PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Is hemoglobin below 7.0 g/dl an optimal trigger for allogenic red blood cell transfusion in patients admitted to intensive care units? A meta-analysis and systematic review
AUTHORS	Yao, Ren; Ren, Chao; Zhang, Zi; Zhu, Yibing; Xia, Zhao Fan; YAO, Yongming

VERSION 1 - REVIEW

REVIEWER	Aryeh Shander TeamHealth Research Institute (THRI) Englewood Health, Englewood New Jersey, USA
REVIEW RETURNED	23-Apr-2019

GENERAL COMMENTS	This is a comprehensive analysis that is restricted to RCT on liberal versus restrictive transfusion of RBC in the critically ill. The authors have focused on transfusion triggers ()thresholds0 of Hgb equal or lower than 7 grams per deciliter. In addition, a subgroup analysis of septic patients was conducted. Although well conducted, the meta-analysis has some limitations mostly in terms of the low number of trails and the low number of endpoints with in these studies that the authors sought in use as their primary and secondary endpoints. A few comments. The objectives as described need to be better focused, The introduction can be improve in terms of the language structure. In many ways, they way it is written, the authors do not describe the controversies around poor benefit/risk ration of RBC transfusions, i.e., improved DO2 but not necessarily VO2. The authors address transfusion in sepsis as if it is part of the therapy, which it isn't. Last, the references used are old and new ones could better support their positions including the global number of units transfused.

REVIEWER	Barnaby Reeves Prof I was chief investigator for a large RCT of alternative transfusion thresholds after cardiac surgery.
REVIEW RETURNED	15-May-2019

GENERAL COMMENTS	This manuscript describes a systematic review and meta-analysis of randomized trials comparing restrictive and liberal transfusion triggers in intensive care patients, restricted to trials in which the

	restrictive trigger was <7 g/dl. I have concern about the choice of research question, some of the review methods used and the reporting of the findings. Abstract: I don't believe that is completely compliant with PRISMA for abstracts. The authors should ensure that it does. Choice of research question: The Introduction states that "no studies have reported the impact of the transfusion threshold of 7 g/dl on the short-term outcomes of critically ill patients or the financial value of a different transfusion strategy. Therefore, we performed a systematic review and meta-analysis in which we investigated differences between the 7 g/dl transfusion threshold and a lower threshold." (p6, 23-28) The justification for the specific eligibility ranges chosen (<7 vs 8.5 to 10 g/dl) is weak, in my view – what is the clinical relevance of restricting inclusion to studies with a restrictive transfusion trigger <7 g/dl (compared to including all studies comparing restrictive and liberal transfusion triggers)? In which direction is a treatment effect hypothesised and why? The rationale for this decision is of key importance because these ranges mean that some important studies are excluded. Otherwise, the review may have arises from an arbitrary choice (motivated by generating a "different" set of included studies and an "original" review, despite the large number of existing reviews) or specifically in order to bias the studies which are eligible (unlikely, given the overall conclusion that the objectives could not be adequately addressed because there insufficient studies/randomized participants). The English in this section of the paper is not of a high standard which makes it difficult to understand the authors' intentions. Review methods: "Only ICU patients were considered, while participants in other hospital departments with critical illnesses were not eligible." (p.8, 12-15) Why did the authors choose to specify eligibility in terms of hospital departments? The precise setting in which similar patients are treated may differ across health care systems. Analysis of length of hospital and intensive care stay as continuous variables (Figures 3 and 4) is inappropriate, especially when a high proportion of patients died in some studies (a patient who dies and is "discharged" to the mortuary is not the same as a patient who survives and is discharged to another care institution or home). At the very least, the authors should describe how they dealt with this issue. What was the justification for using a random effects model, e.g. different specific threshold triggers across trials? I think that publication bias should be described as "small study bias." I am uncertain about the publication status of some included studies (i.e. full paper vs abstract only). This is not clear from the descriptions of (a) eligibility criteria in the Methods, (b) included studies the Results or from the PRISMA diagram (Figure 1). The possibility that some included studies were reported only as abstracts became apparent to me only when reading the Discussion. I don't believe that including studies based on

	abstracts only is a valid approach; there is literature describing the extent to which reports of studies differ between abstracts and full papers. Abstracts are unlikely to report all of the information required to conduct the review. The authors report that they contacted corresponding authors for more information but do not comment on their success and the extent of missing or unclear data affecting the final analysis. Results: The risk of short-term mortality varied hugely across included studies (10% to >50%). The potential limitations of this variation is not considered. Risks of ischaemic / thromboembolic events also varied considerably. Discussion: Some of the points highlighted above should be covered under limitations. The potential strengths of the review depend on better justification of the research question. I am not a critical care doctor and cannot comment critically on the comprehensiveness of the Discussion with respect to other literature on similar research questions. References: Reference numbering is awry. Bergamin is cited in the text (Results, short-term mortality) as reference 19 but is listed as 20 (2014 paper) or 27 (2017 paper) in the reference list. The reference list is not consistently formatted and there are typographic errors in the reference list, e.g. “Holst … New England journal of medicine: 1381-912014.” I was unable to find the 2014 Bergamin trial in PubMed. Figures: Forest plots (X axes) should be labelled conventionally, as “favours restrictive” and “favours liberal” on either side of the line of no effect, for clarity.

REVIEWER	Benjamin Mayer Ulm University, Germany
REVIEW RETURNED	30-Jul-2019

GENERAL COMMENTS	Thank you for giving me the opportunity to review this systematic review and metaanalysis, which is overall well-written. I only have a few point to be reconsidered by the authors: 1) The "objectives" paragraph in the abstract makes no sense to me, something is wrong here or missing in the style of wording. 2) abstract, data sources: the authors could think of writing "standardized mean difference" instead of only "mean difference". 3) abstract, data sources: why did the authors exclusively applied random effects models to the data? I think the usual way is to base the decision for either fixed or random effects model on the I^2 statistic.

	4) materials and methods: i think that the exclusive use of random effects models are not conform with the PRISMA statement. 5) search strategy and information sources: did the authors use MeSh terms (medical subject headings)? 6) data synthesis and analysis: see my comments before (3+4): why was the decision for either fixed or random effects models not based on the I^2 measure as commonly done? 7) conclusions: i missed the relation to the conclusions formulated within the abstract (especially the hint to further studies needed in the field). 8) figures 3,4 and 5 would benefit from applying a fixed effects model in terms of smaller confidence intervals and p-values, respectively.

REVIEWER	R. David Hayward Ascension Saint John Hospital Detroit, Michigan USA
REVIEW RETURNED	31-Jul-2019

GENERAL COMMENTS	This paper presents a meta-analysis of RCTs comparing use of a threshold of 7g/dl hemoglobin for transfusion in adult ICU patients, in comparison to higher threshold. I have been requested to focus on statistical aspects of the paper, and from a methodological and statistical standpoint this is a very strong contribution -- it has been rigorously conducted and well-documented throughout. I have a few comments that I feel could be addressed. 1. The scale on the forest plots in Figures 3 and 4 is so large that it is very difficult to compare the lines. If possible it would be worth considering changing this from -100 - 100 to something like -25 to 25. 2. The explanation of how this study differs from other recent meta-analyses is useful and comprehensive, but comes very late in the manuscript. A briefer summary of how the scope of this meta-analysis differs from others (i.e., focus on studies with specific 7g/dl thresholds only, restriction to adult ICU patients) would be valuable to add in the introduction to provide more context. 3. There are issues with English grammar and usage throughout the manuscript that could be resolved with further editing.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 1
Reviewer Name: Aryeh Shander
Institution and Country: Team Health Research Institute (THRI), Englewood Health, Englewood New Jersey, USA
Please state any competing interests or state ‘None declared’: None
Please leave your comments for the authors below
This is a comprehensive analysis that is restricted to RCT on liberal versus restrictive transfusion of

RBC in the critically ill. The authors have focused on transfusion triggers (thresholds) of Hgb equal or lower than 7 grams per deciliter. In addition, a subgroup analysis of septic patients was conducted. Although well conducted, the meta-analysis has some limitations mostly in terms of the low number of trails and the low number of endpoints within these studies that the authors sought in use as their primary and secondary endpoints.
A few comments. The objectives as described need to be better focused, The introduction can be improve in terms of the language structure. In many ways, they way it is written, the authors do not describe the controversies around poor benefit/risk ration of RBC transfusions, i.e., improved DO_2 but not necessarily VO_2. The authors address transfusion in sepsis as if it is part of the therapy, which it isn't. Last, the references used are old and new ones could better support their positions including the global number of units transfused.
Response: Thanks very much for your comments and kind suggestions. The objective as described in Abstract has been edited to get a more focused description (Page 3, Lines 2-4 in Revised Manuscript without mark). The language structure of introduction has been improved to make a clear description. The controversies around poor benefit/risk ration of RBC transfusion has been provided in the revised manuscript, including the different reports around DO_2 and VO_2 (Page 7, Lines 10-18, Line 22; Page 8, Lines 1-10). As with transfusion in sepsis, it indeed a efficient remedy for septic shock patients, as recommended by Surviving Sepsis Campaign (SCC). The references were re-checked and refreshed for new citations, but some studies published before 2000 was included and cited with providing essential information, which can be removed or refreshed.

Reviewer: 2
Reviewer Name: Prof Barnaby Reeves
Institution and Country: University of Bristol, Bristol Heart Institute
Please state any competing interests or state 'None declared': I was chief investigator for a large RCT of alternative transfusion thresholds after cardiac surgery.
Please leave your comments for the authors below
This manuscript describes a systematic review and meta-analysis of randomized trials comparing restrictive and liberal transfusion triggers in intensive care patients, restricted to trials in which the restrictive trigger was <7 g/dl. I have concern about the choice of research question, some of the review methods used and the reporting of the findings.
Abstract:

I don't believe that is completely compliant with PRISMA for abstracts. The authors should ensure that it does.
Response: Thanks very much for your comments. We have checked and revised the format of the section of Abstract in accordance with the PRISMA checklist (Page 3, Lines 2-25, Page 4, Lines 1-2, in Revised Manuscript without mark).

Choice of research question:
The Introduction states that "no studies have reported the impact of the transfusion threshold of 7 g/dl on the short-term outcomes of critically ill patients or the financial value of a different transfusion strategy. Therefore, we performed a systematic review and meta-analysis in which we investigated differences between the 7 g/dl transfusion threshold and a lower threshold." (p6, 23-28) The justification for the specific eligibility ranges chosen (<7 vs. 8.5 to 10 g/dl) is weak, in my view – what is the clinical relevance of restricting inclusion to studies with a restrictive transfusion trigger <7 g/dl (compared to including all studies comparing restrictive and liberal transfusion triggers)? In which direction is a treatment effect hypothesised and why? The rationale for this decision is of key

importance because these ranges mean that some important studies are excluded. Otherwise, the review may have arises from an arbitrary choice (motivated by generating a “different” set of included studies and an “original” review, despite the large number of existing reviews) or specifically in order to bias the studies which are eligible (unlikely, given the overall conclusion that the objectives could not be adequately addressed because there insufficient studies/randomized participants). The English in this section of the paper is not of a high standard which makes it difficult to understand the authors’ intentions.
Response: Thanks very much for your comments. This study mainly focused on analyzing the impact of the transfusion threshold of 7 g/dl on the short-term outcomes of critically ill patients, which was based on clinical practice and extensive search of literatures. In fact, the transfusion threshold of 7 g/dl has been discussed over 20 years, but it still remains a controversy issue today. Additionally, the guidelines for RBC transfusion in septic settings are different among various organizations, such as the Surviving Sepsis Campaign (SCC), the American College of Critical Care Medicine (ACCM), and the World Health Organization (WHO). The SCC recommends blood transfusion in sepsis when the hemoglobin concentration drops below 7.0 g/dL, while blood transfusion that is initiated at 10 g/dL of hemoglobin concentration is recommended by ACCM. While the WHO suggests transfusion in patients with septic shock ‘if intravenous (IV) fluids do not maintain adequate circulation’, as a supportive measure of last resort. These guidelines on blood transfusion are mainly based on relative long-term outcomes, e.g. 90-day mortality and adverse reactions. The short-term outcomes also deserve to be taken into consideration on assessment of RBC transfusion, as it indicates the ICU stay of most critically ill patients. Therefore, we performed this meta-analysis and systematic review in discussing the impact of blood transfusion on short-term outcomes of critically ill patients when conducted at transfusion threshold of 7 g/dl.

Review methods:
“Only ICU patients were considered, while participants in other hospital departments with critical illnesses were not eligible.” (p.8, 12-15) Why did the authors choose to specify eligibility in terms of hospital departments? The precise setting in which similar patients are treated may differ across health care systems.
Response: Thanks for your comments. Indeed, the source of patients was restricted to ICU only as reported in our manuscript. The major objective of our study was to discuss and evaluate the impact of RBC transfusion at threshold of 7 g/dl on the short-term outcomes of critically ill patients, which involved comparisons in multiple outcomes, including short-term mortality, adverse reactions as well as consumption of RBC products and hospital cost. The ICU that was chosen as the distinct hospital department might be in favor of assessing potential benefits and harms of RBC transfusion in the treatment and cost of critically ill patients, especially when no significant difference was noted in mortality and adverse reactions. Therefore, specific eligibility of hospital departments, ICU as an example, will promote the application of the results into clinical practice. Similar patients might get different health care in different systems, but it doesn’t influence the conclusion with a rigorous inclusion criteria.

Analysis of length of hospital and intensive care stay as continuous variables (Figures 3 and 4) is inappropriate, especially when a high proportion of patients died in some studies (a patient who dies and is “discharged” to the mortuary is not the same as a patient who survives and is discharged to another care institution or home). At the very least, the authors should describe how they dealt with this issue.
Response: Indeed, this issue did exist in the RCTs we had incorporated. Given the fact that we could only obtain limited data as publications presented, which restricted us from controlling such risk of bias. If only we could get detailed data of each RCTs enrolled and performed individual patient data

(IPD) meta-analysis, can we partially tackle this problem. Therefore, we acknowledged this issue, as well as made a statement towards it within the manuscript (Page19, Lines 3-8). In addition, we ranked the outcome as low quality of evidence via GRADE methods.

What was the justification for using a random effects model, e.g. different specific threshold triggers across trials?
Response: We carefully considered reviewer's comments and revised the methodology accordingly. We replaced the exclusive use of random effect model by applying both fixed or random effect model, which was determined by the severity of heterogeneity for each outcome (Page 13, Lines 7-12).

I think that publication bias should be described as "small study bias."
Response: Thanks for your suggestions. The description of publication bias was changed into "small study bias" (Page 13, Line 12, Lines 14-15; Page 18, Lines 8, 9, 10, 12; Page 24, Lines 11-12).

I am uncertain about the publication status of some included studies (i.e. full paper vs. abstract only). This is not clear from the descriptions of (a) eligibility criteria in the Methods, (b) included studies the Results or from the PRISMA diagram (Figure 1). The possibility that some included studies were reported only as abstracts became apparent to me only when reading the Discussion. I don't believe that including studies based on abstracts only is a valid approach; there is literature describing the extent to which reports of studies differ between abstracts and full papers. Abstracts are unlikely to report all of the information required to conduct the review.

Response: The publication status of included studies has been provided in the "Result: Search results and the characteristics of the included studies" of revised manuscript (Page 14, Line 3). We did implement rigorous eligibility criteria for inclusion of studies, and the descriptions of eligibility criteria were edited and detailed in Methods, Results and PRISMA diagram, respectively. We also performed second search of literatures carefully to refresh these included studies, and found that the included abstract needed to be removed from this analysis due to error in the primary search and refresh during major revision. The study by Bergamin F et al, entitled "Transfusion requirements in septic shock patients: a randomized controlled trial" that published in 2014, was actually a part of the results from study of Bergamin F in 2017 entitled "Liberal Versus Restrictive Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial", which was included by mistake. We have removed the date from the abstract of Bergamin F in 2014 and conducted a second analysis. In addition, the abstract by Gobatto A et al was also an abstract that published in the form of conference abstract in 2017, which was found with full paper publication during the major revision of our manuscript. Thus, we checked both publications carefully and replaced the abstract by the full paper, and performed a second systematic analysis. We feel sorry about our careless search of literature in primary manuscript, and really hope the revised manuscript can be up to standard.

The authors report that they contacted corresponding authors for more information but do not comment on their success and the extent of missing or unclear data affecting the final analysis.
Response: The comments on more information that we required from the author of manuscript entitled "Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock" had been included into the revised manuscript (Page 17, Lines 3-9), which was also mentioned in the Acknowledge part (Page 26, Lines 12-15).

Results:
The risk of short-term mortality varied hugely across included studies (10% to >50%). The potential limitations of this variation is not considered. Risks of ischaemic / thromboembolic events also varied considerably.
Response: We greatly appreciate the reviewer's comments. Indeed, heterogeneity did exist in several outcomes, including primary outcome and ischemic events, while several attempts had been done to address this problem: (1) We performed sensitivity analysis and found that study conducted by Bergamin F et al was the main source of heterogeneity, remove of which could dramatically decrease heterogeneity (I^2 statistics from 50% to 29%, P value for χ^2test from 0.04 to 0.21); (2) Subgroup analysis was conducted as well, heterogeneity within sepsis and non-sepsis group displayed no statistical significance (I^2<50% and P>0.1); (3) We further did meta regression analysis by using STATA 12 software to find potential co-variates, while we observed no statistical significance of incorporated variates, including mean age, publication year, SAPS score at admission, sample size and study location; (4) We had mentioned this limitation within the section of Strengths and limitations. Moreover, we had illustrated yet analyzed the results of sensitivity analysis within the Discussion section, and provided rational explanation towards it (Page 19, Lines 15-20). We included an additional sensitivity analysis for the secondary outcome of ischemic events and stated it in the revised version (Page 18, Lines 4-6).

Discussion:
Some of the points highlighted above should be covered under limitations. The potential strengths of the review depend on better justification of the research question. I am not a critical care doctor and cannot comment critically on the comprehensiveness of the Discussion with respect to other literature on similar research questions.
Response: Thanks for your comments. The potential strength of the review was re-checked and edited based on better justification of the research question (Page 23, Lines 21-25; Page 24, Lines 1-2). Currently, the blood transfusion is prudently used in ICU patients, especially patients with septic shock due to a shortage of supply and stringent regulation. Previously published meta-analysis and system review mainly focused on discussing the impact of blood transfusion on long-term outcome of critically ill patients, but scarcely reported on short-term mortality. The short-term mortality, in our view, is much more suitable for assessing the efficiency of blood transfusion on the outcome of ICU patients.

References:
Reference numbering is awry. Bergamin is cited in the text (Results, short-term mortality) as reference 19 but is listed as 20 (2014 paper) or 27 (2017 paper) in the reference list. The reference list is not consistently formatted and there are typographic errors in the reference list, e.g. "Holst … New England journal of medicine: 1381-912014."
I was unable to find the 2014 Bergamin trial in PubMed.
Response: We sincerely appreciate your comments and careful works. We carefully reviewed and checked all the citations within the manuscript. We corrected the wrong format of citations and a few mistakes accordingly. The publication of citation of "2014 Bergamin" was attached below (doi: 10.1186/cc13302)

P112
Transfusion requirements in septic shock patients: a randomized controlled trial
F Bergamin[1], J Almeida[1], C Park[1], E Osawa[1], J Silva[1], F Galas[1], D Nagaoka[1], J Fukushima[1], S Vieira[1], L Candido[1], CO Oshiro[1], JL Vincent[2], L Hajjar[1]
[1]*Instituto do Cancer do Estado de São Paulo, Brazil;* [2]*Erasme Hospital, Université libre de Bruxelles, Brussels, Belgium*
Critical Care 2014, **18(Suppl 1):**P112 (doi: 10.1186/cc13302)

Figures:
Forest plots (X axes) should be labelled conventionally, as “favours restrictive” and “favours liberal” on either side of the line of no effect, for clarity.
Response: Many thanks for your valuable suggestions. We labelled each forest plot by “favors restrictive” and “favors liberal” on X axes (Fig. 2-7).

Reviewer: 3
Reviewer Name: Benjamin Mayer
Institution and Country: Ulm University, Germany
Please state any competing interests or state ‘None declared’: None declared.
Please leave your comments for the authors below
Thank you for giving me the opportunity to review this systematic review and metaanalysis, which is overall well-written. I only have a few point to be reconsidered by the authors:
1) The "objectives" paragraph in the abstract makes no sense to me, something is wrong here or missing in the style of wording.
Response: We are sincerely grateful for your comments. We revised the section of Objectives in the abstract to make it more understandable (Page 3, Lines 2-4 in Revised Manuscript without mark).

2) abstract, data sources: the authors could think of writing "standardized mean difference" instead of only "mean difference".
Response: We sincerely appreciate your comments. We chose mean difference (MD) instead of standardized mean difference (SMD) mainly based on several reasons: the dimension of hospital/ICU length of stay across the studies was of no discrepancy; the numerical value of across the studies was comparable. Given that, we believed that reporting pooled data by MD might be more appropriate than applying SMD.

3) abstract, data sources: why did the authors exclusively applied random effects models to the data? I think the usual way is to base the decision for either fixed or random effects model on the I^2 statistic.
Response: We are grateful for the reviewer’s suggestions. The consistent use of random effect models was based on several published literatures. Indeed, we did think it was inappropriate, and revised our manuscript accordingly. We abated the exclusive use of random effect models. Instead, we applied both χ^2 test and I^2 statistics to determine the severity of heterogeneity for each outcome, thereby choosing the correct model (fixed/random effects model) (Page 3, Line 15).

4) materials and methods: i think that the exclusive use of random effects models are not conform with the PRISMA statement.
Response: We changed the exclusive use of random effect models and stated the new approach in the section of Materials and methods, which was in line with the PRISMA statement in our perspective (Page 13, Lines 7-12).

5) search strategy and information sources: did the authors use MeSh terms (medical subject headings)?
Response: We did implicate several MeSH terms within our search strategy and we listed all the

MeSH terms we used in accordance with your suggestions (Page 10, Lines 8-11). Besides, we provided detailed search strategy in Supplementary File 1.

6) data synthesis and analysis: see my comments before (3+4): why was the decision for either fixed or random effects models not based on the I^2 measure as commonly done?
Response: As you suggests, we had abated the exclusive use of random effect models and applied both χ^2 test and I^2 statistics to determine the severity of heterogeneity for each outcome, thereby choosing the correct model.

7) conclusions: i missed the relation to the conclusions formulated within the abstract (especially the hint to further studies needed in the field).
Response: We revised the Conclusion part within the manuscript and deleted the statement about "Further studies are needed in the field" according to your comments.

8) figures 3,4 and 5 would benefit from applying a fixed effects model in terms of smaller confidence intervals and p-values, respectively.
Response: Thanks for your comments. Due to the mild heterogeneity (P value＞0.1 and I^2＜50%) observed within the outcome of hospital length of stay (Fig. 3), ICU length of stay (Fig. 4), as well as incidence of MI (Fig. 5), we applied fixed effect model according to our new statements. Meanwhile, we corrected Fig. 3-5 accordingly (Fig. 3-5).

Reviewer: 4
Reviewer Name: R. David Hayward
Institution and Country: Ascension Saint John Hospital, Detroit, Michigan, USA
Please state any competing interests or state 'None declared': None declared
Please leave your comments for the authors below
This paper presents a meta-analysis of RCTs comparing use of a threshold of 7g/dl hemoglobin for transfusion in adult ICU patients, in comparison to higher threshold. I have been requested to focus on statistical aspects of the paper, and from a methodological and statistical standpoint this is a very strong contribution -- it has been rigorously conducted and well-documented throughout. I have a few comments that I feel could be addressed.
1. The scale on the forest plots in Figures 3 and 4 is so large that it is very difficult to compare the lines. If possible it would be worth considering changing this from -100 - 100 to something like -25 to 25.
Response: Thanks for your valuable suggestions. We changed the scale of X axes in both Fig. 3 and Fig. 4 according to your recommendations (Fig. 3-4).

2. The explanation of how this study differs from other recent meta-analyses is useful and comprehensive, but comes very late in the manuscript. A briefer summary of how the scope of this meta-analysis differs from others (i.e., focus on studies with specific 7g/dl thresholds only, restriction to adult ICU patients) would be valuable to add in the introduction to provide more context.
Response: Many thanks to reviewer's comments. According to your suggestions, we added a brief summary of other systematic reviews and meta-analyses addressed the same topic. Moreover, we

illustrated the uniqueness of our study at the end of Introduction section as well (Page 8, Lines 1-16; Page 9, Lines 10-18 in Revised Manuscript without mark).

3. There are issues with English grammar and usage throughout the manuscript that could be resolved with further editing.
Response: Many thanks to your comments. We have consulted a native language specialist specialized at similar research field at American Journal Experts (AJE) website, and the editing certificate was provided as a separate file. We further asked an experienced English speaker to help checking and editing the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Benjamin Mayer Ulm University, Germany
REVIEW RETURNED	07-Oct-2019

GENERAL COMMENTS	I would like to thank the authors for carefully addressing my comments raised during the 1st review phase. Now the manuscript has improved and I suggest publication apart from some minor comments to be addressed: page 3, line 17: The authors had valid arguments to use "mean difference" instead of "standardized mean difference", nevertheless the correct terminology according to the cochrane handbook is "standardized mean difference". Please change. http://handbook-5-1.cochrane.org/chapter_9/9_2_3_2_the_standardized_mean_difference.htm page 3, line 18: fixed or random effects model. page 13, line 15: Please use SMD, see my comment above. page 13, line 20/21: random effect models....fixed effect models.

REVIEWER	R. David Hayward Ascension Saint John Hospital Detroit, Michigan USA
REVIEW RETURNED	02-Oct-2019

GENERAL COMMENTS	My comments on the initial draft have been fully addressed.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 4

Reviewer Name: R. David Hayward

Institution and Country:

Ascension Saint John Hospital

Detroit, Michigan

USA

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

My comments on the initial draft have been fully addressed.

Response: We sincerely appreciate your valuable comments and careful work, which largely improve the quality of this manuscript. Meanwhile, we want to express our deepest gratitude to your affirmation.

Reviewer: 3

Reviewer Name: Benjamin Mayer

Institution and Country: Ulm University, Germany

Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below

I would like to thank the authors for carefully addressing my comments raised during the 1st review phase. Now the manuscript has improved and I suggest publication apart from some minor comments to be addressed:

page 3, line 17:

The authors had valid arguments to use "mean difference" instead of "standardized mean difference", nevertheless the correct terminology according to the cochrane handbook is "standardized mean difference". Please change. http://handbook-5-1.cochrane.org/chapter_9/9_2_3_2_the_standardized_mean_difference.htm

Response: Thank you so much for suggestion and careful work. We carefully reviewed the cochrane handbook you provided, and changed the method of pooling continuous data from “mean difference” to “standardized mean difference” in accordance with your suggestion (Page 3, Lines 14-15; Page 13, Lines 6-7). Meanwhile, the figures and results were also revised correspondingly (Page 3, Lines 20-22; Page 17, Lines 18-25; Fig 3; Fig 4).

page 3, line 18:

fixed or random effects model.

Response: We have revised the sentence accordingly (Page 3, Lines 15-16).

page 13, line 15:

Please use SMD, see my comment above.

Response: We have replaced the “mean difference” by “standardized mean difference” accordingly (Page 13, Lines 6-7).

page 13, line 20/21:

random effect models....fixed effect models.

Response: We have revised the sentence accordingly (Page 13, Lines 11-12).