PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomized controlled trials
AUTHORS	Hu, Zhi-Chao; Tang, Qian; Sang, Chang-Min; Tang, Li; Li, Xiaobin; Zheng, Gang; Feng, Zhen-Hua; Xuan, Jiang-Wei; Shen, Zhi-Hao; Shen, Li-Yan; ni, wenfei; Wu, Ai-Min

VERSION 1 – REVIEW

REVIEWER	Pnina Rotman Pikielny Meir Medical Center Israel
REVIEW RETURNED	23-Sep-2018

GENERAL COMMENTS	The clinical question that stands in the basis of this review is legitimate: do vitamin d and calcium supplements reduce the risk of all fractures, vertebral and hip fractures by themselves. In the introduction the authors review nicely the conflicting and confusing data in this matter that results from previous meta-analyses. The methods section is described meticulously. I like the fact that the analysis was divided into several calcium and vitamin d combinations and i think the doses chosen as high vs. low vitamin d and calcium levels are appropriate. The meta-analysis was done on a large number of patients 27102 for the all fractures outcome and 42531 for the vertebral/hip fractures outcome. Yet, I have a few remarks/suggestions: 1. Regarding the selection of RCT: ref. 26 deals with hemodialysis patients. It should be excluded as CRF is associated with metabolic bone disease (exclusion No 5) 2. Four studies (No 4,9,13,18) lasted less than a year, and two of them No 13 and 18 less than 6 months. I think this time-frame is too short to see anti-fracture efficacy. I would include only studies that lasted more than a year, and certainly would discuss the lensgth of the studies in the discussion. 3. The exclusion criteria should include patients treated with steroids. Do any of the studies include such patients? 4. The refernce list should include all the 29 studies included in the meta-analysis. I dont understand why those are included in a seperate refernce list 5. Some studies that had baseline vitamin d had a baseline level of 10ng/dL in contrast to others that started from a sufficient level of 30ng/dL. Did you do an analysis of the studies with baseline vitamin d to see whether people with low baseline gain more from the treatment of vitamin d?

	6. The English should be improved throuout the manuscript. Examples: line 83 should be "it's challenging" and not "it's a challenging", lines 230, 233 the sentences start with the word and. it should be modified 7. Some references are listed as the full name of the paper and some are abbreviated. For example: ref. 20,21 are written in full while ref. 17, 24 are abbreviated. There should be consistency in-line with journal requirements 8. The meta-analysis by Zhao was recently published. There should be a better discussion regarding the similarities and differences between these two meta-analyses

REVIEWER	Professor Robert Clarke Professor Robert Clarke CTSU, Nuffield Department of Population Health University of Oxford Old Road Campus Oxford, OX3 7LF, UK
REVIEW RETURNED	16-Oct-2018

GENERAL COMMENTS	Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomized controlled trials. This meta-analysis combined the result of randomised trials of vitamin D for prevention of fracture. It involved a total of 29 trials and 45,647 participants. The analyses stratified for the effects of treatment for vitamin D <800 IU/day or 800 IU/day or greater. Neither dose had any beneficial effect on risk of fracture. Major comments: 1. The meta-analysis ignored duration of treatment. A substantial proportion of these trials were continued for less than 12 months. 2. The report ignored the effect of treatment with vitamin D on plasma 25-hydroxy-vitamin D concentrations. 3. The report ignored the effect of treatment with vitamin D on sub-types of fracture, such as fragility or osteoporotic fractures. 4. The report ignored the report by Bolann and colleagues that was published in the Lancet in October 2018. 5. The report did not comment on the major large trials of vitamin D that are testing the effects of much higher doses of vitamin D on risk of fracture and other disease outcomes. 6. It is unclear to me that this meta-analysis will be informative to change guidelines on the routine use of vitamin D for the prevention of fractures.

REVIEWER	Erin Michos Johns Hopkins School of Medicine
REVIEW RETURNED	23-Oct-2018

GENERAL COMMENTS	BMJ Open reviewer comments Given the high burden of fractures in older adults, it is imperative to understand effective treatment strategies for prevention. As the

	authors acknowledge, prior data have been mixed/inconclusive regarding the benefits or harms of vitamin D and calcium supplements for the purpose of fracture prevention. The US Preventative Services Task Force (USPSTF) has given vitamin D/calcium supplementation an insufficient (I) recommendation for fracture prevention in community dwelling post-menopausal women. Despite this, vitamin D and calcium supplements are still widely used for this purpose. In this updated meta-analysis, the authors attempt to address this important question. However, there have been several prior meta-analyses about this topic already though. Most recently there was a meta-analysis published in the Lancet 2018 by Bolland et al entitled "Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis." I understand this Bolland meta-analysis was published likely after the authors completed the present work, but nevertheless, since Bolland's meta-analysis has now been published and widely read, the authors should reference and mention this prior meta-analysis and discuss how their current analyses is different. The current meta-analyses submitted by Hu et al does have some notable differences from Bolland's, which do add to this discussion. First, the current submitted analyses included calcium supplementation, where the Bolland one focused on vitamin D. Furthermore, the current meta-analysis used a new approach, a "network meta-analysis" and compared groups of vitamin D and calcium supplements by dose groups (high vs low). There was also was a presentation of ranking by probability of fracture within dose groups. Thus, I do think the current submitted paper is different. At least the Bolland meta-analysis in Lancet and the present analysis came to similar conclusions: "The use of supplements that included calcium, vitamin D, or both was not found to be better than placebo or no treatment in terms of risk of fractures among community-dwelling older adults. It means the routine use of these supplements in community-dwelling older people should be treated more carefully." Thus, both of these meta-analyses should dampen the enthusiasm for the use of vitamin D for fracture prevention consistent with prior USPSTF recommendations. A few additional comments/questions 1) The Bolland 2018 Lancet meta-analysis identified 42 randomized controlled trials that reported on vitamin D and fracture. However, the authors only found 29 trials that met inclusion criteria. What was the difference? Reporting of dose? Not including calcium? 2) In considering all of these published meta-analyses, it is very important to note though that meta-analyses are only as good as the underlying individual trials. The authors did examine risk of bias. But other limitations of the prior individual RCTs worth discussing include:(1)The lack of recruitment of participants specifically with vitamin D deficiency or insufficiency (individuals with adequate 25(OH)D levels likely do not need more vitamin D for supplementation and (2) Not all trials used daily oral vitamin D supplementation (there might be harm with administrating very large non-physiological doses of vitamin D weekly, monthly, or even yearly (like the Sanders 2010 paper of 500,000IUyear))! Some more discussion about the limitations of meta-analyses

	would be helpful, specifically in regards to baseline 25(OH)D concentrations and dosing regimens (not just >800 vs <800 IU, but how they were dosed, daily or otherwise). 3) Do you have any information about populations with baseline low vitamin D in your meta-analyses? The methods section says that the authors collected information on baseline serum 25-hydroxyvitamin D concentration from the individual studies, but I did not see any analyses stratified or checked for interaction by baseline 25(OH)D concentrations. If this cannot be done, I would mention it in the discussion as the effect of supplementation might only help those who are truly deficient. Also, did the authors check for any interaction by trial duration? Shorter trials may have inflated effect sizes. 4) Minor note; please define all abbreviations on first use. Including EU, GDP, RCT used in introduction 5) When the authors refer to "elderly" in the introduction, what do you mean exactly? Are you referring to adults >70 years of age? There is quite a lot of heterogeneity in aging. Some adults over 70 are not frail. The term "elderly" is falling out of favor. 6) Maybe could add some numerical results data to the results text, such as the RR rather than just a broad summary statement of "However, there was still no significant association of vitamin D, calcium or their combination with total fracture." 7) I could not see the third figure very well on my PDF reviewer copy, which I think is the main Forest Plots for the meta-analysis. The figure was so small and blurry; I could not see results, which is why it would be nice to have some results in the text itself. I could see the Forest plots on next Figures a bit better – I think these were supplemental figures 1 and 2. Since Figure 3 seems to be your main results, can you make it bigger and clearer similar to the Supplemental Figures? Perhaps plot A, B, and C separately for total fractures, hip fractures and vertebral fractures so that they are easier to see. 8) In the Bolland meta-analysis there was a non-significant trend that suggested high dose vs low dose vitamin D might benefit fractures. 0·61 (0·36–1·06). I could not see your Figure 3 very well. Did you see a similar hint of benefit for high dose vs low dose? 9) The figures were not labeled in PDF proof and they were all included together. I guess the first three were main figures and all the rest were supplemental figures. But hard to follow since the legends were not included next to the figures so I was struggling to figure out which figure was which. It would be nice if the figures were labeled, but also they could be explained better. 10) The authors state "Based on SUCRA, high calcium plus low vitamin D group (0.726) ranked the first, the second was high calcium plus high vitamin D group (0.642) and the last was low calcium plus high vitamin D group (0.217). " I understand this to mean that the interventions were ranked from best to worst for the best treatment effect for fracture prevention. But I find this ranking confusing when none of the intervention groups were individually

	found to be better than placebo. I found the statistical methods a bit challenging to follow. 11) I was trying to understand the supplemental figures that showed the loop specific heterogeneity, I am not sure I understand these supplemental figures or how an inconsistency model was then developed to deal with this problem for the main analyses. Again, I think the statistical methods could be explained more clearly. 12) I admit I am not familiar with network meta-analysis vs the more commonly presented standard meta-analysis. Can you provide a reference for network meta-analyses? 13) I am a clinician with some Epi background, but these statistical methods for network analyses are unfamiliar to me. Some of it was hard for me to follow. This paper would benefit being reviewed by as statistical reviewer.

REVIEWER	Nick Meader University of York, UK
REVIEW RETURNED	19-Nov-2018

GENERAL COMMENTS	The systematic review methods look fine, and as far as I can see the conclusions appear appropriate. However, I'd recommend two main improvements to the paper: 1) The English in the paper is mostly OK but there are places where it is not quite to sufficient standard. Related to this sometimes the terminology is a little clumsy and not quite clear - e.g. 'Then the operational model was chosen according to the inconsistency test, which was the basis of forest maps' calculation.' This sentence doesn't really make sense to me, there are a few other examples throughout the text. 2) Perhaps more importantly, inconsistency is not discussed in enough detail in the results and as far as I can see is not even mentioned in the discussion. You mention that you use inconsistency models but little more than that. If you've identified important inconsistency in the analyses you need to discuss this in a great deal more detail.Its a substantial limitation to your findings so we need to know much more about the inconsistency you have identified, what's likely driving it, and how this impacts on the validity of your conclusions.

REVIEWER	Richard Jackson University of Liverpool
REVIEW RETURNED	20-Nov-2018

GENERAL COMMENTS	Comparison of Fracture Risk using different supplemental doses of vitamin D, calcium or their compbination: a network meta-analysis of randomized controlled trials. This manuscript details the systematic review and meta-analysis of studies comparing the use of vitamin D, calcium and their combination on the risk of fracture.

	Generally the manuscript is clear and the results presented match the conclusions drawn. There is enough detail presented to give some assurance over the validity of the results however the article would benefit from more detailed methodology as some areas are not sufficiently explained Major The abtract refers to the use of 'confounder adjusted risk ratios'. Details should be provided on how risk ratios are adjusted – e.g. what methodology is applied and what covariates are used to adjust? It is stated in the methods that to be included, treatments must be compared against a Placebo – why is this the case, an RCT comparing Vit D directly to Calcium would be extremely valuable in this network analysis. In the methodology the section beginning 'The model we used was fit for all kinds of networks' needs greater explanation. Also, 'To the only one triangular curcular' – what is meant by 'triangular-circular' are they referring to the 'closed' section of the network???? What is the rational for restricting funnel plots to scenarios where the number of studies is greater than 10. Multiple references are made to an 'inconsistency model'. Some clarification as to what this is should be included in the methods section. Minor point 'Strength and Limitations' – the first bullet point is defining the research being undertaken and is neither a strength/weakness. In some places minor improvement to the English is required. Metods section – given the inclusion criteria is RCT, it is not necessary to include non-randomized trials, observational and experimental studies or case reports as exclusion criteria. It should be stated which authors did the literature search not just 'two-authors' The manuscript refers to 'CI', 'CrI' and there is reference to 'PrI' in the figures. Some definitions and consistency should be employed. There are a large number of figure, not all of which are easy to interpret and the authors should consider ways to reduce these.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Pnina Rotman Pikielny
Institution and Country: Meir Medical Center, Israel
Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below
The clinical question that stands in the basis of this review is legitimate: do vitamin d and calcium supplements reduce the risk of all fractures, vertebral and hip fractures by themselves.
In the introduction the authors review nicely the conflicting and confusing data in this matter that results from previous meta-analyses.
The methods section is described meticulously. I like the fact that the analysis was divided into several calcium and vitamin d combinations and i think the doses chosen as high vs. low vitamin d and calcium levels are appropriate.
The meta-analysis was done on a large number of patients 27102 for the all fractures outcome and 42531 for the vertebral/hip fractures outcome.
Yet, I have a few remarks/suggestions:
1. Regarding the selection of RCT: ref. 26 deals with hemodialysis patients. It should be excluded as CRF is associated with metabolic bone disease (exclusion No 5)
Reply: Sorry for the mistake. We excluded it and made our trial more reasonable.

2. Four studies (No 4,9,13,18) lasted less than a year, and two of them No 13 and 18 less than 6 months. I think this time-frame is too short to see anti-fracture efficacy. I would include only studies that lasted more than a year, and certainly would discuss the length of the studies in the discussion.
Reply: Thanks for your attention. We excluded these studies.

3. The exclusion criteria should include patients treated with steroids. Do any of the studies include such patients?
Reply: Thanks for your suggestion. We updated the exclusion criteria accordingly.

4. The reference list should include all the 29 studies included in the meta-analysis. I don't understand why those are included in a seperate reference list.
Reply: Sorry for the confusion. We corrected the reference list.

5. Some studies that had baseline vitamin d had a baseline level of 10ng/dL in contrast to others that started from a sufficient level of 30ng/dL. Did you do an analysis of the studies with baseline vitamin d to see whether people with low baseline gain more from the treatment of vitamin d?
Reply: Thanks for your suggestion. Actually, we did a subgroup meta-analysis before network meta-analysis study. And no statistical differences was found when the baseline 25OHD level is >20ng/dl or<20ng/dl. Meanwhile, no obvious heterogeneity and inconsistence was observed in all these results according to our inconsistence and heterogeneity check. Most network meta-analysis didn't include a subgroup analysis1-4. They could not perform subgroup analysis or meta-regression analysis to evaluate it due to the extreme complexity or the limitation of statistical method. So before starting a network meta-analysis, we were accustomed to include studies with low heterogeneity. And we added this point to our "Limitations" part accordingly.

6. The English should be improved throuout the manuscript. Examples: line 83 should be "it's challenging" and not "it's a challenging", lines 230, 233 the sentences start with the word and. it should be modified
Reply: Sorry for the mistake. We corrected the expression here and improved the English throughout the manuscript.

7. Some references are listed as the full name of the paper and some are abbreviated. For example: ref. 20,21 are written in full while ref. 17, 24 are abbreviated. There should be consistency in-line with journal requirements
Reply: Sorry for the mistake. We corrected this part.

8. The meta-analysis by Zhao was recently published. There should be a better discussion regarding the similarities and differences between these two meta-analyses
Reply: Thanks for your suggestion. We enriched this part in our discussion part.

Reviewer: 2
Reviewer Name: Professor Robert Clarke
Institution and Country: Professor Robert Clarke, CTSU, Nuffield Department of Population Health; University of Oxford, Old Road Campus, Oxford, OX3 7LF, UK
Please state any competing interests or state 'None declared': I have no competing interests.

Please leave your comments for the authors below
Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomized controlled trials.

This meta-analysis combined the result of randomised trials of vitamin D for prevention of fracture. It involved a total of 29 trials and 45,647 participants. The analyses stratified for the effects of treatment for vitamin D <800 IU/day or 800 IU/day or greater. Neither dose had any beneficial effect on risk of fracture.

Major comments:

1. The meta-analysis ignored duration of treatment. A substantial proportion of these trials were continued for less than 12 months.
Reply: Thanks for your attention. We excluded these studies and included only studies that lasted more than a year.

2. The report ignored the effect of treatment with vitamin D on plasma 25-hydroxy-vitamin D concentrations.
Reply: Thanks for your suggestion. We added this part to our limitation part.

3. The report ignored the effect of treatment with vitamin D on sub-types of fracture, such as fragility or osteoporotic fractures.
Reply: Sorry for the confusion. Our study focused on the osteoporotic fractures. And we enriched it in our limitation section.

4. The report ignored the report by Bolann and colleagues that was published in the Lancet in October 2018.
Reply: Sorry for the confusion. We added Bolland's study in our discussion part.

5. The report did not comment on the major large trials of vitamin D that are testing the effects of much higher doses of vitamin D on risk of fracture and other disease outcomes.
Reply: Sorry for the confusion. We enrich it in our discussion.

6. It is unclear to me that this meta-analysis will be informative to change guidelines on the routine use of vitamin D for the prevention of fractures.
Reply: Sorry for the confusion. Similar to trials reported recently, our trial only reminded that the routine use of these supplements in community-dwelling older people should be treated more carefully. This work does not necessarily preclude any benefit of vitamin D and calcium supplementation in older, frail individuals. However, further research with standardized, unbiased methods and larger sample sizes are still required for deeper analysis.

Reviewer: 3
Reviewer Name: Erin Michos
Institution and Country: Johns Hopkins School of Medicine
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
see attached

Given the high burden of fractures in older adults, it is imperative to understand effective treatment strategies for prevention. As the authors acknowledge, prior data have been mixed/inconclusive regarding the benefits or harms of vitamin D and calcium supplements for the purpose of fracture prevention. The US Preventative Services Task Force (USPSTF) has given vitamin D/calcium supplementation an insufficient (I) recommendation for fracture prevention in community dwelling post-menopausal women. Despite this, vitamin D and calcium supplements are still widely used for this purpose.

In this updated meta-analysis, the authors attempt to address this important question. However, there have been several prior meta-analyses about this topic already though. Most recently there was a meta-analysis published in the Lancet 2018 by Bolland et al entitled "Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis."

I understand this Bolland meta-analysis was published likely after the authors completed the present work, but nevertheless, since Bolland's meta-analysis has now been published and widely read, the authors should reference and mention this prior meta-analysis and discuss how their current analyses is different.

The current meta-analyses submitted by Hu et al does have some notable differences from Bolland's, which do add to this discussion. First, the current submitted analyses included calcium supplementation, where the Bolland one focused on vitamin D. Furthermore, the current meta-analysis used a new approach, a "network meta-analysis" and compared groups of vitamin D and calcium supplements by dose groups (high vs low). There was also was a presentation of ranking by probability of fracture within dose groups. Thus, I do think the current submitted paper is different.

At least the Bolland meta-analysis in Lancet and the present analysis came to similar conclusions: "The use of supplements that included calcium, vitamin D, or both was not found to be better than placebo or no treatment in terms of risk of fractures among community-dwelling older adults. It means the routine use of these supplements in community-dwelling older people should be treated more

carefully." Thus, both of these meta-analyses should dampen the enthusiasm for the use of vitamin D for fracture prevention consistent with prior USPSTF recommendations.

A few additional comments/questions

1. The Bolland 2018 Lancet meta-analysis identified 42 randomized controlled trials that reported on vitamin D and fracture. However, the authors only found 29 trials that met inclusion criteria. What was the difference? Reporting of dose? Not including calcium?
Reply: Sorry for the confusion. Most recently there was a meta-analysis published in the Lancet 2018 by Bolland et al, whose findings suggested that vitamin D supplementation does not prevent fractures or falls, or have clinically meaningful effects on bone mineral density. Although it was similar to our study to some extent, they are really different. First, we only included community-dwelling older people. We found that some meta-analyses equated community-dwelling older people with those in nursing institution. The lack of exercise, dietary intake and exposure to sunlight made people in nursing institution turned more susceptible to the use of supplements including vitamin D, calcium or their combination. Although the studies involving participants living in nursing institution were only a small part, but it could change the whole outcomes and produce false positive results. We found only Avenell's study5 paid attention to this question when they conducted a subgroup analysis, but they did not discussed separately. Furthermore, we only enrolled adults older than 50 years and trials more than 1 year.

2. In considering all of these published meta-analyses, it is very important to note though that meta-analyses are only as good as the underlying individual trials. The authors did examine risk of bias. But other limitations of the prior individual RCTs worth discussing include:(1)The lack of recruitment of participants specifically with vitamin D deficiency or insufficiency (individuals with adequate 25(OH)D levels likely do not need more vitamin D for supplementation and (2) Not all trials used daily oral vitamin D supplementation (there might be harm with administrating very large non-physiological doses of vitamin D weekly, monthly, or even yearly (like the Sanders 2010 paper of 500,000IUyear))! Some more discussion about the limitations of meta-analyses would be helpful, specifically in regards to baseline 25(OH)D concentrations and dosing regimens (not just >800 vs <800 IU, but how they were dosed, daily or otherwise).
Reply: Thanks for your constructive suggestion. We added these to our limitation part.

3. Do you have any information about populations with baseline low vitamin D in your meta-analyses? The methods section says that the authors collected information on baseline serum 25-hydroxyvitamin D concentration from the individual studies, but I did not see any analyses stratified or checked for interaction by baseline 25(OH)D concentrations. If this cannot be done, I would mention it in the discussion as the effect of supplementation might only help those who are truly deficient. Also, did the authors check for any interaction by trial duration? Shorter trials may have inflated effect sizes.
Reply: Thanks for your reminder. We added these to our limitation part about plasma 25-hydroxy-vitamin D concentrations and we excluded trials less than 1 year according to reviewers' suggestion.

4. Minor note; please define all abbreviations on first use. Including EU, GDP, RCT used in introduction
Reply: Sorry for the mistake. We corrected it.

5. When the authors refer to "elderly" in the introduction, what do you mean exactly? Are you referring to adults >70 years of age? There is quite a lot of heterogeneity in aging. Some adults over 70 are not frail. The term "elderly" is falling out of favor.
Reply: Sorry for the confusion. Actually, it referred to adults older than 50 years. We interpreted it in our inclusion criteria according to previous studies6.

6. Maybe could add some numerical results data to the results text, such as the RR rather than just a broad summary statement of “However, there was still no significant association of vitamin D, calcium or their combination with total fracture.”
Reply: Sorry for the confusion. We add some numerical results data to the results text. However, more detailed data was too tedious to add completely because there too many comparison in one forest plot. So we tried our best to make our figure clearer to read.

7. I could not see the third figure very well on my PDF reviewer copy, which I think is the main Forest Plots for the meta-analysis. The figure was so small and blurry; I could not see results, which is why it would be nice to have some results in the text itself. I could see the Forest plots on next Figures a bit better – I think these were supplemental figures 1 and 2. Since Figure 3 seems to be your main results, can you make it bigger and clearer similar to the Supplemental Figures? Perhaps plot A, B, and C separately for total fractures, hip fractures and vertebral fractures so that they are easier to see.
Reply: To avoid confusion, we plotted A, B, and C separately.

8. In the Bolland meta-analysis there was a non-significant trend that suggested high dose vs low dose vitamin D might benefit fractures. 0·61 (0·36–1·06). I could not see your Figure 3 very well. Did you see a similar hint of benefit for high dose vs low dose?
Reply: Yes, we could see a similar hint of benefit for high dose vs low dose (low dose vs high dose vitamin D, CI:1.11, 0.79-1.56). We made our figure clearer and could found that trend in the updated figure.

9. The figures were not labeled in PDF proof and they were all included together. I guess the first three were main figures and all the rest were supplemental figures. But hard to follow since the legends were not included next to the figures so I was struggling to figure out which figure was which. It would be nice if the figures were labeled, but also they could be explained better.
Reply: Sorry for the confusion. We labeled that in our figures according.

10. The authors state “Based on SUCRA, high calcium plus low vitamin D group (0.726) ranked the first, the second was high calcium plus high vitamin D group (0.642) and the last was low calcium plus high vitamin D group (0.217). “ I understand this to mean that the interventions were ranked from best to worst for the best treatment effect for fracture prevention. But I find this ranking confusing when none of the intervention groups were individually found to be better than placebo. I found the statistical methods a bit challenging to follow.
Reply: Sorry for the confusion. According to Zhao’s network meta-analysis, they ranked the interventions though there were no significant differences among them. However, to avoid confusion, we deleted the SUCRA part in our article. Because this ranking is meaningless. SUCRA is only a rank system. We should make a conclusion combined with the results of network forest plots.

11. I was trying to understand the supplemental figures that showed the loop specific heterogeneity, I am not sure I understand these supplemental figures or how an inconsistency model was then developed to deal with this problem for the main analyses. Again, I think the statistical methods could be explained more clearly.
Reply: Sorry for confusion. We enriched this part in our methods.

12. I admit I am not familiar with network meta-analysis vs the more commonly presented standard meta-analysis. Can you provide a reference for network meta-analyses?
Reply: It’s our pleasure to provide that reference4.

13. I am a clinician with some Epi background, but these statistical methods for network analyses are unfamiliar to me. Some of it was hard for me to follow. This paper would benefit being reviewed by as statistical reviewer.
Reply: Thanks for your contribution. Your constructive suggestion really helped us a lot.

Reviewer: 4
Reviewer Name: Nick Meader
Institution and Country: University of York, UK
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
The systematic review methods look fine, and as far as I can see the conclusions appear appropriate.

However, I'd recommend two main improvements to the paper:

1) The English in the paper is mostly OK but there are places where it is not quite to sufficient standard. Related to this sometimes the terminology is a little clumsy and not quite clear - e.g. 'Then the operational model was chosen according to the inconsistency test, which was the basis of forest maps’ calculation.' This sentence doesn't really make sense to me, there are a few other examples throughout the text.
Reply: To avoid confusion. We omitted the sentence and revised the expression throughout our text.

2) Perhaps more importantly, inconsistency is not discussed in enough detail in the results and as far as I can see is not even mentioned in the discussion.
Reply: Sorry for the mistake. Actually, no obvious inconsistency was observed in all these results. We enriched it in our result part.

You mention that you use inconsistency models but little more than that. If you've identified important inconsistency in the analyses you need to discuss this in a great deal more detail. It’s a substantial limitation to your findings so we need to know much more about the inconsistency you have identified, what's likely driving it, and how this impacts on the validity of your conclusions.
Reply: Sorry for the mistake. In fact, we adopted a consistency model in all three groups. The statistical inconsistency between direct and indirect comparisons was generally low according to inconsistency test because the CI values included zero.

Reviewer: 5
Reviewer Name: Richard Jackson
Institution and Country: University of Liverpool
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
Comparison of Fracture Risk using different supplemental doses of vitamin D, calcium or their compbination: a network meta-analysis of randomized controlled trials.

This manuscript details the systematic review and meta-analysis of studies comparing the use of vitamin D, calcium and their combination on the risk of fracture.

Generally the manuscript is clear and the results presented match the conclusions drawn.
There is enough detail presented to give some assurance over the validity of the results however the article would benefit from more detailed methodology as some areas are not sufficiently explained

Major

The abstract refers to the use of 'confounder adjusted risk ratios'. Details should be provided on how risk ratios are adjusted – e.g. what methodology is applied and what covariates are used to adjust?
Reply: Sorry for the confusion. It's really difficult to make the question clear and most network didn't mention this definition7 8. So we revised this part to make it easier to read.

It is stated in the methods that to be included, treatments must be compared against a Placebo – why is this the case, an RCT comparing Vit D directly to Calcium would be extremely valuable in this network analysis.
Reply: Good point. Inconsistent findings in regard to association between different concentrations of vitamin D, calcium or their combination and the risk of fracture have been reported during the past decade. Nowadays, more and more studies dampened the enthusiasm for the use of vitamin D for fracture prevention. So we paid close attention to studies with placebo. If we deleted that inclusion criteria, theoretically, we may include all of the studies without placebo. If none of the intervention groups are individually found to be better than placebo, it's meaningless to add plenty of studies comparing different interventions. Thus, we tried to include higher quality studies with placebo to improve the quality of network meta-analysis.

In the methodology the section beginning 'The model we used was fit for all kinds of networks' needs greater explanation. Also, 'To the only one triangular curcular' – what is meant by 'triangular-circular' are they referring to the 'closed' section of the network????
Reply: To avoid confusion. We changed the expression in this part and made it more pellucid.

What is the rational for restricting funnel plots to scenarios where the number of studies is greater than 10.
Reply: Thanks for your concern. Actually, according to previous studies6 9, publication bias is difficult to evaluate among reviews of 10 or fewer studies (due to lack of power).

Multiple references are made to an 'inconsistency model'. Some clarification as to what this is should be included in the methods section.
Reply: Sorry for the confusion. We updated the included studies and revised our methods section.

Minor point
'Strength and Limitations' – the first bullet point is defining the research being undertaken and is neither a strength/weakness.
Reply: Sorry for the confusion. We corrected this part.

In some places minor improvement to the English is required.
Reply: Thanks for your reminder. We improved the English of the article.

Methods section – given the inclusion criteria is RCT, it is not necessary to include non-randomized trials, observational and experimental studies or case reports as exclusion criteria.
Reply: Sorry for the mistake. We deleted that exclusion criteria.

It should be stated which authors did the literature search not just 'two-authors'
Reply: Sorry for the confusion. We revised this part accordingly.

The manuscript refers to 'CI', 'CrI' and there is reference to 'PrI' in the figures. Some definitions and consistency should be employed.
Reply: Thanks for the suggestion. We add this part in our manuscript

There are a large number of figure, not all of which are easy to interpret and the authors should consider ways to reduce these.
Reply: Thanks for your concern. We reduced the number of figures and make our article clearer and more concise.

1. Zhang L, Cao HY, Zhao S, et al. Effect of exogenous pulmonary surfactants on mortality rate in neonatal respiratory distress syndrome: A network meta-analysis of randomized controlled trials. Pulmonary pharmacology & therapeutics 2015;34:46-54. doi: 10.1016/j.pupt.2015.08.005 [published Online First: 2015/08/25]
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3. Zhao JG, Wang J, Meng XH, et al. Surgical interventions to treat humerus shaft fractures: A network meta-analysis of randomized controlled trials. PloS one 2017;12(3):e0173634. doi: 10.1371/journal.pone.0173634 [published Online First: 2017/03/24]
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5. Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. The Cochrane database of systematic reviews 2014(4):Cd000227. doi: 10.1002/14651858.CD000227.pub4 [published Online First: 2014/04/15]
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7. Li S, Xie P. Efficacy Comparison of Five Different Acupuncture Methods on Pain, Stiffness, and Function in Osteoarthritis of the Knee: A Network Meta-Analysis. 2018;2018:1638904. doi: 10.1155/2018/1638904
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9. Dalton JE, Bolen SD, Mascha EJ. Publication Bias: The Elephant in the Review. Anesthesia and analgesia 2016;123(4):812-3. doi: 10.1213/ane.0000000000001596 [published Online First: 2016/09/17]

VERSION 2 – REVIEW

REVIEWER	Nick Meader University of York, UK
REVIEW RETURNED	30-Jan-2019

GENERAL COMMENTS	I thank the authors for substantially revising the manuscript. I think it reads better now and some of the awkward phrasing has been modified. I think my questions about the methods have been responded to appropriately. Apologies that I didn't raise this previously, generally the principle of choosing the random effects or fixed effect model based on I-squared or chi-squared p-value is not recommended. You should either make a judgement about what is most likely to be appropriate based on the assumptions of the different models or conduct both fixed or random effects and compare which seems to fit the data better.

	A further point in your revised draft (p12) seems to suggest that including covariates in the NMA is not possible with STATA. As far as I'm aware it is possible - so its better to say this should be explore in future analyses rather than suggest its not possible due to limitations with STATA.

REVIEWER	Richard Jackson Liverpool University, UK
REVIEW RETURNED	06-Feb-2019

GENERAL COMMENTS	I am happy to the responses to my comments raised.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4
Reviewer Name: Nick Meader
Institution and Country: University of York, UK
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
I thank the authors for substantially revising the manuscript. I think it reads better now and some of the awkward phrasing has been modified.

I think my questions about the methods have been responded to appropriately. Apologies that I didn't raise this previously, generally the principle of choosing the random effects or fixed effect model based on I-squared or chi-squared p-value is not recommended. You should either make a judgement about what is most likely to be appropriate based on the assumptions of the different models or conduct both fixed or random effects and compare which seems to fit the data better.
Reply: Thanks for your constructive suggestion. We corrected it in our method part accordingly.

A further point in your revised draft (p12) seems to suggest that including covariates in the NMA is not possible with STATA. As far as I'm aware it is possible - so its better to say this should be explore in future analyses rather than suggest its not possible due to limitations with STATA.
Reply: Sorry for the confusion. We updated it in our limitation and made it more reasonable.

Reviewer: 5
Reviewer Name: Richard Jackson
Institution and Country: Liverpool University, UK
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
I am happy to the responses to my comments raised.
Reply: Thank you for careful examination of the manuscript.

VERSION 3 – REVIEW

REVIEWER	Nick Meader University of York, UK
REVIEW RETURNED	23-Aug-2019

GENERAL COMMENTS	Thanks for updating the manuscript, its nearly there however I think one of your changes needs further refinement. You have updated the manuscript by cutting and pasting what I wrote: "To choose the random effects or fixed effects model, we either make a judgement about what is most likely to be appropriate based on the assumptions of the different models or conduct both fixed or random effects and compare which seems to fit the data better" So now this is theoretically correct. However, you now need to go on and tell us what you actually did - i.e. whether you chose fixed or random effects models and why. Otherwise it sounds incomplete.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 4
Reviewer Name: Nick Meader
Institution and Country: University of York, UK
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Thanks for updating the manuscript, its nearly there however I think one of your changes needs further refinement. You have updated the manuscript by cutting and pasting what I wrote:

"To choose the random effects or fixed effects model, we either make a judgement about what is most likely to be appropriate based on the assumptions of the different models or conduct both fixed or random effects and compare which seems to fit the data better"

So now this is theoretically correct. However, you now need to go on and tell us what you actually did - i.e. whether you chose fixed or random effects models and why. Otherwise it sounds incomplete.
Reply: Thanks for your constructive suggestion and sorry for the confusion. We performed both fixed and random effects models in our supplementary Figure 9, supplementary Figure 10 and supplementary Figure 11. In present study, the result of fixed effects models is similar to the random effects models, and no obvious heterogeneity was observed in all these results. Thus, we chose the conventional fixed effect model in this article. We revised this part accordingly to make it more reasonable. Sorry for the confusion again. If you have any other queries, please don't hesitate to contact us.