assessing factors associated with preterm birth (PTB) in Ethiopia with meta-analytic methodology. I acknowledge the scientific relevance of the

study in object, since developing countries such Ethiopia present a greater burden from preterm birth, however I am afraid that the study design needs some methodological restructuring in order to evaluate appropriately the research question raised by the authors "assessing the magnitude and associated factors of preterm birth in Ethiopia".

I have the following comments and criticisms:

Major comments

The major criticism to this protocol is the lack of description of a clear study primary outcome: is it PTB below 37 weeks? Is it PTB below 37 weeks in presence of specific morbidity such as pre-eclampsia? Is it spontaneous PTB? The authors needs to make clear this aspect first.

Subsequently, the authors need to consider inclusion of appropriate secondary outcomes related to PTB according to internationally recognized standard protocols, such as the CROWN initiative. In particular, other clinically relevant thresholds of gestational age needs to be assessed (e.g .34, 32 or 28 weeks) as well as maternal and neonatal variables. (1, 2)

Possibly sub-analyses and sensitivity analyses needs to be considered for assessing the risk of spontaneous or iatrogenic PTB, study with higher quality or lower risk of bias.

Meta-regression for a major covariate related to PTB (e.g. maternal age, bmi) needs to be taken into consideration, should the authors have the luck to find enough data in the original manuscript.

A clear list of risk factors of preterm birth is not included in the protocol. I believe that each of these will need to be assessed separately for association with the primary outcome and secondary outcomes in object.

The dates of the study should be included in the manuscript, with particular interest to study design, literature search, data extraction and data analysis. Anticipated or actual start date published on Prospero was the 23rd of September 2017 and anticipated completion date was the 3rd of April 2018. Why did the authors present a delay of about 3 years in the publication of the present protocol? Were there some problems in relation to the present study? Please, disclose them for readers in the manuscript.

Inclusion and exclusion criteria for studies assessed are not clear enough.

Assessment of risk of bias, random errors and study quality in not discussed. Study quality can be assesses by the Newcastle Ottawa scale. (3)

Minor comments

There were some changes in the coauthors between Prospero publication and the present protocol: please disclose the role of each authors in the study protocol.

The study period was changed from the initial protocol published in Prospero (2007-2017 vs 2009-2019), this change probably reflect the delay of the authors described among the major comments, please disclose this problem in the protocol.

The authors should be aware that a meta-analysis assessing observational studies is by definition destined to present low or very low score at GRADE assessment tool. (4)

Statistical methodology should follow the Cochrane manual (5), anticipation of type of graphical analyses (Forrest plots) and assessment of risk of bias (Funnel Plots) needs to be considered.

References
1. http://www.crown-initiative.org/wp-content/uploads/2016/03/CROWN-announcement-for-BJOG.pdf

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3. Wells GA, Shea B, O'Connel DI, Peterson J, Welch V, Losos M, Tugwel P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Institute website. Available from: http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf; Accessed on the 17th febrauary 2020.

4. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, de Beer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann H. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidem 2011; 64: 383-394.

5. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

VERSION 1 – AUTHOR RESPONSE

II. Response to Reviewer #1

Thank you for the opportunity to review this manuscript. This protocol aims to evaluate the prevalence and associated factors of preterm birth in Ethiopia. The authors stated the importance of the review: preterm birth in Ethiopia is not remarkable reduced. However, I have some questions and concerns below, particularly as relates to the associated factors of preterm birth.

Major concerns:

The study will include all observational studies. As we know, the bias are very common in observational studies. Also, the risk factors for preterm birth are complicated. How the authors avoid the impact of the bias? Is there any statistical method to detect the bias?

Reply: Thank you Dear reviewer, you pointed very important that could come along with observational studies. However, we will use standard JBI critical appraisal tool for each kind of study designs that is expected to assess the overall methodological quality of the studies including bias. Which is included in the subtopic "Critical appraisal" under the methods part of the body of the manuscript.

Minor concerns:

On Page 5 line 38-52, the authors list some risk factors for preterm birth. Some factors are overlapped. For example, pregnancy induced hypertension belongs to obstetric complication. This sentence should be reordered.

Reply: Thank you for this critical view. We have restructured the sentences in line with your suggestion.

Response to Reviewer #2 reports

The present study protocol present a project aimed at assessing factors associated with preterm birth (PTB) in Ethiopia with meta-analytic methodology. I acknowledge the scientific relevance of the study in object, since developing countries such Ethiopia present a greater burden from preterm birth, however I am afraid that the study design needs some methodological restructuring in order to evaluate appropriately the research question raised by the authors "assessing the magnitude and associated factors of preterm birth in Ethiopia".

I have the following comments and criticisms:

Major comments

The major criticism to this protocol is the lack of description of a clear study primary outcome: is it PTB below 37 weeks? Is it PTB below 37 weeks in presence of specific morbidity such as pre-eclampsia? Is it spontaneous PTB? The authors needs to make clear this aspect first.

Reply: Thank you for the comment pointed out. As we have started defining preterm birth at the first line of the introduction, we can easily understand that preterm refers directly births before 37 weeks of gestational period in this study. It may be with the presence of morbidity, spontaneous, and more as listed by the reviewer. However, for further clarity we have now incorporated a phrase describing preterm in various subtopic of the manuscript including the second line under subheading "Eligibility criteria" in the "Methods and Analysis" part of the body.

Subsequently, the authors need to consider inclusion of appropriate secondary outcomes related to PTB according to internationally recognized standard protocols, such as the CROWN initiative. In particular, other clinically relevant thresholds of gestational age needs to be assessed (e.g .34, 32 or 28 weeks) as well as maternal and neonatal variables.

Reply: It would have been good if we can consider various threshold gestational ages including 34, 32, or 28 weeks as well as maternal & neonatal variables as secondary outcome as suggested by the reviewer. However, the current scope of the proposed review is broad (prevalence and all possible associated factors) so that we could not take this into account. Probably we could take it as further direction for researchers in our final report.

Possibly sub-analyses and sensitivity analyses needs to be considered for assessing the risk of spontaneous or iatrogenic PTB, study with higher quality or lower risk of bias. Meta-regression for a major covariate related to PTB (e.g. maternal age, bmi) needs to be taken into consideration, should the authors have the luck to find enough data in the original manuscript.

Reply: Statements about sensitivity analysis and subgroup analysis are also included in the "Data synthesis and statistical analysis" under the "Methods and Analysis" part of the body. Regarding meta-regression, it will be used as one means of solving heterogeneity using continuous covariates. However, from our preliminary search maternal age as well as BMI were reported in categories, not reported in their continuous form. So, better way to deal during occurrence of heterogeneity will be using random effects model and subgroup analysis which we have stated in the document.

A clear list of risk factors of preterm birth is not included in the protocol. I believe that each of these will need to be assessed separately for association with the primary outcome and secondary outcomes in object.

Reply: Thank you for the concern. As we have replied above that we are not going to take those suggested as secondary outcome, no need to differentiate factors for the primary and secondary outcome. However, for the primary outcome (birth before 37 weeks) we will review some factors where the detailed and comprehensive factors are expected as an outcome of the review.

The dates of the study should be included in the manuscript, with particular interest to study design, literature search, data extraction and data analysis.

Reply: Moreover, we believe that anticipated and completion dates of the review are adequate so the details of planned dates for study design, literature search, data extraction, and data analysis may not be relevant.

Anticipated or actual start date published on Prospero was the 23rd of September 2017 and anticipated completion date was the 3rd of April 2018. Why did the authors present a delay of about 3 years in the publication of the present protocol? Were there some problems in relation to the present study? Please, disclose them for readers in the manuscript.

Reply: The PROSPERO study record was registered initially on Nov 3, 2017. However, because of busy schedule of the authors we were not able to conduct by the planned schedule. So, the PROSPERO study record was last edited and submitted on Oct 16 2019 for approval. Now, the record is still under waiting list for the approval and access to latest record is suspended because of the administrative process, as we can understand from the website. The brief details of the changes made while editing will be accessible in PROSPERO record as soon as approved. Furthermore, we would like to disclose that the delay was not related to any problem to the present study. The following disclosure statements are added under the subtopic "Development and review method" in the methods part of the body of the manuscript:

"The initial anticipated or actual start date and anticipated completion date were updated with brief details on Prospero records. We would like to disclose that the delay was not related to any problem to the present study."

Inclusion and exclusion criteria for studies assessed are not clear enough.

Assessment of risk of bias, random errors and study quality in not discussed. Study quality can be assesses by the Newcastle Ottawa scale.

Reply: To make preterm birth as specific as possible, "preterm birth" is replaced by "preterm birth (births before 37 weeks of gestational period). Further, eligibility criteria based on the computation of the magnitude of preterm is included under the subtopic "Eligibility criteria" of "Methods and Analysis" of the body of the manuscript.

Furthermore, we agree on the idea that Newcastle Ottawa scale can be used to assess risk of bias, random errors and study quality. However, JBI tool which we planned to use in our review is also another option. The detailed procedures planned to follow for these assessment are given under the subtopic "Critical appraisal" in the "Methods and Analysis" of the body of the manuscript.

Minor comments

There were some changes in the coauthors between Prospero publication and the present protocol: please disclose the role of each authors in the study protocol.

Reply: Thank you for the comment. The role of the authors in the study protocol are disclosed in detail as "Author contributions" under Declarations.

The study period was changed from the initial protocol published in Prospero (2007-2017 vs 2009-2019), this change probably reflect the delay of the authors described among the major comments, please disclose this problem in the protocol.

Reply: The following sentences are added under the subtopic "Development and review method" of the protocol to disclose:

"The initial anticipated or actual start date and anticipated completion date were updated with brief details on Prospero records. We would like to disclose that the delay was not related to any problem to the present study."

The authors should be aware that a meta-analysis assessing observational studies is by definition destined to present low or very low score at GRADE assessment tool.

Reply: Thank you for this important concern. We are aware of that issue. However, from the preliminary search we have realized that all of the accessed studies in Ethiopia regarding preterm birth are observational studies. So, we hope this review will be with better power and precision providing comprehensive knowledge with available observational studies.

Statistical methodology should follow the Cochrane manual, anticipation of type of graphical analyses (Forrest plots) and assessment of risk of bias (Funnel Plots) needs to be considered.

Reply: Thank you for the comment. It was already stated under "Data synthesis and statistical analysis" of the protocol. That is these techniques, Forrest plots and Funnel will be considered in our analysis.

VERSION 2 – REVIEW

REVIEWER	Paolo Cavoretto
	IRCCS San Raffaele Scientific Centre
	Milan, Italy
REVIEW RETURNED	20-Feb-2020

GENERAL COMMENTS	I am afraid that most issues raised in my previous review remained unresolved. In particular the outcomes of interest were not clarified enough. what is that the authors are looking for? PTB with ipertension? PtB with preeclampsia? It is not enough to look for PTB<37 weeks (it is a weak outcome: please look at PTB<34, 32 or 28 wks as well), in addition secondary outcomes in agreement with the Crown initiative were ignored. I have to decline publication in its present form as it is inadequate. Please restructure the study as suggested should the author wish to align with international standards on PTB research. Meta regression optionis not presented as well as clarification of inclusion and exclusion criteria and subs slides of spontaneous versus iatrogenic PTB.

VERSION 2 – AUTHOR RESPONSE

II. Response to Reviewer #2

I am afraid that most issues raised in my previous review remained unsolved. In particular the outcome of interest were not clarified enough. What is that the authors are looking for? PTB with ipertension? PtB with preeclampsia? It is not enough to look for PTB<37 weeks (it is a weak outcome: please look at PTB<34, 32 or 28 wks as well), in addition secondary outcomes in agreement with the Crown initiative were ignored.

Reply: Thank you for your critical comment that helped us to improve the manuscript. We have tried to make the outcome clear. As suggested, by considering the CROWN initiative, we have included

PTB<34, 32 or 28 weeks as secondary outcomes in addition to the primary outcome PTB<37 weeks. Any type of PTB will be considered among all livebirths. However, specific types regarding morbidities like PTB with preeclampsia and PTB with ipertension were considered for subgroup analysis. Details are available in the abstract as well as in the Methods and Analysis part under subtopic Data synthesis and statistical analysis.

I have to decline publication in its present form as it is inadequate. Please restructure the study as suggested should the author wish to align with international standards on PTB research.

Reply: It has been tried to accommodate the comments and the manuscript is modified accordingly.

Meta regression option is not presented

Reply: Included as suggested. That is the statement "Meta-regression will be considered for major covariates (maternal age and maternal body mass index) related to PTB." have been included in the Methods and Analysis part under subtopic Data synthesis and statistical analysis.

Clarification of inclusion and exclusion criteria

Reply: Included both in the abstract and the body of the manuscript as suggested. The detailed modifications are available in Eligibility Criteria under Data synthesis and statistical analysis part as well as in abstract of the manuscript.

Subs slides of spontaneous versus iatrogenic PTB.

Reply: As suggested, we have included the statement "Subgroup analysis will be sought based on possible characteristics of the studies, specific morbidity (like pre-eclampsia, hypertension), type of PTB (spontaneous or iotrogenic), and quality of study (high quality or low risk)." in the Methods and Analysis part under subtopic Data synthesis and statistical analysis as well as in the abstract.