Author’s response to reviews

Title: Prevalence of Type 2 Diabetes Mellitus among Hepatitis C Virus-Infected Patients: Protocol of a Systematic Review and Meta-Analysis

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Version: 1 Date: 08 Nov 2018

Author’s response to reviews:

Covering letter

Dear Editor-in-chief

We the authors would like to thank for the quick review process of our manuscript “Ambachew S et al. SYSR-D-18-00107: Prevalence of Type Two Diabetes Mellitus among Hepatitis C Virus-Infected Patients: A Systematic Review and Meta-Analysis Protocol and for your consideration for publication in the prestigious journal; Systematic Reviews

We tried to revise and address the comments and issues raised by reviewers. Herein, the point-by-point reply to reviewers’ comments is attached.

Finally, we confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript and agree with its resubmission to Systematic Reviews.

Sintayehu Ambachew

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With kind regards!
Author's response to reviews

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Authors

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Response for reviewers-1

Dear Reviewer,

We thank you very much for your constructive comments and suggestions for the improvement of this manuscript. We have corrected and amended the manuscript based on your comments and suggestions. To visualize the changes made in the manuscript, we enabled the track change feature in Microsoft word.

Reviewer #1:

1-In the search strategy section, please mention the language of the articles you have searched for

Reply: thank you for your concern, we have mentioned the language of the articles that will be searched.
2- Please, present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated.

Reply: thank you, we have added the Search Strategy

3- Please, describe how the strength of the body of evidence will be assessed

Reply: Thank you, we have described that the quality and the strength of evidence will be assessed based on JBI appraisal criteria attached as additional file 1

4- Please review the PRISMA-P checklist for protocols and pay attention to any items not currently reported in this manuscript. Please provide a PRISMA-P checklist for the revised manuscript

Reply: we have reviewed the PRISMA-P checklist and attached as additional file 2

Reviewer #2: The investigators report the protocol for a systematic review with meta-analysis of proportions on the prevalence of diabetes mellitus in patients infected with hepatitis C. I have the following comments:

The abstract is fraught with grammatical errors, making it hard to understand. For example this sentence: "Therefore, this protocol for meta-analysis will support to estimate the overall prevalence of type two diabetes mellitus in patients infected with hepatitis C virus"

The background also has come grammatical errors.

Reply: Now we have improved the quality of written language in collaboration with colleagues and linguistic professionals.

The proposed work does not seem to adequately address the concern of excess risk of diabetes mellitus (DM) in people with HCV. The prevalence of DM in people with HCV should be compared with prevalence of DM in non-HCV populations. This estimate of risk is more informative that a meta-analyses of proportions and could easily be accomplished by selecting analytical studies and pooling the estimate of risk. The choice to pool prevalence should be justified better.

Reply: thanks, we modified the proposed work in an effort to clarify the excess risk of diabetes mellitus (DM) in people with HCV and better justified.

Are there any eligibility criteria regarding sample size?
Reply: no eligibility criteria will be used regarding sample size

The measure of prevalence here is problematic: "The prevalence will be calculated by dividing the number of patients who developed T2DM per total number of HCV infected patients for each study". Firstly, there is no way of establishing temporality (did HCV or DM come first?). Secondly, the definition of "prevalence" doesn't require this knowledge.

Reply: Thanks we have corrected.

In the quality assessment, why is "appropriate statistical analysis" a criteria when you will be pulling the numbers and analysing them yourselves?

Reply: "appropriate statistical analysis’” importantly, the numerator and denominator should be clearly reported, and percentages should be given with confidence intervals. The methods section should be detailed enough for reviewers to identify the analytical technique used and how specific variables were measured. Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

Please provide more details on the sensitivity analyses to check the stability of the estimate.

Reply: it has been modified as “Sensitivity analysis will be done to evaluate the effect of each study on the pooled estimated prevalence of T2DM among HCV infected patients by excluding each study step-by-step from the analysis process.”

The I2 gives an estimate of the magnitude of heterogeneity but not potential sources of heterogeneity.

Reply: thanks we have corrected it.

In the protocol, please report potential sources of heterogeneity that might explain the I2 values you may find. For example, study size, year, location etc.

Reply: We modified to describe potential sources of heterogeneity.

State how the results will be reported. % with 95% confidence intervals?

Reply: thanks, point estimation with a confidence interval of 95% will be used.
This and other studies like it would have been useful in the background:" A systematic review and meta-analysis done by Naing et al. (16) showed an excess risk of T2DM in HCV infected cases than non-HCV infected controls (OR: 1.63, 95% CI: 1.11-2.39)'

Reply: Thanks: we modified the background in an effort to clarify the excess risk of diabetes mellitus (DM) in people with HCV

Reviewer #3: The manuscript presents a protocol of the systematic review and meta-analysis of the prevalence of type 2 diabetes mellitus (T2DM) in people with Hepatitis C Virus (HCV). I find the issue is very interesting and the research questions definitely need to be answered since the risk of developing T2DM later in life increasing 2.5 folds in people with HCV comparing with a general population. It lays a double burden on a health care system and is worsening a patient' outcomes.

While the protocol is clear and structured, I have some remarks and comments to address.

General remarks:

The authors claim that they would like to estimate "global" prevalence of T2DM among people with HCV. However, they expect that "some" countries may not be available. Honestly speaking, I would say that it is quite ambitious statement. There is a huge lack of data sources with respect to T2DM in general population of at least half of countries in the world, and I'm afraid that the evidence in rages to T2DM in people with HCV is even more scarce and few and far between. I would say that the authors should be happy to find at least some studies done outside of the high-income countries.

Reply: Thank you for your concern, a comprehensive literature search will be conducted to identify studies published in English language expecting in "some" countries may not be available.

I would suggest that the biggest heterogeneity factor would be a variation in original study cohorts. The authors did not mention sampling design anywhere while it might vary substantially from source to source.

Reply: thanks, we clarified and explained the factors that might cause biggest heterogeneity including study design.

Also, age and time since diagnosis of HCV are the important risk factors that might play a big role in the study variations.
Reply: we have made a pilot search but those studies that we aimed to do so have not been considered age and time since diagnosis of HCV. Therefore we are forced not to include these issues.

Concrete remarks:

There are a lot of studies, including systematic reviews, that discuss HCV and DM in different aspects. It would be great if the authors provide a brief overview in the introduction.

Reply: Thanks: we modified the introduction part in an effort to clarify HCV and DM in different aspects.

How HCV will be defined - as a chronic known infection? For what time it should last? How should it be diagnosed/proved?

Reply: those patients confirmed to be positive or having HCV from blood sample at any time regardless of the severity of disease will be considered.

The authors defined T2DM by OGTT, FBG and RPG. What is about HbA1c that is quite common as diagnostic criteria? Also, except WHO criteria for diabetes, there are ADA criteria. Do the authors check for it as well?

Reply: We modified the paper in an effort to include the previous comments.

What is about diagnosed/known diabetes? Or do the authors include only screenings for a new cases of T2DM? If we talk about observational cross-sectional studies, the true prevalence of diabetes would contain previously diagnosed cases and new cases found after a test.

Reply: both previously diagnosed cases and new cases found after a test will be included.

Do the authors control if diabetes was diagnosed before an infection or refer only cases that happened after HCV infection?

Reply: we only plan to refer only cases that happened after HCV infection

It would be great if the authors will present the items of this protocol in accordance with the PRISMA-P checklist as an additional file. The PRISMA-P checklist contains 17 items considered to be essential and minimum components of a systematic review or meta-analysis protocol.
Reply: we have reviewed the PRISMA-P checklist and attached as additional file 2

Also, even it is not fully relevant for a prevalence meta-analysis, it would be great to assess your research question in regards to PECO (analogue of PICO for observational studies), the components of a population, exposure, comparator, and outcome list.

Reply: thanks we will consider it.

Do the authors exclude mathematical models, conference abstracts, thesis or other non-primary research articles and if not/yes, why? Would unpublished literature be eligible?

Reply: look the eligibility criteria

Do the authors extract more information about the eligible study population? Gender distribution, age distribution, adjustments, regionality and specificity of sampling, sampling design (population-based, clinic-based, local, regional, cohort-specific etc), non-institutionalised. I would suggest that is some specific populations the prevalence of T2DM might vary quite widely.

Reply: The data extraction format will only include information regarding the country, year of publication, primary author, type of study, study design, study setting, number of participants, the age range of the population, diagnostic criteria for each condition, and the number of T2DM.

The authors include the keyword "prevalence" in the search terms. Why? Do the author aim only for studies where prevalence of T2DM is a primary aim? Would it be better if all other studies on people with HCV also will be included where a study population might be stratified and described in regards to a wide list of chronic conditions?

Reply: thanks so much we will consider it

Did the authors run a sensitivity/specificity pilot search to see of what kind of studies might be found?

Reply: yes we did

It would be great if the authors provide an example of search terms for one of the search engines.

Reply: look at the search strategy
The authors mentioned language restrictions in the limitations. I would recommend to mention in the methods as well. Anyway, would the authors suggest using Google Translate for non-English publications?

Reply: we only plan those studies published in English language

Do the authors limited a publication date range? Is the search limited by study design?

Reply: no restriction of “publication date range” until April 2017.

Are the authors consulted by a professional librarian in preparation of the search strategy?

Reply: not consulted by a professional librarian rather we have trained and got help by those professional having deep knowledge of systematic review and meta-analysis.

Do the authors plan to search the citation lists of included studies (i.e., a snowball search)?

Reply: yes we did plan

How do the authors going to work in Google Scholar while it returns all kinds of documents including not peer-reviewed?

Reply: we will try to extensively look at our topic of interest in Google Scholar though it is a tireless work

The authors mentioned that the sub-group analysis will be conducted based on geographical region. How do they plan to define "a geographical region"? By UN classification? Any other?

Reply: we will consider geographical region by continent of UN classification


Reply: thanks we will consider it.

Small remarks:
Abstract: abbreviations "DM" and "HCV" are used without definition

Reply: thanks it has been corrected as suggested

Objectives: abbreviation "T2DM" is given without definition

Reply: thanks it has been corrected as suggested

Ethics statements: do the review require an ethics committee approval or written informed consent?

Reply: it is to mean ethics committee approval

Introduction: Ref 6 and 7 are quite old. I'm sure there are a plenty of new studies on incidence and mortality from HCV in the world. I would suggest that the authors should update the sources.

Reply: thanks it has been modified

Introduction: Ref 3 is very old. Since 1993 a huge amount literature has been written about diabetes and its complications as well as their pathogenesis.

Reply: thanks it has been modified

Inclusion criteria: I would substitute "diabetes events" to "diabetes cases" since the authors are searching for prevalence and not incidence.

Reply: thanks it has been corrected as suggested

Search strategy: I would say that mentioned source are search engines and not just bibliographical databases.

Reply: thanks it has been corrected as suggested

I assume that the authors mean "data extraction" except "data abstraction".

Reply: thanks it has been corrected as suggested
What does "study setting" mean in this case?

Reply: study setting in this context mean community based, hospital based or list of countries where data had been collected.