Author’s response to reviews

Title: Prevalence of potential drug-drug interactions and associated factors among outpatients and inpatients in Ethiopian Hospitals: a systematic review and Meta-analysis of observational studies

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Author’s response to reviews:

Reviewers comment responses
We used a yellow color on the revised part to indicate modifications
For Reviewer 1
Abstract
1. On the background part, the reviewer comment as it is confusing and missing some punctuation mark. We made it clear.
2. On the method section, the reviewer asked as to add analysis information. We added information on data analysis in the method part on line 6.
Background
The reviewer commented as we describe a lot of information’s on the manuscript and the ideas lacks coherence. Based on this we modified the whole part of the introduction, made it coherent and had 2 pages.
Methods
Study protocol
Reviewer recommendation was given to change conducting to reporting. We already change in the method section line 4.
We also added the Prospero registration number on the second paragraph.
Eligibility criteria
What means sufficient data? In this review sufficient data means when the article fulfils the inclusion criteria, contains the outcome of interest and fulfils the data based on our standard data extraction format.
Data extraction
Since the PRISMA flow chart is presented in the result section we removed it from the data extraction.
Quality assessment
We were used the verb was and now changed into were in line 1
Data processing and statistical analysis
Since the first sentence was described on the data extraction we already removed it. Results
CS; we describe it in paragraph 2 line 8
Paragraph 2 line 12: all 14 included studies
Discussion, limitation and conclusion.
All sentences that need reference are well referenced. One sentence from the conclusion is
removed and added as a limitation part of the final sentence.
For Reviewer 2:
Background
The reviewer commented us to add additional reference Galleli et al, 2017. We add it in this part
paragraph 6 line 1.
Methods
The reviewer commented us to add the role of each author in the selection of references. We add
the author’s role in this review and meta-analysis in the screening and eligibility of studies section.
Results
The reviewer commented us to add the role of nutrients and gender in the development of DDIs
but we did not add the role of nutrients in the development of DDIs because it is not our objective.
Our objective is drug-drug interaction and we also exclude drug interaction with nutrients. The
role of gender in the development of DDIs is mentioned in the “Factors associated with potential
DDIs” section table 5 row 3. None of the articles mentioned the time of DDI development so we
did not mentioned it. We mentioned the effect/risk of interaction in table 6 column 4.
Discussion
The role of age for the development of DDI is discussed in paragraph 6 line 1 whereas the role of
BMI and nutrient is not mentioned because for nutrient it is not our objective and for BMI doesn’t
mentioned by included articles. Gender is not a factor in the development of DDI in this review
and meta-analysis.
For Reviewer 3:
Abstract
The reviewer commented us we include unpublished articles but we doesn’t include in the
methodology and result. Based on this comment we revise it and observed as we did not include
unpublished articles so we removed the sentence unpublished articles. It is also mentioned in the
inclusion criteria line 3 as we include all published articles without time limit were included.
Background
The reviewer commented us to reduce this section so we reorganize and reduced it from 3 pages to
2 pages.
Methods
PRISMA format: we used PRISMA format for reporting in this review. As the reviewersuggested
MOOSE is a formal reporting for observational studies. Yes he/she is correct but different scholars
suggested PRISMA is also used to report observational studies even if basically used for
randomized controlled trials. Because of this we send it to PROSPERO and already registered the
protocol on PROSPERO.
In the exclusion criteria we include “studies that were conducted outside of Ethiopia were
excluded”. We agreed with the reviewer comment and we removed the sentence.
Quality assessment
We commented to mention items used for the evaluation of the quality. We include the 12 quality
assessment items in this section line 3
Assessment of heterogeneity
We mentioned it under data processing and analysis part before the reviewer comment. Now we mentioned it in the separate subtitle and include clinical, methodological and statistical heterogeneity (See the heterogeneity assessment subtitle)

Results
The results of heterogeneity assessment is putted in the result section based on the reviewer comment (see in the Test of heterogeneity, subgroup analysis and publication bias section)
The reviewer commented as to include the five articles that are excluded with justification. We included them in the article search result subtitle section as an additional file 2: table 2.
Based on the reviewer comment, the results of a subtitle sensitivity and subgroup analysis is presented in a separate subtitle.

Conclusion
We mentioned as this review has considerable heterogeneity. So we include this sentence as a limitation in the last sentence of limitation part.

Figures
In Figure 5; the word major is changed to minor.

Tables
Abbreviations are placed as footnotes in the table 2 and 3.
In table 3: based on the reviewer comment for the purpose of comparative purpose we report the rate of major, moderate and minor interactions in percentage and number
In the Table 4, 5 and 6, we mentioned studies that doesn’t mentioned the required item as s footnote.

For Reviewer 4:

Background
The reviewer suggested us to rewrite the introduction and to add alert fatigue. We write the introduction by describing DDI, reasons why DDI occur, impact of DDI on economy and finally why we done this review and meta-analysis. We also include alert fatigue in paragraph 7.

Patients with renal and hepatic insufficiency is mentioned in paragraph 5.

Method
Exclusion criteria: We exclude studies that were conducted in the primary health care setting because our objective is to know the prevalence of DDIs in the Hospitals.

Quality assessment
The details of the quality scores are found in the result section quality of included studies as an additional file 3: table 3.

Results
The reports of CI is presented in percentages

Discussion
The sentence which says 2.67 potential DDIs per one patient is in the first paragraph is removed.
In paragraph 5, the sentence almost all HIV infected patients…. Is changed to all (100%) HIV infected patients treated in outpatient setting….

Figures and table
Table 3 classification of severity is included as a limitation
Table 6 we add a column for PK, PD, Both or unknown. We also add a column for the effect of interaction.