8-24-2023

Abdominal aortic calcification, bone mineral density and fractures: A systematic review and meta-analysis of observational studies

Abadi K. Gebre
Edith Cowan University

Joshua R. Lewis
Edith Cowan University

Kevin Leow

Pawel Szulc

David Scott

See next page for additional authors

10.1093/gerona/glac171

OXFORD UNIVERSITY PRESS | Journal of Gerontology: Medical Scienc

Abdominal aortic calcification, bone mineral density and fractures: a systematic review and meta-analysis of observational studies

Journal:	*Journal of Gerontology: Medical Sciences*
Manuscript ID	JGMS-2022-REV-0161.R1
Manuscript Type:	Review
Date Submitted by the Author:	n/a
Complete List of Authors:	Gebre, Abadi; Edith Cowan University, Institute for Nutrition Research; Mekelle University, School of Pharmacy Lewis, Joshua; Edith Cowan University, Institute for Nutrition Research; The University of Western Australia, Medical School; The University of Sydney Children's Hospital Westmead Clinical School, Centre for Kidney Research Leow, Kevin; The University of Sydney Children's Hospital Westmead Clinical School, Centre for Kidney Research Westmead Szulc, Pawel; INSERM UMR 1033, Epidemiology of Osteoporosis Scott, David; Monash University Faculty of Medicine Nursing and Health Sciences, School of Clinical Sciences at Monash Health Ebeling, Peter; Monash University, Department of Medicine, School of Clinical Sciences, Faculty of Medicine, Nursing and Health Sciences Sim, Marc; Edith Cowan University; University of Western Australia Wong, Germaine; Children\'s Hospital at Westmead Centre for Kidney Research Lim, Wai; The University of Western Australia Schousboe, John ; University of Minnesota Academic Health Center, Park Nicollet Osteoporosis Center and HealthPartners Institute, HealthPartners, Minneapolis, MN 55416, USA, Division of Health Policy and Management Kiel, Doug; Hebrew SeniorLife, Institute for Aging Research Prince, Richard; The University of Western Australia, Medical School Rodríguez, Alexander ; Edith Cowan University; Monash University, Department of Medicine
Keywords:	Osteoporosis, Cardiovascular, Hip Fracture
Alternate Keyword:	vascular calcification

Abdominal aortic calcification, bone mineral density and fractures: a systematic review and meta-analysis of observational studies

Abadi K. Gebre, MSc,[1,2] Joshua R. Lewis, PhD[1,3,4], Kevin Leow, MBBS,[4] Pawel Szulc, PhD,[5] David Scott, PhD,[6,7] Peter R. Ebeling, MD,[7] Marc Sim, PhD,[1,3] Germaine Wong, PhD,[4] Wai H. Lim, PhD,[3,8] John T. Schousboe, MD, PhD,[9] Douglas P. Kiel, MD,[10] Richard L. Prince, MD,[3] and Alexander J. Rodríguez, PhD [1,7*]

[1]Nutrition & Health Innovation Research Institute, School of Medical and Health Sciences, Edith Cowan University, Joondalup, Australia

[2]School of Pharmacy, College of Health Sciences, Mekelle University, Mekelle, Tigray

[3]Medical School, University of Western Australia, Perth, Australia

[4]Centre for Kidney Research, Children's Hospital at Westmead School of Public Health, Sydney Medical School, The University of Sydney, Sydney, Australia

[5]INSERM UMR 1033, University of Lyon, Hospices Civils de Lyon, Lyon, France

[6]Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Geelong, VIC, Australia

[7]Bone and Muscle Health Research Group, Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Victoria, Australia

[8]Department of Renal Medicine, Sir Charles Gairdner Hospital, Western Australia, Australia

[9]Park Nicollet Osteoporosis Center and HealthPartners Institute, HealthPartners, Minneapolis, MN 55416, USA, and Division of Health Policy and Management, University of Minnesota, Minneapolis, MN 55455, USA

[10]Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

Corresponding author:

Alexander J. Rodríguez PhD

Research Fellow - Bone & Muscle Research Group

Department of Medicine, Monash University, Level 7, Translational Research Facility MHTP Building, 51 Kanooka Grove, Clayton VIC 3168

Telephone: [redacted] Email: [redacted]

ORCID: 0000-0002-2955-0642

Word count

Abstract=249

Manuscript=3827

Number of data elements: 4

Running title: AAC, BMD and fracture meta-analysis

Abstract

Background: Abdominal aortic calcification (AAC) has been inconsistently associated with skeletal health. We aimed to investigate the association of AAC with bone mineral density (BMD) and fracture risk by pooling the findings of observational studies.

Methods: Medline, EMBASE, Web of Science and Google Scholar were searched (August 2021). All clinical studies that assessed the association between AAC and BMD or fracture were included. AAC was categorized into AAC any/advanced (all higher reported groups) vs no/less advanced (lowest reported group). Pooled standardized mean differences (SMDs) and risk ratios (RRs) with 95% confidence intervals (CI) were determined for BMD and fracture, respectively, using random-effects models.

Results: Of 2,192 articles screened, 86 (61,553 participants) were included in the review, while 42 provided data for meta-analysis. AAC was associated with lower BMD at the total hip [SMD=-1.05 (95%CI: -1.47 to -0.63); 16 studies], femoral neck [-0.25 (-0.46 to - 0.04); 10] and lumbar spine [-0.67 (-1.21 to -0.12); 20]. AAC was associated with a greater risk of any fracture [RR= 1.73 (95%CI: 1.48 to 2.02); 27]. AAC was also associated with vertebral, non-vertebral and hip fractures. In dose-response analysis, the highest AAC group had greater risks of any, vertebral and non-vertebral fractures.

Conclusions: AAC is associated with lower BMD and increased fracture risk at multiple sites, underscoring the potential importance of vascular disease on skeletal health. Detection of AAC at the time of BMD testing may provide clinicians with prognostic information about bone health to enhance osteoporosis screening programs and fracture risk prediction.

Keywords: Vascular calcification, osteoporosis, fracture

Introduction

Vascular calcification, previously considered an inevitable consequence of aging, is now understood to be an active and dynamic process of mineral deposition within arterial walls. It is closely linked with chronic diseases such as atherosclerosis, chronic kidney disease (CKD), and type 2 diabetes mellitus (1). Specifically, abdominal aortic calcification (AAC) has been identified as a marker of advanced atherosclerotic plaques (2), and is associated with an increased risk of cardiovascular events and poor prognosis (3). AAC has also been associated with poorer skeletal health, such as lower bone mineral density (BMD) (4, 5) and an increased risk of osteoporotic fractures (4, 6, 7).

Vascular calcification and osteoporosis (another disease previously considered a natural consequence of aging) have shared genetic (8) and signalling pathways (9) as well as other risk factors (e.g. smoking, diabetes mellitus, obesity and menopause) suggestive of a common causal origin (10, 11). Vascular calcification may theoretically precede and provoke bone loss by impairing peripheral blood perfusion potentially affecting osteogenesis (12). Vascular disease may also be associated with reduced physical activity and fitness, leading to weak and fragile bone as well as low muscle mass which may predispose to falling (13). Mechanisms underlying these observations, which commonly present during aging, represent potential targets for intervention. However, despite these putative causal links, the findings of the available small studies with different measures of skeletal outcomes and median AAC are often discordant. Thus, synthesis of the available studies is crucial to refining our understanding of the relationship if any, of AAC with skeletal health.

To date, two previous meta-analyses of observational studies have reported on this association, Chen and Yu et al (2016) (14) and Wei et al (2018) (15). However, these studies identified only a limited number of articles (15 and seven, respectively) and failed to investigate potential

sources of between-study heterogeneity such as imaging modality. Moreover, it is unclear whether the association between AAC and BMD or fracture is similar across different skeletal sites and cohorts of differing characteristics. We aimed to assess BMD differences, and risk of fractures in patients with AAC.

Methods

This systematic review and meta-analysis of observational studies was conducted in accordance with PRISMA guidelines and was registered in PROSPERO (CRD42018088019). The protocol was published previously (7).

Data sources and search strategy

Database searches were performed in MEDLINE, EMBASE, Web of Science core collection and Cochrane library for articles published from inception to August 6, 2021 without language restriction using key terms such as vascular calcification, bone mineral density, fracture and additional filters such as human and observational studies as detailed in **Table S1** and previously published protocol (7). We also searched Google Scholar (top 200 by relevancy) manually to retrieve additional relevant articles. Conference abstracts were also assessed. Reference lists of eligible studies were hands-searched and previous meta-analyses were evaluated for potentially relevant articles missing from the main search.

Study selection

Studies were reviewed for eligibility by at least two independently reviewers (AJR, KL or AKG) as described previously (7). Retrieved studies were pooled together into a citation manager with duplicates removed. The remaining articles were screened sequentially by title, then abstract, then full text according to predefined exclusion and inclusion criteria. Disagreements at each level of screening were resolved by consensus or an involvement of a third reviewer (JRL).

Eligibility criteria

As no randomized trials exist, we included observational studies conducted in humans, of any design, that assessed AAC by any methodology and reported BMD at any site by any modality, or prevalent or incident fracture reported by any means as described previously (7).

Risk of bias and quality assessment

The risk of bias was assessed by at least two reviewer (AJR, KL or AKG) using the Newcastle-Ottawa Scale (NOS) (16). The risk of bias for each of the studies included in the meta-analysis was assessed based on the study design (cross-sectional, case-control or cohort studies) grouped into three categories of quality (good, fair or poor) as described previously (17, 18). Summary estimates of the confidence placed on the evidence was evaluated using the Grading of Recommendations Assessment Development and Evaluation (GRADE) for prognosis which starts with high quality evidence that can then be rated down (19). Publication bias was evaluated using visual inspection of funnel plots and Egger's regression tests (20).

AAC reporting

AAC was assessed either semi-quantitatively (radiograph or DXA) or quantitatively (CT). Data used for analysis specifically related to AAC only. Where studies combined data for AAC with calcification from other parts/branches of the aorta, these data were excluded from meta-analysis.In the main quantitative analysis, the lowest reported AAC group (low or none) was used as referent and compared with the combination of all higher reported groups (any/advanced AAC) to compute the standardized mean difference (SMD) for BMD measures, absolute risk difference (ARD) and relative risk (RR) for any and site-specific fractures. For example, if a study has four AAC groups (AAC score: 0-1; 2-5; 6-9 and 9+), analysis combined the highest three groups (2-5; 6-9 and 9+) and compare fracture risks and BMD measures against the lowest group (0-1). We have used this approach to minimize classification bias

given the heterogeneity in AAC group definitions in the included literature. Additionally, we have analysed studies that reported AAC either as: (1) any versus none to assess the relationship between any AAC and fracture outcomes or (2) for studies that reported three or more AAC groups, dose–response analysis was made. To do this, we considered the lowest AAC score as the reference group. Fracture risks in the the middle group(s) and the highest AAC group (high AAC) were compared against this reference group.Where data on more than three groups of AAC were presented, the middle groups were combined as 'moderate AAC'.

Statistical analysis

For BMD measures, estimates were expressed as SMD with 95% confidence intervals (95%CIs) to account for reporting differences (g/cm^2, g/cm^3, g/mm^3). For fracture outcomes, ARD and RR with 95%CI were calculated, from which, a summary estimate was determined using random effects models. Summary estimate fixed effects models were also provided in the forest plots to show internal consistency of the relationship. As an attempt to account for between-study heterogeneity, we conducted several sub-group analyses, identified a priori (7), and potential effect modifiers were explored through meta-regression. Additionally, we conducted an exploratory analysis pooling together adjusted risk estimates as reported in included studies of the association between AAC and fracture as a measure of internal validity. The I^2 (%) and τ^2 statistics were reported as measures of the proportion of total variability due to between-study heterogeneity and between-study variance, respectively. Smaller values indicate less variability and variance in between-study heterogeneity. All analyses were computed using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria (https://www.R-project.org/) and considered statistically significant when the bounds of the 95%CI did not cross one for RR and zero for SMD.

Results

Literature search

2192 unique records were retrieved through database searches. Of these, 1944 records were excluded based on title or abstract, and a further 162 were excluded after full-text screening leaving 86 (61,553 participants) studies for qualitative synthesis [**Figure 1**].

Study characteristics

Study characteristics of all included studies (those contributing to qualitative synthesis only as well as those included in quantitative synthesis) are presented in **Table 1**. The majority of the studies were conducted in an older adult population aged over 65 years (n=57 studies, 67%). Most studies were conducted in Europe (n=32 studies, 37.2%) or North America (n=26 studies, 30.2%), and 63.9% (n=55 studies) were published in 2010 or later. Most studies (n=59 studies, 68.6%) were conducted in the general population of men and women or only in postmenopausal women, and 22.1% (n=19 studies) were conducted in patients with CKD, haemodialysis, or kidney stones (**Table 1**). AAC was evaluated by radiograph in 46 studies (53.4%) by CT in 25 studies (30.2%) and by DXA in 14 studies (16.3%). Detailed characteristics of the studies including the key findings from each study are presented in **Table S2**.

Of the 86 eligible studies included in the qualitative synthesis, 42 studies (two abstracts, 40 full publications) provided extractable data suitable for the meta-analysis [BMD, n=14, fracture, n=12, both BMD and fracture, n=16] [**Figure 1**]. For studies that were not included in the meta-analysis (n=44, 51.2%), these articles were reviewed in the qualitative synthesis only. These studies included reports that did not provide quantitative data to enable an association to be drawn between AAC with BMD or fracture. Abstracts were checked to determine if they were subsequently published after the search date. Where uncertainties were apparent, corresponding authors were contacted for relevant data.

Risk of bias assessment

Risk of bias assessment is presented in **Data S1.** Of the 42 studies included in meta-analysis**,** 40 studies were assessed (two conference abstracts not assessed), 24 studies (60%) were graded as good quality, 14 studies (35 %) graded as fair quality and two (5%) studies graded as poor quality (**Table S3-5)**.

AAC and BMD measures

BMD was reported by 30 studies: 10 studies for femoral neck (n=6981 participants), 16 studies for total hip (n=20277), 20 for lumbar spine (n=17260), four for distal radius (4257 participants), three for proximal radius (n=3476), three for whole body (n=3426), two each for calcaneus (n=2575) and vertebral trabecular vBMD (n=1259) [**Table S6**]. Compared with individuals with no/less advanced AAC, those with any/advanced AAC had lower BMD at the total hip, femoral neck, lumbar spine and calcaneus, all $p<0.05$ [**Figure 2** and **Table S7**]. Marked heterogeneity was evident in all analyses.

Sensitivity analyses in studies reporting BMD as an outcome

Subgroup analyses highlighted women with any/advanced AAC had consistently lower BMD at the femoral neck, total hip, and lumbar spine but these associations were not seen in men except a marginal difference at the total hip. Similarly, lower femoral neck, total hip and lumbar spine BMDs were observed in studies that used radiograph to capture AAC [**Table S8**] whilst this association was only evident for total hip in studies that used DXA to capture AAC. Additionally, any/advanced AAC was significantly associated with lower BMD at the total hip and lumbar spine even after excluding studies with poor and fair quality. However, the magnitude of the association between AAC and femoral neck BMD was attenuated after exclusion of studies with poor and fair quality. In meta-regression, as the proportion of women in each study increased, the effect size between AAC and femoral neck BMD decreased (β=-

0.005). The R^2 value for this association was 0.28 indicating that 28% of the variance in studies that reported the association between AAC, and femoral neck BMD may be explained by the proportion of women included in studies [**Table S9** and **Figure S1**]. In studies that reported the association between AAC and BMD by skeletal sites, a statistically significant evidence of publication bias was only observed for calcaneus [**Table S7** and **Figure S2 A-C]**.

AAC and fracture outcomes

The association between any/advanced AAC and risk of any fracture was reported in 28 studies (n=33748 participants): 22 studies for vertebral (n=23344), 10 for non-vertebral (n=18424) and nine for hip fractures (n=17809) (**Table S10** and **11**). Individuals with any/advanced AAC had a greater absolute risk and relative risk for any [**Figure 3]**, vertebral, non-vertebral and hip fractures [**Figure 4**]. AAC was associated with greater risk for incident fracture and site-specific incident fractures [**Figure 3** and **Table S11**]. In studies that reported three or more AAC groups, the RR for any, vertebral and non-vertebral fractures increased with increasing severity of AAC group [**Table S12**]. Pooled analyses of reported estimates after adjustment for BMD (including a minimum of age, BMI and smoking) revealed AAC was associated with greater risks of prevalent (six studies: OR=2.34 95%CI:1.46 to 3.74, I^2 =71.0%) and incident (six studies: HR=1.45; 95%CI:1.21 to 1.72, I^2 =57.4%) fractures. Marked heterogeneity was evident in all analyses.

Sensitivity analyses in studies reporting fracture outcomes

The association between any/advanced AAC, any and site-specific fractures remained significant after excluding studies with poor and fair quality [**Table S13**]. Subgroup analyses showed a consistent increased RR of any, vertebral, non-vertebral and hip fracture in studies with a sample size greater than 500, studies undertaken in women only, and in studies that utilized radiographs for AAC detection [**Table S14**]. In meta-regression, age explained the

observed between-study heterogeneity for the association between AAC and any (β =-0.038) and vertebral fractures (β=-0.047) by 35.7% and 44.4%, respectively. In addition, percentage of smokers in the cohort explained the observed between study heterogeneity for any (β=-0.012) and vertebral (β=-0.012) fractures by 33.5% and 25.7% respectively [**Figure S3A-D** and **Table S15**].

Publication bias in studies reporting fracture outcomes

Funnel plot and Egger's tests indicated moderate to minimal-study publication bias in studies reporting the association between the presence of any/advanced AAC and risk of any and hip fracture (p=0.02). However, no statistically significant evidence of publication bias was observed in studies that reported vertebral and non-vertebral fractures [**Table S10 and Figure S4A-D]**.

Quality of evidence assessment

There was moderate quality evidence for BMD outcomes. There was moderate-high quality evidence for any, vertebral and non-vertebral fracture outcomes and low-quality evidence for hip fracture outcomes [**Table S16**].

Discussion

Growing evidence suggests a close relationship between the development and progression of cardiovascular disease and osteoporosis, previously thought of as natural consequences of aging. We sought to provide the association of AAC with both BMD and fracture in a single comprehensive report. We observed that, compared with people with no/less advanced AAC, people with any/advanced AAC demonstrated lower BMD across several skeletal sites and higher RR for any and site-specific fractures. These data provide consistent findings linking AAC, a readily quantifiable marker of vascular disease, with poor skeletal health confirming

that AAC and bone metabolism are linked and may improve fracture prediction and reclassification. We also showed that in pooling estimates that accounted for BMD in adjusted analyses, AAC remained a significant predictor of fracture risk. Moreover, the majority of the studies that were included in qualitative synthesis only (namely, studies without data for meta-analysis) reported an inverse relationship between AAC and BMD (more AAC, lower BMD) (21-23) and increased risk of fractures (24-26) in general and specific populations. A few studies included in the qualitative review showed no relationship between AAC, BMD or fractures (26-29). These studies were low powered and conducted in samples not resperesentative of the general population, but the overall meaningful the qualitative analyses generally supports findings from our quantitative synthesis that the presence and severity of AAC indicates poor skeletal health and prognosis.

AAC is speculated to alter blood flow dynamics through aortic stiffening, leading to small vessel disease which may impact the skeletal circulation (30). The skeleton receives about 10% of the cardiac output and for similarly perfused organs, aortic stiffening can induce end-organ damage (31). It has also been speculated that AAC diminishes renal and mesenteric blood flow, therefore retarding the delivery and absorption of essential micro-nutrients needed for bone remodelling (30). This potentially increases oxidative stress, thereby accelerating bone loss and increasing fracture risk (9, 32). The femoral head and neck receives most of its supply via the medial circumflex femoral artery which is a branch of the femoral artery originating from the abdominal aorta via the iliac artery. Thus, this anatomical relation supports the nutrient supply hypothesis (12, 33). Of note, a significant association between AAC and lumbar spine BMD was observed further supporting the nutrient supply theory given the lumbar arteries branch off the abdominal aorta. However, no such relationship was observed with BMD at the distal radius, proximal radius, and whole body. This possibly reflects a lesser contribution of abdominal aortic blood flow to these skeletal areas. This is supported by Szulc et al (2014) (33)

where the association of AAC and hip fracture persisted, but not lower limb fractures, after adjustment for ankle-brachial index (an indirect marker of blood flow dynamics). This suggests that some observed associations may be explained by mechanisms beyond the nutrient supply hypothesis.

Given the well-established association of BMD in the causal pathway for fracture, we expected that associations between AAC and fractures would mirror associations observed for BMD at these sites. Compared with individuals with no/less advanced AAC, we found that those with any/advanced AAC had a 66% increased RR of fracture at any site. Findings were consistent for vertebral, non-vertebral and hip fractures which supports observations from the BMD analysis. This would suggest that AAC may have an important role in increasing the risk of low BMD leading to fracture. Interestingly, AAC was also associated with greater risks of fractures in studies that reported associations of AAC with fracture after adjustment for BMD which suggests that at least some of the excess fracture risk attributable to AAC is not mediated by BMD. Therefore, the presence of AAC in an individual should warrant further observation and follow-up and may have a role in risk stratification and guide decisions about treatment recommendation in those below treatment threshold. Population age of included studies accounted for large proportions of between-study heterogeneity in meta-regression with respect to fractures only and not BMD. Further, the association between AAC and fracture remained in a pooled analysis of available reported multivariable adjusted effect estimates. This suggests unknown (or unaccounted for) factors during aging affecting both the calcification process and fracture risk.

Other mechanisms thought to explain these associations include, the well-described effect of atherosclerosis/vessel calcification on syncope and on compromised muscle strength that can both exacerbate the risk of falls (34) and subsequent fracture (35). Further, traditional risk factors for fracture and CVD such as advanced age, smoking and post-menopausal oestrogen

decline (all having deleterious effects on bone quality and vascular health) may also explain the observed associations (36). To this end, our subgroup analyses showed estimates were consistently stronger in women-only (particularly for BMD analyses) studies compared to men-only or mixed populations. However, there were inconsistent effects of age and smoking in meta-regression, likely related to the small number of studies included in the analysis and/or limited data availability to enable meaningful regression. Older individuals and smokers may have a greater accumulation of other fracture risk factors, reducing the relative contribution of AAC to fracture risk and BMD. This suggests that early detection of AAC could enhance identification of individuals at higher risk of osteoporosis. Overall, absolute fracture risks were large and, importantly, consistent with the magnitude of RR, supporting the notion that clinically meaningful associations are being observed. Although the absolute risks for hip and non-vertebral fractures were modest (likely related to lower event rates consistent with our understanding of these fractures), the healthcare costs and mortality associated with these fractures renders these ARDs clinically important (37). Notably, these findings highlight areas of primary prevention to reduce vascular-bone disease. From a public health standpoint, screening of AAC in patients at risk for fracture and poor skeletal health could enhance risk stratification and represent an opportunity to 'value-add' to existing osteoporosis screening programmes as has been recently demonstrated but has not been adopted in screening guidelines (38).

This report has numerous strengths, providing an additional contribution to the literature beyond what has been previously reported (14, 15). Firstly, the reporting of AAC associations with both BMD and fractures provides internal consistency. We showed consistent associations between AAC with BMD and fractures across skeletal sites underscoring the importance of maintaining BMD in fracture reduction but also highlights how vascular disease is an important contributor to fracture. Secondly, we conducted a comprehensive literature search and

identified 13-21 (87%-300%) more studies than the previous meta-analyses (14, 15). Thirdly, we undertook detailed subgroup and meta-regression analyses to investigate factors that may explain the observed between-study heterogeneity. These subgroup analyses served a secondary purpose of understanding factors that modify observed associations, which could provide clues for putative causal pathways and offer areas to target in intervention trials.

The present study has several limitations. First, high between-study heterogeneity (I^2 53% - 100% and τ^2 0.06-1.53) was noted in several analyses, suggesting the need for a careful interpretation of the findings. This suggests that the range of true effect sizes may yet include the null. Importantly, when we pooled together reported estimates for the association of AAC with fracture after adjustment for BMD, measures of heterogeneity were reduced. This suggests that considering important risk factors enhances confidence in the summary estimates. For this reason, we have attempted to explore such factors through numerous subgroup analyses (where study characteristics were more) homogeneous and meta-regression. Most of these analyses supported the primary analysis, underscoring internal validity. Overall, we are of the view that pooling of studies despite this heterogeneity is justified on clinical grounds as the studies included have sought to investigate the same question. We note that meta-analysing effect estimates from prospective cohort studies yielded reduced heterogeneity, highlighting the putative role AAC may have in fracture and the ongoing need for higher forms of evidence to inform our understanding. Specifically, subgroup analyses revealed findings to be more pronounced in women, possibly reflecting greater statistical power (as there were more studies conducted in women) as well as the known effects of oestrogen decline on skeletal and vascular outcomes. Cohort age and percentage of smokers also explained a considerable amount of the observed between-study heterogeneity in studies that reported the association between AAC, any or vertebral fractures. However, this fits with our understanding of age and smoking as independent risk factors for AAC and fractures. Second, publication bias was noted for studies

that investigated the association between AAC and any and hip fractures. These limitations may have affected the validity of observed associations. Publication biases may be attributable to the inclusion of two conference abstracts; however, we believe inclusion of these data are justified to increase statistical power and only represent a small fraction of the included studies. Third, given that the studies included in these meta-analyses were observational, causality cannot be inferred. Fourth, cut points (thresholds) for AAC groupings that were used to categorise into any/advanced AAC versus no/low were not consistent amongst the studies and this may have contributed to observed effect estimate variance through classification bias which is beyond our capacity as reviewers to control. Dose response analyses were conducted to minimise this limitation. Fifth, many studies provided limited data on the contribution of confounders on the associations between AAC, BMD or fracture. This was primarily driven by the fact that many of the studies were not specifically designed to investigate these associations but had data for extraction that allowed such an association to be explored.

Conclusion

The present study synthesized the available literature and determined that, overall, the presence and severity of AAC is associated with lower BMD and increased fracture risk across multiple sites and across multiple patient populations. Since AAC AAC may be quantified at the time of BMD testing, it may provide prognostic information to clinicians about vascular and bone disease. Future studies should focus on understanding shared risk factors and in developing prevention and treatment strategies that may, concomitantly, reduce both vascular and musculoskeletal disease burden.

Conflict of Interest

None declared

Acknowledgements

PRE has received grant funding to his institution from Amgen, Eli-Lilly and Alexion, and honoraria from Amgen and Sanofi. DPK has received grant funding to his institution from Amgen, Radius, and Solarea Bio. He serves as a member of scientific advisory boards for Solarea Bio and Pfizer and has received royalties for publication in UpToDate from Wolters Kluwer. All other authors declare no conflict of interest. The salary of J.R.L is supported by a National Heart Foundation of Australia Future Leader Fellowship (ID: 102817), and Rebecca L. Cooper Medical Research Foundation grant. Dr Kiel's time was supported by a grant from the National Institute for Arthritis and Musculoskeletal and Skin Diseases (R01 AR 041398). The salary of DS is supported by a National Health and Medical Research Council Australia Investigator Grant (GNT1174886). The salary of AJR is supported by a National Health and Medical Research Council Australia Investigator Grant (GNT1197958). None of these funding agencies had any input into any aspect of the design and management of this study.

Author contributions

AJR, JRL, KL and AKG study concept and design. AJR and KL searched and retrieved the articles. AKG, AJR, and KL extracted the data. AKG and AJR conducted the data analyses. AKG and AJR drafted the manuscript. AJR, JRL and MS supervised the study. AJR co-ordinated the authorship team. All authors read and approved the revised version and final supported versions. AKG and AJR have the primary responsibility for the final content.

References

1. Johnson RC, Leopold JA, Loscalzo J. Vascular calcification: pathobiological mechanisms and clinical implications. Circ Res. 2006;**99**:1044-1059. doi: 10.1161/01.RES.0000249379.55535.21

2. Lewis JR, Schousboe JT, Lim WH, Wong G, Zhu K, Lim EM, et al. Abdominal Aortic Calcification Identified on Lateral Spine Images From Bone Densitometers Are a Marker of Generalized Atherosclerosis in Elderly Women. Arteriosclerosis, thrombosis, and vascular biology. 2016;**36**:166-173. doi: 10.1161/ATVBAHA.115.306383

3. Leow K, Szulc P, Schousboe JT, Kiel DP, Teixeira-Pinto A, Shaikh H, et al. Prognostic Value of Abdominal Aortic Calcification: A Systematic Review and Meta-Analysis of Observational Studies. J Am Heart Assoc. 2021;**10**:e017205. doi: 10.1161/JAHA.120.017205

4. Lewis JR, Eggermont CJ, Schousboe JT, Lim WH, Wong G, Khoo B, et al. Association Between Abdominal Aortic Calcification, Bone Mineral Density, and Fracture in Older Women. J Bone Miner Res. 2019;**34**:2052-2060. doi: 10.1002/jbmr.3830

5. Vogt MT, San Valentin R, Forrest KY, Nevitt MC, Cauley JA. Bone mineral density and aortic calcification: the Study of Osteoporotic Fractures. J Am Geriatr Soc. 1997;**45**:140-145. doi: 10.1111/j.1532-5415.1997.tb04498.x

6. Szulc P. Abdominal aortic calcification: A reappraisal of epidemiological and pathophysiological data. Bone. 2016;**84**:25-37. doi: 10.1016/j.bone.2015.12.004

7. Rodríguez AJ, Leow K, Szulc P, Scott D, Ebeling P, Sim M, et al. Abdominal aortic calcification, bone mineral density and fractures: a systematic review and meta-analysis protocol. BMJ Open. 2019;**9**:e026232. doi: 10.1136/bmjopen-2018-026232

8. Sennerby U, Melhus H, Gedeborg R, Byberg L, Garmo H, Ahlbom A, et al. Cardiovascular diseases and risk of hip fracture. Jama. 2009;**302**:1666-1673. doi: 10.1001/jama.2009.1463

9. Thompson B, Towler DA. Arterial calcification and bone physiology: role of the bone-vascular axis. Nat Rev Endocrinol. 2012;**8**:529-543. doi: 10.1038/nrendo.2012.36

10. Rodriguez AJ, Scott D, Ebeling PR. Exploring the Links Between Common Diseases of Ageing—Osteoporosis, Sarcopenia and Vascular Calcification. Clinical Reviews in Bone and Mineral Metabolism. 2019;**17**:1-23. doi.org/10.1007/s12018-018-9251-2

11. Rubin MR, Silverberg SJ. Vascular calcification and osteoporosis--the nature of the nexus. J Clin Endocrinol Metab. 2004;**89**:4243-4245. doi: 10.1210/jc.2004-1324

12. Ramasamy SK, Kusumbe AP, Schiller M, Zeuschner D, Bixel MG, Milia C, et al. Blood flow controls bone vascular function and osteogenesis. Nature Communications. 2016;**7**:13601. doi: 10.1038/ncomms13601

13. Demer LL, Tintut Y. Mechanisms linking osteoporosis with cardiovascular calcification. Current osteoporosis reports. 2009;**7**:42-46. doi: 10.1007/s11914-009-0008-1

14. Chen Z, Yu Y. Aortic calcification was associated with risk of fractures: A meta-analysis. J Back Musculoskelet Rehabil. 2016;**29**:635-642. doi: 10.3233/bmr-160700

15. Wei D, Zheng G, Gao Y, Guo J, Zhang T. Abdominal aortic calcification and the risk of bone fractures: a meta-analysis of prospective cohort studies. Journal of bone and mineral metabolism. 2018;**36**:439-446. doi: 10.1007/s00774-017-0849-0

16. Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute. 2011.

17. Herzog R, Alvarez-Pasquin M, Diaz C, Del Barrio J, Estrada J, Gil A. Newcastle-Ottawa Scale adapted for cross-sectional studies. BMC Public Health. 2013;**13**:154.

18. Zizzo M, Ruiz CC, Zanelli M, Bassi MC, Sanguedolce F, Ascani S, et al. Damage control surgery for the treatment of perforated acute colonic diverticulitis: A systematic review. Medicine. 2020;**99**. doi: 10.1097/md.0000000000023323

19. Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. Bmj. 2015;**350**:h870. doi: 10.1136/bmj.h870

20. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;**315**:629-634. doi: 10.1136/bmj.315.7109.629

21. Aoki A, Kojima F, Uchida K, Tanaka Y, Nitta K. Associations between vascular calcification, arterial stiffness and bone mineral density in chronic hemodialysis patients. Geriatr Gerontol Int. 2009;**9**:246-252. doi: 10.1111/j.1447-0594.2009.00528.x

22. Avramovski P, Avramovska M, Lazarevski M, Sikole A. Femoral neck and spine bone mineral density-Surrogate marker of aortic calcification in postmenopausal women. Anatol J Cardiol. 2016;**16**:202-209. doi: 10.5152/akd.2015.6016

23. Bolton CE, McEniery CM, Raj V, McDonnell BJ, Dixon AK, Munnery M, et al. Aortic calcification, arterial stiffness and bone mineral density in patients with COPD. Artery Research. 2011;**5**:30-36. doi.org/10.1016/j.artres.2011.01.001

24. Bagger YZ, Rasmussen HB, Alexandersen P, Werge T, Christiansen C, Tankó LB. Links between cardiovascular disease and osteoporosis in postmenopausal women: serum lipids or atherosclerosis per se? Osteoporos Int. 2007;**18**:505-512. doi: 10.1007/s00198-006-0255-2

25. Fusaro M, Tripepi G, Noale M, Vajente N, Plebani M, Zaninotto M, et al. High prevalence of vertebral fractures assessed by quantitative morphometry in hemodialysis patients, strongly associated with vascular calcifications. Calcif Tissue Int. 2013;**93**:39-47. doi: 10.1007/s00223-013-9722-x

26. Rodríguez-García M, Gómez-Alonso C, Naves-Díaz M, Diaz-Lopez JB, Diaz-Corte C, Cannata-Andía JB. Vascular calcifications, vertebral fractures and mortality in haemodialysis patients. Nephrol Dial Transplant. 2009;**24**:239-246. doi: 10.1093/ndt/gfn466

27. Chau K, Martinez G, Elder GJ. Vascular calcification in patients undergoing kidney and simultaneous pancreas-kidney transplantation. Nephrology (Carlton). 2014;**19**:275-281. doi: 10.1111/nep.12212

28. Drinka PJ, Bauwens SF, DeSmet AA. Lack of correlation between aortic calcification and bone density. Wis Med J. 1992;**91**:299-301.

29. Reid IR, Evans MC, Ames R, Wattie DJ. The influence of osteophytes and aortic calcification on spinal mineral density in postmenopausal women. J Clin Endocrinol Metab. 1991;**72**:1372-1374. doi: 10.1210/jcem-72-6-1372

30. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. Journal of applied physiology. 2008;**105**:1652-1660. doi: 10.1152/japplphysiol.90549.2008

31. Mitchell GF. Aortic stiffness, pressure and flow pulsatility, and target organ damage. J Appl Physiol (1985). 2018;**125**:1871-1880. doi: 10.1152/japplphysiol.00108.2018

32. Hak AE, Pols HA, van Hemert AM, Hofman A, Witteman JC. Progression of aortic calcification is associated with metacarpal bone loss during menopause: a population-based longitudinal study. Arterioscler Thromb Vasc Biol. 2000;**20**:1926-1931. doi: 10.1161/01.atv.20.8.1926

33. Szulc P, Blackwell T, Schousboe JT, Bauer DC, Cawthon P, Lane NE, et al. High hip fracture risk in men with severe aortic calcification: MrOS study. J Bone Miner Res. 2014;**29**:968-975. doi: 10.1002/jbmr.2085

34. Gebre AK, Sim M, Rodríguez AJ, Hodgson JM, Blekkenhorst LC, Szulc P, et al. Abdominal aortic calcification is associated with a higher risk of injurious fall-related

hospitalizations in older Australian women. Atherosclerosis. 2021. doi: 10.1016/j.atherosclerosis.2021.05.003

35. Bischoff-Ferrari HA. The role of falls in fracture prediction. Curr Osteoporos Rep. 2011;**9**:116-121. doi: 10.1007/s11914-011-0059-y

36. Farhat GN, Cauley JA. The link between osteoporosis and cardiovascular disease. Clin Cases Miner Bone Metab. 2008;**5**:19-34. pmcid: pmc2781192

37. Schattner A. The burden of hip fractures—why aren't we better at prevention? QJM: An International Journal of Medicine. 2017;**111**:765-767. doi: 10.1093/qjmed/hcx216

38. Schousboe JT, Langsetmo L, Szulc P, Lewis JR, Taylor BC, Kats AM, et al. Joint Associations of Prevalent Radiographic Vertebral Fracture and Abdominal Aortic Calcification With Incident Hip, Major Osteoporotic, and Clinical Vertebral Fractures. J Bone Miner Res. 2021;**36**:892-900. doi: 10.1002/jbmr.4257

Table Title

Table 1. Characteristics of the included studies

Figure Captions

Figure 1: Study selection flow diagram

Figure 2: Forest plot for the association between AAC and BMD taking unadjusted group means by skeletal site

Figure 3: Forest plot for the unadjusted association of AAC with prevalent (top) and incident (bottom) fractures

Figure 4: Forest plot for unadjusted association of AAC with site-specific fracture

Table 1. Characteristics of the included studies

Characteristics	All studies, n (%)	Studies included in meta-analysis, n (%)	Study included only in qualitative synthesis, n (%)
Year of publication			
Pre-2010	31 (36.1)	16 (38.1)	15 (34.1)
2010-2015	33 (38.4)	17 (40.5)	16 (36.4)
2016-2021	22 (24.4)	9 (21.4)	13 (29.5)
Setting			
Chronic kidney disease, kidney stones and patients in haemodialysis	19 (22.1)	2 (4.7)	17 (38.6)
Postmenopausal women only	29 (33.7)	21 (50)	8 (18.2)
General population	30 (34.9)	17 (40.5)	13 (29.5)
Other*	8 (9.3)	2 (4.8)	7 (15.9)
Region			
North America	26 (30.2)	11 (26.2)	15 (34.1)
Europe	32 (37.2)	15 (35.7)	17 (38.6)
Asia	10 (11.6)	5 (11.9)	5 (11.4)
Oceania	9 (10.5)	3 (7.1)	6 (13.6)
Africa	5 (5.8)	5 (11.9)	------
South America	4 (4.7)	3 (7.1)	1 (2.3)
Number of subjects			

<500	48 (55.8)	17 (40.5)	31 (70.5)
>500	38 (44.2)	23 (57.1)	15 (34.1)
Modality of AAC assessment			
Radiography	46 (53.5)	28 (66.7)	18 (40.9)
Quantitative computed tomography	26 (30.2)	4 (9.5)	22 (50.0)
Dual energy x-ray absorptiometry	14 (16.3)	10 (23.8)	4 (9.1)
Sex			
Men only	8 (9.3)	6 (14.2)	2 (4.5)
Women only	33 (38.3)	23 (54.8)	10 (22.7)
Mixed	40 (46.5)	13 (31.0)	27 (61.3)
Not specified	5 (5.8)	-----	5 (11.4)
%People with a smoking history			
<15%	12 (13.9)	9 (21.4)	3 (6.8)
≥ 15%	31 (36.0)	12 (28.6)	19 (43.2)
Not specified	43 (50.0)	21 (50)	22 (50)
Study design			
Prospective	24 (27.9)	15 (35.7)	9 (20.5)
Cross-sectional	58 (67.4)	26 (61.9)	32 (72.7)
Case-control	2 (2.3)?	1 (2.4)	1 (2.3)

*Chronic obstructive pulmonary disease, HIV, Rheumatoid arthritis, and type 2 diabetes mellitus.

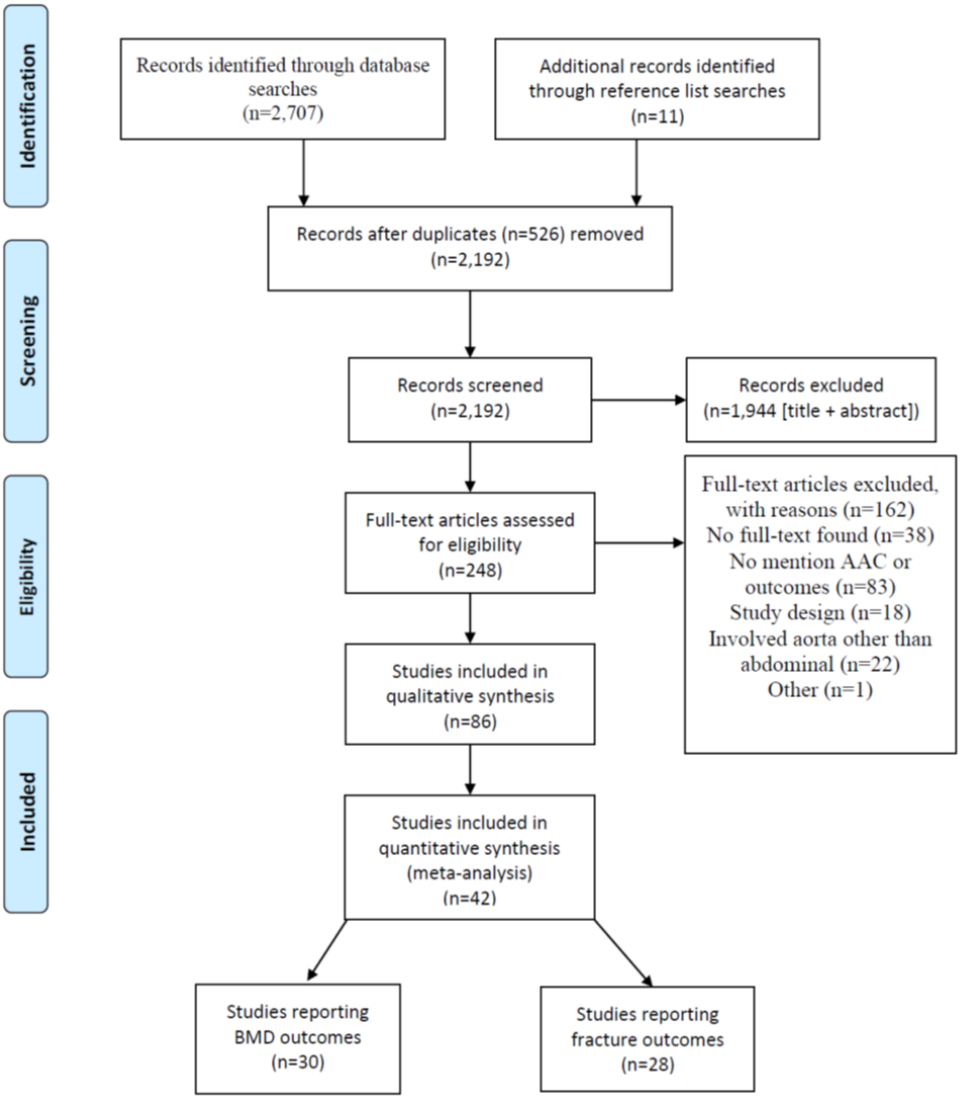

Figure 1: Study selection flow diagram

159x174mm (158 x 159 DPI)

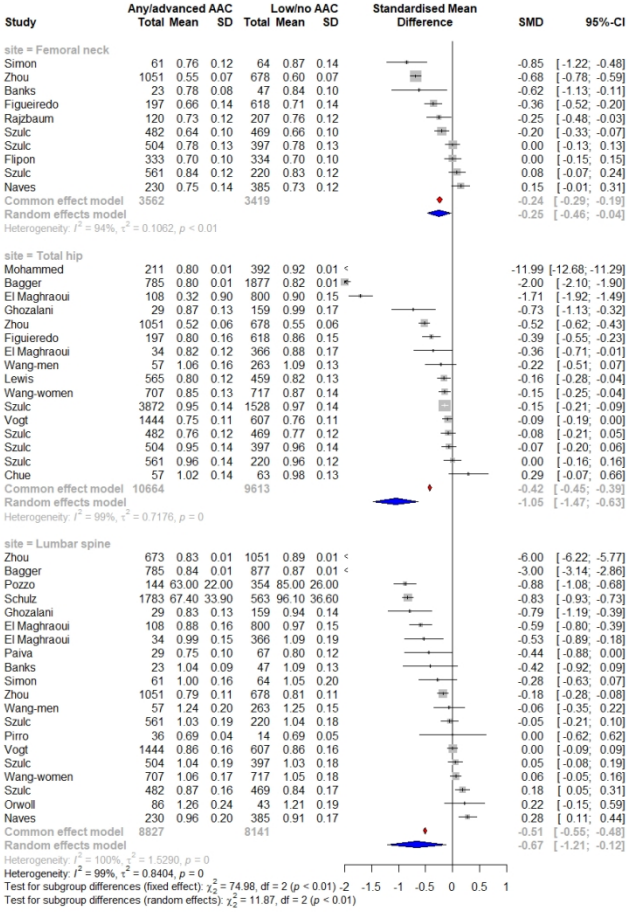

Figure 2: Forest plot for the association between AAC and BMD taking unadjusted group means by skeletal site

370x343mm (96 x 96 DPI)

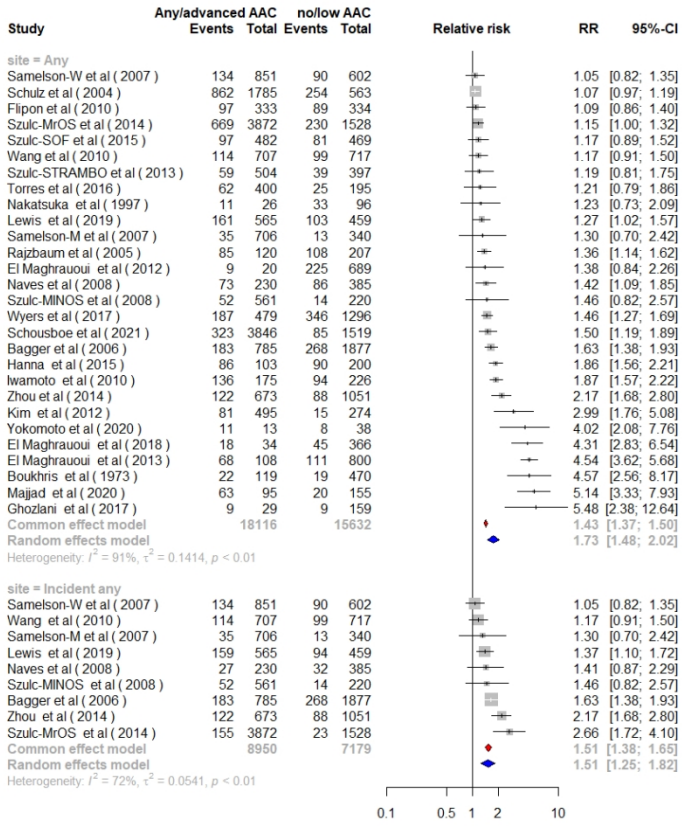

Figure 3: Forest plot for the unadjusted association of AAC with prevalent (top) and incident (bottom) fractures

317x291mm (96 x 96 DPI)

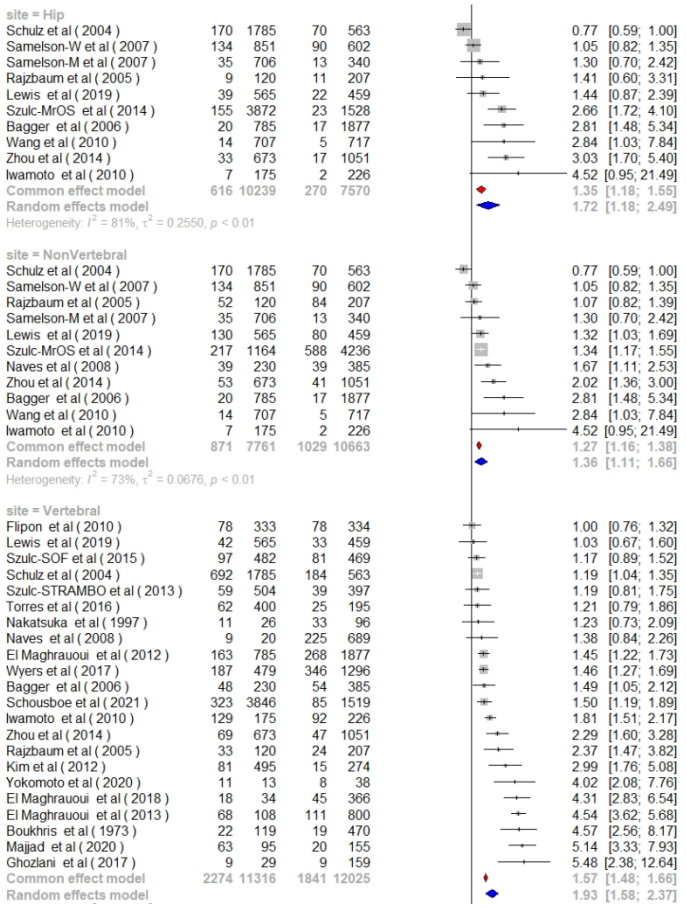

Figure 4: Forest plot for unadjusted association of AAC with site-specific fracture

317x291mm (96 x 96 DPI)

Abdominal aortic calcification, bone mineral density and fractures: a systematic review and meta-analysis of observational studies

Abadi K. Gebre, MSc,[1,2] Joshua R. Lewis, PhD[1,3,4], Kevin Leow, MBBS,[4] Pawel Szulc, PhD,[5] David Scott, PhD,[6,7] Peter R. Ebeling, MD,[7] Marc Sim, PhD,[1,3] Germaine Wong, PhD,[4] Wai H. Lim, PhD,[3,8] John T. Schousboe, MD, PhD,[9] Douglas P. Kiel, MD,[10] Richard L. Prince, MD,[3] and Alexander J. Rodríguez, PhD [1,7*]

[1]Nutrition & Health Innovation Research Institute, School of Medical and Health Sciences, Edith Cowan University, Joondalup, Australia

[2]School of Pharmacy, College of Health Sciences, Mekelle University, Mekelle, Tigray

[3]Medical School, University of Western Australia, Perth, Australia

[4]Centre for Kidney Research, Children's Hospital at Westmead School of Public Health, Sydney Medical School, The University of Sydney, Sydney, Australia

[5]INSERM UMR 1033, University of Lyon, Hospices Civils de Lyon, Lyon, France

[6]Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Geelong, VIC, Australia

[7]Bone and Muscle Health Research Group, Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Victoria, Australia

[8]Department of Renal Medicine, Sir Charles Gairdner Hospital, Western Australia, Australia

[9]Park Nicollet Osteoporosis Center and HealthPartners Institute, HealthPartners, Minneapolis, MN 55416, USA, and Division of Health Policy and Management, University of Minnesota, Minneapolis, MN 55455, USA

[10]Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

Corresponding author:

Alexander J. Rodríguez PhD

Research Fellow - Bone & Muscle Research Group

Department of Medicine, Monash University, Level 7, Translational Research Facility MHTP Building, 51 Kanooka Grove, Clayton VIC 3168

Telephone: +61 (03) 8572 2919 Email: alexander.rodriguez@monash.edu

ORCID: 0000-0002-2955-0642

Word count

Abstract=249

Manuscript=3694

Number of data elements: 3

Running title: AAC, BMD and fracture meta-analysis

Abstract

Background: Abdominal aortic calcification (AAC) has been inconsistently associated with skeletal health. We aimed to investigate the association of AAC with bone mineral density (BMD) and fracture risk by pooling the findings of observational studies.

Methods: Medline, EMBASE, Web of Science and Google Scholar were searched (August 2021). All clinical studies that assessed the association between AAC and BMD or fracture were included. AAC was categorized into AAC any/advanced (all higher reported groups) vs no/less advanced (lowest reported group). Pooled standardized mean differences (SMDs) and risk ratios (RRs) with 95% confidence intervals (CI) were determined for BMD and fracture, respectively, using random-effects models.

Results: Of 2,192 articles screened, 86 (61,553 participants) were included in the review, while 42 provided data for meta-analysis. AAC was associated with lower BMD at the total hip [SMD=-1.05 (95%CI: -1.47 to -0.63); 16 studies], femoral neck [-0.25 (-0.46 to - 0.04); 10] and lumbar spine [-0.67 (-1.21 to -0.12); 20]. AAC was associated with a greater risk of any fracture [RR= 1.73 (95%CI: 1.48 to 2.02); 27]. AAC was also associated with vertebral, non-vertebral and hip fractures. In dose-response analysis, the highest AAC group had greater risks of any, vertebral and non-vertebral fractures.

Conclusions: AAC is associated with lower BMD and increased fracture risk at multiple sites, underscoring the potential importance of vascular disease on skeletal health. Detection of AAC at the time of BMD testing may provide clinicians with prognostic information about bone health to enhance osteoporosis screening programs and fracture risk prediction.

Keywords: Vascular calcification, osteoporosis, fracture

Introduction

Vascular calcification, previously considered an inevitable consequence of aging, is now understood to be an active and dynamic process of mineral deposition within arterial walls. It is closely linked with chronic diseases such as atherosclerosis, chronic kidney disease (CKD), and type 2 diabetes mellitus (1). Specifically, abdominal aortic calcification (AAC) has been identified as a marker of advanced atherosclerotic plaques (2), and is associated with an increased risk of cardiovascular events and poor prognosis (3). AAC has also been associated with poorer skeletal health, such as lower bone mineral density (BMD) (4, 5) and an increased risk of osteoporotic fractures (4, 6, 7).

Vascular calcification and osteoporosis (another disease previously considered a natural consequence of aging) have shared genetic (8) and signalling pathways (9) as well as other risk factors (e.g. smoking, diabetes mellitus, obesity and menopause) suggestive of a common causal origin (10, 11). Vascular calcification may theoretically precede and provoke bone loss by impairing peripheral blood perfusion potentially affecting osteogenesis (12). Vascular disease may also be associated with reduced physical activity and fitness, leading to weak and fragile bone as well as low muscle mass which may predispose to falling (13). Mechanisms underlying these observations, which commonly present during aging, represent potential targets for intervention. However, despite these putative causal links, the findings of the available small studies with different measures of skeletal outcomes and median AAC are often discordant. Thus, synthesis of the available studies is crucial to refining our understanding of the relationship if any, of AAC with skeletal health.

To date, two previous meta-analyses of observational studies have reported on this association, Chen and Yu *et al* (2016) (14) and Wei *et al* (2018) (15). However, these studies identified only a limited number of articles (15 and seven, respectively) and failed to investigate potential

sources of between-study heterogeneity such as imaging modality. Moreover, it is unclear whether the association between AAC and BMD or fracture is similar across different skeletal sites and cohorts of differing characteristics. We aimed to assess BMD differences, and risk of fractures in patients with AAC.

Methods

This systematic review and meta-analysis of observational studies was conducted in accordance with PRISMA guidelines and was registered in PROSPERO (CRD42018088019). The protocol was published previously (7).

Data sources and search strategy

Database searches were performed in MEDLINE, EMBASE, Web of Science core collection and Cochrane library for articles published from inception to August 6, 2021 without language restriction *using key terms such as vascular calcification, bone mineral density, fracture and additional filters such as human and observational studies as detailed in* ***Table S1*** *and previously published protocol* (7). We also searched Google Scholar (top 200 by relevancy) manually to retrieve additional relevant articles. Conference abstracts were also assessed. Reference lists of eligible studies were hands-searched and previous meta-analyses were evaluated for potentially relevant articles missing from the main search.

Study selection

Studies were reviewed for eligibility by at least two independently reviewers (AJR, KL or AKG) as described previously (7). Retrieved studies were pooled together into a citation manager with duplicates removed. The remaining articles were screened sequentially by title, then abstract, then full text according to predefined exclusion and inclusion criteria. Disagreements at each level of screening were resolved by consensus or an involvement of a third reviewer (JRL).

Eligibility criteria

As no randomized trials exist, we included observational studies conducted in humans, of any design, that assessed AAC by any methodology and reported BMD at any site by any modality, or prevalent or incident fracture reported by any means as described previously (7).

Risk of bias and quality assessment

The risk of bias was assessed by at least two reviewer (AJR, KL or AKG) using the Newcastle-Ottawa Scale (NOS) (16). The risk of bias for each of the studies *included in the meta-analysis* was assessed based on the study design (cross-sectional, case-control or cohort studies) grouped into three categories of quality (good, fair or poor) as described previously (17, 18). Summary estimates of the confidence placed on the evidence was evaluated using the Grading of Recommendations Assessment Development and Evaluation (GRADE) for prognosis which starts with high quality evidence that can then be rated down (19). Publication bias was evaluated using visual inspection of funnel plots and Egger's regression tests (20).

AAC reporting

AAC was assessed either semi-quantitatively (radiograph or DXA) or quantitatively (CT). Data used for analysis specifically related to AAC only. Where studies combined data for AAC with calcification from other parts/branches of the aorta, these data were excluded from meta-analysis.In the main quantitative analysis, the lowest reported AAC group (low or none) was used as referent and compared with the combination of all higher reported groups (any/advanced AAC) to compute the standardized mean difference (SMD) for BMD measures, absolute risk difference (ARD) and relative risk (RR) for any and site-specific fractures. For example, if a study has four AAC groups (AAC score: 0-1; 2-5; 6-9 and 9+), analysis combined the highest three groups (2-5; 6-9 and 9+) and compare fracture risks and BMD measures against the lowest group (0-1). We have used this approach to minimize classification bias

given the heterogeneity in AAC group definitions in the included literature. Additionally, we have analysed studies that reported AAC either as: (1) any versus none to assess the relationship between any AAC and fracture outcomes or (2) for studies that reported three or more AAC groups, dose–response analysis was made. To do this, we considered the lowest AAC score as the reference group. Fracture risks in the the middle group(s) and the highest AAC group (high AAC) were compared against this reference group.Where data on more than three groups of AAC were presented, the middle groups were combined as 'moderate AAC'.

Statistical analysis

For BMD measures, estimates were expressed as SMD with 95% confidence intervals (95%CIs) to account for reporting differences (g/cm^2, g/cm^3, g/mm^3). For fracture outcomes, ARD and RR with 95%CI were calculated, from which, a summary estimate was determined using random effects models. Summary estimate fixed effects models were also provided in the forest plots to show internal consistency of the relationship. As an attempt to account for between-study heterogeneity, we conducted several sub-group analyses, identified *a priori* (7), and potential effect modifiers were explored through meta-regression. Additionally, we conducted an exploratory analysis pooling together adjusted risk estimates as reported in included studies of the association between AAC and fracture as a measure of internal validity. The I^2 (%) and τ^2 statistics were reported as measures of the proportion of total variability due to between-study heterogeneity and between-study variance, respectively. Smaller values indicate less variability and variance in between-study heterogeneity. All analyses were computed using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria (https://www.R-project.org/) and considered statistically significant when the bounds of the 95%CI did not cross one for RR and zero for SMD.

Results

Literature search

2192 unique records were retrieved through database searches. Of these, 1944 records were excluded based on title or abstract, and a further 162 were excluded after full-text screening leaving 86 (61,553 participants) studies for qualitative synthesis [**Figure 1**].

Study characteristics

*Study characteristics of all included studies (those contributing to qualitative synthesis only as well as those included in quantitative synthesis) are presented in **Table 1**.* The majority of the studies were conducted in an older adult population aged over 65 years (n=57 studies, 67%). Most studies were conducted in Europe (n=32 studies, 37.2%) or North America (n=26 studies, 30.2%), and 63.9% (n=55 studies) were published in 2010 or later. Most studies (n=59 studies, 68.6%) were conducted in the general population of men and women or only in postmenopausal women, and 22.1% (n=19 studies) were conducted in patients with CKD, haemodialysis, or kidney stones (**Table 1**). AAC was evaluated by radiograph in 46 studies (53.4%) by CT in 25 studies (30.2%) and by DXA in 14 studies (16.3%). Detailed characteristics of the studies including the key findings from each study are presented in **Table S2**.

Of the 86 eligible studies included in the qualitative synthesis, 42 studies (two abstracts, 40 full publications) provided *extractable data suitable for* the meta-analysis [BMD, n=14, fracture, n=12, both BMD and fracture, n=16] [**Figure 1**]. For studies that were not included in the meta-analysis (n=44, 51.2%), *these articles were reviewed in the qualitative synthesis only.* These studies included reports that did not provide quantitative data to enable an association to be drawn between AAC with BMD or fracture. *Abstracts were checked to determine if they were subsequently published after the search date.* Where uncertainties were apparent, corresponding authors were contacted for relevant data.

Risk of bias assessment

Risk of bias assessment is presented in **Data S1.** Of the 42 studies included in meta-analysis**,** 40 studies were assessed (two conference abstracts not assessed), 24 studies (60%) were graded as good quality, 14 studies (35 %) graded as fair quality and two (5%) studies graded as poor quality (**Table S3-5)**.

AAC and BMD measures

BMD was reported by 30 studies: 10 studies for femoral neck (n=6981 participants), 16 studies for total hip (n=20277), 20 for lumbar spine (n=17260), four for distal radius (4257 participants), three for proximal radius (n=3476), three for whole body (n=3426), two each for calcaneus (n=2575) and vertebral trabecular vBMD (n=1259) [**Table S6**]. Compared with individuals with no/less advanced AAC, those with any/advanced AAC had lower BMD at the total hip, femoral neck, lumbar spine and calcaneus, all $p<0.05$ [**Figure 2** and **Table S7**]. Marked heterogeneity was evident in all analyses.

Sensitivity analyses in studies reporting BMD as an outcome

Subgroup analyses highlighted women with any/advanced AAC had consistently lower BMD at the femoral neck, total hip, and lumbar spine but these associations were not seen in men except a marginal difference at the total hip. Similarly, lower femoral neck, total hip and lumbar spine BMDs were observed in studies that used radiograph to capture AAC [**Table S8**] whilst this association was only evident for total hip in studies that used DXA to capture AAC. *Additionally, any/advanced AAC was significantly associated with lower BMD at the total hip and lumbar spine even after excluding studies with poor and fair quality. However, the magnitude of the association between AAC and femoral neck BMD was attenuated after exclusion of studies with poor and fair quality.* In meta-regression, as the proportion of women in each study increased, the effect size between AAC and femoral neck BMD decreased (β=-

0.005). The R^2 value for this association was 0.28 indicating that 28% of the variance in studies that reported the association between AAC, and femoral neck BMD may be explained by the proportion of women included in studies [**Table S9** and **Figure S1**]. In studies that reported the association between AAC and BMD by skeletal sites, a statistically significant evidence of publication bias was only observed for calcaneus [**Table S7** and **Figure S2 A-C**].

AAC and fracture outcomes

The association between any/advanced AAC and risk of any fracture was reported in 28 studies (n=33748 participants): 22 studies for vertebral (n=23344), 10 for non-vertebral (n=18424) and nine for hip fractures (n=17809) (**Table S10** and **11**). Individuals with any/advanced AAC had a greater absolute risk and relative risk for any [**Figure 3**], vertebral, non-vertebral and hip fractures [**Figure 4**]. AAC was associated with greater risk for incident fracture and site-specific incident fractures [**Figure 3** and **Table S11**]. In studies that reported three or more AAC groups, the RR for any, vertebral and non-vertebral fractures increased with increasing severity of AAC group [**Table S12**]. Pooled analyses of reported estimates after adjustment for BMD (including a minimum of age, BMI and smoking) revealed AAC was associated with greater risks of prevalent (six studies: OR=2.34 95%CI:1.46 to 3.74, I^2 =71.0%) and incident (six studies: HR=1.45; 95%CI:1.21 to 1.72, I^2 =57.4%) fractures. Marked heterogeneity was evident in all analyses.

Sensitivity analyses in studies reporting fracture outcomes

*The association between any/advanced AAC, any and site-specific fractures remained significant after excluding studies with poor and fair quality [**Table S13**].* Subgroup analyses showed a consistent increased RR of any, vertebral, non-vertebral and hip fracture in studies with a sample size greater than 500, studies undertaken in women only, and in studies that utilized radiographs for AAC detection [**Table S14**]. In meta-regression, age explained the

observed between-study heterogeneity for the association between AAC and any (β =-0.038) and vertebral fractures (β=-0.047) by 35.7% and 44.4%, respectively. In addition, percentage of smokers in the cohort explained the observed between study heterogeneity for any (β=-0.012) and vertebral (β=-0.012) fractures by 33.5% and 25.7% respectively [**Figure S3A-D** and **Table S15**].

Publication bias in studies reporting fracture outcomes

Funnel plot and Egger's tests indicated moderate to minimal-study publication bias in studies reporting the association between the presence of any/advanced AAC and risk of any and hip fracture (p=0.02). However, no statistically significant evidence of publication bias was observed in studies that reported vertebral and non-vertebral fractures [**Table S10 and Figure S4A-D**].

Quality of evidence assessment

There was moderate quality evidence for BMD outcomes. There was moderate-high quality evidence for any, vertebral and non-vertebral fracture outcomes and low-quality evidence for hip fracture outcomes [**Table S16**].

Discussion

Growing evidence suggests a close relationship between the development and progression of cardiovascular disease and osteoporosis, previously thought of as natural consequences of aging. We sought to provide the association of AAC with both BMD and fracture in a single comprehensive report. We observed that, compared with people with no/less advanced AAC, people with any/advanced AAC demonstrated lower BMD across several skeletal sites and higher RR for any and site-specific fractures. These data provide consistent findings linking AAC, a readily quantifiable marker of vascular disease, with poor skeletal health confirming

that AAC and bone metabolism are linked and may improve fracture prediction and reclassification. We also showed that in pooling estimates that accounted for BMD in adjusted analyses, AAC remained a significant predictor of fracture risk. *Moreover, the majority of the studies that were included in qualitative synthesis only (namely, studies without data for meta-analysis) reported an inverse relationship between AAC and BMD (more AAC, lower BMD) (21-23) and increased risk of fractures (24-26) in general and specific populations. A few studies included in the qualitative review showed no relationship between AAC, BMD or fractures (26-29). These studies were low powered and conducted in samples not resperesentative of the general population, but the overall meaningful the qualitative analyses generally supports findings from our quantitative synthesis that the presence and severity of AAC indicates poor skeletal health and prognosis.*

AAC is speculated to alter blood flow dynamics through aortic stiffening, leading to small vessel disease which may impact the skeletal circulation (30). The skeleton receives about 10% of the cardiac output and for similarly perfused organs, aortic stiffening can induce end-organ damage (31). It has also been speculated that AAC diminishes renal and mesenteric blood flow, therefore retarding the delivery and absorption of essential micro-nutrients needed for bone remodelling (30). This potentially increases oxidative stress, thereby accelerating bone loss and increasing fracture risk (9, 32). The femoral head and neck receives most of its supply via the medial circumflex femoral artery which is a branch of the femoral artery originating from the abdominal aorta via the iliac artery. Thus, this anatomical relation supports the nutrient supply hypothesis (12, 33). Of note, a significant association between AAC and lumbar spine BMD was observed further supporting the nutrient supply theory given the lumbar arteries branch off the abdominal aorta. However, no such relationship was observed with BMD at the distal radius, proximal radius, and whole body. This possibly reflects a lesser contribution of abdominal aortic blood flow to these skeletal areas. This is supported by Szulc *et al* (2014) (33)

where the association of AAC and hip fracture persisted, but not lower limb fractures, after adjustment for ankle-brachial index (an indirect marker of blood flow dynamics). This suggests that some observed associations may be explained by mechanisms beyond the nutrient supply hypothesis.

Given the well-established association of BMD in the causal pathway for fracture, we expected that associations between AAC and fractures would mirror associations observed for BMD at these sites. Compared with individuals with no/less advanced AAC, we found that those with any/advanced AAC had a 66% increased RR of fracture at any site. Findings were consistent for vertebral, non-vertebral and hip fractures which supports observations from the BMD analysis. This would suggest that AAC may have an important role in increasing the risk of low BMD leading to fracture. Interestingly, AAC was also associated with greater risks of fractures in studies that reported associations of AAC with fracture after adjustment for BMD which suggests that at least some of the excess fracture risk attributable to AAC is not mediated by BMD. Therefore, the presence of AAC in an individual should warrant further observation and follow-up and may have a role in risk stratification and guide decisions about treatment recommendation in those below treatment threshold. Population age of included studies accounted for large proportions of between-study heterogeneity in meta-regression with respect to fractures only and not BMD. Further, the association between AAC and fracture remained in a pooled analysis of available reported multivariable adjusted effect estimates. This suggests unknown (or unaccounted for) factors during aging affecting both the calcification process and fracture risk.

Other mechanisms thought to explain these associations include, the well-described effect of atherosclerosis/vessel calcification on syncope and on compromised muscle strength that can both exacerbate the risk of falls (34) and subsequent fracture (35). Further, traditional risk factors for fracture and CVD such as advanced age, smoking and post-menopausal oestrogen

decline (all having deleterious effects on bone quality and vascular health) may also explain the observed associations (36). To this end, our subgroup analyses showed estimates were consistently stronger in women-only (particularly for BMD analyses) studies compared to men-only or mixed populations. However, there were inconsistent effects of age and smoking in meta-regression, likely related to the small number of studies included in the analysis and/or limited data availability to enable meaningful regression. Older individuals and smokers may have a greater accumulation of other fracture risk factors, reducing the relative contribution of AAC to fracture risk and BMD. This suggests that early detection of AAC could enhance identification of individuals at higher risk of osteoporosis. Overall, absolute fracture risks were large and, importantly, consistent with the magnitude of RR, supporting the notion that clinically meaningful associations are being observed. Although the absolute risks for hip and non-vertebral fractures were modest (likely related to lower event rates consistent with our understanding of these fractures), the healthcare costs and mortality associated with these fractures renders these ARDs clinically important (37). Notably, these findings highlight areas of primary prevention to reduce vascular-bone disease. From a public health standpoint, screening of AAC in patients at risk for fracture and poor skeletal health could enhance risk stratification and represent an opportunity to 'value-add' to existing osteoporosis screening programmes as has been recently demonstrated but has not been adopted in screening guidelines (38).

This report has numerous strengths, providing an additional contribution to the literature beyond what has been previously reported (14, 15). Firstly, the reporting of AAC associations with both BMD and fractures provides internal consistency. We showed consistent associations between AAC with BMD and fractures across skeletal sites underscoring the importance of maintaining BMD in fracture reduction but also highlights how vascular disease is an important contributor to fracture. Secondly, we conducted a comprehensive literature search and

identified 13-21 (87%-300%) more studies than the previous meta-analyses (14, 15). Thirdly, we undertook detailed subgroup and meta-regression analyses to investigate factors that may explain the observed between-study heterogeneity. These subgroup analyses served a secondary purpose of understanding factors that modify observed associations, which could provide clues for putative causal pathways and offer areas to target in intervention trials.

The present study has several limitations. First, high between-study heterogeneity *(I^2 53% - 100% and τ^2 0.06-1.53)* was noted in several analyses, suggesting the need for a careful interpretation of the findings. This suggests that the range of true effect sizes may yet include the null. Importantly, when we pooled together reported estimates for the association of AAC with fracture after adjustment for BMD, measures of heterogeneity were reduced. This suggests that considering important risk factors enhances confidence in the summary estimates. For this reason, we have attempted to explore such factors through numerous subgroup analyses (where study characteristics were more) homogeneous and meta-regression. Most of these analyses supported the primary analysis, underscoring internal validity. Overall, we are of the view that pooling of studies despite this heterogeneity is justified on clinical grounds as the studies included have sought to investigate the same question. We note that meta-analysing effect estimates from prospective cohort studies yielded reduced heterogeneity, highlighting the putative role AAC may have in fracture and the ongoing need for higher forms of evidence to inform our understanding. *Specifically, subgroup analyses revealed findings to be more pronounced in women, possibly reflecting greater statistical power (as there were more studies conducted in women) as well as the known effects of oestrogen decline on skeletal and vascular outcomes.* Cohort age and percentage of smokers also explained a considerable amount of the observed between-study heterogeneity in studies that reported the association between AAC, any or vertebral fractures. However, this fits with our understanding of age and smoking as independent risk factors for AAC and fractures. Second, publication bias was noted for studies

that investigated the association between AAC and any and hip fractures. These limitations may have affected the validity of observed associations. Publication biases may be attributable to the inclusion of two conference abstracts; however, we believe inclusion of these data are justified to increase statistical power and only represent a small fraction of the included studies. Third, given that the studies included in these meta-analyses were observational, causality cannot be inferred. Fourth, cut points (thresholds) for AAC groupings that were used to categorise into any/advanced AAC versus no/low were not consistent amongst the studies and this may have contributed to observed effect estimate variance through classification bias which is beyond our capacity as reviewers to control. Dose response analyses were conducted to minimise this limitation. Fifth, many studies provided limited data on the contribution of confounders on the associations between AAC, BMD or fracture. This was primarily driven by the fact that many of the studies were not specifically designed to investigate these associations but had data for extraction that allowed such an association to be explored.

Conclusion

The present study synthesized the available literature and determined that, overall, the presence and severity of AAC is associated with lower BMD and increased fracture risk across multiple sites and across multiple patient populations. Since AAC AAC may be quantified at the time of BMD testing, it may provide prognostic information to clinicians about vascular and bone disease. Future studies should focus on understanding shared risk factors and in developing prevention and treatment strategies that may, concomitantly, reduce both vascular and musculoskeletal disease burden.

Conflict of Interest

None declared

Acknowledgements

PRE has received grant funding to his institution from Amgen, Eli-Lilly and Alexion, and honoraria from Amgen and Sanofi. DPK has received grant funding to his institution from Amgen, Radius, and Solarea Bio. He serves as a member of scientific advisory boards for Solarea Bio and Pfizer and has received royalties for publication in UpToDate from Wolters Kluwer. All other authors declare no conflict of interest. The salary of J.R.L is supported by a National Heart Foundation of Australia Future Leader Fellowship (ID: 102817), and Rebecca L. Cooper Medical Research Foundation grant. Dr Kiel's time was supported by a grant from the National Institute for Arthritis and Musculoskeletal and Skin Diseases (R01 AR 041398). The salary of DS is supported by a National Health and Medical Research Council Australia Investigator Grant (GNT1174886). The salary of AJR is supported by a National Health and Medical Research Council Australia Investigator Grant (GNT1197958). None of these funding agencies had any input into any aspect of the design and management of this study.

Author contributions

AJR, JRL, KL and AKG study concept and design. AJR and KL searched and retrieved the articles. AKG, AJR, and KL extracted the data. AKG and AJR conducted the data analyses. AKG and AJR drafted the manuscript. AJR, JRL and MS supervised the study. AJR co-ordinated the authorship team. All authors read and approved the revised version and final supported versions. AKG and AJR have the primary responsibility for the final content.

References

1. Johnson RC, Leopold JA, Loscalzo J. Vascular calcification: pathobiological mechanisms and clinical implications. Circ Res. 2006;**99**:1044-1059.

2. Lewis JR, Schousboe JT, Lim WH, Wong G, Zhu K, Lim EM, *et al.* Abdominal Aortic Calcification Identified on Lateral Spine Images From Bone Densitometers Are a Marker of Generalized Atherosclerosis in Elderly Women. Arteriosclerosis, thrombosis, and vascular biology. 2016;**36**:166-173.

3. Leow K, Szulc P, Schousboe JT, Kiel DP, Teixeira-Pinto A, Shaikh H, *et al.* Prognostic Value of Abdominal Aortic Calcification: A Systematic Review and Meta-Analysis of Observational Studies. J Am Heart Assoc. 2021;**10**:e017205.

4. Lewis JR, Eggermont CJ, Schousboe JT, Lim WH, Wong G, Khoo B, *et al.* Association Between Abdominal Aortic Calcification, Bone Mineral Density, and Fracture in Older Women. J Bone Miner Res. 2019;**34**:2052-2060.

5. Vogt MT, San Valentin R, Forrest KY, Nevitt MC, Cauley JA. Bone mineral density and aortic calcification: the Study of Osteoporotic Fractures. J Am Geriatr Soc. 1997;**45**:140-145.

6. Szulc P. Abdominal aortic calcification: A reappraisal of epidemiological and pathophysiological data. Bone. 2016;**84**:25-37.

7. Rodríguez AJ, Leow K, Szulc P, Scott D, Ebeling P, Sim M, *et al.* Abdominal aortic calcification, bone mineral density and fractures: a systematic review and meta-analysis protocol. BMJ Open. 2019;**9**:e026232.

8. Sennerby U, Melhus H, Gedeborg R, Byberg L, Garmo H, Ahlbom A, *et al.* Cardiovascular diseases and risk of hip fracture. Jama. 2009;**302**:1666-1673.

9. Thompson B, Towler DA. Arterial calcification and bone physiology: role of the bone-vascular axis. Nat Rev Endocrinol. 2012;**8**:529-543.

10. Rodriguez AJ, Scott D, Ebeling PR. Exploring the Links Between Common Diseases of Ageing—Osteoporosis, Sarcopenia and Vascular Calcification. Clinical Reviews in Bone and Mineral Metabolism. 2019;**17**:1-23.

11. Rubin MR, Silverberg SJ. Vascular calcification and osteoporosis--the nature of the nexus. J Clin Endocrinol Metab. 2004;**89**:4243-4245.

12. Ramasamy SK, Kusumbe AP, Schiller M, Zeuschner D, Bixel MG, Milia C*, et al.* Blood flow controls bone vascular function and osteogenesis. Nature Communications. 2016;**7**:13601.

13. Demer LL, Tintut Y. Mechanisms linking osteoporosis with cardiovascular calcification. Current osteoporosis reports. 2009;**7**:42-46.

14. Chen Z, Yu Y. Aortic calcification was associated with risk of fractures: A meta-analysis. J Back Musculoskelet Rehabil. 2016;**29**:635-642.

15. Wei D, Zheng G, Gao Y, Guo J, Zhang T. Abdominal aortic calcification and the risk of bone fractures: a meta-analysis of prospective cohort studies. Journal of bone and mineral metabolism. 2018;**36**:439-446.

16. Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute. 2011.

17. Herzog R, Alvarez-Pasquin M, Diaz C, Del Barrio J, Estrada J, Gil A. Newcastle-Ottawa Scale adapted for cross-sectional studies. BMC Public Health. 2013;**13**:154.

18. Zizzo M, Ruiz CC, Zanelli M, Bassi MC, Sanguedolce F, Ascani S*, et al.* Damage control surgery for the treatment of perforated acute colonic diverticulitis: A systematic review. Medicine. 2020;**99**.

19. Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B, *et al.* Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. Bmj. 2015;**350**:h870.

20. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;**315**:629-634.

21. Aoki A, Kojima F, Uchida K, Tanaka Y, Nitta K. Associations between vascular calcification, arterial stiffness and bone mineral density in chronic hemodialysis patients. Geriatr Gerontol Int. 2009;**9**:246-252.

22. Avramovski P, Avramovska M, Lazarevski M, Sikole A. Femoral neck and spine bone mineral density-Surrogate marker of aortic calcification in postmenopausal women. Anatol J Cardiol. 2016;**16**:202-209.

23. Bolton CE, McEniery CM, Raj V, McDonnell BJ, Dixon AK, Munnery M, *et al.* Aortic calcification, arterial stiffness and bone mineral density in patients with COPD. Artery Research. 2011;**5**:30-36.

24. Bagger YZ, Rasmussen HB, Alexandersen P, Werge T, Christiansen C, Tankó LB. Links between cardiovascular disease and osteoporosis in postmenopausal women: serum lipids or atherosclerosis per se? Osteoporos Int. 2007;**18**:505-512.

25. Fusaro M, Tripepi G, Noale M, Vajente N, Plebani M, Zaninotto M, *et al.* High prevalence of vertebral fractures assessed by quantitative morphometry in hemodialysis patients, strongly associated with vascular calcifications. Calcif Tissue Int. 2013;**93**:39-47.

26. Rodríguez-García M, Gómez-Alonso C, Naves-Díaz M, Diaz-Lopez JB, Diaz-Corte C, Cannata-Andía JB. Vascular calcifications, vertebral fractures and mortality in haemodialysis patients. Nephrol Dial Transplant. 2009;**24**:239-246.

27. Chau K, Martinez G, Elder GJ. Vascular calcification in patients undergoing kidney and simultaneous pancreas-kidney transplantation. Nephrology (Carlton). 2014;**19**:275-281.

28. Drinka PJ, Bauwens SF, DeSmet AA. Lack of correlation between aortic calcification and bone density. Wis Med J. 1992;**91**:299-301.

29. Reid IR, Evans MC, Ames R, Wattie DJ. The influence of osteophytes and aortic calcification on spinal mineral density in postmenopausal women. J Clin Endocrinol Metab. 1991;**72**:1372-1374.

30. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. Journal of applied physiology. 2008;**105**:1652-1660.

31. Mitchell GF. Aortic stiffness, pressure and flow pulsatility, and target organ damage. J Appl Physiol (1985). 2018;**125**:1871-1880.

32. Hak AE, Pols HA, van Hemert AM, Hofman A, Witteman JC. Progression of aortic calcification is associated with metacarpal bone loss during menopause: a population-based longitudinal study. Arterioscler Thromb Vasc Biol. 2000;**20**:1926-1931.

33. Szulc P, Blackwell T, Schousboe JT, Bauer DC, Cawthon P, Lane NE*, et al.* High hip fracture risk in men with severe aortic calcification: MrOS study. J Bone Miner Res. 2014;**29**:968-975.

34. Gebre AK, Sim M, Rodríguez AJ, Hodgson JM, Blekkenhorst LC, Szulc P*, et al.* Abdominal aortic calcification is associated with a higher risk of injurious fall-related hospitalizations in older Australian women. Atherosclerosis. 2021.

35. Bischoff-Ferrari HA. The role of falls in fracture prediction. Curr Osteoporos Rep. 2011;**9**:116-121.

36. Farhat GN, Cauley JA. The link between osteoporosis and cardiovascular disease. Clin Cases Miner Bone Metab. 2008;**5**:19-34.

37. Schattner A. The burden of hip fractures—why aren't we better at prevention? QJM: An International Journal of Medicine. 2017;**111**:765-767.

38. Schousboe JT, Langsetmo L, Szulc P, Lewis JR, Taylor BC, Kats AM*, et al.* Joint Associations of Prevalent Radiographic Vertebral Fracture and Abdominal Aortic Calcification With Incident Hip, Major Osteoporotic, and Clinical Vertebral Fractures. J Bone Miner Res. 2021;**36**:892-900.

Table Title

Table 1. Characteristics of the included studies

Figure Captions

Figure 1: Study selection flow diagram

Figure 2: Forest plot for the association between AAC and BMD taking unadjusted group means by skeletal site

Figure 3: Forest plot for the unadjusted association of AAC with prevalent (top) and incident (bottom) fractures

Figure 4: Forest plot for unadjusted association of AAC with site-specific fracture

Table 1. Characteristics of the included studies

Characteristics	All studies, n (%)	Studies included in meta-analysis, n (%)	Study included only in qualitative synthesis, n (%)
Year of publication			
Pre-2010	31 (36.1)	16 (38.1)	15 (34.1)
2010-2015	33 (38.4)	17 (40.5)	16 (36.4)
2016-2021	22 (24.4)	9 (21.4)	13 (29.5)
Setting			
Chronic kidney disease, kidney stones and patients in haemodialysis	19 (22.1)	2 (4.7)	17 (38.6)
Postmenopausal women only	29 (33.7)	21 (50)	8 (18.2)
General population	30 (34.9)	17 (40.5)	13 (29.5)
Other*	8 (9.3)	2 (4.8)	7 (15.9)
Region			
North America	26 (30.2)	11 (26.2)	15 (34.1)
Europe	32 (37.2)	15 (35.7)	17 (38.6)
Asia	10 (11.6)	5 (11.9)	5 (11.4)
Oceania	9 (10.5)	3 (7.1)	6 (13.6)
Africa	5 (5.8)	5 (11.9)	------
South America	4 (4.7)	3 (7.1)	1 (2.3)
Number of subjects			

<500	48 (55.8)	17 (40.5)	31 (70.5)
>500	38 (44.2)	23 (57.1)	15 (34.1)
Modality of AAC assessment			
Radiography	46 (53.5)	28 (66.7)	18 (40.9)
Quantitative computed tomography	26 (30.2)	4 (9.5)	22 (50.0)
Dual energy x-ray absorptiometry	14 (16.3)	10 (23.8)	4 (9.1)
Sex			
Men only	8 (9.3)	6 (14.2)	2 (4.5)
Women only	33 (38.3)	23 (54.8)	10 (22.7)
Mixed	40 (46.5)	13 (31.0)	27 (61.3)
Not specified	5 (5.8)	-----	5 (11.4)
%People with a smoking history			
<15%	12 (13.9)	9 (21.4)	3 (6.8)
≥ 15%	31 (36.0)	12 (28.6)	19 (43.2)
Not specified	43 (50.0)	21 (50)	22 (50)
Study design			
Prospective	24 (27.9)	15 (35.7)	9 (20.5)
Cross-sectional	58 (67.4)	26 (61.9)	32 (72.7)
Case-control	2 (2.3)?	1 (2.4)	1 (2.3)

*Chronic obstructive pulmonary disease, HIV, Rheumatoid arthritis, and type 2 diabetes mellitus

Response to Peer Review for Manuscript ID: JGMS-2022-REV-0161

We would like to thank the editors and reviewers for their time to review our work as well as for their valuable comments and suggestions. We have now extensively revised the manuscript to address the feedback. Point by point responses are provided below.

Editor in chief

The reviewer(s) have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript. In addition to responding to the reviewers' comments, I suggest that, to make your article updated and most relevant to the readers, please review and if appropriate, reference recently published papers - including the ones that are published ahead of print online. While we consider this reminder helpful to advancing the scientific conversation, it does not affect the decision process regarding your paper.

Response: We thank the Editor for this advice. We understand the need for recency and relevancy in our meta-analysis. Our submission included titles up until August 2021. For completeness, we re-ran our search for newly published articles or abstracts until the end of May 2022 (August 2021 to May 2022) and found only one full text publication and one abstract that would meet our inclusion criteria.

- Chen et al., 2021 (https://link.springer.com/content/pdf/10.1007/s11657-022-01059-z.pdf) included 90 patients in maintenance haemodialysis for an association between abdominal aortic calcification (AAC) and bone mineral density (BMD). The study compared BMD at the lumbar spine between individuals with severe versus mild AAC.

Compared to patients with mild AAC, those with severe AAC had lower lumbar spine BMD (SMD -0.83 95%CI, -1.32 to -0.33).

- Yoshi et al, (2021) (http://dx.doi.org/10.1136/annrheumdis-2021-eular.269) reported an association between grades of AAC, grades 0 (n=219), 1 (n=428) & 2 (n=278), and fragility fracture in 931 patients with osteoporotic fracture. The subsequent occurrence of fragility fracture for advanced AAC versus no AAC group was 176/706 and 26/219, respectively.

Incorporating the data from the full-text publication did not substantively change the point estimates for our main analysis of the association of AAC with lumbar spine BMD: SMD -0.666 95%CI, (-1.212 to -0.120) when included versus SMD -0.673 95%CI, (-1.205 to -0.145). Equally, incorporating the data from the abstract did not substantively change the point estimates for our main analysis of the association of AAC with any fracture (RR 1.73 95% CI, 1.48 to 2.02 when included versus RR 1.74 95% CI, 1.49 to 2.02, I^2=90.5%.

Associate editor

The authors have done a nice job in putting together this meta-analysis but need to make a stronger case for how it might inform the field, given that this is not a controversial topic. Please also consider the suggestions of the reviewers to improve the quality and readability.

Response: Thank you for the comment regarding justification. We believe our review represents a significant advance from previous reviews. First, we included up to 21 more studies so readers can be assured that this review is a comprehensive report. Second, we included analysis of both BMD and fractures as outcomes in a single report which provides internal validity as BMD is accepted to be on the causal pathway to fracture; and to understand the relative contribution of vascular disease to site-specific fractures as this

evidence suggests stronger links with more central rather than peripheral fractures. Further, these findings highlight the public health potential to value-add osteoporosis screening by capturing AAC at the time of BMD testing. Finally, we have deeply investigated sources of clinical heterogeneity through meta-regression and sub-group analyses. We believe these elements stand this review apart and provide readers with the reliability of findings.

The importance of these findings is recognized for an individual who is close to but not beyond a treatment threshold for fracture prevention therapy, the additional knowledge of their AAC may lead to a recommendation for such therapy. Future research should focus on this concept, namely that identification of AAC improves reclassification and leads to better treatment decision making in terms of fracture risk. For completeness, this was not an explicit aim of our meta-analysis nor that of any of the included studies and hence our call for further research.

Review-1

It would be important to describe at least some of the some of the search terms/strategy in the main manuscript (versus all in supplement or referenced from previous publication #7) as that is so key for readers to interpret systematic reviews.

Response: We have now included key search terms on page 5, lines 58-60, and reads as; Database searches were performed in MEDLINE, EMBASE, Web of Science core collection and Cochrane library for articles published from inception to August 6, 2021, without language restriction *"using key terms such as vascular calcification, bone mineral density, fracture and additional filters such as human and observational studies as detailed in* ***Table S1*** *and previously published protocol (1)*."

- Figure S1 should be in the main text, as well.

Response: We have now moved Figure S1 (study selection flow diagram) to the main text.

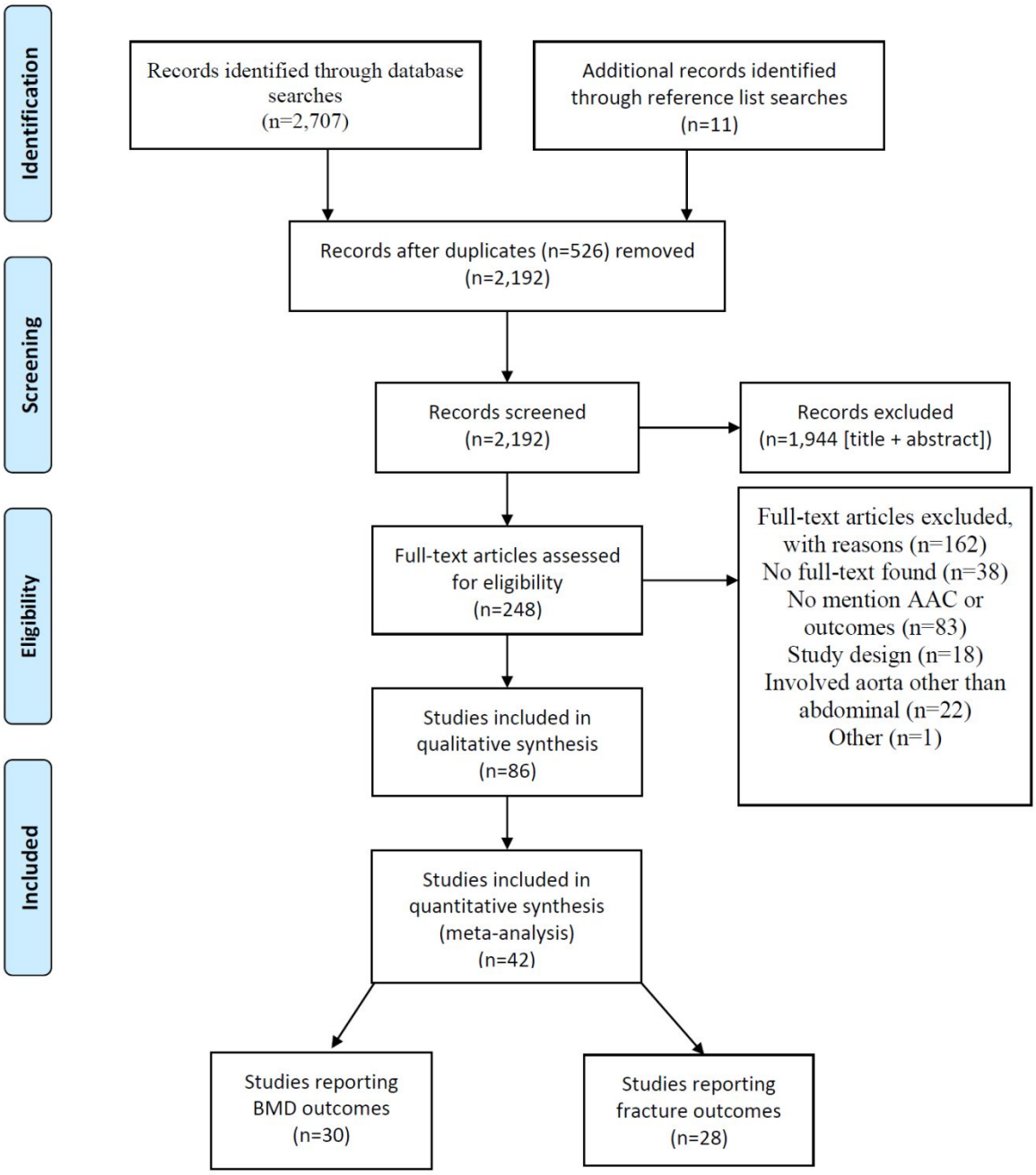

Figure 1: Study selection flow diagram

It should be clarified what it means that "Of the 86 included studies, 42 studies provided data for quantitative analyses…" (page 8). Did the authors sought contact with the corresponding authors of all 86 included studies to get data but only 42 responded? There may be implicit biases in who those 42 were that may influence the meta-analyses.

Response: The statement has now been edited to clarify that of the 86 studies that were eligible based on the full-text screening, only 42 had extractable data for meta-analyses. The edited paragraph can be found in the main manuscript on page 8, lines 135-136 and reads as: "*Of the 86 eligible studies included in the qualitative synthesis, 42 studies (two abstracts, 40 full publications) provided extractable data for the meta-analysis [BMD, n=14, fracture, n=12, both BMD and fracture, n=16] [**Figure 1**].*"

The authors could add description of differences by studies included vs not in meta-analysis re: location, publication year, population studied, AAC and BMD determination modalities, etc. Related, Table 1 should add a column for studies included in the meta-analysis (to compare the distribution of study characteristics between the subgroup and full group of 86).

Response: We have now included additional two columns in **Table 1** (pages 24&25) of the manuscript describing the specific study characteristics (e.g., location, publication year, population studied, AAC and BMD determination modalities) of those included in the meta-analysis as well as the studies which were only included in the qualitative synthesis.

Table 1. Characteristics of the included studies

Characteristics	All studies, n (%)	Studies included in meta-analysis, n (%)	Studies included only in qualitative synthesis, n (%)
Year of publication			
Pre-2010	31 (36.1)	16 (38.1)	15 (34.1)
2010-2015	33 (38.4)	17 (40.5)	16 (36.4)

2016-2021	22 (24.4)	9 (21.4)	13 (29.5)
Setting			
Chronic kidney disease, kidney stones and patients in haemodialysis	19 (22.1)	2 (4.7)	17 (38.6)
Postmenopausal women	29 (33.7)	21 (50)	8 (18.2)
General population	30 (34.9)	17 (40.5)	13 (29.5)
Other	8 (9.3)	2 (4.8)	7 (15.9)
Region			
North America	26 (30.5)	11 (26.2)	15 (34.1)
Europe	32 (37.6)	15 (35.7)	17 (38.6)
Asia	10 (11.7)	5 (11.9)	5 (11.4)
Oceania	9 (10.6)	3 (7.1)	6 (13.6)
Africa	5 (5.9)	5 (11.9)	------
South America	4 (4.6)	3 (7.1)	1 (2.3)
Number of subjects			
<500	48 (55.8)	17 (40.5)	31 (70.5)
>500	38 (44.2)	23 (57.1)	15 (34.1)
Modality of AAC assessment			
Radiography	46 (53.5)	28 (66.7)	18 (40.9)
Quantitative computed tomography	26 (30.2)	4 (9.5)	22 (50.0)
Dual energy x-ray absorptiometry	14 (16.3)	10 (23.8)	4 (9.1)
Sex			
Men only	8 (9.3)	6 (14.2)	2 (4.5)
Women only	33 (38.3)	23 (54.8)	10 (22.7)
Mixed	40 (46.5)	13 (31.0)	27 (61.3)
Not specified	5 (5.8)	-----	5 (11.4)
%People with a smoking history			
<15%	12 (13.9)	9 (21.4)	3 (6.8)
≥ 15%	31 (36.0)	12 (28.6)	19 (43.2)
Not specified	43 (50)	21 (50)	22 (50)
Study design			
Prospective	24 (27.9)	15 (35.7)	9 (20.5)
Cross-sectional	58 (67.4)	26 (61.9)	32 (72.7)
Case-control	2 (2.3)?	1 (2.4)	1 (2.3)

Sensitivity analyses should be conducted for the meta-analysis after excluding "poor" and perhaps "fair" bias quality.

Response: Thank you for the suggestion. Sensitivity analyses have now been done after excluding the studies with poor and fair quality. A new table (Table S13) is added on page 24 of the supplementary online material. Additionally, descriptions highlighting the results are included on pages 9 lines 162-165: *"Additionally, any/advanced AAC was associated with lower BMD at the total hip and lumbar spine even after excluding the studies with poor and fair quality. However, the association between AAC and femoral neck BMD was attenuated after exclusion of studies with poor and fair quality."*

And, Page 10 lines186-187: "The association between any/advanced AAC, any and site-specific fractures remained significant after excluding studies with poor and fair quality [Table S13]."

Table S 13: Pooled analyses showing the association between any/advanced AAC, BMD and fracture after excluding studies with poor and fair quality.

		Number of studies (patients)	SMD (95%CI)	I^2 (%)
BMD (SMD 95%CI)	**Femoral neck**			
	No/low AAC	7 (2569)	1 (referent)	
	Any/advanced AAC	7 (2724)	-0.26 (-0.55 to 0.03)	95.7
	Total Hip			
	No/low AAC	10 (6842)	1 (referent)	
	Any/advanced AAC	10 (8688)	-1.26 (-1.70 to -0.82)	99.2
	Lumbar spine			
	No/low AAC	10 (5372)	1 (referent)	
	Any/advanced AAC	10 (4804)	-1.05 (-2.07 to -0.03)	99.8
Fracture (OR 95%CI)	**Any/All fracture**			
	No/low AAC	17 (2011/13242)	1 (referent)	
	Any/ advanced AAC	17 (1438/10047)	1.68 (1.43 to 1.99)	82.2
	Vertebral fracture			
	No/ low AAC	12 (943/6201)	1 (referent)	
	Any/advanced AAC	12 (1254/5088)	1.97 (1.53 to 2.53)	84.8
	Non-vertebral fracture			
	No/low AAC	7 (540/6553)	1 (referent)	

	Any/advanced AAC	7 (1122/9022)	1.30 (1.04 to 1.64)	77.0
	Hip fracture			
	No/low AAC	5 (230/5961)	1 (referent)	
	Any/advanced AAC	5 (547/8672)	1.63 (1.01 to 2.63)	88.1%

It would be useful for the subgroup analyses should be presented in Tables/Figures as well, as they have major implications (eg. Findings stronger in women) but aren't clear from the figures.

Response: We thank the reviewer for the suggestion. We have presented the detailed subgroup analyses in Tables S8 and S14 on pages 19 &25 of the supplementary online material. Whilst we understand the attraction of presenting all sub-groups in a single forest plot, we believe this may compromise the overall quality readability of the figures.

Table S8. Subgroup analysis showing a standardized mean difference in BMD by skeletal sites in people with any/advanced AAC

Site	Subgroup analysis		Number of studies (n)	SMD (95%CI)	I^2 (%)
Femoral neck	Gender	Women only	5 (2140)	-0.32 (-0.54 to -0.09)	81.1
		Men only	2 (1682)	0.04 (-0.07 to 0.14)	0.0
		Mixed	3 (3159)	-0.31 (-0.82 to 0.21)	97.5
	Study location	Europe	6 (2819)	-0.18 (-0.40 to 0.05)	85.7
		North America	2 (1618)	-0.10 (-0.30 to 0.09)	74.4
		South America	1 (815)	-0.36 (-0.52 to -0.20)	-
		Asia	1 (1729)	-0.68 (-0.78 to -0.59)	-
	Imaging modality	Radiograph	8 (5465)	-0.34 (-0.59 to -0.10)	93.9
		DXA	2 (1516)	0.07 (-0.08 to 0.22)	53.0
	Sample size	<500	3 (522)	-0.55 (-0.95 to -0.14)	74.4
		>500	7 (6459)	-0.15 (-0.41 to 0.11)	96.0
Total hip	Gender	Women only	8 (9608)	-0.66 (-1.27 to -0.04)	99.4
		Men only	4 (7402)	-0.11 (-0.18 to -0.04)	21.9
		Mixed	4 (3267)	-3.09 (-5.03 to -1.15)	99.7
	Study location	Europe	5 (5067)	-2.69 (-4.29 to -1.09)	99.8
		North America	3 (8402)	-0.12 (-0.17 to -0.08)	-0.0
		South America	1 (815)	-0.39 (-0.56 to -0.23)	-
		Asia	1 (1729)	-0.52 (-0.62 to -0.43)	-
		Oceania	2 (2768)	-0.16 (-0.24 to -0.08)	0.0
		Africa	3 (1496)	-0.94 (-1.84 to -0.04)	95.8

	Imaging modality	Radiograph	8 (14509)	-0.37 (-0.87 to -0.13)	99.4
		DXA	7 (5768)	-1.84 (-2.73 to -0.95)	99.5
	Sample size	<500	4 (1028)	-0.25 (-0.63 to 0.14)	79.3
		>500	12 (19249)	-1.32 (-1.81 to -0.82)	99.6
Lumbar spine	Gender	Women only	16 (12914)	-0.89 (-1.64 to -0.14)	99.6
		Men only	3 (2002)	0.00 (-0.09 to 0.10)	0.0
		Mixed	2 (2344)	0.04 (-0.41 to 0.49)	95.5
	Study location	Europe	7 (4204)	-0.49 (-1.62 to 0.63)	99.6
		North America	4 (5477)	-0.12 (-0.65 to 0.42)	98.6
		South America	2 (594)	-0.71 (-1.13 to -0.29)	68.3
		Asia	2 (3453)	-3.09 (-8.79 to 2.61)	100
		Africa	3 (1496)	-0.61 (-0.78 to -0.45)	0.0
		Oceania	2 (2036)	0.04 (-0.05 to 0.14)	0.0
	Imaging modality	Radiograph	11 (9368)	-0.91 (-1.92 to 0.10)	99.7
		CT	2 (2844)	-0.84 (-0.93 to -0.75)	0.0
		DXA	7 (5048)	-0.19 (-0.44 to 0.05)	91.3
	Sample size	<500	10 (2168)	-0.37 (-0.65 to -0.09)	81.6
		>500	11 (15092)	-0.92 (-1.69 to -14)	99.8

Table S14: Subgroup analysis showing risks of fractures in people with any/advanced AAC

Site	Subgroup analysis		Number of studies (n)	Relative Risk (95%CI)	I^2 (%)
Any fracture	Gender	Women only	15 (15217)	1.85 (1.43 to 2.39)	94.1
		Men only	7 (15977)	1.33 (1.19 to 1.48)	20.1
		Mixed	6 (2554)	1.97 (1.52 to 2.55)	00.0
	Study location	Europe	8 (8323)	1.33 (1.21 to 1.45)	20.0
		North America	8 (17455)	1.40 (1.13 to 1.72)	86.9
		Asia	5 (3067)	2.14 (1.64 to 2.79)	62.7
		Africa	5 (2455)	3.74 (2.41 to 5.78)	80.8
		Oceania	2 (2448)	1.23 (1.04 to1.44)	0.0
	Imaging modality	Radiograph	19 (26251)	1.49 (1.32 to 1.68)	77.9
		CT	2 (3117)	1.73 (0.63 to 4.72)	94.3
		DXA	7 (4380)	2.68 (1.53 to 4.70)	94.0
	Sample size	<500	8 (2042)	2.02 (1.55 to 2.63)	86.04
		>500	20 (31706)	1.62 (1.34 to 1.96)	91.6
Vertebral fracture	Gender	Women only	13 (10293)	2.12 (1.48 to 3.03)	93.3
		Men only	4 (10703)	1.45 (1.31 to 1.60)	0.0
		Mixed	5 (2345)	2.12 (1.39 to 3.24)	79.8
	Study location	Europe	7 (5589)	1.36 (1.14 to 1.62)	49.5
		North America	4 (9253)	1.57 (1.12 to 2.21)	86.4

		Asia	5 (3067)	2.17 (1.59 to 2.95)	65.1
		Africa	5 (4408)	3.71 (1.93 to 7.12)	95.2
		Oceania	1 (1024)	1.03 (0.66 to 1.60)	-
	Imaging modality	Radiograph	13 (13891)	1.64 (1.37 to 1.96)	75.5
		CT	2 (3117)	1.81 (0.74 to 4.48)	90.9
		DXA	7 (6333)	2.62 (1.52 to 4.50)	94.6
	Sample size	<500	7 (1739)	2.97 (1.94 to 4.56)	85.3
		>500	15 (21602)	1.62 (1.30 to 2.03)	90.5
Non-vertebral fracture	Gender	Women only	7 (10962)	1.35 (1.08 to 1.69)	77.0
		Men only	2 (6446)	1.30 (0.70 to 2.42)	-
		Mixed	2 (1016)	2.05 (0.94 to 4.47)	31.4
	Study location	Europe	3 (3604)	1.49 (1.20 to 1.85)	48.0
		North America	4 (10247)	0.95 (0.72 to 1.26)	52.2
		Asia	2 (2125)	2.12 (1.44 to 3.11)	0.0
		Oceania	2 (2448)	1.64 (0.83 to 3.23)	51.4
	Imaging modality	Radiograph	9 (15052)	1.52 (1.25 to 1.84)	56.1
		CT	1 (2348)	0.77 (0.59 to 1.00)	-
		DXA	1 (1024)	1.32 (1.03 to 1.70)	-
	Sample size	<500	2 (728)	1.91 (0.63 to 5.75)	56.9
		>500	9 (17696)	1.39 (1.11 to 1.73)	71.4
Hip fracture	Gender	Women only	7 (10962)	1.56 (1.03 to 2.36)	81.3
		Men only	2 (6446)	1.93 (0.96 to 3.88)	70.9
		Mixed	1 (401)	4.52 (0.95 to 21.49)	-
	Study location	Europe	2 (2989)	2.11 (1.09 to 4.12)	37.8
		North America	4 (10247)	1.26 (0.77 to 2.06)	87.3
		Asia	2 (2125)	3.18 (1.85 to 5.47)	0.0
		Oceania	2 (2448)	1.74 (0.96 to 3.17)	27.2
	Imaging modality	Radiograph	8 (14437)	2.02 (1.33 to 3.07)	74.5
		CT	1 (2348)	0.77 (0.59 to 1.00)	-
		DXA	1 (1024)	1.44 (0.87 to 2.39)	-
	Study size	<500	2 (728)	2.09 (0.71 to 6.13)	39.4
		>500	8 (17081)	1.67 (1.12 to 2.50)	84.4

Similarly, it would be good to show results for the investigations of heterogeneity between studies that are described in the discussion (limitations section specifically).

Response: We thank the reviewer for the comment. We have explored heterogeneity extensively by way of subgroup analyses (representing clinically homogeneous groups in

an attempt to minimize these known contributors to heterogeneity) and through meta-regression. We recognize that heterogeneity cannot be entirely eliminated, but we have applied these statistical methods to address the observed heterogeneity to improve the internal validity of our primary findings. The findings for heterogeneity, I^2 (%), have been presented in all the figures (**Figure 2-4**) and supplementary tables (Tables S7 (page 18) and 8 (page 19), 11-14 (pages 22-25) highlighting between-study heterogeneity. Additionally, we have now clarified the context that we want to refer to when we say high between-study heterogeneity in the limitation on page 15, lines 292-293. *First, high between-study heterogeneity "(I^2>60% and τ^2 >0.05)" was noted in several analyses, suggesting the need for a careful interpretation of the findings*. The potential causes for this high heterogeneity include, population characteristics (older age groups) women-only, CKD), design (cross-sectional, prospective) and measurement of exposures (radiographs, CT, DXA). We have chosen to preferentially present in the pooled estimates of the data from the total cohort analysis, and this would likely have the greatest statistical power as well. We acknowledge the high heterogeneity in these analyses is not fully overcome by increasing sample size. Further, as can be viewed from our various subgroup analyses, heterogeneity is not fully overcome by increasing clinical homogeneity. This suggests that there is a significant amount of residual confounding when examining the association between bone and vascular calcification, and potentially highlights how vascular calcification may capture underappreciated risk factors for skeletal outcomes. Rather than be discouraged by this we believe that there is a need to further explore the role of specific biological factors in the understanding of the association between AAC and bone health.

Reviewer-2

Sensitivity analyses would be easier to understand if Table 1 characteristics were provided for the 42 studies included in the meta-analysis- the number of studies differs markedly in women vs men and by imaging modality (while number of studies is provided the n is not).

Response: Thank you, we have now included additional two columns to Table 1 and presented the detailed characteristics of the studies included in the meta-analysis.

Table 2. Characteristics of the included studies

Characteristics	All studies, n (%)	Studies included in meta-analysis, n (%)	Studies included only in qualitative synthesis, n (%)
Year of publication			
Pre-2010	31 (36.1)	16 (38.1)	15 (34.1)
2010-2015	33 (38.4)	17 (40.5)	16 (36.4)
2016-2021	22 (24.4)	9 (21.4)	13 (29.5)
Setting			
Chronic kidney disease, kidney stones and patients in haemodialysis	19 (22.1)	2 (4.7)	17 (38.6)
Postmenopausal women	29 (33.7)	21 (50)	8 (18.2)
General population	30 (34.9)	17 (40.5)	13 (29.5)
Other	8 (9.3)	2 (4.8)	7 (15.9)
Region			
North America	26 (30.5)	11 (26.2)	15 (34.1)
Europe	32 (37.6)	15 (35.7)	17 (38.6)
Asia	10 (11.7)	5 (11.9)	5 (11.4)
Oceania	9 (10.6)	3 (7.1)	6 (13.6)
Africa	5 (5.9)	5 (11.9)	------
South America	4 (4.6)	3 (7.1)	1 (2.3)
Number of subjects			
<500	48 (55.8)	17 (40.5)	31 (70.5)
>500	38 (44.2)	23 (57.1)	15 (34.1)
Modality of AAC assessment			
Radiography	46 (53.5)	28 (66.7)	18 (40.9)

Quantitative computed tomography	26 (30.2)	4 (9.5)	22 (50.0)
Dual energy x-ray absorptiometry	14 (16.3)	10 (23.8)	4 (9.1)
Sex			
Men only	8 (9.3)	6 (14.2)	2 (4.5)
Women only	33 (38.3)	23 (54.8)	10 (22.7)
Mixed	40 (46.5)	13 (31.0)	27 (61.3)
Not specified	5 (5.8)	-----	5 (11.4)
%People with a smoking history			
<15%	12 (13.9)	9 (21.4)	3 (6.8)
≥ 15%	31 (36.0)	12 (28.6)	19 (43.2)
Not specified	43 (50)	21 (50)	22 (50)
Study design			
Prospective	24 (27.9)	15 (35.7)	9 (20.5)
Cross-sectional	58 (67.4)	26 (61.9)	32 (72.7)
Case-control	2 (2.3)?	1 (2.4)	1 (2.3)

Could power be the explanation for associations seen in women but not men? For associations seen in radiograph studies but not DEXA or CT? Also, the proportion of studies by imaging modality that are included in the meta-analysis is very different (only 5 of 26 CT studies likely because the CT studies were not originally conducted to examine skeletal health).

Response: We thank the reviewer for the comment. We agree that power may partly explain some of the statistically significant associations. Specifically for women we acknowledged in the discussion (page 15, lines 305-308) that power may contribute to the associations. "*Specifically, subgroup analyses revealed findings to be more pronounced in women, possibly reflecting greater statistical power (as there were more studies conducted in women) as well as the known effects of oestrogen decline on skeletal and vascular outcomes*". We believe a similar phenomenon is taking place regarding the modality used for AAC determination. Encouragingly associations were in the same direction across the

imaging modality subgroups suggesting imaging modality does not affect our clinical interpretation.

Can the authors explain the qualitative analysis? Is this limited to the data provided in Table S1? How does this information support the findings in this study?

Response: Thank you for the opportunity to clarify this area. Qualitative analysis includes all studies that met our inclusion-exclusion criteria. We have now added an additional column to Table S2 (pages 4-12 of the supplementary online material, **also available at the end of this response letter**) describing the key findings of each study. Additionally, a few sentences highlighting the qualitative outcomes are now included in the discussion on page 12, lines 216-224. *"Moreover, the majority of the studies that were included in qualitative synthesis only (namely, studies without data for meta-analysis) reported an inverse relationship between AAC and BMD (more AAC, less BMD) (2-4) and increased risk of fractures (5-7) in general and specific populations. Most recently published studies that are not included in this review also support the aforementioned relationships (8, 9). A few studies included in the qualitative synthesis showed no relationship between AAC, BMD or fractures (7, 10-12) but overall the qualitative synthesis generally supports findings from our quantitative synthesis that the presence and severity of AAC indicates poor skeletal health and prognosis."*

Abstracts often present preliminary results- did the authors check with the investigators of the abstracts included in the meta-analysis to confirm the reported abstract associations would not change once final manuscript prepared for publication?

Response: We did not follow up with investigators to confirm if abstracts had been published but we did search for full text articles from the same investigators. The following statement is also added on pages 8, lines 140-141: "*Abstracts were checked if they were*

subsequently published after the search date." Where uncertainties were apparent, corresponding authors were contacted for relevant data.

Can the authors shade or highlight the studies in Tables S3-S5 included in the meta-analysis so that the reader can easily identify the included studies and associated quality without having to search back to Table S2?

Response: Thank you for this suggestion. Quality assessment was made only for studies which were included for the meta-analysis. To provide more clarity on this, we have added a new statement on page 6, lines 77-78. The risk of bias for each of the studies "*included in the meta-analysis"* was assessed based on the study design (cross-sectional, case-control or cohort studies) grouped into three categories of quality (good, fair or poor) as described previously. Similar phrases are also included in the headings of Tables S3-S5 (pages 13-15, supplementary online material).

How did the authors approach the studies that investigated settings other than general population samples? Table 1, > 15% of studies were CKD- did this contribute to heterogeneity? Did authors consider subgroup analysis investigating this population?

Response: Thank you for raising this important point, we have indeed considered several subgroups of clinical interest, and the results of these analyses are provided in above-mentioned Tables S9 and S15, available on pages 19 and 25 of the online supplementary material, respectively. For studies conducted in patients with CKD, there were not enough studies to be considered for subgroup analyses. Of the 19 studies conducted in patients with CKD, haemodialysis or kidney stones, only two studies, Torres et al (2016) (DOI: 10.1016/j.nefro.2016.03.004) and Chue et al (2012) (doi: 10.1371/journal.pone.0039241) provided quantitative data suitable for meta-analysis. Unfortunately, these studies reported different outcome measures limiting the ability for

pooled analysis. Torres et al (2012) reported an association between AAC and vertebral fracture, while Chue et al (2012) reported an association between AAC and femoral neck BMD. The remaining 17 studies did not provide quantitative data for an association between AAC and BMD/fracture to be derived. By way of example, studies by Fusaro et al (2013) and Aoki et al (2009) reported associations between calcification, fracture and BMD, respectively. However, in both studies, the calcification measurement included areas of the aorta beyond the abdominal region without providing effect estimates specifically for AAC. While these studies fulfilled our eligibility criteria the exposure variables used in these studies are not equivalent to that of our analyses. This is replicated amongst other studies that examined the association between AAC and BMD/fracture in patients with CKD.

Table S 2

Table S2: Detailed characteristics of each of the included studies

Included studies (61553 participants)						
Study, year	Country	Study design, participants, groups, and sample size	Imaging modality	AAC modelled as	Outcome measure (s)	Key finding (s)
Aleksova et al,(13) 2018	Australia	Cross sectional, study populations: 48 years;25.9 kg/m^2; 100%chronic kidney disease (CKD);40%women;53%smoker;36%diabetes;10 %HRT;37%fracture; sample size (n=146).	X-ray	AAC24 score≥1, mean AAC AAC24 score	Trabecular bone score (TBS), T-score and aBMD (g/cm2) at lumbar spine, femoral neck, proximal femur, ultra-distal radius and 1/3 radius	AAC scores were inversely related to the TBS but not to DXA-derived BMD parameters.
Alfieri et al,(14) 2015 abstract	Italy	Prospective, study populations:12 months of follow up; 100% CKD; two groups of AAC, present (n=179) versus absent (n=114)	X-ray	Present/absent AAC2 continuous	BMD (g/cm2) at femoral neck	The presence and progression of AAC was related with abnormal femoral neck BMD.
Aoki et al, (2) 2009	Japan	Cross sectional, study populations: 59.3 years;30%women;100%CKD;38.6% diabetets;72.3% medications; sample size (n=83)	CT	aortic calcification index (ACI)	BMD (mmAl) at metacarpal bone	Aortic calcification index (ACI) was inversely correlated with Metacarpal BMD
Avramovski et al,(3) 2016	Macedonia	Cross sectional, study populations:59 years; 27.7 kg/m^2;100%CKD;100%women;25%smoker;21.4 % diabetes;53.5%HTN; sample size (n=56)	X-ray	AAC24 continuous	BMD (g/cm2) at lumbar spine and total hip	AAC was significantly correlated with subtracted femoral neck BMD from lumbar spine BMD.
Bagger et al,(5) 2007	Denmark	Cross sectional, study populations:69.3 years; 26.4 kg/m^2;100%women;24.6%smoker; sample size (n=1176)	X-ray	Mean AAC score and AAC24≥6 AAC24 score	Vertebral and hip fractures	Severe AAC (score≥6) was associated with hip fracture (OR 4.4 95%CI, 1.6 to 12.9) but not vertebral fracture (1.2 95%CI, 0.9 to 1.7) or wrist (95%CI 1.4 1.0 to 2.1) after adjustment to age.
Bolton et al.,(15) 2011	UK	Cross sectional, study populations:66 years; 29 kg/m^2;40%women;13% diabetes;38% HTN;2.2%HRT; 22.2%CVD medications; sample size (n=45)	CT	Volume scoring method	BMD (g/cm2) at lumbar spine, hip, femoral neck, intertrochanteric and trochanter	Aortic calcification was inversely related to BMD.

Canepa et al, (16) 2014	USA	Cross sectional, study populations:67 years;27 kg/m^2;51%women;45%smoker;22%diabetes;42% HTN;42%CVD medication; four groups based on number of aortic segments with apparent calcification (0 (n=687), 1 (n=214), 2 (n=191), 3 (n=75)	CT	Present/absent AAC severity score (0-3)	BMD (g/cm2) at whole body and femoral neck	Aortic calcification was inversely related with bone mineral density.
Carr et al,(17) 2008	USA	Cross sectional, study population: 62.4 years;32.8 kg/m2;50%women;23.9%smoker;100%diabets;22 .4%HTN; sample size (n=1023)	CT	Present/absent	vBMD at thoracic and lumbar spine measured CT and DXA	Atherosclerotic calcified plaque was inversely associated with vBMD.
Chan et al, (18) 2015	USA	Cross sectional, study population:60 years;29 kg/m^2;52.3%women 11%smoker; sample size (n=1317)	CT	Agatston score	Integral and trabecular vBMD	AAC was inversely related with spine BMD.
Chau et al, (10) 2014	Australia	Prospective, study population:42 years;42%women;100% kidney or pancreas-kidney transplant;39.3%smoker;10.6%diabetes; sample size (n=650)	X-ray	Present/absent AAC24	Lumbar spine Z score	No significant inverse association of between AAC and BMD was noted.
Chow et al,(19) 2008	USA	Cross sectional, study population:57.4 years; 27.4 kg/m^2; 54%women;42.7%smoker;22.5%HRT;21.2%fracture; sample size (n=693)	CT	Agatston score	vBMD at lower vertebral trabecular, total femoral neck and femoral neck trabecular	AAC was inversely associated with vBMD.
Dawson-Hughes and Dallal, (20) 1990	USA	Cross sectional, study population:100%women; sample size (n=293)	X-ray	Present/absent	BMD (g/cm^2) at spine radius	AAC was inversely associated with BMD (g/cm^2) at spine radius.
Divers et al, (21) 2011	USA	Cross sectional, study population:60%women;100%diabetes; sample size (n=753)	CT	Agatston score	vBMD at thoracic and lumbar spine	Calcified atherosclerotic plaque was inversely associated with vertebral BMD.
Drinka et al, (11) 1992	USA	Cross sectional, study population:71.9 years; 100% male; sample size (n=113)	X-ray	Present/absent	BMD (g/cm^2) at lumbar spine	No significant correlation between aortic calcification and bone mineral density was observed.
Frye et al, (22) 1992	USA	Cross sectional, study population:100%women; sample size (n=200)	X-ray	Grades of calcification (0,1, and 2)	BMD at spine, femur neck, trochanter, femur shaft, distal radius and BMC midradius	Aortic calcification was not associated with lumbar spine BMD.

					Vertebral fracture	
Fusaro et al, (6) 2013	Italy	Cross sectional, study population:64.2 years; 37%women;100% CKD 36.8%smoker;22%diabetes;77.8%HTN; sample size (n=387)	X-ray	Length of the calcium deposits along the aortic wall (0.1 to 5 cm, 5.1 to 10 cm and >10 cm)	Vertebral fracture	Aortic calcification was associated with greater odds of vertebral fracture (OR 1.77 95%CI, 1.00 to 3.14).
Grant et al,(23) 2017	Canada	Cross sectional, study population: 68.9 years; 28.4 kg/m^2;71%women;11% diabetes;30%HTN; sample size (n=112)	X-ray	AAC severity categories based on lesion length	BMD (g/cm^2) at lumbar spine	Quantified AAC was negatively associated with hip and spine BMD.
Hampson et al, (24) 2013	UK	Cross sectional, study population:61.6 years;24.8 kg/m^2; 100%women;36%smoker;28%previous fracture; sample size (n=149)	DXA	AAC8&24 score	BMD (g/cm^2) at lumbar spine	AAC was negatively correlated with BMD.
Hyder et al, (25) 2009	USA	Cross sectional, study population:50%women; sample size (n=1833)	CT	AAC score	vBMD at lumbar spine	Aortic calcification was associated with lower vBMD.
Iannotti et al, (26) 2014	Italy	Cross sectional, study population: 100%HIV; sample size (n=280)	X-ray	AAC8 score	BMD (g/cm^2) Vertebral fracture	AAC (≥1) was predictor of low BMD and with vertebral fracture (OR 2.87 95%CI, 1.30 to 6.31).
Iba et al,(27) 2004	Japan	Cross sectional, study population:100%women; 100% osteoporosis; sample size (n=135)	X-ray	Present/absent	BMD	Abdominal aortic calcification was not associated with BMD.
Idoate et al,(28) 2017	Spain	Cross sectional, study population:91 years; 24.4 kg/m^2; 74%women; sample size (n=42)	CT	Present/absent	Vertebral BMD	Femoral artery calcification was significantly negatively correlated with BMD.
Jensky et al,(29) 2011	USA	Prospective, study population;64 years; 100%women; 36 months; sample size (n=936)	CT	Agatston score	BMD	Calcified atherosclerosis was inversely associated with vBMD
Kim et al,(30) 2021	South Korea	Cross sectional, study population:65 years;23.7 kg/m^2;43.6%women;47.9%diabetes;100%CKD;23.1%HTN; sample size (n=117)	CT	AAC volume in Hounsfield units	vBMD (mg/cm3)	AAC volume was negatively correlated with BMD.
Kinsella et al,(31) 2015	Ireland	Cross sectional, study population:47 years;100%CKD; 39%women;15.6%diabetes;	CT	Aortic calcification index	Trabecular and cortical vBMD	Aortic Calcification Index was inversely associated with volumetric BMD.

		43.8%smoker; two groups of AAC, present (n=22) versus absent (n=42)				
Kuipers et al, (32) 2014	Caribbean Islands	Cross sectional, study population:56 years;27.9 kg/m^2; 10.1% smoker;100%women;24.5% diabetes;45.3%HTN; two groups of AAC, present (n=190) versus absent (n=88)	CT	Present/absent	Trabecular and cortical BMD (mg/cm^3) at tibia and radius	Vascular calcification was associated with low BMD.
Lampropoulos et al, (33) 2016	Greece	Cross sectional, study population:100%women; sample size (n=29)	X-ray	AAC24 score	Osteoporosis	Aortic calcification was associated with osteoporosis.
Lee et al, 2017 (34)	South Korea	Cross sectional, study populations:58.3 years; 23 kg/m^2;56%women;29%diabetes;100%CKD; sample size (n=55)	X-ray	AAC24 score ≥5	Bone mass forearm	AAC was associated with low bone mass at the forearm.
Li et al,(35) 2020	China	Cross sectional, study populations:61.8 years;63%women;21.2%smoker;12.7%diabetes;40.7%HTN; sample size (n=3431)	CT	Agatston score	vBMD	AAC is inversely associated with vBMD in men but not in women.
Paccou et al, (36)2014	France	Case control, study populations:60.5 years; 27.1 kg/m^2;76%women;17.9%smoker;4.6% diabetes;33.4%HTN; 100% rheumatoid arthritis; sample size (n=150)	CT	Abdominal aortic calcium score	BMD (mg/cm^3) at lumbar spine, femoral neck, and total hip	AAC was significantly correlated with BMD.
Pelletier et al, (37) 2015	France	Cross sectional, study populations:50.9 years; 25kg/m^2; 40%women;56.6%smoker;24.5%diabetes; 100%; two groups of AAC24 score, <6 (n=34) versus ≥6 (n=19)	DXA	AAC24 score <6 versus ≥6	Cortical bone structure	Severe AAC was associated with poorer tibia cortical bone structure.
Pirlamarla et al, (38) 2017 Abstract	USA	Case-control, study populations: 100% Kidney stones; sample size (n=925)	CT	Present/absent	BMD	AAC and its severity was associated with osteoporosis.
Reid et al,(39) 1991	New Zealand	Prospective, study populations;100%women; 58 years; four groups of AAC, 0 (n=97), 1 (n=21), 2 (n=12), 3 (n=0)	X-ray	Calcification score (0,1,2 and 3)	BMD at spine and femur	AAC was not correlated with BMD.
Rodriguez et al, (40) 2017	Australia	Cross sectional, study populations;70 years;28.1kg/m^2;61%women;43%smoker;31.6% HTN; sample size (n=337)	X-ray	Present/absent AAC severity groups (0, 1 to 5, ≥6) AAC24 score	BMD (g/cm^2) at femoral neck and total hip	AAC was associated with femoral neck BMD.

Rodrıguez-Garcia et al, (7) 2009	Spain	Prospective, study populations;64 years; 100% CKD; 37.3% women; sample size (n=193)	X-ray	Mild, moderate, and severe calcification	Vertebral fracture	Vascular calcifications in the medium calibre arteries (OR 6.5 95%CI, 1.4 to 29.8) were associated with a higher rate of prevalent vertebral fractures. Such association were observed at large (OR 3.8 95%CI, 0.5 to 31.6) and small (0.96 95%CI, 0.3 to 3.1)) calibre arteries.
Salam et al, (41) 2019 Abstract	UK	Cross sectional, study populations;100%CKD; sample size (n=69)	DXA	AAC-8 score	Distal tibia cortical bone microstructure, cortical thickness, and cortical porosity, BMD t-score at total hip and 1/3 distal radius	Vascular calcification was associated with worse cortical bone microstructure of distal tibia.
Shavit et al, (42) 2015	UK	Case-control, study populations;100% kidney stones; 43% women; sample size (n=111)	CT	Present/absent Calcification severity (≤10%, 11%-50%, ≥51% calcification)	BMD	AAC was associated with lower BMD.
Shen et al,(43) 2007	USA	Prospective, study populations;36% months of follow up;55.9%women; sample size (n=682)	CT	Agatston method	BMD	Vascular calcification was not associated with lower BMD.
Sotomayer et al, (44) 2020	The Netherlands	Cross sectional, study populations;51 years;25.5 kg/m^2;100%kindney transplantation; 42%women;21%smoker;14%diabetes;81%HTN; 22.5% fracture; sample size (n=678)	DXA	AAC-8 score	Areal BMD at lumbar spine	AAC was independently associated with BMD.
Tanko et al, (45) 2002	Denmark	Cross sectional, study populations;100% osteoporotic women; sample size (n=963)	X-ray	AAC24 score	BMD at hip	AAC was inversely correlated with lower BMD.
Toussaint et al,(46) 2008	Australia	Cross sectional, study populations;64.5 years;31.3 kg/m^2;29%women; 30.4%smoker;100%CKD; sample size (n=48)	CT	Present/absent Median AAC score in Hounsfield units	BMD (g/cm2) at spine and femur	Vascular calcification was inversely associated with femoral BMD.
Toussaint et al, (47) 2009	Australia	Cross sectional, study populations;58 years; 26.4 kg/m^2;36%women;38%diabetes;100%CKD; sample size (n=45)	CT	Present/absent Median AAC score in Hounsfield units	BMD (g/cm2) at spine and femur	Aortic calcification was associated with lower BMD.

Wagenknecht et al,(48) 2016	USA	Prospective, study populations;55.1 years;35.3%smoker; 34.7 kg/m2;100% type 2 diabetes; 50%women; 38.7%CKD;80.7%HTN; sample size (n=300)	CT	Present/absent AAC score in Hounsfield units	vBMD at thoracic and lumbar	Progression of abdominal aorta was associated with vBMD.
Woisetschlager and Spångeus, (49) 2018	Sweden	Prospective, study populations; 71 years; 26 kg/cm^2; 50%women; sample size (n=50)	CT	Aortic calcium score	DXA BMD	AAC was not correlated with BMD.
Study included in the meta-analysis						
Aoyagi et al,(50) 2001	USA	Prospective, study populations: 61.8 years; 23.4 kg/m^2;100%women;10%smoker;6.7%diabetes; two groups of AAC, present (n=220) versus absent (n=304)	X-ray	Present/absent	BMD (mg/cm2) at proximal and distal radius, and calcaneus	The differences in BMD in those with versus without calcification were attenuated after adjustment for age.
Bagger et al,(51) 2006	Denmark	Prospective, study populations:64.9 years; 25.1 kg/m^2; 90 months of follow up;100%women;21.6%smoker;5.2%diabetes; two groups of AAC, AAC24≥3 (n=1877) versus <3 (n=785)	X-ray	AAC24≥3/AAC24<3 AAC24 continuous	BMD (g/cm2) at lumbar spine and total hip as well as incident (vertebral and hip) fracture	AAC was significantly associated with lower BMD and accelerated bone loss from the proximal femur, hip and vertebral fractures
Banks et al,(52) 1994	UK	Cross sectional, study populations:56.1 years;100%women; sample size (n=115)	X-ray and CT	Present/absent	BMD (g/cm) at femoral neck and ward triangle	AAC was associated with lower proximal femur bone density.
Boukhris et a,(53) 1973	USA	Cross sectional, study populations:49%women; had fracture at baseline; sample size (n=589)	X-ray	Present/absent	Vertebral fracture	AAC was associated with osteoporosis and fracture.
Bristow et al,(54) 2019	New Zealand	Prospective, study populations:73 years; 26.6 kg/m^2;100%women;60 months follow up;2%smoker;37%fracture; four groups of AAC, AAC8 score 0 (n=166), 1 to 2 (n=102), 3 to 6 (n=24)	DXA	AAC8 score categories (0, 1-2,3-6,7-8)	BMD (g/cm2), BMC (g), bone area (cm2) at lumbar spine, hip, and femoral neck	The presence of AAC was not related to changes in BMD at the total hip or femoral neck, nor to BMD at the spine.
Chue et al,(55) 2012	UK	Cross sectional, study population: 55 years;29 kg/m^2;35%women;64%smoker; 100% CKD; two groups of AAC, calcification (n=57), no calcification (n=63)	X-ray	Present/absent AAC24	BMD (g/cm^2) at femoral neck.	AAC was not associated with lower BMD at femoral neck.
Paiva et al, (56) 2002	Brazil	Cross sectional, study population:64 years;100%women;100% osteoporosis; sample size (n=96)	X-ray	Present/absent	BMD (g/cm^2) at lumbar spine	AAC was associated with lower BMD.

El Maghraoui et al, (57) 2012	Morocco	Prospective, study population:62.4 years; 100% male;26.4 kg/m^2; 7.3% smoker; sample size (n=709)	DXA	AAC24 score ≥5 versus<5 AAC24 score	Vertebral fracture	Advanced AAC was associated with prevalent vertebral fractures.
El Maghraoui et al, (58) 2013	Morocco	Cross sectional, study population:60.9 years; 100%women;0.4% smoker;13% history of peripheral fractures; two groups of AAC, AAC24≥5 (n=108) versus <5 (n=800)	DXA	AAC24 score ≥5 versus <5 AAC24 score	BMD (g/cm^2) at lumbar spine and total hip Vertebral fracture	The presence of AAC was significantly associated with vertebral fracture and lower BMD at total hip.
El Maghraoui et al, (59) 2018	Morocco	Cross sectional, study population:59.5 years; 29.9 kg/m^2; 100%women; all non-smokers;13.3% history of fracture; two groups of AAC, AAC24≥5 (n=34) versus <5 (n=366)	DXA	AAC24 score ≥5 versus <5 AAC24 score	BMD (g/cm^2) at lumbar spine and total hip Vertebral fracture	The presence of AAC was significantly associated with vertebral fracture and lower BMD.
Farhat et al, (60) 2006	USA	Prospective, study population: 100% women; three AAC scores, 0 (n=146), 1 to 74 (n=221), ≥75 (n=123)	CT	Agatston scoring method	vBMD (g/cm)	Higher AAC was associated with lower vBMD.
Figueiredo et al,(61) 2012	Brazil	Cross sectional, study population:73 years; 27.9 kg/m^2;58%women; 12.3%smoker;21.2%diabetes;63.5%HRT;13%histroy of fragility fracture; two groups of AAC, AAC24≥7 (n=197) versus <7 (n=618)	X-ray	AAC24 score ≥7 versus <7 AAC24 score	BMD (g/cm^2) and t-score at femoral neck and total femur	Advanced AAC was associated with lower BMD.
Flipon et al,(62) 2010	France	Prospective, study population:100%women;15% smokers; two groups of AAC, AAC24≥median (n=333) versus <median (n=334)	X-ray	AAC24 score ≥median versus <median AAC24 score	BMD (g/cm^2) at femoral neck and osteoporotic fracture	Aortic calcification score was not associated with lower BMD and osteoporotic fractures.
Ghozlani et al,(63) 2017	Morocco	Cross sectional, study population:57.9 years;30.4 kg/m^2;100%women; two groups of AAC, AAC24≥5 (n=159) versus <5 (n=29)	DXA	AAC24 score ≥5 versus <5 AAC24 score	BMD (g/cm^2) and T-score at total hip and lumbar spine Vertebral fracture	Advanced AAC was associated with lower BMD and higher vertebral fracture
Hanna et al,(64) 2015	USA	Cross sectional, study population:53 years;67.2%women; two groups of AAC, present (n=103) versus absent (n=200)	X-ray	Present/absent	Lumbar fracture	AAC was associated with low velocity impact fractures and lower BMD.
Iwamoto et al,(65) 2010	Japan	Cross sectional, study population:72.4 years;94%women; two groups of AAC, present (n=175) versus absent (n=226)	X-ray	Present/absent	Vertebral fractures	Severity of abdominal aortic calcification was associated with vertebral fractures.

Jamal et al,(66) 2005	Canada	Cross sectional, study population:65.8 years;100%CKD;29% women; 9%smokers; sample size (n=57)	X-ray	AAC24 score, every unit increase in AAC	Fracture	Lumbar aortic calcification was associated with increased fracture risk.
Kim et al, (67) 2012	South Korea	Cross sectional, study population:64.7 years;22.9 kg/m^2;100%women;9%smoker;16% diabetes;31%HTN;16.8%previous fracture; two groups of AAC, present (n=274) versus absent (n=495)	CT	Agatston score	vBMD at total hip, femoral neck and vertebral Fracture	Aortic calcium score was associated with low trabecular BMD
Lewis et al,(68) 2019	Australia	Prospective, study populations:75 years; 27 kg/m^2;120 months of follow up; 100%women;35.9%smoker;5.6%diabetes;25.8%previous fracture; three groups of AAC, 0 to 1 (n=459), 2 to 5 (n=373) and ≥6 (n=192)	DXA	AAC24 score (0 to 1, 2 to 5, and ≥6)	Area, BMC, BMD (g/m$^{2)}$ at total hip, prevalent fracture, vertebral fracture	Advanced AAC was associated with lower BMD and increased fracture risk.
Majjad et al, (69) 2020	Morocco	Cross sectional, study populations: 55 years;100%women; 28.5 kg/m^2; 2.8% peripheral fracture; sample size (n=250)	DXA	Present/absent AAC24 score	Vertebral fracture	AAC was independently associated with prevalent vertebral fractures.
Mohammed et al,(70) 2014	Ireland	Cross sectional, study populations:57 years; 27 kg/m^2; 71%women;43%smoker; 17%diabetes;23%HTN; two groups of AAC, present (n=211) versus absent (n=392)	DXA	Present/absent AAC24 score	BMD (g/cm^2) and T-score at hip	AAC was associated with lower BMD.
Nakatsuka et al, (71) 1997	Turkey	Case control, study populations:68.6 years; 100%women; sample size (n=122)	X-ray	Present/absent	Vertebral fracture	AAC was not associated with vertebral fractures.
Naves et al, (72) 2008	Spain	Prospective, study populations:48 months follow up;50.6%women;17.2%smoker;9.1%diabets; two groups of AAC, present (n=230) versus absent (n=385)	DXA	Present/absent	Lumbar, femoral neck BMD and osteoporotic fracture	AAC was positively associated with osteoporotic fractures. The progression of AAC was also positively associated with the rate of decline in BMD at lumbar spine.
Pirro et al, (73) 2013	Italy	Cross sectional, study populations:64.3 years;26.4 kg/m^2; 100% women; two groups of AAC, present (n=36) versus absent (n=14)	X-ray	Present/absent	BMD (g/cm^2) at lumbar spine	AAC was not significantly associated with lumbar spine BMD.

Pozzo et al, (74) 2006 abstract	Argentina	Cross sectional, study populations: 100%women; two groups of AAC, AAC≤1 (n=354) versus > 1(n=144)	CT	AAC score ≤ 1 versus >1	BMD (mg/cm3) at lumbar spine	AAC was associated with lower BMD.
Orwoll et al, (75) 1990	USA	Cross sectional, study populations:64 years; 100%men; four groups of AAC, Grade 0 (n=43), 1(n=44), 2(n=26), 3(n=16)	X-ray	Grad 0 to 4 calcification	BMD at spine and hip	Vascular calcification had very minimal effect on BMD.
Rajzbaum et al,(76) 2005	France	Cross sectional, study populations;63.5 years; 100%women;24.2 kg/m^2; 20%smoker; 20%HTN;2% diabetes; two groups of AAC, present (n=120) versus absent (n=207)	X-ray	Present/absent	Wrist, hip, vertebral and other fractures BMD (g/cm^2) at femoral neck, t-score and z-score	AAC was associated with lower BMD and increased risk of fracture.
Samelson et al, (77) 2007	USA	Prospective, study populations;60 years;27 kg/m^2; 3.4% smoker; 0.5% diabetes; 50%women;420 months of follow up; AAC present (n=1557), absent (n=942)	X-ray	Present/absent AAC24 score	Incident hip fracture	Severity of aortic calcification was not associated with hip fracture.
Schousboe et al, (78) 2021	USA	Prospective, study populations; 100%women; 62.5%smokers; two AAC groups, 0 to 1 (n=1519), 2 to 4 (n=1456), 5 to 8 (n=1231), ≥9 (n=1159)	X-ray	AAC-24 score	Prevalent vertebral and incident osteoporotic fractures	AAC was associated with a higher risk of incident hip and major osteoporotic fractures.
Schulz et al,(79) 2004	USA	Cross sectional, study populations;68.3 years;24.9 kg/m^2; 100%women; two groups of AAC, present (n=1785) versus absent (n=563)	CT	Present/absent	Vertebral bone density (mg/m^2) and vertebral fracture	Aortic calcification was associated with low bone density and fragility fractures.
Simon et al, (80) 2014	Romania	Cross sectional, study populations;67.6 years; 29.5 kg/m^2; 100%women;21.6%diabetes;4.8%smoker; two groups of AAC, present (n=61) versus absent (n=64)	X-ray	Present/absent AAC24 score	BMD (mg/m^2) at lumbar spine, femoral neck, and trochanter	AAC was associated with low BMD.
Szulc et al, (81) 2008-MINOS	France	Prospective, study populations;120 months of follow up; 100%men; two groups of AAC, present (n=181) versus absent (n=220)	X-ray	Present/absent AAC24 score	BMD (mg/m^2) at lumbar spine, femoral neck, trochanter, total hip, whole body, distal forearm, and ultra distal radius Incident fracture	AAC (>6) was associated with incident fractures.

Szulc et al, (82) 2013 STRAMBO	France	Cross sectional, study populations;70 years; 100%men; 67.9%smoker;37%HTN; 11% diabetes; four groups of AAC, 0 (n=397), 1 to 2 (n=242), 3 to 6 (n=151), >6 (n=111)	DXA	AAC24 score (0, 1 to 2, 3 to 6, >6)	BMD (g/cm^2) at lumbar spine, femoral neck, total hip, trochanter,1/3 distal radius, ultra-distal radius and whole body Vertebral fracture	AAC (>6) was associated with fracture but not BMD.
Szulc et al,(83) 2014-MrOs	USA	Prospective, study populations;100%men;62.4%smokers; four groups of AAC, 0 to 1 (n=1528), 2 to 4 (n=1468), 5 to 8 (n=1240), >9+(n=1164)	X-ray	AAC24 score (0-1, 2 to 4, 5 to 8, >9+)	BMD (g/cm^2) at total hip Hip and non-spine fracture	AAC was associated with lower BMD and higher fracture risk.
Szulc et al, (84) 2015-SOF	USA	Prospective, study populations;100%women;180 months of follow up; 41%smokers; three groups of AAC, 0 (n=469), 1 to 4 (n=244), ≥5 (n=238)	X-ray	AAC24 score (0, 1 to 4, ≥5)	BMD at lumbar spine, total hip and femoral neck Vertebral fracture	AAC was associated with lower BMD but not vertebral fracture.
Torres et al, (85) 2016	Spain	Cross sectional, study populations;55.2 years;26.7 kg/m^2;39%women; 100%CKD; four groups of AAC, 0 (n=195), 1 to 6 (n=195), >6 (n=205), had baseline fracture	X-ray	AAC24 score	Vertebral fracture	AAC was not associated with fracture.
Vogt et al, (86) 1997	USA	Cross sectional, study populations; 100%women; two groups of AAC, present (n=1444) and absent (n=607)	X-ray	Present/absent	BMD (g/cm2) at hip, lumbar spine, proximal radius, distal radius and calcaneus	AAC was associated with lower BMD.
Wang et al, (87) 2010	New Zealand	Prospective, study populations; 81.6% women; sample size (n=1424)	X-ray	Present/absent AAC-8 score	BMD (g/cm^2) at lumbar spine, total femur, and body, osteoporotic and total fractures	AAC was not associated with lower BMD.
Wyers et al, (88) 2017 Abstract	The Netherlands	Cross sectional, study populations;71 years; 60%women;100% clinical fracture; two AAC groups, present (n=479) and absent (n=1296)	X-ray	AAC-8 score	Vertebral fracture	AAC was associated with vertebral fracture.
Yokomoto,(89) 2020	Japan	Cross sectional, study populations;58 years; 22.4 kg/m^2; 55%women;27%diabetes;47% HTN; 100% with pheochromocytoma; two AAC groups, AAC24≥3 (n=13) and <3 (n=38)	X-ray	AAC-24 score	Vertebral fracture	AAC was associated with vertebral fracture.

Zhou et al, (90) 2013	China	Prospective, study populations;46%women; 60 months of follow up; two AAC groups, 0 (n=678), 1 to 2 (n=431), 3 to 6 (n=336), >6 (n=284)	X-ray	AAC-24 score	BMD (g/cm^2) at vertebra, femoral neck, femoral tuberosity and total hip	AAC was associated with lower BMD.
Zhou et al, (91) 2014	China	Prospective, study populations;69.3 years;21.6 kg/m^2; 100%women; 3.1%smoker;22.2%diabets; 31.1%HTN; two AAC groups, present (n=673), absent (n=1051)	X-ray	Present/absent AAC-8 score	Vertebral, hip, and other fractures	AAC was associated with vertebral fracture.

1. Rodríguez AJ, Leow K, Szulc P, Scott D, Ebeling P, Sim M, et al. Abdominal aortic calcification, bone mineral density and fractures: a systematic review and meta-analysis protocol. BMJ Open. 2019;9(4):e026232.

2. Aoki A, Kojima F, Uchida K, Tanaka Y, Nitta K. Associations between vascular calcification, arterial stiffness and bone mineral density in chronic hemodialysis patients. Geriatr Gerontol Int. 2009;9(3):246-52.

3. Avramovski P, Avramovska M, Lazarevski M, Sikole A. Femoral neck and spine bone mineral density-Surrogate marker of aortic calcification in postmenopausal women. Anatol J Cardiol. 2016;16(3):202-9.

4. Bolton CE, McEniery CM, Raj V, McDonnell BJ, Dixon AK, Munnery M, et al. Aortic calcification, arterial stiffness and bone mineral density in patients with COPD. Artery Research. 2011;5(1):30-6.

5. Bagger YZ, Rasmussen HB, Alexandersen P, Werge T, Christiansen C, Tankó LB. Links between cardiovascular disease and osteoporosis in postmenopausal women: serum lipids or atherosclerosis per se? Osteoporos Int. 2007;18(4):505-12.

6. Fusaro M, Tripepi G, Noale M, Vajente N, Plebani M, Zaninotto M, et al. High prevalence of vertebral fractures assessed by quantitative morphometry in hemodialysis patients, strongly associated with vascular calcifications. Calcif Tissue Int. 2013;93(1):39-47.

7. Rodríguez-García M, Gómez-Alonso C, Naves-Díaz M, Diaz-Lopez JB, Diaz-Corte C, Cannata-Andía JB. Vascular calcifications, vertebral fractures and mortality in haemodialysis patients. Nephrol Dial Transplant. 2009;24(1):239-46.

8. Chen TY, Yang J, Zuo L, Wang L, Wang LF. Relationship of abdominal aortic calcification with lumbar vertebral volumetric bone mineral density assessed by quantitative computed tomography in maintenance hemodialysis patients. Arch Osteoporos. 2022;17(1):24.

9. Yoshii I. AB0606 IMPACT OF ABDOMINAL AORTIC CALCIFICATION AND SERUM CREATININE-TO-CYSTATIN C RATIO TO BONE FRAGILITY FRACTURE. Annals of the Rheumatic Diseases. 2021;80(Suppl 1):1339-.

10. Chau K, Martinez G, Elder GJ. Vascular calcification in patients undergoing kidney and simultaneous pancreas-kidney transplantation. Nephrology (Carlton). 2014;19(5):275-81.

11. Drinka PJ, Bauwens SF, DeSmet AA. Lack of correlation between aortic calcification and bone density. Wis Med J. 1992;91(6):299-301.

12. Reid IR, Evans MC, Ames R, Wattie DJ. The influence of osteophytes and aortic calcification on spinal mineral density in postmenopausal women. J Clin Endocrinol Metab. 1991;72(6):1372-4.

13. Aleksova J, Kurniawan S, Vucak-Dzumhur M, Kerr P, Ebeling PR, Milat F, et al. Aortic vascular calcification is inversely associated with the trabecular bone score in patients receiving dialysis. Bone. 2018;113:118-23.

14. Alfieri CM, Regalia A, Meneghini M, Gandolfo MT, Binda V, Cresseri D, et al. FP869RELATION BETWEEN FEMORAL BONE MINERAL DENSITY AND AORTIC CALCIFICATIONS IN A COHORT OF RENAL TRANSPLANTED PATIENTS. Nephrology dialysis transplantation. 2015;30(suppl_3):iii367-iii.

15. Bolton CE, McEniery CM, Raj V, McDonnell BJ, Dixon AK, Munnery M, et al. Aortic calcification, arterial stiffness and bone mineral density in patients with COPD. Artery Research. 2011;5(1):30-6.

16. Canepa M, Ameri P, AlGhatrif M, Pestelli G, Milaneschi Y, Strait JB, et al. Role of bone mineral density in the inverse relationship between body size and aortic calcification: results from the Baltimore Longitudinal Study of Aging. Atherosclerosis. 2014;235(1):169-75.

17. Carr JJ, Register TC, Hsu FC, Lohman K, Lenchik L, Bowden DW, et al. Calcified atherosclerotic plaque and bone mineral density in type 2 diabetes: the diabetes heart study. Bone. 2008;42(1):43-52.

18. Chan JJ, Cupples LA, Kiel DP, O'Donnell CJ, Hoffmann U, Samelson EJ. QCT Volumetric Bone Mineral Density and Vascular and Valvular Calcification: The Framingham Study. J Bone Miner Res. 2015;30(10):1767-74.

19. Chow JT, Khosla S, Melton LJ, 3rd, Atkinson EJ, Camp JJ, Kearns AE. Abdominal aortic calcification, BMD, and bone microstructure: a population-based study. J Bone Miner Res. 2008;23(10):1601-12.

20. Dawson-Hughes B, Dallal GE. Effect of radiographic abnormalities on rate of bone loss from the spine. Calcif Tissue Int. 1990;46(4):280-1.

21. Divers J, Register TC, Langefeld CD, Wagenknecht LE, Bowden DW, Carr JJ, et al. Relationships between calcified atherosclerotic plaque and bone mineral density in African Americans with type 2 diabetes. J Bone Miner Res. 2011;26(7):1554-60.

22. Frye MA, Melton LJ, 3rd, Bryant SC, Fitzpatrick LA, Wahner HW, Schwartz RS, et al. Osteoporosis and calcification of the aorta. Bone Miner. 1992;19(2):185-94.

23. Grant M, Turner ME, Murray-Guenther J, Anastassiades T, Hopman WM, Adams SM, et al. A novel quantitative approach to the measurement of abdominal aortic calcification as applied to the Canadian Multicenter Osteoporosis Study (CaMOS). Bone. 2017;97:201-8.

24. Hampson G, Edwards S, Conroy S, Blake GM, Fogelman I, Frost ML. The relationship between inhibitors of the Wnt signalling pathway (Dickkopf-1(DKK1) and sclerostin), bone mineral density, vascular calcification and arterial stiffness in post-menopausal women. Bone. 2013;56(1):42-7.

25. Hyder JA, Allison MA, Barrett-Connor E, Detrano R, Wong ND, Sirlin C, et al. Bone mineral density and atherosclerosis: the Multi-Ethnic Study of Atherosclerosis, Abdominal Aortic Calcium Study. Atherosclerosis. 2010;209(1):283-9.

26. Iannotti N, Gazzola L, Savoldi A, Suardi E, Cogliandro V, Bai F, et al. Association between abdominal aortic calcifications, bone mineral density and vertebral fractures in a cohort of HIV-positive patients. J Int AIDS Soc. 2014;17(4 Suppl 3):19715.

27. Iba K, Takada J, Yamashita T. The serum level of bone-specific alkaline phosphatase activity is associated with aortic calcification in osteoporosis patients. J Bone Miner Metab. 2004;22(6):594-6.

28. Idoate F, Cadore EL, Casas-Herrero A, Zambom-Ferraresi F, Martínez-Velilla N, Rodriguez-Mañas L, et al. Noncoronary Vascular Calcification, Bone Mineral Density, and Muscle Mass in Institutionalized Frail Nonagenarians. Rejuvenation Res. 2017;20(4):298-308.

29. Jensky NE, Hyder JA, Allison MA, Wong N, Aboyans V, Blumenthal RS, et al. The association of bone density and calcified atherosclerosis is stronger in women without dyslipidemia: the multi-ethnic study of atherosclerosis. J Bone Miner Res. 2011;26(11):2702-9.

30. Kim K, Song SH, Kim IJ, Jeon YK. Is dual-energy absorptiometry accurate in the assessment of bone status of patients with chronic kidney disease? Osteoporos Int. 2021.

31. Kinsella S, Murphy K, Breen M, O'Neill S, McLaughlin P, Coyle J, et al. Comparison of single CT scan assessment of bone mineral density, vascular calcification and fat mass with standard clinical measurements in renal transplant subjects: the ABC HeART study. BMC Nephrology. 2015;16(1):188.

32. Kuipers AL, Zmuda JM, Carr JJ, Terry JG, Patrick AL, Ge Y, et al. Association of volumetric bone mineral density with abdominal aortic calcification in African ancestry men. Osteoporos Int. 2014;25(3):1063-9.

33. Lampropoulos CE, Kalamara P, Konsta M, Papaioannou I, Papadima E, Antoniou Z, et al. Osteoporosis and vascular calcification in postmenopausal women: a cross-sectional study. Climacteric. 2016;19(3):303-7.

34. Lee SM, Lee HW, Son YK, Kim SE, An WS. Abdominal aortic calcification score among several vascular calcification scores of plain radiograph is the most reliable predictor of severe coronary artery calcification in dialysis patients. Renal failure. 2017;39(1):729-35.

35. Li S, Yin L, Li K, Hu B, Wang L, Wang Y, et al. Relationship of volumetric bone mineral density by quantitative computed tomography with abdominal aortic calcification. Bone. 2020;133:115226.

36. Paccou J, Mentaverri R, Renard C, Liabeuf S, Fardellone P, Massy Z, et al. The relationships between serum sclerostin, bone mineral density, and vascular calcification in rheumatoid arthritis. The Journal of Clinical Endocrinology & Metabolism. 2014;99(12):4740-8.

37. Pelletier S, Confavreux CB, Haesebaert J, Guebre-Egziabher F, Bacchetta J, Carlier MC, et al. Serum sclerostin: the missing link in the bone-vessel cross-talk in hemodialysis patients? Osteoporos Int. 2015;26(8):2165-74.

38. Pirlamarla AK, Agalliu I, DiVito J, Stern JM. MP19-04 THE RELATIONSHIP BETWEEN VASCULAR CALCIFICATION AND KIDNEY STONE FORMERS IN A HOSPITAL-BASED CASE CONTROL STUDY. The Journal of Urology. 2017;197(4S):e230-e.

39. REID IR, EVANS MC, AMES R, WATTIE DJ. The Influence of Osteophytes and Aortic Calcification on Spinal Mineral Density in Postmenopausal Women*. The Journal of Clinical Endocrinology & Metabolism. 1991;72(6):1372-4.

40. Rodríguez AJ, Scott D, Hodge A, English DR, Giles GG, Ebeling PR. Associations between hip bone mineral density, aortic calcification and cardiac workload in community-dwelling older Australians. Osteoporos Int. 2017;28(7):2239-45.

41. Salam S, Paggiosi M, Gallagher O, Eastell R, Khwaja A. FP610 Vascular calcification in advanced CKD and its relationship with bone microstructures. Nephrology Dialysis Transplantation. 2019;34(Supplement_1):gfz106. FP610.

42. Shavit L, Girfoglio D, Vijay V, Goldsmith D, Ferraro PM, Moochhala SH, et al. Vascular calcification and bone mineral density in recurrent kidney stone formers. Clin J Am Soc Nephrol. 2015;10(2):278-85.

43. Shen H, Bielak LF, Streeten EA, Ryan KA, Rumberger JA, Sheedy PF, 2nd, et al. Relationship between vascular calcification and bone mineral density in the Old-order Amish. Calcif Tissue Int. 2007;80(4):244-50.

44. Sotomayor CG, Benjamens S, Gomes-Neto AW, Pol RA, Groothof D, Te Velde-Keyzer CA, et al. Bone Mineral Density and Aortic Calcification: Evidence for a Bone-vascular Axis After Kidney Transplantation. Transplantation. 2021;105(1):231-9.

45. Tankó LB, Qin G, Alexandersen P, Bagger YZ, Christiansen C. Effective doses of ibandronate do not influence the 3-year progression of aortic calcification in elderly osteoporotic women. Osteoporos Int. 2005;16(2):184-90.

46. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG. Associations between vascular calcification, arterial stiffness and bone mineral density in chronic kidney disease. Nephrol Dial Transplant. 2008;23(2):586-93.

47. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG. Determination and validation of aortic calcification measurement from lateral bone densitometry in dialysis patients. Clin J Am Soc Nephrol. 2009;4(1):119-27.

48. Wagenknecht LE, Divers J, Register TC, Russell GB, Bowden DW, Xu J, et al. Bone Mineral Density and Progression of Subclinical Atherosclerosis in African-Americans With Type 2 Diabetes. J Clin Endocrinol Metab. 2016;101(11):4135-41.

49. Woisetschläger M, Spångeus A. Model for improved correlation of BMD values between abdominal routine Dual energy CT data and DXA scans. European journal of radiology. 2018;99:76-81.

50. Aoyagi K, Ross PD, Orloff J, Davis JW, Katagiri H, Wasnich RD. Low bone density is not associated with aortic calcification. Calcif Tissue Int. 2001;69(1):20-4.

51. Bagger YZ, Tankó LB, Alexandersen P, Qin G, Christiansen C. Radiographic measure of aorta calcification is a site-specific predictor of bone loss and fracture risk at the hip. J Intern Med. 2006;259(6):598-605.

52. Banks LM, Lees B, MacSweeney JE, Stevenson JC. Effect of degenerative spinal and aortic calcification on bone density measurements in post-menopausal women: links between osteoporosis and cardiovascular disease? Eur J Clin Invest. 1994;24(12):813-7.

53. Boukhris R, Becker KL. Calcification of the aorta and osteoporosis. A roentgenographic study. Jama. 1972;219(10):1307-11.

54. Bristow SM, Gamble GD, Horne AM, Reid IR. Longitudinal changes in bone mineral density, bone mineral content and bone area at the lumbar spine and hip in postmenopausal women, and the influence of abdominal aortic calcification. Bone Rep. 2019;10:100190.

55. Chue CD, Wall NA, Crabtree NJ, Zehnder D, Moody WE, Edwards NC, et al. Aortic calcification and femoral bone density are independently associated with left ventricular mass in patients with chronic kidney disease. PLoS One. 2012;7(6):e39241.

56. Paiva LC, Filardi S, Pinto-Neto AM, Samara A, Marques Neto JF. Impact of degenerative radiographic abnormalities and vertebral fractures on spinal bone density of women with osteoporosis. Sao Paulo Med J. 2002;120(1):9-12.

57. El Maghraoui A, Rezqi A, Mounach A, Achemlal L, Bezza A, Ghozlani I. Relationship between vertebral fracture prevalence and abdominal aortic calcification in men. Rheumatology (Oxford). 2012;51(9):1714-20.

58. El Maghraoui A, Rezqi A, Mounach A, Achemlal L, Bezza A, Dehhaoui M, et al. Vertebral fractures and abdominal aortic calcification in postmenopausal women. A cohort study. Bone. 2013;56(1):213-9.

59. El Maghraoui A, Hamza T, Sadni S, El Maataoui A, Majjad A, Rezqi A, et al. Vitamin D status and abdominal aortic calcification in postmenopausal women. J Bone Miner Metab. 2018;36(2):229-37.

60. Farhat GN, Cauley JA, Matthews KA, Newman AB, Johnston J, Mackey R, et al. Volumetric BMD and vascular calcification in middle-aged women: the Study of Women's Health Across the Nation. J Bone Miner Res. 2006;21(12):1839-46.

61. Figueiredo CP, Rajamannan NM, Lopes JB, Caparbo VF, Takayama L, Kuroishi ME, et al. Serum phosphate and hip bone mineral density as additional factors for high vascular calcification

scores in a community-dwelling: the São Paulo Ageing & Health Study (SPAH). Bone. 2013;52(1):354-9.

62. Flipon E, Liabeuf S, Fardellone P, Mentaverri R, Ryckelynck T, Grados F, et al. Is vascular calcification associated with bone mineral density and osteoporotic fractures in ambulatory, elderly women? Osteoporos Int. 2012;23(5):1533-9.

63. Ghozlani I, El Maataoui A, Ghazi M, Kherrab A, Niamane R. FRI0548 Influence of homocysteine and vertebral fractures on prevalent abdominal aortic calcification in postmenopausal women: a multicentric cross-sectional study. BMJ Publishing Group Ltd; 2017.

64. Hanna TN, Zygmont ME, Harmouche E, Salastekar N, Johnson JO, Khosa F. Association of lumbar fractures, abdominal aortic calcification, and osteopenia. Clin Imaging. 2015;39(4):662-6.

65. Iwamoto J, Matsumoto H, Takeda T, Sato Y, Uzawa M. A radiographic study on the associations of age and prevalence of vertebral fractures with abdominal aortic calcification in Japanese postmenopausal women and men. J Osteoporos. 2010;2010:748380.

66. Jamal SA, Leiter RE, Bauer DC. Hyperhomocysteinaemia and aortic calcification are associated with fractures in patients on haemodialysis. Qjm. 2005;98(8):575-9.

67. Kim KJ, Kim KM, Park KH, Choi HS, Rhee Y, Lee YH, et al. Aortic calcification and bone metabolism: the relationship between aortic calcification, BMD, vertebral fracture, 25-hydroxyvitamin D, and osteocalcin. Calcif Tissue Int. 2012;91(6):370-8.

68. Lewis JR, Eggermont CJ, Schousboe JT, Lim WH, Wong G, Khoo B, et al. Association Between Abdominal Aortic Calcification, Bone Mineral Density, and Fracture in Older Women. J Bone Miner Res. 2019;34(11):2052-60.

69. Majjad A, Ghassem MA, Toufik H, Sadni S, Debbarh Z, Djossou JH, et al. Relationship between vertebral fracture prevalence and abdominal aortic calcification in women with rheumatoid arthritis. Bone. 2020;141:115599.

70. Mohammad A, Lohan D, Bergin D, Mooney S, Newell J, O'Donnell M, et al. The Prevalence of Aortic Calcification on Vertebral Fracture Assessment Imaging Among Patients With Rheumatoid Arthritis. Journal of Clinical Densitometry. 2014;17(1):72-7.

71. Nakatsuka K, Sirtori PL, McCloskey EV, Khan SA, Orgee JM, O'neill TW, et al. Preliminary study on relationship between vertebral fracture and aortic calcification in postmenopausal women. Journal of bone and mineral metabolism. 1997;15(4):218-22.

72. Naves M, Rodríguez-García M, Díaz-López JB, Gómez-Alonso C, Cannata-Andía JB. Progression of vascular calcifications is associated with greater bone loss and increased bone fractures. Osteoporos Int. 2008;19(8):1161-6.

73. Pirro M, Manfredelli MR, Schillaci G, Helou RS, Bagaglia F, Melis F, et al. Association between circulating osteoblast progenitor cells and aortic calcifications in women with postmenopausal osteoporosis. Nutr Metab Cardiovasc Dis. 2013;23(5):466-72.

74. Pozzo M, Lozano M, Ilera V, Hermberg HC. Relation between aortic calcifications and bone mineral density measured by quantitative computed tomography (QCT). Bone. 2006;5(38):S11-S2.

75. Orwoll ES, Oviatt SK, Mann T. The impact of osteophytic and vascular calcifications on vertebral mineral density measurements in men. J Clin Endocrinol Metab. 1990;70(4):1202-7.

76. Rajzbaum G, Roger VL, Bézie Y, Chauffert M, Bréville P, Roux F, et al. French women, fractures and aortic calcifications. J Intern Med. 2005;257(1):117-9.

77. Samelson EJ, Cupples LA, Broe KE, Hannan MT, O'Donnell CJ, Kiel DP. Vascular calcification in middle age and long-term risk of hip fracture: the Framingham Study. J Bone Miner Res. 2007;22(9):1449-54.

78. Schousboe JT, Langsetmo L, Szulc P, Lewis JR, Taylor BC, Kats AM, et al. Joint Associations of Prevalent Radiographic Vertebral Fracture and Abdominal Aortic Calcification With Incident Hip, Major Osteoporotic, and Clinical Vertebral Fractures. J Bone Miner Res. 2021;36(5):892-900.

79. Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V. Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab. 2004;89(9):4246-53.

80. Simon SP, Fodor D, Muntean L, Poanta L, Cristea P, Rednic S. Bone mineral density, vertebral fractures and body mass index in postmenopausal women with abdominal aortic calcification. Endocr Res. 2014;39(1):1-6.

81. Szulc P, Kiel DP, Delmas PD. Calcifications in the abdominal aorta predict fractures in men: MINOS study. J Bone Miner Res. 2008;23(1):95-102.

82. Szulc P, Samelson EJ, Sornay-Rendu E, Chapurlat R, Kiel DP. Severity of aortic calcification is positively associated with vertebral fracture in older men--a densitometry study in the STRAMBO cohort. Osteoporos Int. 2013;24(4):1177-84.

83. Szulc P, Blackwell T, Schousboe JT, Bauer DC, Cawthon P, Lane NE, et al. High hip fracture risk in men with severe aortic calcification: MrOS study. J Bone Miner Res. 2014;29(4):968-75.

84. Szulc P, Blackwell T, Kiel DP, Schousboe JT, Cauley J, Hillier T, et al. Abdominal aortic calcification and risk of fracture among older women — The SOF study. Bone. 2015;81:16-23.

85. Torres A, Torregrosa V, Marcen R, Campistol JM, Arias M, Hernández D, et al. Mineral metabolism disorders, vertebral fractures and aortic calcifications in stable kidney transplant recipients: The role of gender (EMITRAL study). Nefrologia. 2016;36(3):255-67.

86. Vogt MT, San Valentin R, Forrest KY, Nevitt MC, Cauley JA. Bone mineral density and aortic calcification: the Study of Osteoporotic Fractures. J Am Geriatr Soc. 1997;45(2):140-5.

87. Wang TK, Bolland MJ, van Pelt NC, Horne AM, Mason BH, Ames RW, et al. Relationships between vascular calcification, calcium metabolism, bone density, and fractures. J Bone Miner Res. 2010;25(12):2777-85.

88. Wyers CE, Vranken L, Schousboe JT, van der Velde RY, de Bruin IJ, Janzing HM, et al. Systematic Evaluation of Abdominal Aortic Calcification Reveals Unknown Cardiovascular Disease Risk in Patients Visiting a Fracture Liaison Service. Journal of Bone and Mineral Research. 2017;32:S361-S.

89. Yokomoto-Umakoshi M, Umakoshi H, Ogata M, Fukumoto T, Matsuda Y, Miyazawa T, et al. Coexistence of osteoporosis and atherosclerosis in pheochromocytoma: new insights into its long-term management. Osteoporos Int. 2020;31(11):2151-60.

90. Zhou R, Zhou H, Cui M, Wang Y, Tan J, Sawmiller D, et al. Association between aortic calcification and the risk of osteoporosis in a chinese cohort: the Chongqing osteoporosis study. Calcif Tissue Int. 2013;93(5):419-25.

91. Zhou R, Zhou H, Cui M, Chen L, Xu J. The association between aortic calcification and fracture risk in postmenopausal women in China: the prospective Chongqing osteoporosis study. PLoS One. 2014;9(5):e93882.

Supplementary Material for Review and Online Publication

Data S1. Newcastle-Ottawa scoring

Newcastle-Ottawa Scale adapted for cross-sectional studies

Selection:

1. Representativeness of the sample:
    a) Truly representative of the average in the target population. * (all subjects or random sampling)
    b) Somewhat representative of the average in the target group. * (non-random sampling)
    c) Selected group of users/convenience sample.
    d) No description of the derivation of the included subjects.
2. Sample size:
    a) Justified and satisfactory (including sample size calculation). *
    b) Not justified.
    c) No information provided
3. Non-respondents:
    a) Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded. *
    b) Unsatisfactory recruitment rate, no summary data on non-respondents.
    c) No information provided
4. Ascertainment of the exposure (risk factor):
    a) Clinic registers/hospital records only. **
    b) Parental or personal recall and hospital records. *
    c) Parental/personal recall only.

Comparability: (Maximum 2 stars)

5. Comparability of subjects in different outcome groups on the basis of design or analysis. Confounding factors controlled.
    a) Data/ results adjusted for relevant predictors/risk factors/confounders. **
    b) Data/results not adjusted for all relevant confounders/risk factors/information not provided.

Outcome:

6. Assessment of outcome:
    a) Independent blind assessment **
    b) Record linkage**
    c) Self-report
    d) No description
7. Statistical test:
    a) Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and probability level (p value). *
    b) Statistical test not appropriate, not described or incomplete.

Newcastle- Ottawa Quality Assessment Scale - Cohort Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for comparability.

Selection

1. Representativeness of the exposed cohort
    a) Truly representative of the average population (e.g., general population) of that age in the community *
    b) Somewhat representative of the average population (general population) of that age in the community *
    c) Selected group of users e.g., nurses, volunteers
    d) no description of the derivation of the cohort
2. Selection of the non-exposed cohort
    a) drawn from the same community as the exposed cohort *
    b) drawn from a different source
    c) no description of the derivation of the non-exposed cohort
3. Ascertainment of exposure

a) Secure record (e.g., surgical records) *
b) Structured interview *
c) Written self-report
d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes *
b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) Study controls for previous history lower BMD and/or fracture *
b) Study controls for any additional conventional osteoporosis and/or fracture risk factors *

Outcome

1) Assessment of outcome
a) independent blind assessment *
b) record linkage *
c) self-report
d) no description
2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) *
b) no
3) Adequacy of follow up of cohorts
a) complete follow up-all subjects accounted for *
b) subjects lost to follow up unlikely to introduce bias- small number lost - > 20% lost to follow up, or description provided of those lost) *
c) follow up rate < 20% and no description of those lost
d) no statement

Table S1: Search strategy

Keyword	MEDLINE	EMBASE
Population= adults	No search strategy	No search strategy
Intervention/test=aortic calcification	exp Vascular Calcification/or exp Calcinosis/ or exp Vascular Diseases/or arterial calcification. mp or exp Arteriosclerosis/or exp Arterial Occlusive Diseases/or exp Aortic Diseases/ oraortic.mp or vascular calcifications.mp. or exp Vascular Calcification/or calcified atherosclerosis.mp or calcification.mp or calcified atherosclerotic plaque.mp or arterial calcium.mp or aortic calcification.mp or aorta calcification.mp and aort$.mp and calc$.mp	vascular calcification.mp. or exp blood vessel calcification/or artery calcification.mp. or exp artery calcification/or exp coronary artery disease/or exp arteriosclerosis/or calcified atherosclerosis.mp or arterial calcium. mp or calcified atherosclerotic plaque.mp or calcification.mp or aortic calcification. mp or aorta calcification.mp or vascular calcifications.mp or arteriosclerosis.mp or extracoronary.mp and aort$.mp and calc$.mp
Methodology=observational	No search strategy	No search strategy
Comparator= None	No search strategy	No search strategy
Outcome=	bone mineral density.mp or exp Bone Density/ or Fracture.mp or Fractures.mp	bone mineral density.mp or exp bone density/ or fracture.mp or fractures.mp or exp fracture/
Additional specific filters	Human	Human

Table S1: Detailed characteristics of each of the included studies

Included studies (61553 participants)						
Study, year	Country	Study design, participants, groups, and sample size	Imaging modality	AAC modelled as	Outcome measure (s)	Key finding (s)
Aleksova et al,(1) 2018	Australia	Cross sectional, study populations: 48 years;25.9 kg/m^2; 100%chronic kidney disease (CKD);40%women;53%smoker;36%diabetes;10 %HRT;37%fracture; sample size (n=146).	X-ray	AAC24 score≥1, mean AAC AAC24 score	Trabecular bone score (TBS), T-score and aBMD (g/cm2) at lumbar spine, femoral neck, proximal femur, ultra-distal radius and 1/3 radius	AAC scores were inversely related to the TBS but not to DXA-derived BMD parameters.
Alfieri et al,(2) 2015 abstract	Italy	Prospective, study populations:12 months of follow up; 100% CKD; two groups of AAC, present (n=179) versus absent (n=114)	X-ray	Present/absent AAC2 continuous	BMD (g/cm2) at femoral neck	The presence and progression of AAC was related with abnormal femoral neck BMD.
Aoki et al, (3) 2009	Japan	Cross sectional, study populations: 59.3 years;30%women;100%CKD;38.6% diabetets;72.3% medications; sample size (n=83)	CT	aortic calcification index (ACI)	BMD (mmAl) at metacarpal bone	Aortic calcification index (ACI) was inversely correlated with Metacarpal BMD
Avramovski et al,(4) 2016	Macedonia	Cross sectional, study populations:59 years; 27.7 kg/m^2;100%CKD;100%women;25%smoker;21.4 % diabetes;53.5%HTN; sample size (n=56)	X-ray	AAC24 continuous	BMD (g/cm2) at lumbar spine and total hip	AAC was significantly correlated with subtracted femoral neck BMD from lumbar spine BMD.
Bagger et al,(5) 2007	Denmark	Cross sectional, study populations:69.3 years; 26.4 kg/m^2;100%women;24.6%smoker; sample size (n=1176)	X-ray	Mean AAC score and AAC24≥6 AAC24 score	Vertebral and hip fractures	Severe AAC (score≥6) was associated with hip fracture (OR 4.4 95%CI, 1.6 to 12.9) but not vertebral fracture (1.2 95%CI, 0.9 to 1.7) or wrist (95%CI 1.4 1.0 to 2.1) after adjustment to age.
Bolton et al.,(6) 2011	UK	Cross sectional, study populations:66 years; 29 kg/m^2;40%women;13% diabetes;38% HTN;2.2%HRT; 22.2%CVD medications; sample size (n=45)	CT	Volume scoring method	BMD (g/cm2) at lumbar spine, hip, femoral neck, intertrochanteric and trochanter	Aortic calcification was inversely related to BMD.

Canepa et al, (7) 2014	USA	Cross sectional, study populations:67 years;27 kg/m^2;51%women;45%smoker;22%diabetes;42% HTN;42%CVD medication; four groups based on number of aortic segments with apparent calcification (0 (n=687), 1 (n=214), 2 (n=191), 3 (n=75)	CT	Present/absent AAC severity score (0-3)	BMD (g/cm2) at whole body and femoral neck	Aortic calcification was inversely related with bone mineral density.
Carr et al,(8) 2008	USA	Cross sectional, study population: 62.4 years;32.8 kg/m2;50%women;23.9%smoker;100%diabets;22 .4%HTN; sample size (n=1023)	CT	Present/absent	vBMD at thoracic and lumbar spine measured CT and DXA	Atherosclerotic calcified plaque was inversely associated with vBMD.
Chan et al, (9) 2015	USA	Cross sectional, study population:60 years;29 kg/m^2;52.3%women 11%smoker; sample size (n=1317)	CT	Agatston score	Integral and trabecular vBMD	AAC was inversely related with spine BMD.
Chau et al, (10) 2014	Australia	Prospective, study population:42 years;42%women;100% kidney or pancreas-kidney transplant;39.3%smoker;10.6%diabetes; sample size (n=650)	X-ray	Present/absent AAC24	Lumbar spine Z score	No significant inverse association of between AAC and BMD was noted.
Chow et al,(11) 2008	USA	Cross sectional, study population:57.4 years; 27.4 kg/m^2; 54%women;42.7%smoker;22.5%HRT;21.2%fract ure; sample size (n=693)	CT	Agatston score	vBMD at lower vertebral trabecular, total femoral neck and femoral neck trabecular	AAC was inversely associated with vBMD.
Dawson-Hughes and Dallal, (12) 1990	USA	Cross sectional, study population:100%women; sample size (n=293)	X-ray	Present/absent	BMD (g/cm^2) at spine radius	AAC was inversely associated with BMD (g/cm^2) at spine radius.
Divers et al, (13) 2011	USA	Cross sectional, study population:60%women;100%diabetes; sample size (n=753)	CT	Agatston score	vBMD at thoracic and lumbar spine	Calcified atherosclerotic plaque was inversely associated with vertebral BMD.
Drinka et al, (14) 1992	USA	Cross sectional, study population:71.9 years; 100% male; sample size (n=113)	X-ray	Present/absent	BMD (g/cm^2) at lumbar spine	No significant correlation between aortic calcification and bone mineral density was observed.
Frye et al, (15) 1992	USA	Cross sectional, study population:100%women; sample size (n=200)	X-ray	Grades of calcification (0,1, and 2)	BMD at spine, femur neck, trochanter, femur shaft, distal radius and BMC midradius Vertebral fracture	Aortic calcification was not associated with lumbar spine BMD.
Fusaro et al, (16) 2013	Italy	Cross sectional, study population:64.2 years; 37%women;100% CKD 36.8%smoker;22%diabetes;77.8%HTN;	X-ray	Length of the calcium deposits along the aortic wall	Vertebral fracture	Aortic calcification was associated with greater odds of

		sample size (n=387)		(0.1 to 5 cm, 5.1 to 10 cm and >10 cm)		vertebral fracture (OR 1.77 95%CI, 1.00 to 3.14).
Grant et al,(17) 2017	Canada	Cross sectional, study population: 68.9 years; 28.4 kg/m^2;71%women;11% diabetes;30%HTN; sample size (n=112)	X-ray	AAC severity categories based on lesion length	BMD (g/cm^2) at lumbar spine	Quantified AAC was negatively associated with hip and spine BMD.
Hampson et al, (18) 2013	UK	Cross sectional, study population:61.6 years;24.8 kg/m^2; 100%women;36%smoker;28%previous fracture; sample size (n=149)	DXA	AAC8&24 score	BMD (g/cm^2) at lumbar spine	AAC was negatively correlated with BMD.
Hyder et al, (19) 2009	USA	Cross sectional, study population:50%women; sample size (n=1833)	CT	AAC score	vBMD at lumbar spine	Aortic calcification was associated with lower vBMD.
Iannotti et al, (20) 2014	Italy	Cross sectional, study population: 100%HIV; sample size (n=280)	X-ray	AAC8 score	BMD (g/cm^2) Vertebral fracture	AAC (≥1) was predictor of low BMD and with vertebral fracture (OR 2.87 95%CI, 1.30 to 6.31).
Iba et al,(21) 2004	Japan	Cross sectional, study population:100%women; 100% osteoporosis; sample size (n=135)	X-ray	Present/absent	BMD	Abdominal aortic calcification was not associated with BMD.
Idoate et al,(22) 2017	Spain	Cross sectional, study population:91 years; 24.4 kg/m^2; 74%women; sample size (n=42)	CT	Present/absent	Vertebral BMD	Femoral artery calcification was negatively correlated with BMD.
Jensky et al,(23) 2011	USA	Prospective, study population;64 years; 100%women; 36 months; sample size (n=936)	CT	Agatston score	BMD	Calcified atherosclerosis was inversely associated with vBMD
Kim et al,(24) 2021	South Korea	Cross sectional, study population:65 years;23.7 kg/m^2;43.6%women;47.9%diabetes;100%CKD;23.1%HTN; sample size (n=117)	CT	AAC volume in Hounsfield units	vBMD (mg/cm3)	AAC volume was negatively correlated with BMD.
Kinsella et al,(25) 2015	Ireland	Cross sectional, study population:47 years;100%CKD; 39%women;15.6%diabetes; 43.8%smoker; two groups of AAC, present (n=22) versus absent (n=42)	CT	Aortic calcification index	Trabecular and cortical vBMD	Aortic Calcification Index was inversely associated with volumetric BMD.
Kuipers et al, (26) 2014	Caribbean Islands	Cross sectional, study population:56 years;27.9 kg/m^2; 10.1% smoker;100%women;24.5% diabetes;45.3%HTN; two groups of AAC, present (n=190) versus absent (n=88)	CT	Present/absent	Trabecular and cortical BMD (mg/cm^3) at tibia and radius	Vascular calcification was associated with low BMD.
Lampropoulos et al, (27) 2016	Greece	Cross sectional, study population:100%women; sample size (n=29)	X-ray	AAC24 score	Osteoporosis	Aortic calcification was associated with osteoporosis.
Lee et al, 2017 (28)	South Korea	Cross sectional, study populations:58.3 years; 23 kg/m^2;56%women;29%diabetes;100%CKD; sample size (n=55)	X-ray	AAC24 score ≥5	Bone mass forearm	AAC was associated with low bone mass at the forearm.

Li et al,(29) 2020	China	Cross sectional, study populations:61.8 years;63%women;21.2%smoker;12.7%diabetes;40.7%HTN; sample size (n=3431)	CT	Agatston score	vBMD	AAC was inversely associated with vBMD in men but not in women.
Paccou et al, (30)2014	France	Case control, study populations:60.5 years; 27.1 kg/m^2;76%women;17.9%smoker;4.6% diabetes;33.4%HTN; 100% rheumatoid arthritis; sample size (n=150)	CT	Abdominal aortic calcium score	BMD (mg/cm^3) at lumbar spine, femoral neck, and total hip	AAC was significantly correlated with BMD.
Pelletier et al, (31) 2015	France	Cross sectional, study populations:50.9 years; 25kg/m^2; 40%women;56.6%smoker;24.5%diabetes; 100%; two groups of AAC24 score, <6 (n=34) versus ≥6 (n=19)	DXA	AAC24 score <6 versus ≥6	Cortical bone structure	Severe AAC was associated with poorer tibia cortical bone structure.
Pirlamarla et al, (32) 2017 Abstract	USA	Case-control, study populations: 100% Kidney stones; sample size (n=925)	CT	Present/absent	BMD	AAC and its severity was associated with osteoporosis.
Reid et al,(33) 1991	New Zealand	Prospective, study populations;100%women; 58 years; four groups of AAC, 0 (n=97), 1 (n=21), 2 (n=12), 3 (n=0)	X-ray	Calcification score (0,1,2 and 3)	BMD at spine and femur	AAC was not correlated with BMD.
Rodriguez et al, (34) 2017	Australia	Cross sectional, study populations;70 years;28.1kg/m^2;61%women;43%smoker;31.6% HTN; sample size (n=337)	X-ray	Present/absent AAC severity groups (0, 1 to 5, ≥6) AAC24 score	BMD (g/cm^2) at femoral neck and total hip	AAC was associated with femoral neck BMD.
Rodrıguez-Garcia et al, (35) 2009	Spain	Prospective, study populations;64 years; 100% CKD; 37.3% women; sample size (n=193)	X-ray	Mild, moderate, and severe calcification	Vertebral fracture	Vascular calcifications in the medium calibre arteries (OR 6.5 95%CI, 1.4 to 29.8) were associated with a higher rate of prevalent vertebral fractures. Such association were observed at large (OR 3.8 95%CI, 0.5 to 31.6) and small (0.96 95%CI, 0.3 to 3.1)) calibre arteries.
Salam et al, (36) 2019 Abstract	UK	Cross sectional, study populations;100%CKD; sample size (n=69)	DXA	AAC-8 score	Distal tibia cortical bone microstructure, cortical thickness, and cortical porosity, BMD t-score at total hip and 1/3 distal radius	Vascular calcification was associated with worse cortical bone microstructure of distal tibia.

Shavit et al, (37) 2015	UK	Case-control, study populations;100% kidney stones; 43% women; sample size (n=111)	CT	Present/absent Calcification severity (≤10%, 11%-50%, ≥51% calcification)	BMD	AAC was associated with lower BMD.
Shen et al,(38) 2007	USA	Prospective, study populations;36% months of follow up;55.9%women; sample size (n=682)	CT	Agatston method	BMD	Vascular calcification was not associated with lower BMD.
Sotomayer et al, (39) 2020	The Netherlands	Cross sectional, study populations;51 years;25.5 kg/m^2;100%kindney transplantation; 42%women;21%smoker;14%diabetes;81%HTN; 22.5% fracture; sample size (n=678)	DXA	AAC-8 score	Areal BMD at lumbar spine	AAC was independently associated with BMD.
Tanko et al, (40) 2002	Denmark	Cross sectional, study populations;100% osteoporotic women; sample size (n=963)	X-ray	AAC24 score	BMD at hip	AAC was inversely correlated with lower BMD.
Toussaint et al,(41) 2008	Australia	Cross sectional, study populations;64.5 years;31.3 kg/m^2;29%women; 30.4%smoker;100%CKD; sample size (n=48)	CT	Present/absent Median AAC score in Hounsfield units	BMD (g/cm2) at spine and femur	Vascular calcification was inversely associated with femoral BMD.
Toussaint et al, (42) 2009	Australia	Cross sectional, study populations;58 years; 26.4 kg/m^2;36%women;38%diabetes;100%CKD; sample size (n=45)	CT	Present/absent Median AAC score in Hounsfield units	BMD (g/cm2) at spine and femur	Aortic calcification was associated with lower BMD.
Wagenknecht et al,(43) 2016	USA	Prospective, study populations;55.1 years;35.3%smoker; 34.7 kg/m2;100% type 2 diabetes; 50%women; 38.7%CKD;80.7%HTN; sample size (n=300)	CT	Present/absent AAC score in Hounsfield units	vBMD at thoracic and lumbar	Progression of abdominal aorta was associated with vBMD.
Woisetschlager and Spångeus, (44) 2018	Sweden	Prospective, study populations; 71 years; 26 kg/cm^2; 50%women; sample size (n=50)	CT	Aortic calcium score	DXA BMD	AAC was not correlated with BMD.
Study included in the meta-analysis						
Aoyagi et al,(45) 2001	USA	Prospective, study populations: 61.8 years; 23.4 kg/m^2;100%women;10%smoker;6.7%diabetes; two groups of AAC, present (n=220) versus absent (n=304)	X-ray	Present/absent	BMD (mg/cm2) at proximal and distal radius, and calcaneus	The differences in BMD in those with versus without calcification were attenuated after adjustment for age.
Bagger et al,(46) 2006	Denmark	Prospective, study populations:64.9 years; 25.1 kg/m^2; 90 months of follow up;100%women;21.6%smoker;5.2%diabetes; two groups of AAC, AAC24≥3 (n=1877) versus <3 (n=785)	X-ray	AAC24≥3/AAC24<3 AAC24 continuous	BMD (g/cm2) at lumbar spine and total hip as well as incident (vertebral and hip) fracture	AAC was significantly associated with lower BMD and accelerated bone loss from the proximal femur, hip and vertebral fractures
Banks et al,(47) 1994	UK	Cross sectional, study populations:56.1 years;100%women; sample size (n=115)	X-ray and CT	Present/absent	BMD (g/cm) at femoral neck and ward triangle	AAC was associated with lower proximal femur bone density.

Boukhris et a,(48) 1973	USA	Cross sectional, study populations:49%women; had fracture at baseline; sample size (n=589)	X-ray	Present/absent	Vertebral fracture	AAC was associated with osteoporosis and fracture.
Bristow et al,(49) 2019	New Zealand	Prospective, study populations:73 years; 26.6 kg/m^2;100%women;60 months follow up;2%smoker;37%fracture; four groups of AAC, AAC8 score 0 (n=166), 1 to 2 (n=102), 3 to 6 (n=24)	DXA	AAC8 score categories (0, 1-2,3-6,7-8)	BMD (g/cm2), BMC (g), bone area (cm2) at lumbar spine, hip, and femoral neck	The presence of AAC was not related to changes in BMD at the total hip or femoral neck, nor to BMD at the spine.
Chue et al,(50) 2012	UK	Cross sectional, study population: 55 years;29 kg/m^2;35%women;64%smoker; 100% CKD; two groups of AAC, calcification (n=57), no calcification (n=63)	X-ray	Present/absent AAC24	BMD (g/cm^2) at femoral neck.	AAC was not associated with lower BMD at femoral neck.
Paiva et al, (51) 2002	Brazil	Cross sectional, study population:64 years;100%women;100% osteoporosis; sample size (n=96)	X-ray	Present/absent	BMD (g/cm^2) at lumbar spine	AAC was associated with lower BMD.
El Maghraoui et al, (52) 2012	Morocco	Prospective, study population:62.4 years; 100% male;26.4 kg/m^2; 7.3% smoker; sample size (n=709)	DXA	AAC24 score ≥5 versus<5 AAC24 score	Vertebral fracture	Advanced AAC was associated with prevalent vertebral fractures.
El Maghraoui et al, (53) 2013	Morocco	Cross sectional, study population:60.9 years; 100%women;0.4% smoker;13% history of peripheral fractures; two groups of AAC, AAC24≥5 (n=108) versus <5 (n=800)	DXA	AAC24 score ≥5 versus <5 AAC24 score	BMD (g/cm^2) at lumbar spine and total hip Vertebral fracture	The presence of AAC was significantly associated with vertebral fracture and lower BMD at total hip.
El Maghraoui et al, (54) 2018	Morocco	Cross sectional, study population:59.5 years; 29.9 kg/m^2; 100%women; all non-smokers;13.3% history of fracture; two groups of AAC, AAC24≥5 (n=34) versus <5 (n=366)	DXA	AAC24 score ≥5 versus <5 AAC24 score	BMD (g/cm^2) at lumbar spine and total hip Vertebral fracture	The presence of AAC was significantly associated with vertebral fracture and lower BMD.
Farhat et al, (55) 2006	USA	Prospective, study population: 100% women; three AAC scores, 0 (n=146), 1 to 74 (n=221), ≥75 (n=123)	CT	Agatston scoring method	vBMD (g/cm)	Higher AAC was associated with lower vBMD.
Figueiredo et al,(56) 2012	Brazil	Cross sectional, study population:73 years; 27.9 kg/m^2;58%women; 12.3%smoker;21.2%diabetes;63.5%HRT;13%history of fragility fracture; two groups of AAC, AAC24≥7 (n=197) versus <7 (n=618)	X-ray	AAC24 score ≥7 versus <7 AAC24 score	BMD (g/cm^2) and t-score at femoral neck and total femur	Advanced AAC was associated with lower BMD.
Flipon et al,(57) 2010	France	Prospective, study population:100%women;15% smokers; two groups of AAC, AAC24≥median (n=333) versus <median (n=334)	X-ray	AAC24 score ≥median versus <median AAC24 score	BMD (g/cm^2) at femoral neck and osteoporotic fracture	Aortic calcification score was not associated with lower BMD and osteoporotic fractures.

Ghozlani et al,(58) 2017	Morocco	Cross sectional, study population:57.9 years;30.4 kg/m^2;100%women; two groups of AAC, AAC24≥5 (n=159) versus <5 (n=29)	DXA	AAC24 score ≥5 versus <5 AAC24 score	BMD (g/cm^2) and T-score at total hip and lumbar spine Vertebral fracture	Advanced AAC was associated with lower BMD and higher vertebral fracture
Hanna et al,(59) 2015	USA	Cross sectional, study population:53 years;67.2%women; two groups of AAC, present (n=103) versus absent (n=200)	X-ray	Present/absent	Lumbar fracture	AAC was associated with low velocity impact fractures and lower BMD.
Iwamoto et al,(60) 2010	Japan	Cross sectional, study population:72.4 years;94%women; two groups of AAC, present (n=175) versus absent (n=226)	X-ray	Present/absent	Vertebral fractures	Severity of abdominal aortic calcification was associated with vertebral fractures.
Jamal et al,(61) 2005	Canada	Cross sectional, study population:65.8 years;100%CKD;29% women; 9%smokers; sample size (n=57)	X-ray	AAC24 score, every unit increase in AAC	Fracture	Lumbar aortic calcification was associated with increased fracture risk.
Kim et al, (62) 2012	South Korea	Cross sectional, study population:64.7 years;22.9 kg/m^2;100%women;9%smoker;16% diabetes;31%HTN;16.8%previous fracture; two groups of AAC, present (n=274) versus absent (n=495)	CT	Agatston score	vBMD at total hip, femoral neck and vertebral Fracture	Aortic calcium score was associated with low trabecular BMD
Lewis et al,(63) 2019	Australia	Prospective, study populations:75 years; 27 kg/m^2;120 months of follow up; 100%women;35.9%smoker;5.6%diabetes;25.8%previous fracture; three groups of AAC, 0 to 1 (n=459), 2 to 5 (n=373) and ≥6 (n=192)	DXA	AAC24 score (0 to 1, 2 to 5, and ≥6)	Area, BMC, BMD (g/m^2) at total hip, prevalent fracture, vertebral fracture	Advanced AAC was associated with lower BMD and increased fracture risk.
Majjad et al, (64) 2020	Morocco	Cross sectional, study populations: 55 years;100%women; 28.5 kg/m^2; 2.8% peripheral fracture; sample size (n=250)	DXA	Present/absent AAC24 score	Vertebral fracture	AAC was independently associated with prevalent vertebral fractures.
Mohammed et al,(65) 2014	Ireland	Cross sectional, study populations:57 years; 27 kg/m^2; 71%women;43%smoker; 17%diabetes;23%HTN; two groups of AAC, present (n=211) versus absent (n=392)	DXA	Present/absent AAC24 score	BMD (g/cm^2) and T-score at hip	AAC was associated with lower BMD.
Nakatsuka et al, (66) 1997	Turkey	Case control, study populations:68.6 years; 100%women; sample size (n=122)	X-ray	Present/absent	Vertebral fracture	AAC was not associated with vertebral fractures.
Naves et al, (67) 2008	Spain	Prospective, study populations:48 months follow up;50.6%women;17.2%smoker;9.1%diabets; two groups of AAC, present (n=230) versus absent (n=385)	DXA	Present/absent	Lumbar, femoral neck BMD and osteoporotic fracture	AAC was positively associated with osteoporotic fractures. The progression of AAC was also positively associated with

						the rate of decline in BMD at lumbar spine.
Pirro et al, (68) 2013	Italy	Cross sectional, study populations:64.3 years;26.4 kg/m^2; 100% women; two groups of AAC, present (n=36) versus absent (n=14)	X-ray	Present/absent	BMD (g/cm^2) at lumbar spine	AAC was not significantly associated with lumbar spine BMD.
Pozzo et al, (69) 2006 abstract	Argentina	Cross sectional, study populations: 100%women; two groups of AAC, AAC≤1 (n=354) versus > 1(n=144)	CT	AAC score ≤ 1 versus >1	BMD (mg/cm3) at lumbar spine	AAC was associated with lower BMD.
Orwoll et al, (70) 1990	USA	Cross sectional, study populations:64 years; 100%men; four groups of AAC, Grade 0 (n=43), 1(n=44), 2(n=26), 3(n=16)	X-ray	Grad 0 to 4 calcification	BMD at spine and hip	Vascular calcification had very minimal effect on BMD.
Rajzbaum et al,(71) 2005	France	Cross sectional, study populations;63.5 years; 100%women;24.2 kg/m^2; 20%smoker; 20%HTN;2% diabetes; two groups of AAC, present (n=120) versus absent (n=207)	X-ray	Present/absent	Wrist, hip, vertebral and other fractures BMD (g/cm^2) at femoral neck, t-score and z-score	AAC was associated with lower BMD and increased risk of fracture.
Samelson et al, (72) 2007	USA	Prospective, study populations;60 years;27 kg/m^2; 3.4% smoker; 0.5% diabetes; 50%women;420 months of follow up; AAC present (n=1557), absent (n=942)	X-ray	Present/absent AAC24 score	Incident hip fracture	Severity of aortic calcification was not associated with hip fracture.
Schousboe et al, (73) 2021	USA	Prospective, study populations; 100%women; 62.5%smokers; two AAC groups, 0 to 1 (n=1519), 2 to 4 (n=1456), 5 to 8 (n=1231), ≥9 (n=1159)	X-ray	AAC-24 score	Prevalent vertebral and incident osteoporotic fractures	AAC was associated with a higher risk of incident hip and major osteoporotic fractures.
Schulz et al,(74) 2004	USA	Cross sectional, study populations;68.3 years;24.9 kg/m^2; 100%women; two groups of AAC, present (n=1785) versus absent (n=563)	CT	Present/absent	Vertebral bone density (mg/m^2) and vertebral fracture	Aortic calcification was associated with low bone density and fragility fractures.
Simon et al, (75) 2014	Romania	Cross sectional, study populations;67.6 years; 29.5 kg/m^2; 100%women;21.6%diabetes;4.8%smoker; two groups of AAC, present (n=61) versus absent (n=64)	X-ray	Present/absent AAC24 score	BMD (mg/m^2) at lumbar spine, femoral neck, and trochanter	AAC was associated with low BMD.
Szulc et al, (76) 2008-MINOS	France	Prospective, study populations;120 months of follow up; 100%men; two groups of AAC, present (n=181) versus absent (n=220)	X-ray	Present/absent AAC24 score	BMD (mg/m^2) at lumbar spine, femoral neck, trochanter, total hip, whole body, distal forearm, and ultra distal radius Incident fracture	AAC (>6) was associated with incident fractures.

Szulc et al, (77) 2013 STRAMBO	France	Cross sectional, study populations;70 years; 100%men; 67.9%smoker;37%HTN; 11% diabetes; four groups of AAC, 0 (n=397), 1 to 2 (n=242), 3 to 6 (n=151), >6 (n=111)	DXA	AAC24 score (0, 1 to 2, 3 to 6, >6)	BMD (g/cm^2) at lumbar spine, femoral neck, total hip, trochanter,1/3 distal radius, ultra-distal radius and whole body Vertebral fracture	AAC (>6) was associated with fracture but not BMD.
Szulc et al,(78) 2014-MrOs	USA	Prospective, study populations;100%men;62.4%smokers; four groups of AAC, 0 to 1 (n=1528), 2 to 4 (n=1468), 5 to 8 (n=1240), >9+(n=1164)	X-ray	AAC24 score (0-1, 2 to 4, 5 to 8, >9+)	BMD (g/cm^2) at total hip Hip and non-spine fracture	AAC was associated with lower BMD and higher fracture risk.
Szulc et al, (79) 2015-SOF	USA	Prospective, study populations;100%women;180 months of follow up; 41%smokers; three groups of AAC, 0 (n=469), 1 to 4 (n=244), ≥5 (n=238)	X-ray	AAC24 score (0, 1 to 4, ≥5)	BMD at lumbar spine, total hip and femoral neck Vertebral fracture	AAC was associated with lower BMD but not vertebral fracture.
Torres et al, (80) 2016	Spain	Cross sectional, study populations;55.2 years;26.7 kg/m^2;39%women; 100%CKD; four groups of AAC, 0 (n=195), 1 to 6 (n=195), >6 (n=205), had baseline fracture	X-ray	AAC24 score	Vertebral fracture	AAC was not associated with fracture.
Vogt et al, (81) 1997	USA	Cross sectional, study populations; 100%women; two groups of AAC, present (n=1444) and absent (n=607)	X-ray	Present/absent	BMD (g/cm2) at hip, lumbar spine, proximal radius, distal radius and calcaneus	AAC was associated with lower BMD.
Wang et al, (82) 2010	New Zealand	Prospective, study populations; 81.6% women; sample size (n=1424)	X-ray	Present/absent AAC-8 score	BMD (g/cm^2) at lumbar spine, total femur, and body, osteoporotic and total fractures	AAC was not associated with lower BMD.
Wyers et al, (83) 2017 Abstract	The Netherlands	Cross sectional, study populations;71 years; 60%women;100% clinical fracture; two AAC groups, present (n=479) and absent (n=1296)	X-ray	AAC-8 score	Vertebral fracture	AAC was associated with vertebral fracture.
Yokomoto,(84) 2020	Japan	Cross sectional, study populations;58 years; 22.4 kg/m^2; 55%women;27%diabetes;47% HTN; 100% with pheochromocytoma; two AAC groups, AAC24≥3 (n=13) and <3 (n=38)	X-ray	AAC-24 score	Vertebral fracture	AAC was associated with vertebral fracture.
Zhou et al, (85) 2013	China	Prospective, study populations;46%women; 60 months of follow up; two AAC groups, 0 (n=678), 1 to 2 (n=431), 3 to 6 (n=336), >6 (n=284)	X-ray	AAC-24 score	BMD (g/cm^2) at vertebra, femoral neck, femoral tuberosity and total hip	AAC was associated with lower BMD.
Zhou et al, (86) 2014	China	Prospective, study populations;69.3 years;21.6 kg/m^2; 100%women; 3.1%smoker;22.2%diabets;	X-ray	Present/absent AAC-8 score	Vertebral, hip, and other fractures	AAC was associated with vertebral fracture.

		31.1%HTN; two AAC groups, present (n=673), absent (n=1051)				

Table S3. Risk of bias assessment of cross-sectional studies included in the meta-analysis

Reference	Selection				Comparability	Outcome			
Study, year	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure	Confounding factors are controlled	Assessment of the outcome	Statistical test	Total (10)	Quality
Aoyagi et al, 2001	*	*		**	**	**	*	9	Good
Banks et al, 1994	*			**		**		5	Fair
Boukhris et al, 1973								0	Poor
Chue et al, 2012	*			**		**	*	6	Fair
Paiva et al, 2002				**		**	*	5	Fair
El Maghraoui et al, 2012	*	*		**		**	*	7	Good
El Maghraoui et al, 2013	*	*		**		**		6	Fair
El Maghraoui et al, 2018	*	*		**	**	**	*	9	Good
Figueredo et al, 2012	*	*		**		**	*	7	Good
Flipon et al, 2010	*	*		**		**		6	Fair
Ghozlani et al, 2017				**	**	**	*	7	Good
Hanna et al, 2015	*	*		*	**	**	*	8	Good
Iwamoto et al, 2010	*	*		**		**		6	Fair
Jamal et al, 2005	*	*	*	**	**	**	*	10	Good
Kim et al, 2012	*	*		**	**	**	*	9	Good
Majjad et al, 2020				**		**	*	5	Fair
Mohammed et al, 2014				**	**	**	*	7	Good
Nakatsuka et al, 1997	*			**		**	*	6	Fair
Orwoll et al, 1990		*		**		**		5	Fair
Pirro et al, 2013				**		**	*	5	Fair
Rajzbaum et al, 2005	*	*		**	**	**	*	9	Good
Schulz et al, 2004	*	*		**		**		6	Fair
Szulc et al, 2013-STRAMBO	*	*		**	**	**	*	9	Good
Simon et al, 2014	*	*		**		**	*	7	Good
Torres et al, 2016	*	*		**		**	*	7	Good
Vogt et al, 1997	*	*		**	**	**	*	9	Good

A study can be awarded a maximum of one star for each numbered item within the selection categories. A maximum of two stars can be given for comparability and outcomes for assessment of the outcome

Table S4. Risk of bias assessment of case-control studies included in the meta-analysis

Reference	Selection				Comparability	Exposure				
Study, year	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same ascertainment of exposure for cases and control	Non-response rate	Total (9)	Quality
Yokomoto et al, 2020	*		*	*	*	*	*	*	7	Good

A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability

Table S5. Risk of bias assessment of prospective cohort studies included in the meta-analysis

Reference	Selection				Comparability	Outcome				
Study, year	Representativeness exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up	Total (9)	Quality
Bagger et al, 2006	*	*	*		**	*	*		7	Good
Bristow et al, 2019			*		**	*	*	*	5	Poor
Farhat et al, 2006	*	*	*		**	*		*	7	Good
Naves et al, 2008	*	*	*		**	*	*	*	8	Good
Lewis et al, 2019	*		*		**	*	*	*	7	Fair
Samelson et al, 2007	*	*	*		**	*	*	*	8	Good
Schousboe et al, 2021	*	*	*		**	*		*	7	Good
Szulc et al, 2008-MINOS	*	*	*		**		*	*	7	Good
Szulc et al, 2014-MrOS	*	*	*		**	*	*	*	8	Good
Szulc et al, 2015-SOF	*		*		**	*	*	*	7	Fair
Wang et al, 2010	*		*		**	*	*		6	Fair
Zhou et al, 2013	*	*	*	*	**	*	*		8	Good
Zhou et al, 2014	*	*	*		**	*	*		7	Good

A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability

Table S6. Standardized mean difference of BMD in people with any/advanced AAC for studies included on the BMD meta-analysis

Study	Characteristics		BMD [SMD (95%CI)]						
	Age, y	Test	Femoral neck	Total hip	Lumbar spine	Distal radius	Proximal radius	Whole body	Calcaneus
Aoyagi et al, 2001	66.1	X-ray	…	…		-0.28 (-0.45, -0.11)	-0.29 (-0.46, -0.11)		-0.21 (-0.39, -0.04)
Bagger et al, 2006	65	X-ray	…	-0.36 (-0.45, -0.28)	-3.00 (-3.14, -2.86)	…	…	…	…
Banks et al, 1994	55.2	X-ray	-0.62 (-1.13, -0.11)	…	-0.42 (-0.92, 0.09)	…	…	…	…
Bristow et al, 2019	73	X-ray	…	…	…	…	…	…	…
Chue et al, 2012	55	X-ray	…	0.30 (-0.07, 0.66)	…	…	…	…	…
El Maghraoui et al, 2013	60.9	X-ray	…	-1.70 (-1.92, -1.49)	-0.60 (-0.80, -0.39)	…	…	…	…
El Maghraoui et al, 2018	59.3	X-ray	…	-0.36 (-0.71, -0.01)	-0.53 (-0.89, -0.18)	…	…	…	…
Farhat et al, 2006 (vBMD)	50.0	CT	…	…	-0.28 (-0.48, -0.09)	…	…	…	…
Figueiredo et al, 2013	73	X-ray	-0.36 (-0.52, -0.20)	-0.39 (-0.55, -0.23)	…	…	…	…	…
Flipon et al, 2012	80.1	X-ray	0.00 (-0.15, 0.15)	…	…	…	…	…	…
Ghozalani et al, 2017	57.7	X-ray	…	-0.73 (-1.13, -0.32)	0.79 (-1.20, -0.39)	…	…	…	…
Kim et al, 2012 (vBMD)	64.7	CT	…	…	-0.73 (-0.88, -0.57)		…	…	…
Lewis et al, 2019	75	DXA	…	-0.16 (-0.28, -0.04)	…	…	…	…	…
Kim et al, 2012 (vBMD)	64.7	CT	…		-0.73 (-0.88, -0.57)		…	…	…
Mohammed et al, 2014	57	DXA	…	-11.99 (-12.68, -11.29)	…	…	…	…	…
Naves et al, 2008	65.2	X-ray	0.15 (-0.01, 0.31)	…	0.28 (0.11 to 0.44)	…	…	…	…
Orwoll et al, 1990	64	X-ray	…	…	0.22 (-0.15, 0.59)	…	…	…	…
Paiva et al, 2002	64	X-ray	…	…	-0.44 (-0.88, -0.003)	…	…	…	…
Pirro et al, 2013	74.2	CT	…	…	0.00 (-0.62, 0.62)	…	…	…	…
Pozzo et al, 2006	-	CT	…	…	-0.88 (-1.08, -0.68)	…	…	…	…
Rajzbaum et al,2005	63.5	X-ray	-0.25 (-0.48, -0.03)	…	…	…	…	…	…
Schulz et al, 2004	68.3	CT	…	…	-0.83 (-0.93, -0.73)	…	…	…	…
Simone et al, 2014	67.7	X-ray	-0.85 (-1.22, -0.49)	…	-0.28 (-0.63, 0.07)	…	…	…	…
Szulc et al, 2008-MINOS	65	X-ray	0.08 (-0.07, 0.24)	0.00 (-0.16, 0.16)	-0.05 (-0.21, 0.10)	-0.17 (-0.32, -0.01)	…	-0.19 (-0.34, -0.03)	…
Szulc et al, 2013-STRAMBO	70 .0	DXA	0.00 (-0.13, 0.13)	-0.07 (-0.21, 0.06)	0.05 (-0.08, 0.19)	0.08 (-0.05, 0.21)	0.03 (-0.11, 0.16)	0.11 (-0.02, 0.24)	…
Szulc et al, 2014- MrOS	73.3	X-ray	…	-0.15 (-0.21, -0.09)	…	…	…	…	…
Szulc et al, 2015-SOF	71.8	X-ray	-0.20 (-0.33, -0.07)	-0.08 (-0.21, 0.05)	0.18 (0.05, 0.31)	…	…	…	…
Vogt et al, 1997	70	X-ray	…	-0.09 (-0.19, 0.004)	0.00 (-0.10, 0.10)	-0.149 (-0.24, -0.05)	-0.11 (-0.21, -0.02)	…	-0.12 (-0.22, -0.03)
Wang et al, 2010-M	56.4	X-ray	…	-0.22 (-0.51, 0.07)	-0.06 (-0.35, 0.22)	…	…	-0.22 (-0.51, 0.07)	…
Wang et al, 2010-W	74.2	X-ray	…	-0.15 (-0.25, -0.04)	0.06 (-0.05, 0.16)	…	…	-0.11 (-0.22, -0.01)	…
Zhou et al, 2013	72	X-ray	-0.69 (-0.78, 0.59)	-0.52 (-0.62, -0.43)	-0.18 (-0.28, -0.08)	…	…	…	…
Zhou et al, 2014	69.3	X-ray	…	…	-6.00 (-6.22, -5.78)	…	…	…	…

Alexova et al (2018) showed an inverse association between AAC and trabecular bone score but not DXA derived BMD. Avramovski et al (2013) reported an inverse correlation between AAC and BMD, while Shen et al (2007) revealed no association

Table S7: Pooled standardised mean difference of BMD in people with any/advanced AAC

Skeletal site	Number of studies (patients)	SMD (95%CI)	I^2 (%)	Egger's test	Certainty of evidence (GRADE)
Femoral neck					
No/low AAC	10 (3419)	1 (referent)			
Any/advanced AAC	10 (3562)	-0.25 (-0.46 to -0.04)	94.1	0.79	Moderate
Total Hip					
No/low AAC	16 (9613)	1 (referent)			
Any/advanced AAC	16 (10664)	-1.05 (-1.47 to -0.63)	99.4	0.21	Moderate
Lumbar spine					
No/low AAC	21 (8307)	1 (referent)			
Any/advanced AAC	21 (8953)	-0.67 (-1.21 to -0.12)	99.6	0.49	Moderate
Distal radius					
No/low AAC	4 (1528)	1 (referent)			
Any/advanced AAC	4 (2729)	-0.12 (-0.26 to 0.02)	76.7	0.83	…….
Proximal radius					
No/low AAC	3 (1308)	1 (referent)			
Any/advanced AAC	3 (2168)	-0.11 (-0.26 to 0.04)	74.8	0.77	…….
Whole body					
No/low AAC	4 (1597)	1 (referent)			
Any/advanced AAC	4 (1829)	-0.09 (-0.23 to 0.06)	72.2	0.71	…….
Calcaneus					
No/low AAC	2 (911)	1 (referent)			
Any/advanced AAC	2 (1664)	-0.14 (-0.23 to -0.06)	0.0	< 0.01	…….
Vertebral trabecular vBMD					
No/low AAC	2 (420)	1 (referent)			
Any/advanced AAC	2 (839)	-0.51 (-0.94 to -0.07)	92.0		…….

Egger's test<0.05 was considered significant and the test is more reliable for analyses of more than ten studies

Table S8. Subgroup analysis showing a standardised mean difference in BMD by skeletal sites in people with any/advanced AAC

Site	Subgroup analysis		Number of studies (n)	SMD (95%CI)	I^2 (%)
Femoral neck	Gender	Women only	5 (2140)	-0.32 (-0.54 to -0.09)	81.1
		Men only	2 (1682)	0.04 (-0.07 to 0.14)	0.0
		Mixed	3 (3159)	-0.31 (-0.82 to 0.21)	97.5
	Study location	Europe	6 (2819)	-0.18 (-0.40 to 0.05)	85.7
		North America	2 (1618)	-0.10 (-0.30 to 0.09)	74.4
		South America	1 (815)	-0.36 (-0.52 to -0.20)	-
		Asia	1 (1729)	-0.68 (-0.78 to -0.59)	-
	Imaging modality	Radiograph	8 (5465)	-0.34 (-0.59 to -0.10)	93.9
		DXA	2 (1516)	0.07 (-0.08 to 0.22)	53.0
	Sample size	<500	3 (522)	-0.55 (-0.95 to -0.14)	74.4
		≥500	7 (6459)	-0.15 (-0.41 to 0.11)	96.0
Total hip	Gender	Women only	8 (9608)	-0.66 (-1.27 to -0.04)	99.4
		Men only	4 (7402)	-0.11 (-0.18 to -0.04)	21.9
		Mixed	4 (3267)	-3.09 (-5.03 to -1.15)	99.7
	Study location	Europe	5 (5067)	-2.69 (-4.29 to -1.09)	99.8
		North America	3 (8402)	-0.12 (-0.17 to -0.08)	-0.0
		South America	1 (815)	-0.39 (-0.56 to -0.23)	-
		Asia	1 (1729)	-0.52 (-0.62 to -0.43)	-
		Oceania	2 (2768)	-0.16 (-0.24 to -0.08)	0.0
		Africa	3 (1496)	-0.94 (-1.84 to -0.04)	95.8
	Imaging modality	Radiograph	8 (14509)	-0.37 (-0.87 to -0.13)	99.4
		DXA	7 (5768)	-1.84 (-2.73 to -0.95)	99.5
	Sample size	<500	4 (1028)	-0.25 (-0.63 to 0.14)	79.3
		≥500	12 (19249)	-1.32 (-1.81 to -0.82)	99.6
Lumbar spine	Gender	Women only	16 (12914)	-0.89 (-1.64 to -0.14)	99.6
		Men only	3 (2002)	0.00 (-0.09 to 0.10)	0.0
		Mixed	2 (2344)	0.04 (-0.41 to 0.49)	95.5
	Study location	Europe	7 (4204)	-0.49 (-1.62 to 0.63)	99.6
		North America	4 (5477)	-0.12 (-0.65 to 0.42)	98.6
		South America	2 (594)	-0.71 (-1.13 to -0.29)	68.3
		Asia	2 (3453)	-3.09 (-8.79 to 2.61)	100
		Africa	3 (1496)	-0.61 (-0.78 to -0.45)	0.0
		Oceania	2 (2036)	0.04 (-0.05 to 0.14)	0.0
	Imaging modality	Radiograph	11 (9368)	-0.91 (-1.92 to 0.10)	99.7
		CT	2 (2844)	-0.84 (-0.93 to -0.75)	0.0
		DXA	7 (5048)	-0.19 (-0.44 to 0.05)	91.3
	Sample size	<500	10 (2168)	-0.37 (-0.65 to -0.09)	81.6
		≥500	11 (15092)	-0.92 (-1.69 to -14)	99.8

Table S9. Modifiers of the association between any/advanced AAC and BMD by skeletal sites

Site	Modifier	Number of studies	β-coefficient	p-value
Femoral neck	Age	10	0.007	0.681
	BMI	9	0.027	0.611
	%Smokers in the cohort	8	-0.003	0.843
	%Women in the cohort	10	-0.005	0.018
Total hip	Age	16	0.144	0.126
	BMI	12	0.185	0.715
	%Smokers in the cohort	11	-0.072	0.181
	%Women in the cohort	16	-0.006	0.755
Lumbar spine	Age	20	-0.004	0.943
	BMI	13	0.281	0.082
	%Smokers in the cohort	8	0.030	0.708
	%Women in the cohort	20	-0.010	0.204

Table S10: Absolute (ARD = absolute risk difference) and relative risks (RR) of fractures in people with any/advanced AAC for studies included in the fracture meta-analysis

Study	Characteristics		Any/All fractures		Vertebral fracture		Non-vertebral fracture		Hip fracture	
	Age, y	Test	% Events no/low vs any/advanced (ARD)	RR (95% CI)	% Events no/low vs any/advanced (ARD)	RR (95% CI)	% Events no/low vs any/advanced (ARD)	RR (95% CI)	% Events no/low vs any/advanced (ARD)	RR (95% CI)
Bagger et al, 2006	65	X-ray	14.3 vs 23.3 (+9.0)	1.63 (1.38, 1.93)	14.0 vs 20.9 (+6.9)	1.48 (1.05, 2.12)	0.9 vs 2.5 (+1.6)	2.81 (1.48, 5.34)	0.9 vs 2.5 (+1.6)	2.81 (1.48, 5.34)
Boukhris et al, 1973		X-ray	4.0 vs 18.5 (+14.5)	4.57 (2.56, 8.17)	4.0 vs 18.5 (+14.5)	4.57 (2.56, 8.17)	…	…	…	…
El Maghrauoui et al, 2012	62.4	DXA	32.7 vs 45.0 (+12.3)	1.38 (0.84, 2.26)	14.3 vs 20.8 (+6.5)	1.45 (1.22, 1.73)	…			
El Maghrauoui et al, 2013	60.9	DXA	13.9 vs 63.0 (+49.1)	4.54 (3.62, 5.68)	13.9 vs 63.0 (+49.1)	4.54 (3.62, 5.69)	…	…	…	…
El Maghrauoui et al, 2018	59.3	DXA	12.3 vs 52.9 (+40.6)	4.31 (2.83, 6.54)	12.3 vs 52.9 (+40.6)	4.30 (2.83, 6.55)	…	…	…	…
Flipon et al, 2010	80.1	X-ray	26.6 vs 29.1 (+2.5)	1.09 (0.86, 1.40)	23.4 vs 23.3 (+0.1)	1.00 (0.76, 1.32)	…			
Ghozlani et al, 2017	57.7	DXA	5.7 vs 31.0 (+25.3)	5.48 (2.38, 12.63)	5.7 vs 31.0 (+25.3)	5.48 (2.38, 12.64)	…	…	…	…
Hanna et al, 2015	53	X-ray	45.0 vs 83.5 (+38.5)	1.86 (1.56, 2.21)	…		…	…	…	…
Iwamoto et al, 2010	73.8	X-ray	41.6 vs 77.7 (+30.1)	1.87 (1.57, 2.22)	40.7 vs 73.7 (+33.0)	1.81 (1.51, 2.17)	0.9 vs 4.0 (+3.1)	4.52 (0.95, 21.49)	0.9 vs 4.0 (+3.1)	4.52 (0.95, 21.49)
Kim et al, 2012	64.7	CT	5.5 vs 16.4 (+10.9)	2.99 (1.76, 5.08)	5.5 vs 16.4 (+10.9)	2.99 (1.76, 5.08)	…			
Lewis et al, 2019	75	DXA	22.4 vs 28.5 (+6.1)	1.27 (1.03, 1.57)	7.2 vs 7.4 (+0.2)	1.03 (0.66, 1.60)	17.4 vs 23.0 (+5.6)	1.32 (1.03, 1.70)	4.8 vs 6.9 (+2.1)	1.44 (0.87, 2.39)
Majjad (2020)	55	DXA	66.3 vs 12.9 (+53.4)	5.14 (3.33, 7.93)	66.3 vs 12.9 (+53.4)	5.14 (3.33, 7.93)				
Nakatsuka et al, 1997	68.6	X-ray	34.4 vs 42.3 (+7.9)	1.23 (0.73, 2.09)	34.4 vs 42.3 (+7.9)	1.23 (0.73, 2.09)	…			
Naves et al, 2008	65.2	X-ray	22.3 vs 31.7 (+9.4)	1.42 (1.09, 1.85)	32.7 vs 45.0 (+12.3)	1.38 (0.84, 2.26)	10.1 vs 17.0 (+6.9)	1.67 (1.11, 2.53)		
Rajzbaum et al, 2005	63.5	X-ray	52.2 vs 70.8 (+18.6)	1.36 (1.14, 1.62)	11.6 vs 27.5 (+15.9)	2.37 (1.48, 3.82)	40.6 vs 43.3 (+2.7)	1.07 (0.82, 1.39)	5.3 vs 7.5 (+2.2)	1.41 (0.60, 3.31)
Samelson et al, 2007-m	60	X-ray	3.8 vs 5.0 (+1.2)	1.30 (0.70, 2.42)	…		3.8 vs 5.0 (+1.2)	1.30 (0.70, 2.42)	3.8 vs 5.0 (+1.2)	1.30 (0.70, 2.42)
Samelson et al, 2007-w	61	X-ray	15 vs 15.7 (+0.7)	1.05 (0.82, 1.35)	…		15.0 vs 15.7 (+0.7)	1.05 (0.82, 1.35)	15.0 vs 15.7 (+0.7)	1.05 (0.82, 1.35)
Schousboe (2021)	74.9	DXA	8.3 vs 5.60 (+2.8)	1.50 (1.19, 1.89)	8.3 vs 5.60 (+2.8)	1.50 (1.19, 1.89)				
Schulz et al, 2004	68.3	CT	45.1 vs 48.3 (+3.2)	1.07 (0.97, 1.19)	32.7 vs 38.8 (+5.1)	1.19 (1.04, 1.35)	9.5 vs 12.4 (+2.9)	0.77 (0.59, 1.00)	12.4 vs 9.5 (-2.9)	0.77 (0.59, 1.00)
Szulc et al, 2008-MINOS	65	X-ray	6.4 vs 9.3 (+2.9)	1.46 (0.82, 2.57)	…		…	…	…	…
Szulc et al, 2013-STRAMBO	70	DXA	9.8 vs 11.7 (+1.9)	1.19 (0.81, 1.75)	9.8 vs 11.7 (+1.9)	1.19 (0.81, 1.75)	…	…	…	…
Szulc et al, 2014-MrOS	73.3	X-ray	15.0 vs 17.3 (+2.3)	1.15 (1.00, 1.32)	…	…	12.2 vs 16.1 (+3.9)	1.32 (1.14, 1.54)	1.5 vs 4.0 (+2.5)	2.70 (1.72, 4.10)
Szulc et al, 2015-SOF	71.8	X-ray	17.3 vs 20.1 (+2.8)	1.17 (0.89, 1.52)	17.3 vs 20.1 (+2.8)	1.17 (0.89,1.52)	…	…	…	…
Torres et al, 2016	55.2	X-ray	12.8 vs 15.5 (+2.7)	1.21 (0.79, 1.86)	12.8 vs 15.5 (+2.7)	1.21 (0.79, 1.86)	…	…	…	…
Wang et al, 2010	71	X-ray	13.8 vs 16.1 (+2.3)	1.17 (0.91, 1.50)	…	…	0.7 vs 2.0 (+1.3)	2.84 (1.03, 7.84)	0.7 vs 2.0 (+1.3)	2.84 (1.03, 7.84)
Wyers et al, 2017	66	X-ray	26.7 vs 39.0 (+12.3)	1.46 (1.27, 1.69)	26.7 vs 39.0 (+12.3)	1.46 (1.27, 1.69)	…			
Yokomoto et al, 2020	57	X-ray	21.0 vs 84.6 (+63.6)	4.02 (2.08, 7.76)	21.1 vs 84.6 (+63.5)	4.02 (2.08, 7.76)	…			
Zhou et al, 2014	69.3	X-ray	8.4 vs 18.1 (+9.7)	2.17 (1.68, 2.80)	4.5 vs 10.3 (+5.8)	2.29 (1.60, 3.28)	3.9 vs 7.9 (+4.0)	2.02 (1.36, 3.00)	1.6 vs 4.9 (+3.3)	3.03 (1.70, 5.40)

Jamal et al, 2005 reported adjusted odds ratio and was included in the BMD adjusted analysis.

Table S11: Pooled relative risk of fracture in people with any/advanced AAC compared to those with no/less advanced AAC

AAC group	Fracture type	Number of studies (No. Events/ No. Group)	Absolute Risk Difference (95%CI)	Relative Risk (95%CI)	I^2 (%)	Egger's test (p value)
Any/advanced AAC	**Any/All fracture**					
	No/low AAC	27 (2687/15632)	1 (referent)	1 (referent)		
	Any/ advanced AAC	27 (3829/18116)	+12.9 (+9.6 to +16.2)	1.73 (1.48 to 2.02)	91.0	0.02
	Vertebral fracture					
	No/ low AAC	22 (1841/12025)	1 (referent)	1 (referent)		
	Any/advanced AAC	22 (2274/319)	+14.1(+10.0 to +18.1)	1.93 (1.58 to 2.36)	90.5	0.66
	Non-vertebral fracture					
	No/low AAC	10 (611/7955)	1 (referent)	1 (referent)		
	Any/advanced AAC	10 (1277/10469)	+2.1 (+0.9 to +3.3)	1.36 (1.11 to 1.66)	72.3	0.17
	Hip fracture					
	No/low AAC	10 (270/7570)	1 (referent)	1 (referent)		
	Any/advanced AAC	10 (616/10239)	+1.7 (+0.9 to +2.6)	1.72 (1.18 to 2.49)	81.1	0.02
	Incident any/all fracture					
	No/low AAC	8 (721/7179)	1 (referent)	1 (referent)		
	Any/advanced AAC	8 (981/8950)	+4.2 (+2.1 to +6.4)	1.51 (1.25 to 1.82)	71.7	0.87
	Incident vertebral fracture					
	No/low AAC	3 (335/3387)	1 (referent)	1 (referent)		
	Any/advanced AAC	3 (280/2023)	+5.4 (+3.8 to +7.1)	1.80 (1.30 to 2.47)	64.1	0.36
	Incident non-vertebral fracture					
	No/low AAC	6 (834/9282)	1 (referent)	1 (referent)		
	Any/advanced AAC	6 (603/5451)	+2.4 (+1.2 to +3.5)	1.46 (1.19 to 1.79)	60.1	0.17
	Incident hip fracture					
	No/low AAC	6 (187/6240)	1 (referent)	1 (referent)		
	Any/advanced AAC	6 (430/8159)	+2.0 (+1.4 to +2.5)	1.79 (1.25 to 2.58)	71.8	0.07

Jamal et al, 2005 (n=52 participants) reported adjusted odds ratio and was included in the BMD adjusted analysis.

Table S12: Pooled relative risk of fracture in people with any and different thresholds of AAC

	Fracture type	Number of studies (No. Events/ No. Group)	Absolute Risk Difference (95%CI)	Relative Risk (95%CI)	I^2 (%)
Any detectable AAC	**Any/All fracture**				
	No detectable AAC	18 (1403/7420)	1 (referent)	1 (referent)	
	Any detectable AAC	18 (2208/8268)	+13.3 (+8.6 to+18.0)	1.68 (1.41 to 2.01)	88.3
	Vertebral fracture				
	No detectable AAC	13 (880/5186)	1 (referent)	1 (referent)	
	Any detectable AAC	13 (1442/5245)	+11.3 (+6.8 to 15.9)	1.79 (1.45 to 2.21)	83.5
	Non-vertebral fracture				
	No detectable AAC	7 (305/3706)	1 (referent)	1 (referent)	
	Any detectable AAC	7 (465/5017)	+1.4 (-0.2 to +3.0)	1.27 (0.93 to 1.73)	74.2
	Hip fracture				
	No detectable AAC	6 (206/3480)	1 (referent)	1 (referent)	
	Any detectable AAC	6 (395/4842)	+1.1 (-0.5 to 2.7)	1.38 (0.91 to 2.09)	78.4
Increasing severity of AAC	**Any/All fracture**				
	Lowest reported AAC group	8 (737/6486)	1 (referent)	1 (referent)	
	Middle/combined AAC group (s)	8 (1040/8161)	+2.5 (+0.8 to +4.2)	1.26 (1.07 to 1.49)	61.2
	Highest AAC reported group	8 (533/3403)	+ 4.6 (+1.6 to +7.7)	1.49 (1.19 to 1.85)	71.3
	Vertebral fracture				
	Lowest reported AAC group	6 (331/4016)	1 (referent)	1 (referent)	
	Middle/combined AAC group (s)	6 (404/4164)	+2.7 (+0.8 to +4.7)	1.34 (1.07 to 1.67)	53.0
	Highest AAC reported group	6 (254/1971)	+ 5.6 (+2.20 to +9.0)	1.67 (1.26 to 2.22)	67.9
	Non-vertebral fracture				
	Lowest reported AAC group	4 (369/3906)	1 (referent)	1 (referent)	
	Middle/combined AAC group (s)	4 (597/4642)	+2.5 (+1.2 to +3.8)	1.28 (1.07 to 1.53)	34.4
	Highest AAC reported group	4 (282/1690)	+3.9 (-0.2 to +7.9)	1.53 (1.14 to 2.05)	53.2
	Hip fracture				
	Lowest reported AAC group	3 (143/3521)	1 (referent)	1 (referent)	
	Middle/combined AAC group (s)	3 (254/4515)	+2.0 (+1.2 to +2.8)	1.71 (1.02 to 2.88)	80.2
	Highest AAC reported group	3 (102/1587)	+2.1 (-0.8 to +4.9)	1.81 (0.79 to 4.12)	84.8

Table S 13: Pooled analyses showing the association between any/advanced AAC, BMD and fracture after excluding studies with poor and fair quality.

		Number of studies (patients)	SMD (95%CI)	I^2 (%)
BMD (SMD 95%CI)	**Femoral neck**			
	No/low AAC	7 (2569)	1 (referent)	
	Any/advanced AAC	7 (2724)	-0.26 (-0.55 to 0.03)	95.7
	Total Hip			
	No/low AAC	10 (6842)	1 (referent)	
	Any/advanced AAC	10 (8688)	-1.26 (-1.70 to -0.82)	99.2
	Lumbar spine			
	No/low AAC	10 (5372)	1 (referent)	
	Any/advanced AAC	10 (4804)	-1.05 (-2.07 to -0.03)	99.8
Fracture (OR 95%CI)	**Any/All fracture**			
	No/low AAC	17 (2011/13242)	1 (referent)	
	Any/ advanced AAC	17 (1438/10047)	1.68 (1.43 to 1.99)	82.2
	Vertebral fracture			
	No/ low AAC	12 (943/6201)	1 (referent)	
	Any/advanced AAC	12 (1254/5088)	1.97 (1.53 to 2.53)	84.8
	Non-vertebral fracture			
	No/low AAC	7 (540/6553)	1 (referent)	
	Any/advanced AAC	7 (1122/9022)	1.30 (1.04 to 1.64)	77.0
	Hip fracture			
	No/low AAC	5 (230/5961)	1 (referent)	
	Any/advanced AAC	5 (547/8672)	1.63 (1.01 to 2.63)	88.1%

Table S14: Subgroup analysis showing risks of fractures in people with any/advanced AAC

Site	Subgroup analysis		Number of studies (n)	Relative Risk (95%CI)	I^2 (%)
Any fracture	Gender	Women only	15 (15217)	1.85 (1.43 to 2.39)	94.1
		Men only	7 (15977)	1.33 (1.19 to 1.48)	20.1
		Mixed	6 (2554)	1.97 (1.52 to 2.55)	00.0
	Study location	Europe	8 (8323)	1.33 (1.21 to 1.45)	20.0
		North America	8 (17455)	1.40 (1.13 to 1.72)	86.9
		Asia	5 (3067)	2.14 (1.64 to 2.79)	62.7
		Africa	5 (2455)	3.74 (2.41 to 5.78)	80.8
		Oceania	2 (2448)	1.23 (1.04 to1.44)	0.0
	Imaging modality	Radiograph	19 (26251)	1.49 (1.32 to 1.68)	77.9
		CT	2 (3117)	1.73 (0.63 to 4.72)	94.3
		DXA	7 (4380)	2.68 (1.53 to 4.70)	94.0
	Sample size	<500	8 (2042)	2.02 (1.55 to 2.63)	86.04
		>500	20 (31706)	1.62 (1.34 to 1.96)	91.6
Vertebral fracture	Gender	Women only	13 (10293)	2.12 (1.48 to 3.03)	93.3
		Men only	4 (10703)	1.45 (1.31 to 1.60)	0.0
		Mixed	5 (2345)	2.12 (1.39 to 3.24)	79.8
	Study location	Europe	7 (5589)	1.36 (1.14 to 1.62)	49.5
		North America	4 (9253)	1.57 (1.12 to 2.21)	86.4
		Asia	5 (3067)	2.17 (1.59 to 2.95)	65.1
		Africa	5 (4408)	3.71 (1.93 to 7.12)	95.2
		Oceania	1 (1024)	1.03 (0.66 to 1.60)	-
	Imaging modality	Radiograph	13 (13891)	1.64 (1.37 to 1.96)	75.5
		CT	2 (3117)	1.81 (0.74 to 4.48)	90.9
		DXA	7 (6333)	2.62 (1.52 to 4.50)	94.6
	Sample size	<500	7 (1739)	2.97 (1.94 to 4.56)	85.3
		>500	15 (21602)	1.62 (1.30 to 2.03)	90.5
Non-vertebral fracture	Gender	Women only	7 (10962)	1.35 (1.08 to 1.69)	77.0
		Men only	2 (6446)	1.30 (0.70 to 2.42)	-
		Mixed	2 (1016)	2.05 (0.94 to 4.47)	31.4
	Study location	Europe	3 (3604)	1.49 (1.20 to 1.85)	48.0
		North America	4 (10247)	0.95 (0.72 to 1.26)	52.2
		Asia	2 (2125)	2.12 (1.44 to 3.11)	0.0
		Oceania	2 (2448)	1.64 (0.83 to 3.23)	51.4
	Imaging modality	Radiograph	9 (15052)	1.52 (1.25 to 1.84)	56.1
		CT	1 (2348)	0.77 (0.59 to 1.00)	-
		DXA	1 (1024)	1.32 (1.03 to 1.70)	-
	Sample size	<500	2 (728)	1.91 (0.63 to 5.75)	56.9
		>500	9 (17696)	1.39 (1.11 to 1.73)	71.4
Hip fracture	Gender	Women only	7 (10962)	1.56 (1.03 to 2.36)	81.3
		Men only	2 (6446)	1.93 (0.96 to 3.88)	70.9
		Mixed	1 (401)	4.52 (0.95 to 21.49)	-
	Study location	Europe	2 (2989)	2.11 (1.09 to 4.12)	37.8
		North America	4 (10247)	1.26 (0.77 to 2.06)	87.3
		Asia	2 (2125)	3.18 (1.85 to 5.47)	0.0
		Oceania	2 (2448)	1.74 (0.96 to 3.17)	27.2
	Imaging modality	Radiograph	8 (14437)	2.02 (1.33 to 3.07)	74.5
		CT	1 (2348)	0.77 (0.59 to 1.00)	-
		DXA	1 (1024)	1.44 (0.87 to 2.39)	-
	Study size	<500	2 (728)	2.09 (0.71 to 6.13)	39.4
		>500	8 (17081)	1.67 (1.12 to 2.50)	84.4

Table S15: Modifiers of the association between any/advanced AAC with risk of fractures

Site	Modifier	Number of studies	β-coefficient	p-value
Any fracture	Age	26	-0.038	<0.001
	BMI	21	0.038	0.505
	%Smokers in the cohort	17	-0.012	0.007
	%Women in the cohort	27	0.001	0.764
	AAC24 cut point	27	0.077	0.126
Vertebral fracture	Age	20	-0.047	< 0.001
	BMI	18	0.035	0.556
	% Smokers in the cohort	14	-0.012	0.031
	% Women in the cohort	22	0.00	0.943
	AAC24 cut point	22	0.043	0.443
Non-vertebral fracture	Age	11	0.015	0.613
	BMI	9	-0.039	0.629
	% Smokers	8	-0.005	0.434
	%Women	11	-0.001	0.864
	AAC24 cut point	11	-0.001	0.974
Hip fracture	Age	10	0.043	0.279
	BMI	8	-0.072	0.605
	% Smokers	7	-0.001	0.913
	%Women	10	0.003	0.636
	AAC24 cut point	10	0.159	0.360

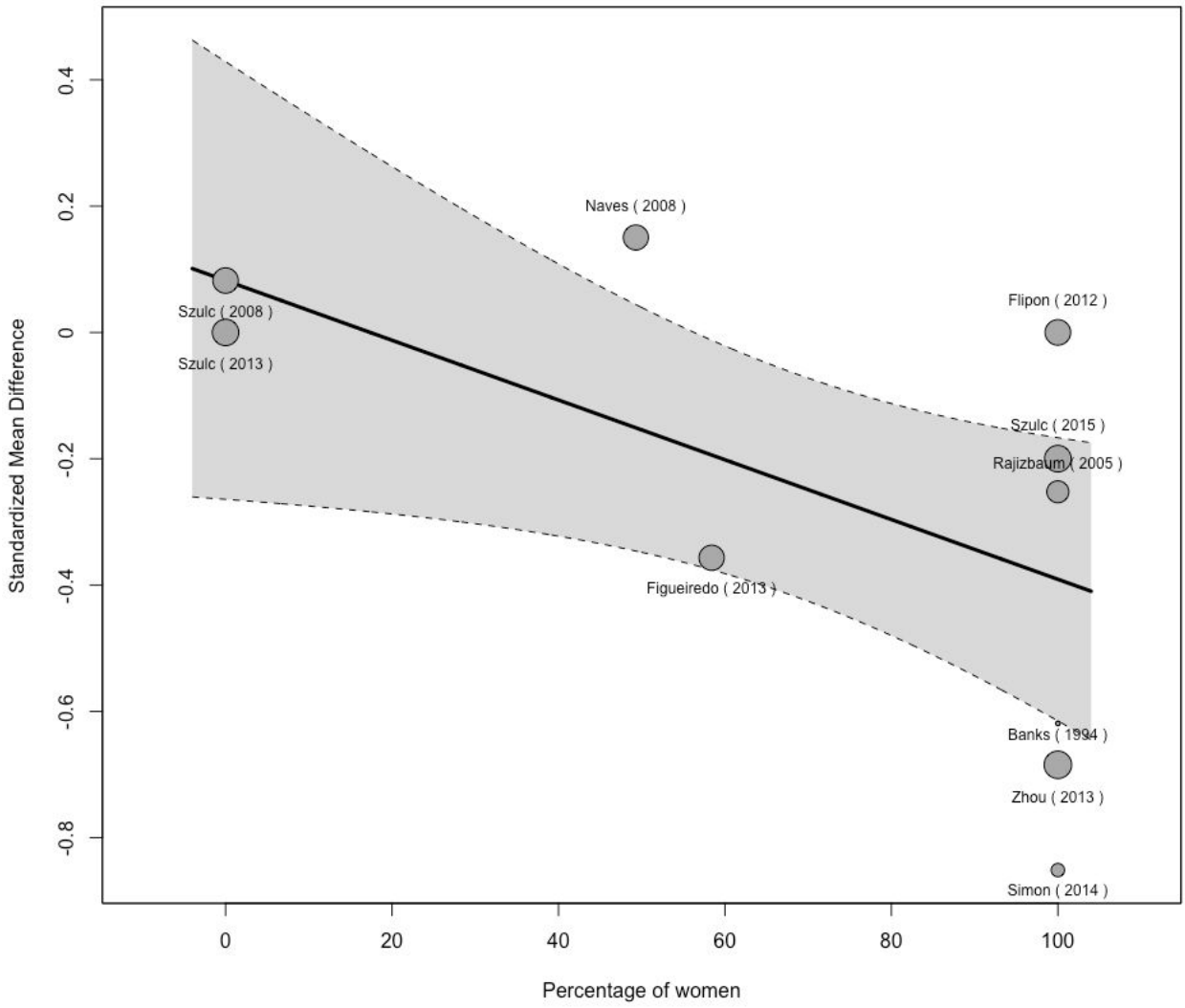

Figure S1: Meta-regression of the modifying effect of percentage women on the association between AAC and femoral neck BMD. Studies with greater percentages of women had greater differences in AAC (negative standardised differences indicate that BMD was lower in those with higher AAC)

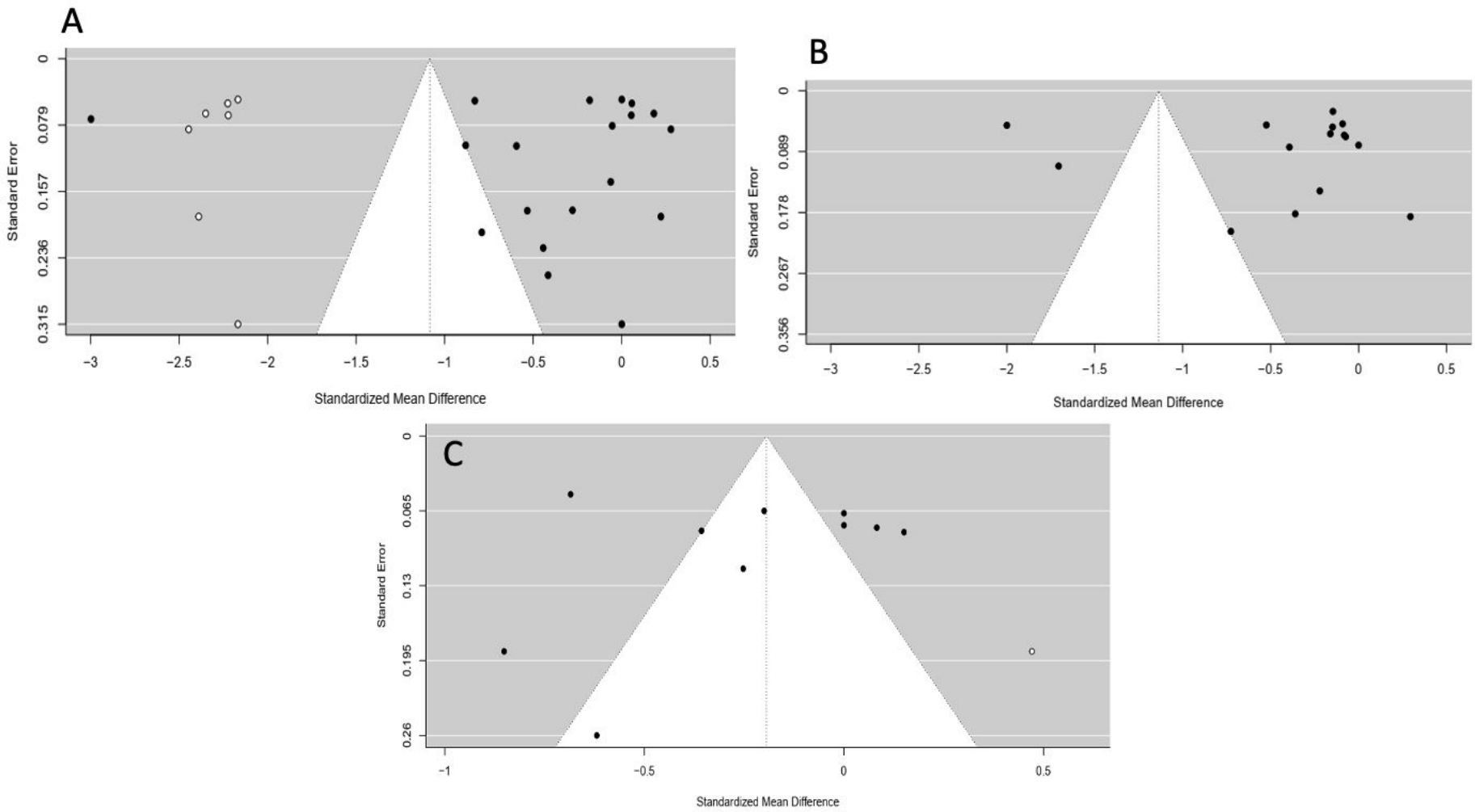

Figure S2: Funnel plots (trim and fill method) showing publication bias on the association between any/advanced AAC and (A) lumbar spine BMD, (B) total hip BMD and (C) Femoral neck BMD

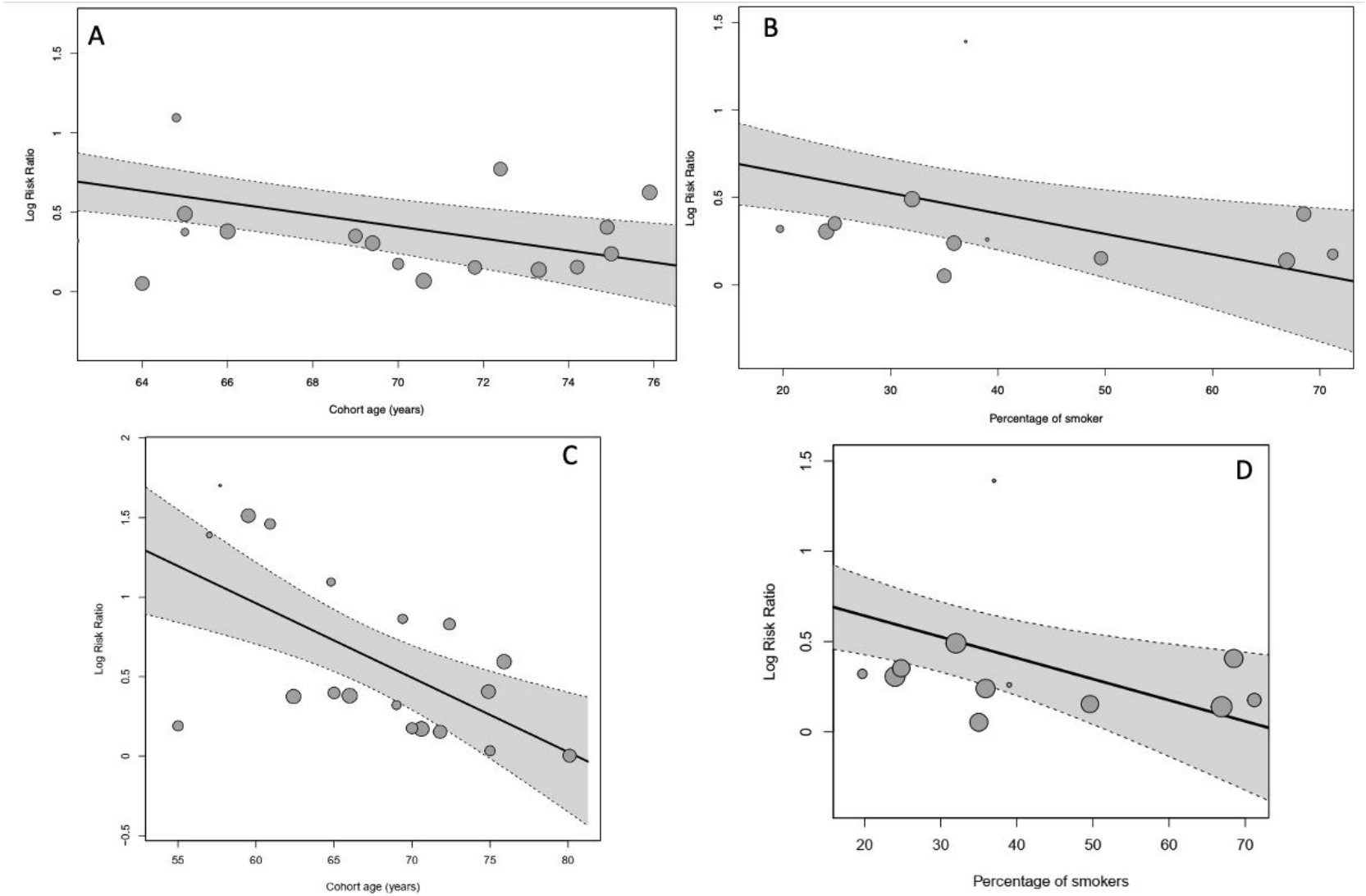

Figure S3: Meta-regression, (**A**) age and log RR of any fracture, (**B**) Percentage of smokers in the cohort and log RR of any fracture, (**C**) age and log RR of vertebral fracture, (**D**) Percentage of smokers in the cohort and log RR of vertebral fracture

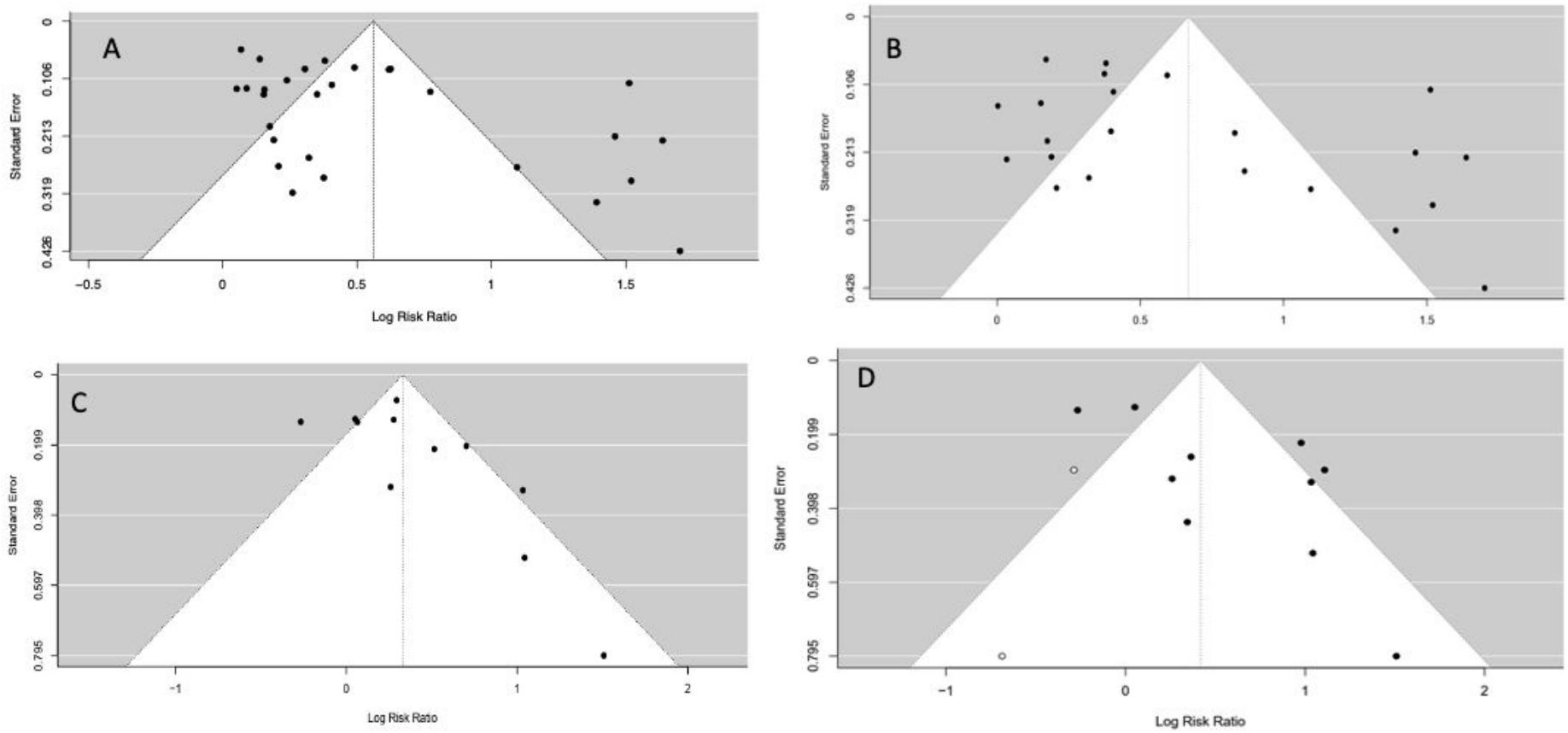

Figure S4: Funnel plots (trim and fill method) showing publication bias on the association between any/advanced AAC and (A) any fracture, (B) vertebral fracture, (C) non-vertebral fracture and (D) hip fracture

Table S16. Detailed GRADE assessment for outcomes in people with any/advanced AAC compared to those with no/less advanced AAC.

			Quality Assessment				Summary of findings			
Outcome		Studies (subjects)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size/Dose response	SMD/RR (95%CI)	Test for heterogeneity	Certainty of Evidence
BMD	Femoral neck	10 (6981)	-	↓1 between-study heterogeneity	pop. generalizable	No serious imprecision		-0.25 (-0.46 to -0.04)	I^2=94.1%, p-value<0.001	Moderate
	Total hip	16 (20277)	-	↓1 between-study heterogeneity	pop. generalizable	No serious imprecision		-1.05 (-1.47 to -0.63)	I^2=99.4%, p-value<0.001	Moderate
	Lumbar Spine	21 (17260)	-	↓1 between-study heterogeneity	pop. generalizable	No serious imprecision		-0.67 (-1.21 to -0.12)	I^2=99.6%, p-value<0.001	Moderate
Fracture	Any	28 (34458)	evidence of publication bias (↓1)	↓1 between-study heterogeneity	pop. generalizable	No serious imprecision	0/↑1	1.73 (1.48 to 2.02)	I^2=91.0, p-value<0.001	Moderate
	Vertebral	22 (23344)	-	↓1 between-study heterogeneity	pop. generalizable	No serious imprecision	0/↑1	1.93 (1.58 to 2.36)	I^2=90.5, p-value<0.001	High
	Non-vertebral	11 (18424)	-	↓1 between-study heterogeneity	pop. generalizable	No serious imprecision	0/↑1	1.36 (1.11 to 1.66)	I^2=72.3, p-value<0.001	High
	Hip	10 (17809)	evidence of publication bias (↓1)	↓1 between-study heterogeneity	pop. generalizable	No serious imprecision	0/0	1.71 (1.18 to 2.48)	I^2=81.1, p-value<0.001	Low

Scores are based on the GRADE for assessment of evidence about prognosis where the evidence begins as high quality evidence.(87)These criteria are based on; a) 5 domains diminishing confidence (-1 for risk of bias, inconsistency, imprecision, indirectness, and publication bias) and b) 2 situations increasing confidence (+1 or +2 for large (RR >2) to very large (RR >4) effect size and a +1 for a dose-response gradient [increasing pooled relative risks for any fracture, vertebral fracture, non-vertebral fracture and hip fractures with increasing severity of AAC]).(87)

References

1. Aleksova J, Kurniawan S, Vucak-Dzumhur M, Kerr P, Ebeling PR, Milat F*, et al.* Aortic vascular calcification is inversely associated with the trabecular bone score in patients receiving dialysis. Bone. 2018;**113**:118-123.

2. Alfieri CM, Regalia A, Meneghini M, Gandolfo MT, Binda V, Cresseri D*, et al.* FP869RELATION BETWEEN FEMORAL BONE MINERAL DENSITY AND AORTIC CALCIFICATIONS IN A COHORT OF RENAL TRANSPLANTED PATIENTS. Nephrology dialysis transplantation. 2015;**30**:iii367-iii367.

3. Aoki A, Kojima F, Uchida K, Tanaka Y, Nitta K. Associations between vascular calcification, arterial stiffness and bone mineral density in chronic hemodialysis patients. Geriatr Gerontol Int. 2009;**9**:246-252.

4. Aoyagi K, Ross PD, Orloff J, Davis JW, Katagiri H, Wasnich RD. Low bone density is not associated with aortic calcification. Calcif Tissue Int. 2001;**69**:20-24.

5. Avramovski P, Avramovska M, Lazarevski M, Sikole A. Femoral neck and spine bone mineral density-Surrogate marker of aortic calcification in postmenopausal women. Anatol J Cardiol. 2016;**16**:202-209.

6. Bagger YZ, Tankó LB, Alexandersen P, Qin G, Christiansen C. Radiographic measure of aorta calcification is a site-specific predictor of bone loss and fracture risk at the hip. J Intern Med. 2006;**259**:598-605.

7. Bagger YZ, Rasmussen HB, Alexandersen P, Werge T, Christiansen C, Tankó LB. Links between cardiovascular disease and osteoporosis in postmenopausal women: serum lipids or atherosclerosis per se? Osteoporos Int. 2007;**18**:505-512.

8. Banks LM, Lees B, MacSweeney JE, Stevenson JC. Effect of degenerative spinal and aortic calcification on bone density measurements in post-menopausal women: links between osteoporosis and cardiovascular disease? Eur J Clin Invest. 1994;**24**:813-817.

9. Bolton CE, McEniery CM, Raj V, McDonnell BJ, Dixon AK, Munnery M*, et al.* Aortic calcification, arterial stiffness and bone mineral density in patients with COPD. Artery Research. 2011;**5**:30-36.

10. Boukhris R, Becker KL. Calcification of the aorta and osteoporosis. A roentgenographic study. Jama. 1972;**219**:1307-1311.

11. Bristow SM, Gamble GD, Horne AM, Reid IR. Longitudinal changes in bone mineral density, bone mineral content and bone area at the lumbar spine and hip in postmenopausal women, and the influence of abdominal aortic calcification. Bone Rep. 2019;**10**:100190.

12. Canepa M, Ameri P, AlGhatrif M, Pestelli G, Milaneschi Y, Strait JB*, et al.* Role of bone mineral density in the inverse relationship between body size and aortic calcification: results from the Baltimore Longitudinal Study of Aging. Atherosclerosis. 2014;**235**:169-175.

13. Carr JJ, Register TC, Hsu FC, Lohman K, Lenchik L, Bowden DW*, et al.* Calcified atherosclerotic plaque and bone mineral density in type 2 diabetes: the diabetes heart study. Bone. 2008;**42**:43-52.

14. Chan JJ, Cupples LA, Kiel DP, O'Donnell CJ, Hoffmann U, Samelson EJ. QCT Volumetric Bone Mineral Density and Vascular and Valvular Calcification: The Framingham Study. J Bone Miner Res. 2015;**30**:1767-1774.

15. Chau K, Martinez G, Elder GJ. Vascular calcification in patients undergoing kidney and simultaneous pancreas-kidney transplantation. Nephrology (Carlton). 2014;**19**:275-281.

16. Chow JT, Khosla S, Melton LJ, 3rd, Atkinson EJ, Camp JJ, Kearns AE. Abdominal aortic calcification, BMD, and bone microstructure: a population-based study. J Bone Miner Res. 2008;**23**:1601-1612.

17. Chue CD, Wall NA, Crabtree NJ, Zehnder D, Moody WE, Edwards NC*, et al.* Aortic calcification and femoral bone density are independently associated with left ventricular mass in patients with chronic kidney disease. PLoS One. 2012;**7**:e39241.

18. Paiva LC, Filardi S, Pinto-Neto AM, Samara A, Marques Neto JF. Impact of degenerative radiographic abnormalities and vertebral fractures on spinal bone density of women with osteoporosis. Sao Paulo Med J. 2002;**120**:9-12.

19. Dawson-Hughes B, Dallal GE. Effect of radiographic abnormalities on rate of bone loss from the spine. Calcif Tissue Int. 1990;**46**:280-281.

20. Divers J, Register TC, Langefeld CD, Wagenknecht LE, Bowden DW, Carr JJ*, et al.* Relationships between calcified atherosclerotic plaque and bone mineral density in African Americans with type 2 diabetes. J Bone Miner Res. 2011;**26**:1554-1560.

21. Drinka PJ, Bauwens SF, DeSmet AA. Lack of correlation between aortic calcification and bone density. Wis Med J. 1992;**91**:299-301.

22. El Maghraoui A, Rezqi A, Mounach A, Achemlal L, Bezza A, Ghozlani I. Relationship between vertebral fracture prevalence and abdominal aortic calcification in men. Rheumatology (Oxford). 2012;**51**:1714-1720.

23. El Maghraoui A, Rezqi A, Mounach A, Achemlal L, Bezza A, Dehhaoui M*, et al.* Vertebral fractures and abdominal aortic calcification in postmenopausal women. A cohort study. Bone. 2013;**56**:213-219.

24. El Maghraoui A, Hamza T, Sadni S, El Maataoui A, Majjad A, Rezqi A, *et al.* Vitamin D status and abdominal aortic calcification in postmenopausal women. J Bone Miner Metab. 2018;**36**:229-237.

25. Farhat GN, Cauley JA, Matthews KA, Newman AB, Johnston J, Mackey R, *et al.* Volumetric BMD and vascular calcification in middle-aged women: the Study of Women's Health Across the Nation. J Bone Miner Res. 2006;**21**:1839-1846.

26. Figueiredo CP, Rajamannan NM, Lopes JB, Caparbo VF, Takayama L, Kuroishi ME, *et al.* Serum phosphate and hip bone mineral density as additional factors for high vascular calcification scores in a community-dwelling: the São Paulo Ageing & Health Study (SPAH). Bone. 2013;**52**:354-359.

27. Flipon E, Liabeuf S, Fardellone P, Mentaverri R, Ryckelynck T, Grados F, *et al.* Is vascular calcification associated with bone mineral density and osteoporotic fractures in ambulatory, elderly women? Osteoporos Int. 2012;**23**:1533-1539.

28. Frye MA, Melton LJ, 3rd, Bryant SC, Fitzpatrick LA, Wahner HW, Schwartz RS, *et al.* Osteoporosis and calcification of the aorta. Bone Miner. 1992;**19**:185-194.

29. Fusaro M, Tripepi G, Noale M, Vajente N, Plebani M, Zaninotto M, *et al.* High prevalence of vertebral fractures assessed by quantitative morphometry in hemodialysis patients, strongly associated with vascular calcifications. Calcif Tissue Int. 2013;**93**:39-47.

30. Ghozlani I, El Maataoui A, Ghazi M, Kherrab A, Niamane R. FRI0548 Influence of homocysteine and vertebral fractures on prevalent abdominal aortic calcification in postmenopausal women: a multicentric cross-sectional study. BMJ Publishing Group Ltd; 2017.

31. Grant M, Turner ME, Murray-Guenther J, Anastassiades T, Hopman WM, Adams SM, *et al.* A novel quantitative approach to the measurement of abdominal aortic calcification as applied to the Canadian Multicenter Osteoporosis Study (CaMOS). Bone. 2017;**97**:201-208.

32. Hampson G, Edwards S, Conroy S, Blake GM, Fogelman I, Frost ML. The relationship between inhibitors of the Wnt signalling pathway (Dickkopf-1(DKK1) and sclerostin), bone mineral density, vascular calcification and arterial stiffness in post-menopausal women. Bone. 2013;**56**:42-47.

33. Hanna TN, Zygmont ME, Harmouche E, Salastekar N, Johnson JO, Khosa F. Association of lumbar fractures, abdominal aortic calcification, and osteopenia. Clin Imaging. 2015;**39**:662-666.

34. Hyder JA, Allison MA, Barrett-Connor E, Detrano R, Wong ND, Sirlin C*, et al.* Bone mineral density and atherosclerosis: the Multi-Ethnic Study of Atherosclerosis, Abdominal Aortic Calcium Study. Atherosclerosis. 2010;**209**:283-289.

35. Iannotti N, Gazzola L, Savoldi A, Suardi E, Cogliandro V, Bai F*, et al.* Association between abdominal aortic calcifications, bone mineral density and vertebral fractures in a cohort of HIV-positive patients. J Int AIDS Soc. 2014;**17**:19715.

36. Iba K, Takada J, Yamashita T. The serum level of bone-specific alkaline phosphatase activity is associated with aortic calcification in osteoporosis patients. J Bone Miner Metab. 2004;**22**:594-596.

37. Idoate F, Cadore EL, Casas-Herrero A, Zambom-Ferraresi F, Martínez-Velilla N, Rodriguez-Mañas L*, et al.* Noncoronary Vascular Calcification, Bone Mineral Density, and Muscle Mass in Institutionalized Frail Nonagenarians. Rejuvenation Res. 2017;**20**:298-308.

38. Iwamoto J, Matsumoto H, Takeda T, Sato Y, Uzawa M. A radiographic study on the associations of age and prevalence of vertebral fractures with abdominal aortic calcification in Japanese postmenopausal women and men. J Osteoporos. 2010;**2010**:748380.

39. Jamal SA, Leiter RE, Bauer DC. Hyperhomocysteinaemia and aortic calcification are associated with fractures in patients on haemodialysis. Qjm. 2005;**98**:575-579.

40. Jensky NE, Hyder JA, Allison MA, Wong N, Aboyans V, Blumenthal RS*, et al.* The association of bone density and calcified atherosclerosis is stronger in women without dyslipidemia: the multi-ethnic study of atherosclerosis. J Bone Miner Res. 2011;**26**:2702-2709.

41. Kim KJ, Kim KM, Park KH, Choi HS, Rhee Y, Lee YH*, et al.* Aortic calcification and bone metabolism: the relationship between aortic calcification, BMD, vertebral fracture, 25-hydroxyvitamin D, and osteocalcin. Calcif Tissue Int. 2012;**91**:370-378.

42. Kim K, Song SH, Kim IJ, Jeon YK. Is dual-energy absorptiometry accurate in the assessment of bone status of patients with chronic kidney disease? Osteoporos Int. 2021.

43. Kinsella S, Murphy K, Breen M, O'Neill S, McLaughlin P, Coyle J*, et al.* Comparison of single CT scan assessment of bone mineral density, vascular calcification and fat mass with standard clinical measurements in renal transplant subjects: the ABC HeART study. BMC Nephrology. 2015;**16**:188.

44. Kuipers AL, Zmuda JM, Carr JJ, Terry JG, Patrick AL, Ge Y*, et al.* Association of volumetric bone mineral density with abdominal aortic calcification in African ancestry men. Osteoporos Int. 2014;**25**:1063-1069.

45. Lampropoulos CE, Kalamara P, Konsta M, Papaioannou I, Papadima E, Antoniou Z, *et al.* Osteoporosis and vascular calcification in postmenopausal women: a cross-sectional study. Climacteric. 2016;**19**:303-307.

46. Lee MJ, Shin DH, Kim SJ, Oh HJ, Yoo DE, Ko KI, *et al.* Progression of aortic arch calcification over 1 year is an independent predictor of mortality in incident peritoneal dialysis patients. PLoS One. 2012;**7**:e48793.

47. Lewis JR, Eggermont CJ, Schousboe JT, Lim WH, Wong G, Khoo B, *et al.* Association Between Abdominal Aortic Calcification, Bone Mineral Density, and Fracture in Older Women. J Bone Miner Res. 2019;**34**:2052-2060.

48. Li S, Yin L, Li K, Hu B, Wang L, Wang Y, *et al.* Relationship of volumetric bone mineral density by quantitative computed tomography with abdominal aortic calcification. Bone. 2020;**133**:115226.

49. Majjad A, Ghassem MA, Toufik H, Sadni S, Debbarh Z, Djossou JH, *et al.* Relationship between vertebral fracture prevalence and abdominal aortic calcification in women with rheumatoid arthritis. Bone. 2020;**141**:115599.

50. Mohammad A, Lohan D, Bergin D, Mooney S, Newell J, O'Donnell M, *et al.* The Prevalence of Aortic Calcification on Vertebral Fracture Assessment Imaging Among Patients With Rheumatoid Arthritis. Journal of Clinical Densitometry. 2014;**17**:72-77.

51. Nakatsuka K, Sirtori PL, McCloskey EV, Khan SA, Orgee JM, O'neill TW, *et al.* Preliminary study on relationship between vertebral fracture and aortic calcification in postmenopausal women. Journal of bone and mineral metabolism. 1997;**15**:218-222.

52. Naves M, Rodríguez-García M, Díaz-López JB, Gómez-Alonso C, Cannata-Andía JB. Progression of vascular calcifications is associated with greater bone loss and increased bone fractures. Osteoporos Int. 2008;**19**:1161-1166.

53. Paccou J, Renard C, Liabeuf S, Kamel S, Fardellone P, Massy ZA, *et al.* Coronary and abdominal aorta calcification in rheumatoid arthritis: relationships with traditional cardiovascular risk factors, disease characteristics, and concomitant treatments. J Rheumatol. 2014;**41**:2137-2144.

54. Pelletier S, Confavreux CB, Haesebaert J, Guebre-Egziabher F, Bacchetta J, Carlier MC, *et al.* Serum sclerostin: the missing link in the bone-vessel cross-talk in hemodialysis patients? Osteoporos Int. 2015;**26**:2165-2174.

55. Pirlamarla AK, Agalliu I, DiVito J, Stern JM. MP19-04 THE RELATIONSHIP BETWEEN VASCULAR CALCIFICATION AND KIDNEY STONE FORMERS IN A

HOSPITAL-BASED CASE CONTROL STUDY. The Journal of Urology. 2017;**197**:e230-e230.

56. Pirro M, Manfredelli MR, Schillaci G, Helou RS, Bagaglia F, Melis F*, et al.* Association between circulating osteoblast progenitor cells and aortic calcifications in women with postmenopausal osteoporosis. Nutr Metab Cardiovasc Dis. 2013;**23**:466-472.

57. Pozzo M, Lozano M, Ilera V, Hermberg HC. Relation between aortic calcifications and bone mineral density measured by quantitative computed tomography (QCT). Bone. 2006;**5**:S11-S12.

58. Orwoll ES, Oviatt SK, Mann T. The impact of osteophytic and vascular calcifications on vertebral mineral density measurements in men. J Clin Endocrinol Metab. 1990;**70**:1202-1207.

59. Rajzbaum G, Roger VL, Bézie Y, Chauffert M, Bréville P, Roux F*, et al.* French women, fractures and aortic calcifications. J Intern Med. 2005;**257**:117-119.

60. REID IR, EVANS MC, AMES R, WATTIE DJ. The Influence of Osteophytes and Aortic Calcification on Spinal Mineral Density in Postmenopausal Women*. The Journal of Clinical Endocrinology & Metabolism. 1991;**72**:1372-1374.

61. Rodríguez AJ, Scott D, Hodge A, English DR, Giles GG, Ebeling PR. Associations between hip bone mineral density, aortic calcification and cardiac workload in community-dwelling older Australians. Osteoporos Int. 2017;**28**:2239-2245.

62. Rodríguez-García M, Gómez-Alonso C, Naves-Díaz M, Diaz-Lopez JB, Diaz-Corte C, Cannata-Andía JB. Vascular calcifications, vertebral fractures and mortality in haemodialysis patients. Nephrol Dial Transplant. 2009;**24**:239-246.

63. Samelson EJ, Cupples LA, Broe KE, Hannan MT, O'Donnell CJ, Kiel DP. Vascular calcification in middle age and long-term risk of hip fracture: the Framingham Study. J Bone Miner Res. 2007;**22**:1449-1454.

64. Salam S, Paggiosi M, Gallagher O, Eastell R, Khwaja A. FP610 Vascular calcification in advanced CKD and its relationship with bone microstructures. Nephrology Dialysis Transplantation. 2019;**34**:gfz106. FP610.

65. Schousboe JT, Langsetmo L, Szulc P, Lewis JR, Taylor BC, Kats AM*, et al.* Joint Associations of Prevalent Radiographic Vertebral Fracture and Abdominal Aortic Calcification With Incident Hip, Major Osteoporotic, and Clinical Vertebral Fractures. J Bone Miner Res. 2021;**36**:892-900.

66. Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V. Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab. 2004;**89**:4246-4253.

67. Shavit L, Girfoglio D, Vijay V, Goldsmith D, Ferraro PM, Moochhala SH, *et al.* Vascular calcification and bone mineral density in recurrent kidney stone formers. Clin J Am Soc Nephrol. 2015;**10**:278-285.

68. Shen H, Bielak LF, Streeten EA, Ryan KA, Rumberger JA, Sheedy PF, 2nd, *et al.* Relationship between vascular calcification and bone mineral density in the Old-order Amish. Calcif Tissue Int. 2007;**80**:244-250.

69. Simon SP, Fodor D, Muntean L, Poanta L, Cristea P, Rednic S. Bone mineral density, vertebral fractures and body mass index in postmenopausal women with abdominal aortic calcification. Endocr Res. 2014;**39**:1-6.

70. Sotomayor CG, Benjamens S, Gomes-Neto AW, Pol RA, Groothof D, Te Velde-Keyzer CA, *et al.* Bone Mineral Density and Aortic Calcification: Evidence for a Bone-vascular Axis After Kidney Transplantation. Transplantation. 2021;**105**:231-239.

71. Szulc P, Kiel DP, Delmas PD. Calcifications in the abdominal aorta predict fractures in men: MINOS study. J Bone Miner Res. 2008;**23**:95-102.

72. Szulc P, Samelson EJ, Sornay-Rendu E, Chapurlat R, Kiel DP. Severity of aortic calcification is positively associated with vertebral fracture in older men--a densitometry study in the STRAMBO cohort. Osteoporos Int. 2013;**24**:1177-1184.

73. Szulc P, Blackwell T, Schousboe JT, Bauer DC, Cawthon P, Lane NE, *et al.* High hip fracture risk in men with severe aortic calcification: MrOS study. J Bone Miner Res. 2014;**29**:968-975.

74. Szulc P, Blackwell T, Kiel DP, Schousboe JT, Cauley J, Hillier T, *et al.* Abdominal aortic calcification and risk of fracture among older women — The SOF study. Bone. 2015;**81**:16-23.

75. Tankó LB, Qin G, Alexandersen P, Bagger YZ, Christiansen C. Effective doses of ibandronate do not influence the 3-year progression of aortic calcification in elderly osteoporotic women. Osteoporos Int. 2005;**16**:184-190.

76. Torres A, Torregrosa V, Marcen R, Campistol JM, Arias M, Hernández D, *et al.* Mineral metabolism disorders, vertebral fractures and aortic calcifications in stable kidney transplant recipients: The role of gender (EMITRAL study). Nefrologia. 2016;**36**:255-267.

77. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG. Associations between vascular calcification, arterial stiffness and bone mineral density in chronic kidney disease. Nephrol Dial Transplant. 2008;**23**:586-593.

78. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG. Determination and validation of aortic calcification measurement from lateral bone densitometry in dialysis patients. Clin J Am Soc Nephrol. 2009;**4**:119-127.

79. Vogt MT, San Valentin R, Forrest KY, Nevitt MC, Cauley JA. Bone mineral density and aortic calcification: the Study of Osteoporotic Fractures. J Am Geriatr Soc. 1997;**45**:140-145.

80. Wagenknecht LE, Divers J, Register TC, Russell GB, Bowden DW, Xu J*, et al.* Bone Mineral Density and Progression of Subclinical Atherosclerosis in African-Americans With Type 2 Diabetes. J Clin Endocrinol Metab. 2016;**101**:4135-4141.

81. Wang TK, Bolland MJ, van Pelt NC, Horne AM, Mason BH, Ames RW*, et al.* Relationships between vascular calcification, calcium metabolism, bone density, and fractures. J Bone Miner Res. 2010;**25**:2777-2785.

82. Woisetschläger M, Spångeus A. Model for improved correlation of BMD values between abdominal routine Dual energy CT data and DXA scans. European journal of radiology. 2018;**99**:76-81.

83. Wyers CE, Vranken L, Schousboe JT, van der Velde RY, de Bruin IJ, Janzing HM*, et al.* Systematic Evaluation of Abdominal Aortic Calcification Reveals Unknown Cardiovascular Disease Risk in Patients Visiting a Fracture Liaison Service. Journal of Bone and Mineral Research. 2017;**32**:S361-S361.

84. Yokomoto-Umakoshi M, Umakoshi H, Ogata M, Fukumoto T, Matsuda Y, Miyazawa T*, et al.* Coexistence of osteoporosis and atherosclerosis in pheochromocytoma: new insights into its long-term management. Osteoporos Int. 2020;**31**:2151-2160.

85. Zhou R, Zhou H, Cui M, Wang Y, Tan J, Sawmiller D*, et al.* Association between aortic calcification and the risk of osteoporosis in a chinese cohort: the Chongqing osteoporosis study. Calcif Tissue Int. 2013;**93**:419-425.

86. Zhou R, Zhou H, Cui M, Chen L, Xu J. The association between aortic calcification and fracture risk in postmenopausal women in China: the prospective Chongqing osteoporosis study. PLoS One. 2014;**9**:e93882.

87. Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B*, et al.* Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. Bmj. 2015;**350**:h870.