Author’s response to reviews

Title: Association of Micronutrient Deficiency and Acute Respiratory Infections in Healthy Adults: A Systematic Review of Observational Studies

Authors:

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Author’s response to reviews:

Reviewer reports:

Reviewer #1:

1. The paper is interesting to those who have same interest. However, I find the paper is not focused on the association between vitamin D and cold but in reality the paper is discussed other variables. I think it is better to summarise. (Editor note: reviewer #1’s comments and suggestions are provided in the attached file.)

Authors: We sincerely thank you for your comments. Indeed, this review is not solely focused on the association between vitamin D and common cold. Our review paper aimed to assess the association between any single micronutrient deficiency and acute respiratory infections, especially the common cold. We have since included “common cold” under “acute respiratory infections” as a broad term to account for the broad search strategy utilised in this study.

2. Title: cold - What you mean by cold, cold weather?

Authors: Thank you for highlighting this. We were referring to the acute common cold, which is an acute respiratory infection. We have revised our title at Line 1-2 to “Association between Micronutrient Deficiency and Acute Respiratory Infections in Healthy Adults: A Systematic Review of Observational Studies” to reflect that more accurately.

3. Line 25: Vitamin D deficiency (VDD) - when the focus here on Vitamin D and its relation with cold weather i think it is better to change the paper subject to what you focused on?

Authors: Thank you for your comment. We have further clarified in Lines 26 – 29 to reflect our focus on the association between any single micronutrient deficiency and acute respiratory infection incidence and its associated severity.
4. Line 36: Introduction - It seems that vitamin D is the focus of this study and i think the introduction should be focused on vitamin D as well.

Authors: This review is focused on the deficiency in any single micronutrient in general, rather than that of vitamin D only. Therefore, the introduction covered evidence from a variety of micronutrient deficiencies rather than focusing on vitamin D deficiency only. Interestingly, only studies focusing on vitamin D deficiency on the outcomes of interest were eligible and selected as the final selection of studies. However, studies focusing on other micronutrient deficiencies did not fulfilled the eligibility criteria.

5. Line 177: Table 4 - I can’t understand what you mean by study quality in this context? Based on what the categories was high, low or fair?

Authors: Study quality in this review referred to the methodological and reporting quality of each study included. Currently, there is no universally accepted guidelines to classify the quality of the methodology and/or reporting measures of observational studies. Thus, we have developed a framework to assign the various quality categories in this review, which are broad enough to generalise to all observational studies. The specific methods used to assess the methodological and reporting quality of each study and their rationale have been documented in Additional File 3.

6. Line 260: these variables - what are these variables?

Authors: The variables referred to are namely: any single micronutrient deficiency, ARI incidence, duration and severity or ARI-associated pneumonia incidence, duration and severity. These variables are also mentioned in lines 265-266 in the text “…The association assessment also included ARI-associated pneumonia incidence, duration and severity in a healthy population. .”

Reviewer #2:

1. Methods section

Please check line 69 "Specific search terms defined with the PEOS criteria" What is PEOS in full?, not mentioned anywhere before.

Authors: Thank you for highlighting this. The PEOS stands for Population, Exposure, Outcome, Study Design and the non-abbreviated form is now added in lines 75 – 76 “Specific search terms defined with the Population, Exposure, Outcome, Study Design (PEOS) criteria and strategies …”.

2. Results section

One of the outcomes of interest is incidence of cold. In line 201-203, "You write Incidence of cold was reported in five studies [21, 23-25, 28], whilst one study reported on the incidence of
CAP [22]. Odd ratios (ORs), relative risks (RRs) and the percentage of population infected with cold reported for the various vitamin D categories suggested that cold incidence.

Do odds ratios provide risk for prevalence studies/cross-sectional studies or even risk for follow-up studies (in this case incidence)?

Authors: Thank you for raising this point. While we do acknowledged that the relative risk is the most appropriate measure for risk in prevalence/cross-sectional studies, we are unable to provide the relative risk as a summary estimate since all but two studies reported odds ratio for cold incidence in the different vitamin D groups, as shown in Table 3A. Since we are limited by data availability of the primary studies, we presented the risk of cold incidence with vitamin D deficiency with the risk estimate presented in majority of the included studies i.e. odds ratio. The two studies (Laaksi, 2007 [1]; Sabetta, 2010 [2]) that reported relative risks were also highlighted with “ * “ in Table 3A.

References


Reviewer #3:

General comments

1. Well stated review; see and revise for grammatical and spelling.

Authors: Thank you. We have checked and revised the manuscript for grammatical and spelling errors.

2. Avoid some unnecessary headings in the method part and others section.

Authors: Thank you for your comment. We have revised all headings in our review and since merged the “Search Strategy and Data Sources” and “Inclusion and Exclusion criteria” subheading into a single “Study Identification and Selection” subheading at line 72. We left other subheadings intact as we believe it aids in reader orientation and results presentation.

3. Where are the keywords you use for search engines (please show all keywords included under quotation conjuncted by or, and)?
Authors: The keywords used were related to the Population, Exposure, Outcome, Study Design (PEOS) criteria for this review. Exact search terms differed according to search syntaxes of each database and have been documented in Table A2 in Additional File 1.


Specific comments

4. Line 1= need title modification. it is preferable as =Association between Micronutrient Deficiency and Common Cold in Healthy Adults: A Systematic Review of Observational Studies

Authors: Thank you for your suggestion. We have since revised our title to “Association between Micronutrient Deficiency and Acute Respiratory Infections in Healthy Adults: A Systematic Review of Observational Studies”, in the revised manuscript in line 1 after considering this and the subsequent comment from you.

5. Line 1= your finding deals with "Micronutrient Deficiency and Cold in Healthy Adults" but your literatures includes pneumonia, influenza, RTI and URTIs. So, how did you conclude these all terms by "cold" only?

Authors: We acknowledge that the common cold and influenza are not exactly the same disease, but have similar symptoms which may result in misclassification of the disease. Our original intention was to account for this possible misclassification through inclusion of “influenza” or “influenza-like illnesses” in our literature search. Nonetheless, we agree with you that our title may be misleading, given the fact that we also searched for URTI and RTI under the assumption that these diseases have similar etiologies to the common cold and hence, may be used as synonyms by different clinicians.
As such, we have revised our title to “Association between Micronutrient Deficiency and Acute Respiratory Infections in Healthy Adults: A Systematic Review of Observational Studies” to reflect the diseases included in our search strategy for more accurately. As mentioned in lines 101 – 104, “This review defines an acute respiratory infection episode as any upper respiratory tract infection, influenza, influenza-like illnesses and common cold episodes ...”.

Lastly, our literature searches also included “pneumonia” as ARI-associated pneumonia incidence and its associated severity was defined as a secondary outcome for our review, but actually not included in our “ARI” definition.

6. Line 1= where is the place this study is conducted? Or what is the context or setting of this review?

Authors: There is not specific location/setting where this study is conducted as this review was aimed to involve studies focusing on healthy adult population, regardless of which country it is conducted in the world.

7. Line16= use "common cold' rather than "cold "only throughout your document. Because the word "cold" by itself has more than one meaning.

Authors: Thank you for your suggestion, which will definitely aid in clarifying what we are referring to when “cold” was mentioned in the manuscript. While we are unable to implement this suggestion due to word count limitation, we have replaced “cold(s)” with “ARI” throughout the manuscript when relevant, and have also mentioned in the methods section of the manuscript (lines 101 – 104) that “ARI” are referring to any upper respiratory tract infection, influenza, influenza-like illnesses and common cold episodes, regardless whether the illness was clinically diagnosed, laboratory-confirmed or self-reported as defined by the study.

8. Line 29= who are deficient group and non-deficient groups? What mean deficient group and non-deficient groups

Authors: The participants in the micronutrient deficient and non-deficient groups were based on the “cut-offs” as defined by the respective authors of the included studies, as mentioned in lines 116 – 117 and detailed in Table 2.

9. Line 44= micronutrient deficiency is a part of undernutrition. So, how did you see this sentence?

Authors: Thank you for raising this. Micronutrient deficiency could be caused by a multitude of factors, including inadequacies in food intake especially in the populations from developing countries (due to socioeconomic factors) and in the elderly (due to personal preferences or socioeconomic factors as well). Thus, we have edited in the line 47.

10. Line 67-68=why you are only limited to four electronic data bases (PubMed, Cochrane Library, Embase and Scopus) were searched in January 2019 to identify observational studies?
Authors: These were the only four databases available and accessible. Furthermore, they are the major databases indexing articles with broad topics relevant to our discipline, particularly PubMed. These four large databases are also the main databases used for most systematic review studies.

11. Line 72= you are saying that language restrictions were not applied in the search strategy. But you are also saying in line 78-80= "Types of studies: Observational studies which included a comparator group in the study design i.e. case-control, cross-sectional and cohort study designs, and were reported in English". How did you see this contradiction?

Authors: Thank you for pointing this out. We did not apply language restrictions in the search strategy as we wanted to identify all studies relevant to our research question. After the primary screening stage, we found five non-English studies. We did attempt to get the English-translated version of the full article through our university library. However, the library could not find any English-translated version of the full-text. Since we were not able to interpret its contents, these studies were excluded.

We have added in the clarification above in lines 79 – 81: “However, only studies published in English were eventually selected as the reviewers were unable to accurately interpret the five potentially eligible non-English studies” and in the limitation sections in line 353-355 on publication bias.

12. Line 86= what about the mineral "iodine" which is the prevalent problem globally?

Authors: Thank you for pointing this out. We acknowledge that we should have had, but did not specifically include this mineral in our search strategy as we based our search mostly on micronutrients highlighted in the review by Maggini et al. (2007) [1]. At the point that review was published, the direct effects of iodine on the immune system remains elusive, although its importance in thyroid hormone synthesis is well established. This was until a cell study published in 2012 suggested a direct impact of thyroid-related molecules on the immune cells, highlighting the importance of iodine in the regulation of human immune cell function [2]. However, the aforementioned study was conducted in vitro and in vivo results could possibly differ. Thus, as iodine was not included in the review by Maggini et al (2007), it was not specifically searched for in the strategy. However, our search strategy (specifically the portion on “(deficiency[subheading] OR deficien*[Title/Abstract]) AND “(Micronutrients[MeSH] OR "micronutrient*"[Title/Abstract]) OR (Minerals[MeSH] OR mineral*[Title/Abstract])”) was sufficiently comprehensive and sensitive to include deficiency of all micronutrients, including iodine, even if they were not explicitly specified in the strategy.

Moreover, the latest score card from the Iodine Global Network suggests that insufficient iodine intake may not be as globally prevalent anymore, given that only 25 out of 174 countries surveyed had insufficient iodine intake based on the median urinary iodine concentration in school-age children [3]. Nevertheless, we have highlighted this point under the limitation section in line 345-347.
Reference:


13. Line 89-90= this criteria is not clearly consistent with your title/objective and is not well addressed. =Types of outcome measures: Reported episodes, duration (in days) and/or severity scores of cold (primary outcome) or CAP episodes (secondary outcome)???

Authors: We seek to clarify that the criteria mentioned in these lines are referring to the ARI incidence, especially the common cold, and its associated severity in healthy adults, which is explicitly stated as the aim in lines 66 – 68 in the manuscript. We were also interested in the association between CAP incidence and its associated severity as a secondary outcome, and thus included it as an outcome of interest in lines 96 – 97.

The criteria stated in lines 96 – 97 was consistent with our aim as the reported ARI or CAP episodes will indicate the respective disease incidence in the various micronutrient status groups, while the episode duration and/or severity scores correspond to the associated severity of the reported episode. The episode duration is considered a measure of severity as a more severe episode will require a longer recovery period, likewise for severity scores which translates subjective symptom severity into tangible scores. Thus, we believe that we will be able to measure the risk of ARI, specifically the common cold or CAP incidence and the associated severity across different micronutrient status groups with the criteria stated in lines 96 – 97.

14. Line 159=what information is missed? Try to explain it

Authors: Thank you for your suggestion. The missing information mentioned included mean population age and an explicit indication of a healthy status in the sample population. These missing information are already explained in lines 153 – 155, before Figure 1 was presented in Line 158.

15. Line 261-296=could you think that VDD can estimate or delegate for all the other micronutrients? Why you are trying to modify your title according to this sentence? "the small number of studies included in this review and identification of vitamin D as the sole micronutrient studied for the outcomes of interest in our target population highlights the paucity of such studies in this population" (my personal view).
Authors: Thank you for your comment. We do not think that the association between VDD and the outcomes of interest can be extrapolated to other micronutrients deficiency, and hence would like to highlight the need for more studies on other micronutrients’ deficiency on ARI, especially the common cold, or CAP incidence and their associated severity in our target population. This is so as our results clearly show a lack of studies on this area in a healthy adult population, given that our search only yielded studies on VDD although we searched for deficiency in micronutrients (general and specific micronutrients shown to have an effect on the immune system). Thus, we were not attempting to modify the review title through this sentence, but rather trying to show the need for more research in this area, in the healthy adult population in the future.

16. Line 322-324 = “Quality” in research refers to both methodological and reporting quality of a study” what is the point you give for the quality of the literatures? Or what is the criteria to high qualified literature?

Authors: Most reviews are only referring to the methodological quality of their included studies when the term “quality” was used, but our review was referring to both methodological and reporting quality. While the reporting quality of a study is not often assessed, it is of equal importance as methodological quality can affect the latter’s rating. This is so as a poorly reported study is more likely to misreport or omit key features needed for methods assessment of a primary study. Thus, it is also possible that the methodological quality of a well-designed and conducted study can be underestimated if it has a poor reporting quality. Therefore, I explicitly addressed the fact that quality of a study is relating to a study’s methods and reporting quality through this sentence in our review.

Currently, there is no universally accepted guidelines to classify the methodological and/or reporting quality of observational studies. Thus, we developed a framework to assign the various quality categories in this review, which are broad enough to be generalised to all observational studies. The specific methods used to assess the methodological and reporting quality of each study and their rationale have been documented in Additional File 3.