PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Abdominal aortic calcification, bone mineral density and fractures: a systematic review and meta-analysis protocol
AUTHORS	Sim, Marc; Rodriguez, Alex; Leow, Kevin; Szulc, Pawel; Scott, David; Ebeling, Peter; Wong, Germaine; Lim, Wai H.; Schousboe, John; Kiel, Douglas; Prince, Richard; R. Lewis, Joshua

VERSION 1 - REVIEW

REVIEWER	Chen zexin second affiliated hospital of zhejiang university school of medicine , zhejiang, China
REVIEW RETURNED	20-Sep-2018

GENERAL COMMENTS	just a usual meta-analysis protocol,lack of innovation

REVIEWER	Licheng Zhang Chinese PLA General Hospital, China
REVIEW RETURNED	01-Oct-2018

GENERAL COMMENTS	1 Full name of CVD is missing. 2 The retrospective nature of the studies will be included, which will weaken the robustness of explaining causality between AAC, BMD, and fractures. 3 It is inappropriate to address two important issues, the associations between AAC or BMD, and fractures, and between AAC and BMD, in one single study. 4 The authors tried to investigate the effect of the association between AAC and BMD on the hypothesized causal pathway to fracture. However, there has been a prospective study (Szulc P. J Bone Miner Res. 2008 Jan;23(1):95-102) reporting that severe AAC and lower BMD are jointly but independently associated with vertebral fractures. 5 Two meta-analysis studies on this topic have been published, including the prospective study of Wei et al 2017, make other meta-analysis studies or protocols unnecessary.

REVIEWER	Rosa Olivia Méndez Estrada. México. Centro de Investigación en Alimentación y Desarrollo, Mexico
REVIEW RETURNED	27-Nov-2018

GENERAL COMMENTS	The manuscript " Abdominal aortic calcification, bone mineral density and fractures: a systematic review and meta-analysis protocol", presents sufficient information that supports the procedure to evaluate the association between AAC and bone mineral density, prevalence of fractures and incident fractures. Suggestion: In objective 4 it is necessary to specify the modifiers that will be evaluated.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Comment: "Just a usual meta-analysis protocol, lack of innovation":

Response: This comment is unusual as meta-analyses are generally not considered innovative but address clinically important issues. They are designed to combine results from an adequate number of published reports to increase statistical power, provide more reliable estimates of the size or direction of an association/effect or to resolve uncertainty and highlight areas for future studies. All of which are applicable to this issue. Second, this will be the first meta-analysis to investigate the relationship between AAC and BMD in the context of fractures. Third, in contrast to previous meta-analyses, we are employing meta-regression to determine effect modifiers which add significant innovation to our manuscript. Fourthly, we aim to investigate the threshold of AAC severity which imposes increased fracture risk by performing pre-specified sub-group analyses investigating fracture risk across different AAC severity criteria. This is important as several studies show negative relationships, but the thresholds applied may be too low. Further, there appears to be site-specific differences in associations where AAC is associated with vertebral and hip fractures but data on the link with other sites and all fractures remains inconsistent. In a pre-specified sub-analysis, we are aiming to determine these links. As such, our meta-analysis will substantially expand the scope and completeness compared with previous meta-analyses on this topic, adding innovation. Overall, this protocol will not only provide a platform to address important clinical questions in this area but will provide a platform for future meta-analyses in other areas of clinical importance by taking inspiration from the innovative techniques planned in this analysis.

Reviewer 2:

1. Full name of CVD is missing.

Response: We have now updated this in the manuscript.

2. The retrospective nature of the studies will be included, which will weaken the robustness of explaining causality between AAC, BMD, and fractures.

Response: Retrospective and prospective studies will be analyzed as a separate subgroup analysis, in addition to using all studies (outlined under “Further Analyses”). Notwithstanding the planned analysis of only the prospective studies, causality cannot be established by observational studies. By determining effect modifiers from meta-regression, we may be able to identify subgroups with clinical risk profiles where AAC is most strongly related to low BMD and increased fracture risk – which currently remains a clinical conundrum.

3. It is inappropriate to address two important issues, the associations between AAC or BMD, and fractures, and between AAC and BMD, in one single study.

Response: We are unclear why the reviewer considers it inappropriate to consider both these outcomes in a single study. The rationale is that AAC is inversely associated with BMD leading to

increased fracture risk. This is supported by our recently published paper in BMJ (Trajanoska K, et al. BMJ. 2018 Aug 29;362:k3225) that the main genetic fracture risk factors are BMD-related traits. The reported associations between AAC and BMD have been weak, potentially site-specific and inconsistent, hence the need for a meta-analysis to clarify current understanding. As such, we believe investigating the relationship between AAC with BMD and fracture in a single meta-analysis is appropriate and makes for a complete investigation of this area of clinical interest.

4. The authors tried to investigate the effect of the association between AAC and BMD on the hypothesized causal pathway to fracture. However, there has been a prospective study (Szulc P. J Bone Miner Res. 2008 Jan;23(1):95-102) reporting that severe AAC and lower BMD are jointly but independently associated with vertebral fractures.

Response: The reviewer incorrectly reports that AAC and lower BMD are independently associated with vertebral fractures. Dr Pawel Szulc (an author of this meta-analysis) and colleagues (2008 paper) reported on the relationship between AAC and incident clinical fracture in one cohort of older men. By contrast, the paper showing that severe AAC and low BMD are associated jointly but independently with vertebral fractures is cross-sectional, not prospective (Szulc P, Osteoporos Int, 2013, 24, 1177-1184). Other published work has not tested whether these findings are independent of BMD or did not find independence. The heterogeneity of conclusions again reinforces the motivation for the current meta-analysis.

5. Two meta-analysis studies on this topic have been published, including the prospective study of Wei et al 2017, make other meta-analysis studies or protocols unnecessary.

Response: As mentioned in the protocol and the above responses, this meta-analysis will undertake a more sensitive and comprehensive approach than the previous two meta-analyses that have not fully explored the true nature of the relationship between AAC, BMD and fracture risk. This is evidenced by our recent search that has identified over 60 eligible studies to date. Additionally, the previous meta-analysis searches only included studies up until December 2016. Hence a more comprehensive meta-analysis (including meta-regression) with an additional 2 years of studies is planned.

Reviewer 3

The manuscript " Abdominal aortic calcification, bone mineral density and fractures: a systematic review and meta-analysis protocol", presents sufficient information that supports the procedure to evaluate the association between AAC and bone mineral density, prevalence of fractures and incident fractures.

Suggestion: In objective 4 it is necessary to specify the modifiers that will be evaluated.

Response: We thank the reviewer for this suggestion, and we have added more specific details to Objective #4 so that it now reads: “To assess the impact of potential effect modifiers, including aspects clinical, methodological and statistical heterogeneity on previous published findings.” As the objectives represent a general overview of planned analyses we did not include all planned sub-group analyses here as they are listed later in the manuscript under Study Design.

Cohort characteristics for meta-regression (where available)

- Cohort age (cohort mean)
- Gender (% female)
- Years since menopause (cohort mean)
- Hormone replacement therapy (%)

- Modality of assessing AAC (DXA, standard radiograph or CT).
- Cut points choses for comparison (low vs high, tertiles etc.)
- Diabetes (% of cohort)
- Current smoker (% of cohort)
- History of smoking (% of cohort)
- Body mass index (cohort mean)
- Chronic kidney disease (% of cohort)
- History of CVD (% of cohort)
- Location of study (Europe, Asia-Pacific, North America), i.e. are association consistent across ethnicities and nation wealth
- Prevalence of CVD medication use (% of cohort)
- History of fracture (% of cohort)