Author's response to reviews

Title: Association between metabolic syndrome and bone fractures: a meta-analysis of observational studies

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Author's response to reviews: see over
Responses to the editor:

Manuscript MS: 8605666111101822 entitled “Association between metabolic syndrome and bone fractures: a meta-analysis of observational studies”.

Dear Prof. April Rada and Prof. Dianna Magliano,

Thank you very much for having given us the opportunity to revise the manuscript. Following your suggestion, we carefully addressed the comments of the reviewer point-by-point and changed our manuscript accordingly. In our response to the reviewers, the comments of the reviewers are in bold, and our responses are in italics.

We hope that with these changes and clarifications, our manuscript will be acceptable for publication in BMC Endocrine Disorders.

Sincerely

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Reviewer's report

Title: Association between metabolic syndrome and bone fractures: a meta-analysis of observational studies

Version: 5 Date: 19 January 2014

Reviewer: Claudia Gagnon

Reviewer's report:

Sun K et al. conducted a meta-analysis of observational studies (both cross-sectional and prospective cohort studies) on the association between metabolic syndrome (MetS) and fractures. They found that there was no association between MetS and fractures in both the cross-sectional and prospective cohort studies. There was however a significant heterogeneity among the prospective cohort studies (n=3). Results from published observational studies on the topic have been inconsistent. The main reason for the discordant results is the fact that MetS is a heterogeneous syndrome that requires the presence of at least 3/5 criteria for its diagnosis (NCEP-ATPIII criteria). Predominance of different components of the MetS in the various studies may contribute to the discrepant results. The relationship between each of the components of the MetS and bone is extremely complex. One of the components may have a positive effect on bone while another component may have a deleterious effect. Moreover, the confounders that were adjusted for in the studies were highly variable and may further contribute to the discordant results. I am thus unsure that looking at the MetS as a whole is the best way to assess clinically whether this syndrome impact on fracture risk. I think that it would be more useful to know which components of the MetS are associated with an increased or a reduced risk of fracture.

Discretionary revisions

1. The authors correctly acknowledge in their discussion (p.13, first para) that evaluating the association between individual components of MetS and fractures would be more appropriate. I think that this meta-analysis would contribute greatly to the current knowledge if it could evaluate, in some way,
the impact of the components of MetS on fracture risk. Would it be possible to do a meta-analysis of the association between each of the components of MetS and bone fractures in the same studies (n=8)?

Response 1:
Thank you for your revision and we appreciate very much for your comments. We fully agree with your suggestion that it must be better if we could analyse the association between each of the components of MetS and bone fractures. However, only the MINOS Study has provided data that evaluated the association between individual components of MetS and fractures. Actually, we thought it could be another limitation for our study.

2. To help the reader better assess the validity of the studies, it would be interesting to add somewhere (perhaps in Table 1) the following information for each study: RR (or OR) and their 95% CI, factors that were adjusted for in the analyses, the number of fractures observed and finally, the duration of follow-up for the prospective cohort studies.

Response 2:
We appreciate very much for your comments. Information for RR (or OR) and their 95% CI has been given in Figure-2 & 3 of the manuscript. In the revised manuscript, the number of fractures observed and the duration of follow-up for the prospective cohort studies have been provided in table 1. For most of the included studies, lots of factors have been adjusted in the analyses and make no space for providing such information in table 1, for example “the MINOS Study adjusted for: age, BMI, education level, prevalent fractures, history of two or more falls during the year preceding recruitment, and aortic calcification score ( >6 vs 0 to 6), ischemic heart disease and whole-body BMD” and study done by “Kyong-Chol Kim adjusted for: age, body weight, percentage body fat, smoking status, alcohol consumption, total
energy expenditure, total calcium intake, total fat and cholesterol intake.”

3. In the discussion, lines 5-6 from the bottom: another cause of heterogeneity among cohort studies is the duration of follow-up. The Rancho Bernardo Study, that found an increased risk of fractures in people with the MetS, had a very short follow-up of about 2 years while the other two studies (Tromso and MINOS), that found a reduced risk of fractures in people with the MetS, had a longer follow-up of 6 and 10 years, respectively. More details on the 3 cohort studies could be provided. For instance, the Tromso study used non-fasting samples for glucose and triglycerides, they also used BMI in the definition instead of waist circumference and the fractures were not limited to non-trauma fractures.

Response 3:
We agree with your comments and provided details of the 3 cohort studies in table 1 and further added other information the 3 cohort studies in the following discussion section: “First, the distinct definition of metabolic syndrome might provide biased estimates on bone fractures. Moreover, the Tromsø Study took non-fasting samples for testing glucose and triglycerides levels and used BMI instead of waist circumference to define metabolic syndrome.” and “Finally, a substantial degree of heterogeneity, partly due to diversity in fractures types and the duration of follow up, was detected among cohort studies. For example, fractures in the Tromsø Study were not limited to non-trauma fractures. Moreover, the Rancho Bernardo Study found an increased risk of fractures in people with metabolic syndrome had only 2 years of follow-up. In the Tromsø Study and the MINOS Study, had a longer follow-up of 6 and 10 years, respectively, found a reduced risk of fractures in people with metabolic syndrome. However, such heterogeneity was not surprising because of unavoidable variations in study population and distinct adjustments across studies. Moreover, overall risk estimates of cohort studies did not substantially modified through the sensitivity analyses.”
4. Subgroup analyses were only done for cross-sectional studies (Table 2). Did the addition of the 3 cohort studies change the results?

Response 4:
Thank you for your revision and we appreciate very much for your comments. Actually, compared with prospective data, cross-sectional data on the association between metabolic syndrome and risk of fracture is limited in establishing causality and suffer from excessive bias. However, as only 3 prospective cohort studies were included in the meta-analysis, we conducted the subgroup analyses by only adopting the cross-sectional data. Moreover, cross-sectional studies and prospective studies were two different design of study and usually do not pooled together in most meta-analysis. As a result, we select cross-sectional studies to assess the overall association.

Minor essential revisions

1. Results p.11, 2nd para: MINOS study did not report cross-sectional data. Did you want to mention the Rancho Bernardo study instead?

Response 1:
We appreciate very much for your comment and following your suggestion, we changed relevant sentence in the revised manuscript.

2. The paper is generally well written although I found some mistakes throughout the text. I would suggest that the paper be reviewed by the authors before publication.

Response 2:
Thank you very much for your revision. We have carefully checked our manuscript
again, for the grammatical mistakes.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests.
Reviewer's report

Title: Association between metabolic syndrome and bone fractures: a meta-analysis of observational studies

Version: 5 Date: 16 January 2014
Reviewer: Peter Ebeling

Reviewer's report:

In this well written paper, Sun et al. have conducted a meta-analysis of observational studies to determine the association between metabolic syndrome and fractures. They included eight epidemiological studies involving 39,938 participants. In the overall analysis, metabolic syndrome was not associated with either prevalent fractures (OR 0.93, 95% CI 0.84 - 1.03) in cross-sectional studies or incident fractures (RR 0.88, 95% CI 0.37 - 2.12) in prospective cohort studies. A substantial heterogeneity was detected in cohort studies, but there was no indication of significant publication bias. Estimates of total effects were substantially consistent in the sensitivity and stratification analyses. The authors conclude this meta-analysis of observational studies suggests that metabolic syndrome may not increase the risk of bone fractures.

This reviewer has the following comments/questions:

Major Compulsory Revisions
1. The conclusion of the abstract is vague as currently written. Is there no effect on bone fractures or not? Please amend accordingly.

Response 1:
Thank you for your revision and we appreciate very much for your comments. Related part was presented in the revised manuscript as “The present meta-analysis of observational studies suggests that metabolic syndrome have no explicit effect on bone fractures.”

2. Perhaps a lack of effect is surprising as some recent papers have shown that both obesity and type 2 diabetes have been associated with an increased risk of

Response 2:

Thank you very much for your suggestion. Following your suggestion, we changed relevant discussion in the revised manuscript. Related part was presented in the revised manuscript as “Some of other metabolic syndrome components may just play a discordant role in the relationship between metabolic syndrome and fractures. Metabolic syndrome is a risk factor for diabetes which might expect an increase in fracture risk. Actually, patients with type 2 diabetes had an increased fracture risk in spite of a higher BMD level, which may partly cause by the increased risk of falling [26]. Strotmeyer et al. [27] found that subjects with type 2 diabetes mellitus may suffer from higher risk of osteoporotic fractures. However, impaired fasting plasma glucose is not associated with fracture risk in the same study. Gagnon C et al. [28] reported that incident fractures were reduced in individuals with elevated 2 hours plasma glucose levels and pre-diabetes independently of BMI and fasting insulin levels. Therefore, increased awareness of the association between metabolic syndrome and fractures is still needed in view of the above argument and growing population of patients with diabetes and impaired glucose regulation [29]. In addition, obesity is a risk factor for fractures of the humerus and ankle but protects against fractures of hip and vertebral [30-32]. Additionally, the association between obesity and fractures appears to vary with age. Dimitri et al. [33] found that obesity is a risk factor of fractures in children but a protective factor of fractures in adults. Future studies are needed to search for more credible evidence and identify the exact mechanisms that link obesity to fracture risk [34]. Base on the above arguments, we assume that the concept of metabolic syndrome may be slightly far-fetched in the
context of fractures. The controversial results of the included studies in this meta-analysis may mainly depend on the discrepancy between each individual component of metabolic syndrome and bone fractures. Moreover, the negative findings of current meta-analysis, to some extent, just verify this viewpoint.”

3. The article by Gagnon C et al. Osteoporos Int. 21:2067-74 2010 showed incident fractures were reduced in individuals with elevated 2-h PG levels and pre-diabetes independently of BMI and fasting insulin levels. This paper should also be cited.

Response 3:
Thank you for your revision and we appreciate very much for your comments. Following your suggestion, we changed relevant discussion in the revised manuscript. Related part was presented in the revised manuscript as “Gagnon C et al. [28] reported that incident fractures were reduced in individuals with elevated 2 hours plasma glucose levels and pre-diabetes independently of BMI and fasting insulin levels. Therefore, increased awareness of the association between metabolic syndrome and fractures is still needed in view of the above argument and growing population of patients with diabetes and impaired glucose regulation.”

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests