

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of Five Types of Selenium Supplementation for Treatment of Kashin-Beck disease in children: A Systematic Review and Network Meta-analysis
AUTHORS	Xie, Dongmei Liao, Yulin Yue, Jirong Zhang, Chao Wang, Yanyan Deng, Chuanyao Chen, Ling

VERSION 1 – REVIEW

REVIEWER	Jose M. Ordonez-Mena University of Oxford, Nuffield Department of Primary Care and Health Sciences, Medical Statistics Group
REVIEW RETURNED	07-Jun-2017

GENERAL COMMENTS	<p>The authors have used a novel approach to consider all Selenium-related treatments for Kashin-Beck Disease (KBD).</p> <p>My main concern is the lack of direct evidence for some of the comparisons, which does not mean that network meta-analysis is not plausible, but that the indirectness of the network meta-analysis estimates needs to be considered. Plus, there is substantial risk of bias in the included RCTs. Thus, the confidence in the estimates will probably need to be down rated using the GRADE approach. SUCRA values may be misleading and need to be considered jointly with the GRADE confidence in the estimates for each comparison. The authors need to take this into consideration in the discussion of their findings and mention it in the abstract.</p> <p>Furthermore, I miss the implications of their research on practice (at least in the abstract). What treatments is then recommended firstly and under which conditions should the other treatments then be used (e.g. when the first treatment is too expensive or unavailable in other countries in which this disease is prevalent).</p> <p>Major Points:</p> <p>1) Authors need to use the GRADE approach to rate the quality of the evidence: http://www.bmj.com/content/349/bmj.g5630. The authors should also include some information about the risk of bias and quality of the evidence in the abstract. Consider deleting other less relevant information from the abstract.</p> <p>2) Was the assumption of transitivity evaluated? See relevant reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4084629/</p>
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3) Authors could combine pairwise and network meta-analysis estimates in Table 1 to enable readers to directly compare them in one single table/figure. In footnote “#” I suggest writing: “ORs represent odds of repair in row-treatment versus column-treatment. ORs larger than 1 denote higher repair rate in row-treatment than column-treatment”.

4) The authors need to include a Summary of Findings Table at least for each intervention in comparison to placebo including confidence in the estimates of effect (estimated using GRADE approach for network meta-analysis) as shown in: http://handbook.cochrane.org/chapter_11/figure_11_5_a_example_of_a_summary_of_findings_table.htm

5) Please, provide a table with number allocated to intervention and number healed to allow others to reproduce your findings.

6) In page 8 paragraph “Intervention-control pairwise meta-analyses”, it is mentioned “A few RCTs reported direct comparisons among active interventions” however, it is not specified which ones and the OR estimates from meta-analysis and individual studies are mixed in the same sentence (see lines 190 to 193).

7) In line204: “For the comparison between active treatments, no significant differences were found”, which means that aside from placebo, neither of these drugs is better than each other. This is also seen in the figure including the ranking of treatments using SUCRA.

8) In lines 206-208: There was no inconsistency between direct and indirect evidences according to the design by-treatment interaction model ($P=0.88$), implying that direct and indirect evidence were mainly consistent (Fig 4).” Or alternatively that there is insufficient power to detect inconsistencies due to the lack of direct comparisons for the majority of designs.

9) Authors need to provide more detail in Figure 4 for authors unfamiliar with network meta-analysis methods: What are the labels? What design does each row correspond to? What does IF means (inconsistency factor?). What is the x-axis (SMD)? What is the vertical line (no inconsistency, $SMD=0$)?. Why are 95%CIs truncated? 95%CIs including the null, indicate insufficient evidence of inconsistency, etc.

Minor Points:

1) Provide list of excluded studies (full-text) in the appendix.

2) Fig 1 typo in penultimate box: “studies included in qualitative synthesis(n”. Please correct.

3) Please, highlight more clearly multi-arm trials in Fig 1 and also in Appendix Table 1.

3) Check Fig 2 and Fig 4 label for Placebo and not “Palcebo”

4) Consider using full intervention names instead of abbreviations in Fig 2, or at least provide the names in the figure legend. Also applicable to other tables and figures.

5) Please, delete diamonds for comparisons “se vs VC”, “Se vs Se+VC”, “Se vs Selenium yeast”, and “selenium yeast vs placebo” as only one study was available and thus no meta-analysis was performed. Plus, the squares are annoyingly overlapping with the diamonds.

6) Choice of random effects model in pairwise meta-analysis is mentioned for the first time in the results. Please, motivate the choice in the methods section. Is it random effects also used in network meta-analysis?

	<p>7) There is a typo in the 95% CI in line 191, the upper confidence limit is shown as 8.20, while in figure 3 it shows 8.02.</p> <p>8) In line 193 the authors wrote "in these group". Suggest writing "...in these groups..." of "...for these drugs...".</p> <p>9) In lines 196-97, the sentence "There were no significant differences were noted in other active interventions comparisons" does not make sense. Remove the second "were".</p> <p>10) In line 210: "...showing a trend to be coincide with direct results". Replace by "...showing a trend to coincide with direct results".</p> <p>11) Table 2, there is a typo in he</p>
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REVIEWER	Fangfang Yu Institution and Country
REVIEW RETURNED	20-Jul-2017

GENERAL COMMENTS	<p>This manuscript mainly was to compare the effectiveness of five kinds of selenium supplementation (Se tablet, Se salt, Se enriched yeast, Se + VE, as well as Se + VC) for the treatment with Kashin-Beck disease (KBD), and rank their effectiveness based on their performance. Different meta-analysis and systematic review have confirmed the benefits of selenium supplementation for the primary prevention of children KBD. Therefore, the conclusion has shown some novel foundation about the effective of selenium salt ranked most. So, I would like suggest it could be publication after a minor revision. The main comments and suggestion for this manuscript are as the following:</p> <p>[1] Line 76 in Page 3: The onset age of KBD patients were most occurred in the children aged 5~15 years old. Selenium supplement was used to prevent the incidence of KBD in Children. Therefore, it is not part of potential limitations. Please revise it.</p> <p>[2] Line 82-84 in Page 4: The distribution of KBD patients were covered in 14 Provinces, not just Hei Longjiang, Gan Su, Shan Xi, Qing Hai, Si-chuan and Tibet provinces. The Shan Xi also has been written incorrectly. Please revise it.</p> <p>[3] Eligibility criteria in Page 5: The diagnostic criteria for KBD patients haven't been described in eligibility criteria. Please list it.</p> <p>[4] Line 133-135 in Page 6: Fingers of KBD patients may occur the metaphyseal and epiphysis lesions in X-ray film. Why you just choose the repair of metaphyseal consider as judgment standard of X-ray for treatment effect of KBD?</p> <p>[5] In the Appendix table 1: The outcome index included X-ray improvement and improvement of metaphyseal lesions on X-ray, they are two different outcome indexes to measure the benefits of selenium. So, why you can pool the ORs in Fig. 3 and Fig.4 using the different outcome indexes?</p> <p>[6] In the Appendix table 2: The risk of bias of included studies hasn't been described in the statistical analysis.</p>
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REVIEWER	Shijie Ren University of Sheffield
REVIEW RETURNED	23-Aug-2017

GENERAL COMMENTS	<p>Xie et al performed a systematic review and network meta-analysis to determine the efficacy of five types of selenium supplementation for treating Kashin-Beck disease in children in China. The PRISMA guidelines were followed, but there are several issues with the conducted network meta-analysis.</p> <p>Data were extracted to the nearest 12 months. Duration of the follow-up varied from 6 to 36 months. But there were no assessment and discussion on the potential impact of the time. The statistical analysis was conducted using STATA, but there was no description of the actual model used, for example a fixed effect vs. a random effects model. The network meta-analysis computed in STATA uses a frequentist approach instead of a Bayesian approach. However, authors still describe their results using credible intervals as if it was from a Bayesian network meta-analysis. The OR from Cai 2005 was estimated with a point estimate of 303.55 and 95% CI (16.03, 5746.39) which doesn't seem to be very plausible. However, authors didn't provide the data used in the analysis. Hence, it's difficult to determine the cause of this rather large OR in this particular study.</p>
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VERSION 1 – AUTHOR RESPONSE

Dear Editor,

Thank you for giving us the opportunity to revise our manuscript. We have considered the reviewers' comments and responded to each of them below. We have made changes in the manuscript and have kept them in blue writing for your convenience. In addition, the typographical/grammatical errors have been corrected in the revised manuscript. Dr. Joseph H. Flaherty has thoroughly proofread and revised the article.

Sincerely,

Jirong Yue

Responses to Comments of Editor

Editor's Comments to Author:

Editorial Requirements:

- Please work to improve the quality of the English throughout your manuscript. We encourage you to ask a native English speaking colleague to assist you.

Author's Response: Thank you for the suggestion, the typographical/grammatical errors have been corrected in the revised manuscript. Dr. Joseph H. Flaherty has thoroughly proofread and revised the article.

Comments from the Associate Editor:

In the Methods please give a clinical perspective on how the condition is diagnosed and managed.

Author's Response: Thank you for the comments. We have revised in METHODS.

1. What dose of Selenium is used in the supplements?

Author's Response: Thank you for the comments. In the included studies, dosage and course of each type of selenium supplementation varied across studies. In fact, we have provided the information of the dosage regimen of each study. More details please see in the Appendix table 1 Characteristics of included trials. In addition, we add a sentence to clarify it: "the characteristics (e.g. interventions dosage, route of administration, duration of treatment, the follow-up period, and outcomes) are presented in the online supplementary Appendix table 2"

2. The search dates in Abstract and Methods don't match (Abstract says up to Oct 2016, Methods says March 2017)

Author's Response: Thank you for the suggestion. It is a typo. The search dates has been revised in Abstract.

3. The dates of the studies are all very old – the most recent was 2005 – 12 years ago. Can you explain why this is?

Author's Response: There are 2 reasons: (1) After implementation of comprehensive prevention measures of KBD, the incidence of KBD has decreased to 0.3% since 2000. The low incidence of KBD also may explain why there has not been any studies about Se treatment for KBD published in recent years; (2) Since KBD among children has almost disappeared, it unlikely that government will support studies to demonstrate the clinically relevant benefit of any selenium supplementation for children with KBD. We have explained this in Discussion.

4. Can you provide an overall assessment of study quality for each study.

Author's Response: Thank you for the suggestion. We have added an overall assessment of study quality in Result and Discussion. More details please see in the Appendix table 2 Risk of Bias of Included Studies. In addition, we applied GRADE system based GRADE working group (see table 1).

5. Can you say in the Discussion what your findings mean for clinical practice?

Author's Response: We are glad you asked about this and that we have the opportunity to revise this section: "Se salt was ranked the most effective, it can be an economical and convenient strategy for control KBD in endemic areas. However, selenium over-dose will be toxic. Therefore, suitable dosage should be strictly controlled and content of selenium should be closely monitored in order to avoid harmful effects on health."

Responses to Comments of Reviewer 1

Reviewer Name: Jose M. Ordonez-Mena

Reviewers' Comments to Author:

The authors have used a novel approach to consider all Selenium-related treatments for Kashin-Beck Disease (KBD).

My main concern is the lack of direct evidence for some of the comparisons, which does not mean that network meta-analysis is not plausible, but that the indirectness of the network meta-analysis estimates needs to be considered. Plus, there is substantial risk of bias in the included RCTs. Thus, the confidence in the estimates will probably need to be down rated using the GRADE approach. SUCRA values may be misleading and need to be considered jointly with the GRADE confidence in the estimates for each comparison. The authors need to take this into consideration in the discussion of their findings and mention it in the abstract.

Furthermore, I miss the implications of their research on practice (at least in the abstract). What treatments is then recommended firstly and under which conditions should the other treatments then be used (e.g. when the first treatment is too expensive or unavailable in other countries in which this disease is prevalent).

1. Major Points:

1) Authors need to use the GRADE approach to rate the quality of the evidence:

<http://www.bmj.com/content/349/bmj.g5630>. The authors should also include some information about the risk of bias and quality of the evidence in the abstract. Consider deleting other less relevant information from the abstract.

Author's Response: This is a great point. We totally agree with your suggestions. We have used the GRADE approach to rate the quality of the evidence (see table 1). In addition, we add some sentence to explain how to do the GRADE: *"In our review, we applied GRADE system to NMAs based GRADE working group. The methods of rating the quality of direct comparison are the same to use GRADE in traditional meta-analysis. We downgraded the evidence from "high quality" by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, inconsistency, imprecision of effect estimates or potential publication bias. The rating of the quality of the indirect estimates is based on the ratings of the two pairwise estimates that contributes to the indirect estimate of the comparison of interest. The lower confidence rating of the two direct comparisons constitutes the confidence rating of the indirect comparison. When both direct and indirect evidence are available, we used the higher of the two quality ratings as the quality rating for NMA estimate."* Moreover, we have revised abstract.

2) Was the assumption of transitivity evaluated? See relevant reference:
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4084629/>

Author's Response: This is a very valid point. We have evaluated the intransitivity in the GRADE and presented it in Method Section: *"In addition, we need to concern that the intransitivity among different groups and the inconsistency between direct comparison and indirect comparison."*

3) Authors could combine pairwise and network meta-analysis estimates in Table 1 to enable readers to directly compare them in one single table/figure. In footnote "#" I suggest writing: "ORs represent odds of repair in row-treatment versus column-treatment. ORs larger than 1 denote higher repair rate in row-treatment than column-treatment".

Author's Response: Thank you very much for your comments and suggestions. As suggested, we have combine pair-wise and network meta-analysis estimates in Table 1(now is table 2). In addition, we have revised the footnote.

4) The authors need to include a Summary of Findings Table at least for each intervention in comparison to placebo including confidence in the estimates of effect (estimated using GRADE approach for network meta-analysis) as shown in:
http://handbook.cochrane.org/chapter_11/figure_11_5_a_example_of_a_summary_of_findings_table.htm

Author's Response: Thank you for the suggestion. We have added a Summary of Findings Table for each intervention in comparison to placebo . Please see in Table 3 Summary of findings for more details.

5) Please, provide a table with number allocated to intervention and number healed to allow others to reproduce your findings.

Author's Response: Thank you for your suggestion and we totally agree. We have added a table to present the number allocated to intervention and number healed. More details please see in the Appendix table 4.

6) In page 8 paragraph "Intervention-control pairwise meta-analyses", it is mentioned "A few RCTs reported direct comparisons among active interventions" however, it is not specified which ones and the OR estimates from meta-analysis and individual studies are mixed in the same sentence (see lines 190 to 193).

Author's Response: Thank you for your comments very much. We have rewritten this section and clarified it: "There were two RCTs compared Se with VC, and the result of traditional meta-analysis showed that no significant difference was found between Se and VC^{23, 31}. For Se+ VC compared to VC, the pooled OR of two RCTs also showed no significant difference existed (OR 1.15, 95% CI: 0.51 – 2.63, P=0.93)^{31, 33}. There was only one RCT for Se vs. Se +VC³¹, Se vs. Se yeast²⁶, Se salt vs. Se + VC³¹, Se salt vs. VC³¹, respectively."

7) In line204: "For the comparison between active treatments, no significant differences were found", which means that aside from placebo, neither of these drugs is better than each other. This is also seen in the figure including the ranking of treatments using SUCRA.

Author's Response: We are glad you asked about this and that we have the opportunity to explain it. Whether there is a significant differences only represented the result of direct comparison between two treatments. A ranking of SUCRA represented the ranking probability for all treatments, which was not associated with the result of direct comparison.

8)In lines 206-208: There was no inconsistency between direct and indirect evidences according to the design by-treatment interaction model (P=0.88), implying that direct and indirect evidence were mainly consistent (Fig 4)." Or alternatively that there is insufficient power to detect inconsistencies due to the lack of direct comparisons for the majority of designs.

Author's Response: Thank you so much for your comments. The results were calculated based on the current sample size. $P=0.88$ means that the overall result was consistent. In fact, there was no necessary correlation between consistency and the lack of direct comparison.

9) Authors need to provide more detail in Figure 4 for authors unfamiliar with network meta-analysis methods: What are the labels? What design does each row correspond to? What does IF means (inconsistency factor?). What is the x-axis (SMD)? What is the vertical line (no inconsistency, $SMD=0$?). Why are 95% CIs truncated? 95% CIs including the null, indicate insufficient evidence of inconsistency, etc.

Author's Response: This is a great point. We have already revised Figure 4 and Figure Legends according to your suggestions.

2. Minor Points:

1) Provide list of excluded studies (full-text) in the appendix.

Author's Response: Thank you for your suggestion. We have added a list of excluded studies in the appendix table 1.

2) Fig 1 typo in penultimate box: "studies included in qualitative synthesis(n". Please correct.

Author's Response: Thank you for bringing attention to this. It is a typo. We have corrected the errors.

3) Please, highlight more clearly multi-arm trials in Fig 1 and also in Appendix Table 1.

Author's Response: Thank you for your suggestion. We have revised.

3) Check Fig 2 and Fig 4 label for Placebo and not "Palcebo"

Author's Response: Thank you for the suggestion. It is a typo. We have corrected the errors in Figures.

4) Consider using full intervention names instead of abbreviations in Fig 2, or at least provide the names in the figure legend. Also applicable to other tables and figures.

Author's Response: Thank you for the suggestion. We have provided the full intervention names of each intervention in the figures legends and tables' footnotes.

5) Please, delete diamonds for comparisons "se vs VC", "Se vs Se+VC", "Se vs Selenium yeast", and "selenium yeast vs placebo" as only one study was available and thus no meta-analysis was performed. Plus, the squares are annoyingly overlapping with the diamonds.

Author's Response: Thank you for your suggestion. We have used a new figure 3 to replace old one.

6) Choice of random effects model in pairwise meta-analysis is mentioned for the first time in the results. Please, motivate the choice in the methods section. Is it random effects also used in network meta-analysis?

Author's Response: Thank you for the suggestion. We have added a sentence to describe the choice of model in the methods section. A random effects model was used both in the pairwise and network meta-analyses.

7) There is a typo in the 95% CI in line 191, the upper confidence limit is shown as 8.20, while in figure 3 it shows 8.02.

Author's Response: Thank you for bringing attention to this. We have corrected this typo in the revised manuscript.

8) In line 193 the authors wrote "in these group". Suggest writing "...in these groups..." or "...for these drugs...".

Author's Response: Thank you for the suggestion. We have revised it.

9) In lines 196-97, the sentence "There were no significant differences were noted in other active interventions comparisons" does not make sense. Remove the second "were".

Author's Response: Thank you for the suggestion. We have corrected this typo.

10) In line 210: "...showing a trend to be coincide with direct results". Replace by "...showing a trend to coincide with direct results".

Author's Response: Thank you for the comment. We have made the revision according to your suggestion.

11) Table 2, there is a typo in heading of column 2, authors wrote "SCURA" instead of "SUCRA". Show abbreviations in a footnote.

Author's Response: Thank you for reminding me of this typo. We have corrected this typo in Table 2 and add a footnote to interpret the meaning of abbreviations.

Responses to Comments of Reviewer 2

Reviewer Name: Fangfang Yu

Reviewers' Comments to Author:

This manuscript mainly was to compare the effectiveness of five kinds of selenium supplementation (Se tablet, Se salt, Se enriched yeast, Se + VE, as well as Se + VC) for the treatment with Kashin-Beck disease (KBD), and rank their effectiveness based on their performance. Different meta-analysis and systematic review have confirmed the benefits of selenium supplementation for the primary prevention of children KBD. Therefore, the conclusion has shown some novel foundation about the effective of selenium salt ranked most. So, I would like suggest it could be publication after a minor revision. The main comments and suggestion for this manuscript are as the following:

[1] Line 76 in Page 3: The onset age of KBD patients were most occurred in the children aged 5~15 years old. Selenium supplement was used to prevent the incidence of KBD in Children. Therefore, it is not part of potential limitations. Please revise it.

Author's Response: Thank you for the suggestion. We have deleted this sentence.

[2] Line 82-84 in Page 4: The distribution of KBD patients were covered in 14 Provinces, not just Hei Longjiang, Gan Su, Shan Xi, Qing Hai, Si-chuan and Tibet provinces. The Shan Xi also has been written incorrectly. Please revise it.

Author's Response: Thank you for the comment. We have revised it. To keep a sentence to describe the distribution: "KBD is prevalent in 377 counties of 14 provinces in China, with 0.64 million cases" and delete the specific list of those provinces.

[3] Eligibility criteria in Page 5: The diagnostic criteria for KBD patients haven't been described in eligibility criteria. Please list it.

Author's Response: Thank you for your suggestion. We have added these sentence: "The diagnostic criteria for KBD is Diagnosis Criteria for Kashin-Beck Disease (GB16003-1995), which was developed by National Health and Family Planning Commission of the People's Republic of China."

[4] Line 133-135 in Page 6: Fingers of KBD patients may occur the metaphyseal and epiphysis lesions in X-ray film. Why you just choose the repair of metaphyseal consider as judgment standard of X-ray for treatment effect of KBD?

Author's Response: Thank you for bringing attention to this. Only five studies reported repairing rate at the distal end of phalanges in hands on X-ray films. The number of included RCTs is too small to do a network meta-analysis. Therefore, we just choose the repair of metaphyseal consider as judgment standard of X-ray for treatment effect of KBD.

[5] In the Appendix table 1: The outcome index included X-ray improvement and improvement of metaphyseal lesions on X-ray, they are two different outcome indexes to measure the benefits of selenium. So, why you can pool the ORs in Fig. 3 and Fig.4 using the different outcome indexes?

Author's Response: Thank you for bringing attention to this. "X-ray improvement" means the study reported two kinds of outcomes: "Improvement of metaphyseal lesions on X-ray & Repairing rate at the distal end of phalanges in hands on X-ray films." Sorry for bringing misunderstanding, we have revised in the Appendix table.

[6] In the Appendix table 2: The risk of bias of included studies hasn't been described in the statistical analysis.

Author's Response: Thank you for your suggestion. We have used the GRADE approach to rate the quality of the evidence (see table 1). In addition, we add some sentence to explain how to do the GRADE: *In our review, we applied GRADE system to NMAs based GRADE working group. The methods of rating the quality of direct comparison are the same to use GRADE in traditional meta-analysis. We downgraded the evidence from "high quality" by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, inconsistency, imprecision of effect estimates or potential publication bias. The rating of the quality of the indirect estimates is based on the ratings of the two pairwise estimates that contributes to the indirect estimate of the comparison of interest. The lower confidence rating of the two direct comparisons constitutes the confidence rating of the indirect comparison. When both direct and indirect evidence are available, we used the higher of the two quality ratings as the quality rating for NMA estimate.*

Responses to Comments of Reviewer 3

Reviewer Name: Shijie Ren

Reviewers' Comments to Author:

Data were extracted to the nearest 12 months. Duration of the follow-up varied from 6 to 36 months. But there were no assessment and discussion on the potential impact of the time. The statistical

analysis was conducted using STATA, but there was no description of the actual model used, for example a fixed effect vs. a random effects model. The network meta-analysis computed in STATA uses a frequentist approach instead of a Bayesian approach. However, authors still describe their results using credible intervals as if it was from a Bayesian network meta-analysis. The OR from Cai 2005 was estimated with a point estimate of 303.55 and 95% CI (16.03, 5746.39) which doesn't seem to be very plausible. However, authors didn't provide the data used in the analysis. Hence, it's difficult to determine the cause of this rather large OR in this particular study.

Author's Response: Thank you very much for your valuable comments and suggestions, and I will answer your questions one by one as follow:

- 1) In our study, we conducted pair-wise meta-analysis by using a random effects model in STATA. We have already added the information about the selection of models in the method section.
- 2) We performed network meta-analysis in STATA by using a frequency approach, and we calculated the OR and its 95% confidence intervals (CI) as the effect estimates as described in the method section. It is a typo in the results section. We have corrected this typo in the revised manuscript.
- 3) In the study of Cai 2005, the patients were divided into sodium selenite group (N=31) and placebo group (N=31). According to the original data of this study, all patients in the sodium selenite group showing improvement of metaphyseal lesions on X-ray, while only 5 patients in placebo group. The result of this RCT showed that sodium selenite was far superior to placebo in repairing metaphyseal lesions. This may explain the reason of the large OR and wide confidence intervals of this particular study.

VERSION 2 – REVIEW

REVIEWER	Jose M. Ordonez-Mena Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
REVIEW RETURNED	17-Oct-2017

GENERAL COMMENTS	<p>The authors have taken into account most of the reviewers' comments and I believe the manuscript has greatly improved. However, there are still some issues that I would like to point out to the authors:</p> <p>1) The Summary of Findings Table 2 could be labelled clearer, what do the absolute numbers represent? Is it number of patients with a repaired metaphyseal lesion? If so, risk may not be the best wording to define these two columns as it has negative connotations. Rate is a more appropriate term. However, a quotient of these two absolute risks/rates should produce a relative risk and not an odds ratio (OR). While the ORs could be directly calculated from the data, it may be useful to show in the columns the odds of repair. Also, expressing absolute effects in thousands maybe an exaggeration, taking into account that the largest study included a bit over 200 patients. Maybe the authors want to consider expressing these in hundreds?</p> <p>2) Figure 1 Network Plot. The authors should highlight the multi-arm</p>
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	<p>trials i.e. Zhou et al 1991 (4 arms), Cui et al 1984 (3 arms), and Chen et al 2003 (3 arms).</p> <p>3) Figure 4. Please revise the typo within the figure's subtitle. It is placebo and not "palcebo". Also, it is unclear what number is shown next to 0 in the X-axis. The x-axis appears to be in the logarithmic scale, because of the definition of IF as the absolute value of the difference between the direct and indirect evidence log odd ratios. The actual wording in the figure caption is confusing: "IF is the absolute inconsistency factor, meaning the logarithm of the rate ratio for OR (RoR) of direct and indirect evidence for each comparison loop". I believe you meant: "IF is the absolute inconsistency factor, meaning the logarithm of the ratio of odds ratios (RoR) of direct and indirect evidence for each comparison loop".</p> <p>4) Se+VE vs. placebo in Table 1 has a GRADE of Low, while in Very Low in Table 2. Please, correct.</p> <p>5) I suggest the authors remove table 4 and add SUCRA (%) column to Summary of Findings Table 2. Please, also consider ranking the rows in Table 2 according to SUCRA values.</p> <p>6) In the limitations of the study, it is acknowledged that heterogeneity was high. However, I see no I² estimates in the results or tables. Please, report these.</p> <p>7) Please correct the formatting of all tables i.e. vertical and horizontal lines are showing/missing at random.</p> <p>8) Conclusion: The ranking of Se salt and Se + VE is nearly the same (1.8 vs. 2) so I would refrain from concluding (both in the abstract and in the discussion) that Se salt ranked the most effective. In fact, the results for Se salt are just based on one trial with 59 participants, 4 interventions, and unclear risk of bias. I would rather limit the conclusion to saying that all interventions were more effective than placebo and so that selenium supplementation is of help in repairing metaphyseal lesions. The quality of the evidence is insufficient to draw a conclusion about what method of selenium supplementation is most effective.</p>
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REVIEWER	Yu Fang Fang Xi'an Jiaotong University
REVIEW RETURNED	18-Oct-2017

GENERAL COMMENTS	The response to reviewers have not been found out in the author's manuscript. Therefore, it is difficult to check the response to my suggestion. Please upload it.
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REVIEWER	Shijie Ren University of Sheffield, UK
REVIEW RETURNED	21-Oct-2017

GENERAL COMMENTS	The revised manuscript has addressed most of the comments. However, there were still no assessment and discussion on the potential impact of different study follow-ups.
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	<p>Minor comments:</p> <p>p8 line 51: change “predictive” to “prediction”</p> <p>p8 line 51: modify the sentence “The PrI interval shows the degree of uncertainty around estimated treatment effects.” so that it reflects that both CI and PrI provide uncertainty around the estimated effects. PrI gives a range for the predicted parameter value in a new study.</p> <p>p9 line 13: change “chi-square” to “chi-squared”</p> <p>Page18 line 9: the claim “Consequently, estimates in our analysis were more precise than the pair-wise meta-analyses.” is not necessarily true. Some of the results from NMA were less precise than the pair-wise MA.</p> <p>It will be useful to provide the data used in the analyses.</p> <p>Use capital “T” for table.</p>
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VERSION 2 – AUTHOR RESPONSE

Dear Editor,

Thank you for giving us the opportunity to revise our manuscript again. We have considered the reviewers’ comments and responded to each of them below.

Sincerely,
Jirong Yue

Reviewer: 1

The authors have taken into account most of the reviewers’ comments and I believe the manuscript has greatly improved.

However, there are still some issues that I would like to point out to the authors:

1) The Summary of Findings Table 2 could be labelled clearer, what do the absolute numbers represent? Is it number of patients with a repaired metaphyseal lesion? If so, risk may not be the best wording to define these two columns as it has negative connotations. Rate is a more appropriate term. However, a quotient of these two absolute risks/rates should produce a relative risk and not an odds ratio (OR). While the ORs could be directly calculated from the data, it may be useful to show in the columns the odds of repair. Also, expressing absolute effects in thousands maybe an exaggeration, taking into account that the largest study included a bit over 200 patients. Maybe the authors want to consider expressing these in hundreds?

Thank you for your suggestion and we agree with you. We have revised Table 2 as: “Risk \diamond Repair rate”; “per 1000 \diamond per 100”. The reason of using OR for relative effect is that we want to keep consistence with the data in table 3.

2) Figure 1 Network Plot. The authors should highlight the multi-arm trials i.e. Zhou et al 1991 (4 arms), Cui et al 1984 (3 arms), and Chen et al 2003 (3 arms).

Thank you for the suggestion. We have revised the figure 1 and added note in Figure 2 caption.

3) Figure 4. Please revise the typo within the figure’s subtitle. It is placebo and not “palcebo”. Also, it is unclear what number is shown next to 0 in the X-axis. The x-axis appears to be in the logarithmic scale, because of the definition of IF as the absolute value of the difference between the direct and

indirect evidence log odd ratios. The actual wording in the figure caption is confusing: "IF is the absolute inconsistency factor, meaning the logarithm of the rate ratio for OR (RoR) of direct and indirect evidence for each comparison loop". I believe you meant: "IF is the absolute inconsistency factor, meaning the logarithm of the ratio of odds ratios (RoR) of direct and indirect evidence for each comparison loop".

Thank you for the suggestion. We have revised the figure 4 and figure caption.

4) Se+VE vs. placebo in Table 1 has a GRADE of Low, while in Very Low in Table 2. Please, correct. Thank you for the comment. Se+VE vs. placebo has a "very low" grade rating in direct evidence which is consistent with the quality of evidence in table 2. However, it has a "Low" grade rating in indirect evidence. When both direct and indirect evidence are available, we used the higher of the two quality ratings as the quality rating for the NMA estimate. So we rate the quality of network meta-analysis evidence as "low" instead of "very low".

5) I suggest the authors remove table 4 and add SUCRA (%) column to Summary of Findings Table 2. Please, also consider ranking the rows in Table 2 according to SUCRA values.

Thank you for the suggestion. However, table 4 is the probabilistic ranking of effectiveness of different interventions. Table 2 is the summary of finding for each selenium supplements compare to placebo and did not included indirect evidence. Therefore, we think Table 4 cannot be removed.

6) In the limitations of the study, it is acknowledged that heterogeneity was high. However, I see no I² estimates in the results or tables. Please, report these.

Thank you for the suggestion. We have added I² in the text of Results. Some comparisons have only 1 RCT, in this condition, I² was not applicable.

7) Please correct the formatting of all tables i.e. vertical and horizontal lines are showing/missing at random.

Thank you for the suggestion. We have revised all the tables.

8) Conclusion: The ranking of Se salt and Se + VE is nearly the same (1.8 vs. 2) so I would refrain from concluding (both in the abstract and in the discussion) that Se salt ranked the most effective. In fact, the results for Se salt are just based on one trial with 59 participants, 4 interventions, and unclear risk of bias. I would rather limit the conclusion to saying that all interventions were more effective than placebo and so that selenium supplementation is of help in repairing metaphyseal lesions. The quality of the evidence is insufficient to draw a conclusion about what method of selenium supplementation is most effective.

Thank you for the suggestion. We have revised the manuscript in ABSTRACT-conclusions and in the DISCUSSION.

Reviewer: 2

Reviewer Name: Yu Fang Fang

The response to reviewers have not been found out in the author's manuscript. Therefore, it is difficult to check the response to my suggestion. Please upload it.

Dear Pro. Yu,

Thank you for reviewing our manuscript. We have responded your comments. However, it was invisible by mistake. I pasted them again, please see below:

[1] Line 76 in Page 3: The onset age of KBD patients were most occurred in the children aged 5~15 years old. Selenium supplement was used to prevent the incidence of KBD in Children. Therefore, it is not part of potential limitations. Please revise it.

Author's Response: Thank you for the suggestion. We have deleted this sentence.

[2] Line 82-84 in Page 4: The distribution of KBD patients were covered in 14 Provinces, not just Hei Longjiang, Gan Su, Shan Xi, Qing Hai, Si-chuan and Tibet provinces. The Shan Xi also has been written incorrectly. Please revise it.

Author's Response: Thank you for the comment. We have revised it. To keep a sentence to describe the distribution: "KBD is prevalent in 377 counties of 14 provinces in China, with 0.64 million cases" and delete the specific list of those provinces.

[3] Eligibility criteria in Page 5: The diagnostic criteria for KBD patients haven't been described in eligibility criteria. Please list it.

Author's Response: Thank you for your suggestion. We have added these sentence: "The diagnostic criteria for KBD is Diagnosis Criteria for Kashin-Beck Disease (GB16003-1995), which was developed by National Health and Family Planning Commission of the People's Republic of China."

[4] Line 133-135 in Page 6: Fingers of KBD patients may occur the metaphyseal and epiphysis lesions in X-ray film. Why you just choose the repair of metaphyseal consider as judgment standard of X-ray for treatment effect of KBD?

Author's Response: Thank you for bringing attention to this. Only five studies reported repairing rate at the distal end of phalanges in hands on X-ray films. The number of included RCTs is too small to do a network meta-analysis. Therefore, we just choose the repair of metaphyseal consider as judgment standard of X-ray for treatment effect of KBD.

[5] In the Appendix table 1: The outcome index included X-ray improvement and improvement of metaphyseal lesions on X-ray, they are two different outcome indexes to measure the benefits of selenium. So, why you can pool the ORs in Fig. 3 and Fig.4 using the different outcome indexes?

Author's Response: Thank you for bringing attention to this. "X-ray improvement" means the study reported two kinds of outcomes: "Improvement of metaphyseal lesions on X-ray & Repairing rate at the distal end of phalanges in hands on X-ray films." Sorry for bringing misunderstanding, we have revised in the Appendix table.

[6] In the Appendix table 2: The risk of bias of included studies hasn't been described in the statistical analysis.

Author's Response: Thank you for your suggestion. We have used the GRADE approach to rate the quality of the evidence (see table 1). In addition, we add some sentence to explain how to do the GRADE: "In our review, we applied GRADE system to NMAs based GRADE working group. The methods of rating the quality of direct comparison are the same to use GRADE in traditional meta-analysis. We downgraded the evidence from "high quality" by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, inconsistency, imprecision of effect estimates or potential publication bias. The rating of the quality of the indirect estimates is based on the ratings of the two pairwise estimates that contributes to the indirect estimate of the comparison of interest. The lower confidence rating of the two direct comparisons constitutes the confidence rating of the indirect comparison. When both direct and indirect evidence are available, we used the higher of the two quality ratings as the quality rating for NMA estimate."

Reviewer: 3

The revised manuscript has addressed most of the comments. However, there were still no assessment and discussion on the potential impact of different study follow-ups.

Minor comments:

p8 line 51: change "predictive" to "prediction"

Thank you for your suggestion. We have revised it.

p8 line 51: modify the sentence “The PrI interval shows the degree of uncertainty around estimated treatment effects.” so that it reflects that both CI and PrI provide uncertainty around the estimated effects. PrI gives a range for the predicted parameter value in a new study.

Thank you for your suggestion. We have revised it as: “The PrI shows the predicted parameter value around estimated treatment effects in the future study.”.

p9 line 13: change “chi-square” to “chi-squared”

Thank you for your suggestion. We have revised it.

Page18 line 9: the claim “Consequently, estimates in our analysis were more precise than the pair-wise meta-analyses.” is not necessarily true. Some of the results from NMA were less precise than the pair-wise MA.

Thank you for your suggestion. We have deleted this sentence.

It will be useful to provide the data used in the analyses.

Thank you for your suggestion. We have provided raw data in Appendix table 4.

Use capital “T” for table.

Thank you for your suggestion. We have revised it.

VERSION 3 – REVIEW

REVIEWER	Shijie Ren University of Sheffield
REVIEW RETURNED	29-Nov-2017

GENERAL COMMENTS	The authors did not provide response to the following comment: there were still no assessment and discussion on the potential impact of different study follow-ups. Appendix Table 4 includes the data used for the NMA. But it only shows for each comparison, which is not helpful. Individual study data should be provided.
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REVIEWER	Yu Fang Fang Xi'an Jiaotong University
REVIEW RETURNED	04-Dec-2017

GENERAL COMMENTS	I has reviewed the Responses to Comments of Reviewer 2. The author have been answered all the questions, there is no other issues. Therefore, the manuscript can be accepted according to the author's revised manuscript.
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REVIEWER	JM Ordonez Mena Nuffield Department of Primary Care Health Sciences, University of Oxford
REVIEW RETURNED	04-Dec-2017

GENERAL COMMENTS	The authors have taken into account all the comments from the reviewers. I think the take-home message of the paper is now better supported by the findings. There is nothing much to add but just the following minor points:
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	<p>1) The authors have conducted a network meta-analysis and therefore the Summary of Findings table should include the findings from network meta-analysis, not those from traditional pairwise meta-analyses. Hence why I suggested they included also a column with the ranking according to SUCRA. This should also apply to the ORs and to the Quality of the Evidence columns in the table (see any example of a Cochrane systematic review including a network meta-analysis).</p> <p>2) The authors should also include the name of the comparison in the first row, which appears to be deleted by accident. Also in the second row, the repair rate in the placebo group should be 35 per 100 (not per 1,00).</p> <p>3) The authors should specify in the methods why Odds Ratios were used instead of Risk Ratios (also known as Relative Risks). Odds Ratios give a more dramatic magnitude of effect than RRs when the outcome is common (>20% which is the case of the repair rate in this study). Surely, the network STATA package can also do network meta-analysis with RRs.</p>
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VERSION 3 – AUTHOR RESPONSE

Dear Editor,

Thank you for giving us the opportunity to revise our manuscript again. We have considered the reviewers' comments and responded to each of them below.

Sincerely,
Jirong Yue

Reviewer: 1
Reviewer Name: JM Ordonez Mena

The authors have taken into account all the comments from the reviewers. I think the take-home message of the paper is now better supported by the findings. There is nothing much to add but just the following minor points:

1) The authors have conducted a network meta-analysis and therefore the Summary of Findings table should include the findings from network meta-analysis, not those from traditional pairwise meta-analyses. Hence why I suggested they included also a column with the ranking according to SUCRA. This should also apply to the ORs and to the Quality of the Evidence columns in the table (see any example of a Cochrane systematic review including a network meta-analysis).

Thank you for this suggestion. We have revised the Table 2: added this column and ranked them according to SUCRA.

2) The authors should also include the name of the comparison in the first row, which appears to be deleted by accident. Also in the second row, the repair rate in the placebo group should be 35 per 100 (not per 1,00).

Thank you for this suggestion. We have corrected them.

3) The authors should specify in the methods why Odds Ratios were used instead of Risk Ratios (also known as Relative Risks). Odds Ratios give a more dramatic magnitude of effect than RRs when the outcome is common (>20% which is the case of the repair rate in this study). Surely, the network STATA package can also do network meta-analysis with RRs.

Thank you for bringing attention to this. We have added the following in the methods:
 The reason why OR were used instead of Risk Ratios (RR) was following: inferential fallacies with use of RR in indirect comparison provide scope for abuse with respect to choice in framing of outcomes, and confound decision making where both results are presented. The use of ORs overcomes this inferential fallacy, consistently informing inference with respect to direction of treatment effect in indirect comparisons.

Reviewer: 2
 Reviewer Name: Yu Fang Fang

I has reviewed the Responses to Comments of Reviewer 2. The author have been answered all the questions, there is no other issues. Therefore, the manuscript can be accepted according to the author's revised manuscript.
 Thank you.

Reviewer: 3
 Reviewer Name: Shijie Ren

The authors did not provide response to the following comment: there were still no assessment and discussion on the potential impact of different study follow-ups.
 Thank you for this suggestion. We are sorry for missing that question in first round revision. We added the following text in discussion:

“Potential limitations to this review exist. Firstly, the duration of follow-up diverse widely which varied from 6 to 36 months. However, follow-up period of most studies are concentrated in 12 months. So the data were extracted to the nearest 12 months. Even so, the best beneficial duration of therapy time frame remains unclear for KBD. Conferring with other RCT about osteoarthritis, 36 months of therapy duration may be appropriate for observing X-ray repairing changes of KBD.”

Appendix Table 4 includes the data used for the NMA. But it only shows for each comparison, which is not helpful. Individual study data should be provided.

This is a great point. We have revised the appendix table 4 and added an appendix figures to clarify the data of individual study.

VERSION 4 – REVIEW

REVIEWER	JM Ordonez Mena Nuffield Department of Primary Care Health Sciences, University of Oxford, UK
REVIEW RETURNED	21-Dec-2017

GENERAL COMMENTS	<p>The authors have address nearly all my comments. In relation to point 3, the authors seem to have copy-pasted the conclusion of this article: https://www.ncbi.nlm.nih.gov/pubmed/19179043 In order for this not to be considered plagiarism, the authors must cite this paper, and add quotation marks " " to the text that they have literally copy-pasted.</p> <p>I have no further comments but I am now concerned about the rest of the manuscript. I hope that the authors can check that this does not apply to any other sentence in the text, and additionally the editorial board must use a plagiarism software such as iThenticate to confirm this.</p>
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REVIEWER	Shijie Ren University of Sheffield, UK
REVIEW RETURNED	21-Dec-2017
GENERAL COMMENTS	All comments were addressed.

VERSION 4 – AUTHOR RESPONSE

Dear Editor,

Thank you for giving us the opportunity to revise our manuscript again. We have considered the reviewers' comments and responded to each of them below.

Sincerely,

Jirong Yue

Reviewer: 1

The authors have address nearly all my comments. In relation to point 3, the authors seem to have copy-pasted the conclusion of this article: <https://www.ncbi.nlm.nih.gov/pubmed/19179043>

In order for this not to be considered plagiarism, the authors must cite this paper, and add quotation marks " " to the text that they have literally copy-pasted.

I have no further comments but I am now concerned about the rest of the manuscript. I hope that the authors can check that this does not apply to any other sentence in the text, and additionally the editorial board must use a plagiarism software such as iThenticate to confirm this.

Thank you for bringing attention to this. When we answered the question "why OR were used instead of RR", we consulted a statistician. This sentence were provided by our statistician. We did not recognized that it was copy-pasted. I'm sorry to bring the misunderstanding.

In order to not be considered as plagiarism, we have rephrased this sentence and cited this paper. We have checked although the manuscript, there are no other sentence were copy-pasted. Some part of the methodology is inevitable similar with other paper. However, we have the confidence this manuscript can be tested by any plagiarism software.

Reviewer: 3

Reviewer Name: Shijie Ren

Institution and Country: University of Sheffield, UK

Please state any competing interests: None declared.

Please leave your comments for the authors below

All comments were addressed.

Thank you!

