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SYSTEMATIC REVIEW AND META-ANALYSIS

# Prognostic Value of Abdominal Aortic Calcification: A Systematic Review and Meta-Analysis of Observational Studies

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**BACKGROUND:** The prognostic importance of abdominal aortic calcification (AAC) viewed on noninvasive imaging modalities remains uncertain.

**METHODS AND RESULTS:** We searched electronic databases (MEDLINE and Embase) until March 2018. Multiple reviewers identified prospective studies reporting AAC and incident cardiovascular events or all-cause mortality. Two independent reviewers assessed eligibility and risk of bias and extracted data. Summary risk ratios (RRs) were estimated using random-effects models comparing the higher AAC groups combined (any or more advanced AAC) to the lowest reported AAC group. We identified 52 studies (46 cohorts, 36 092 participants); only studies of patients with chronic kidney disease (57%) and the general older-elderly (median, 68 years; range, 60–80 years) populations (26%) had sufficient data to meta-analyze. People with any or more advanced AAC had higher risk of cardiovascular events (RR, 1.83; 95% CI, 1.40–2.39), fatal cardiovascular events (RR, 1.85; 95% CI, 1.44–2.39), and all-cause mortality (RR, 1.98; 95% CI, 1.55–2.53). Patients with chronic kidney disease with any or more advanced AAC had a higher risk of cardiovascular events (RR, 3.47; 95% CI, 2.21–5.45), fatal cardiovascular events (RR, 3.68; 95% CI, 2.32–5.84), and all-cause mortality (RR, 2.40; 95% CI, 1.95–2.97).

**CONCLUSIONS:** Higher-risk populations, such as the elderly and those with chronic kidney disease with AAC have substantially greater risk of future cardiovascular events and poorer prognosis. Providing information on AAC may help clinicians understand and manage patients' cardiovascular risk better.

**Key Words:** abdominal aortic calcification ■ all-cause mortality ■ cardiovascular events and deaths ■ chronic kidney disease ■ general population

The presence of coronary artery calcification, an established marker of subclinical atherosclerosis, has been shown to predict future risk of cardiovascular events and mortality.[1] Calcifications in other extracoronary vascular beds such as the carotid, iliac, and abdominal aorta are also common, but fewer studies have investigated the prognostic importance of these calcified vascular lesions. Vascular calcification at these sites is often observed in high-risk patients such as those with advanced age, diabetes mellitus, advanced atherosclerosis, or chronic kidney disease (CKD). A number of noninvasive, safe, and widely available modalities can be used to assess vascular calcification at these sites, particularly of the abdominal aorta.[2]

The abdominal aorta is one of the first vascular beds where atherosclerotic calcification is observed,

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## CLINICAL PERSPECTIVE

### What Is New?

- We demonstrate that the presence and severity of abdominal aortic calcification detected using any imaging modality is an underappreciated measure of structural vascular disease that identifies people with substantially higher risk of clinical cardiovascular events and poorer long-term prognosis.

### What Are the Clinical Implications?

- Fortuitous findings of abdominal aortic calcification in patients with no known disease or information on cardiovascular risk factors, should be considered to be an indication for diagnostic testing such as lipid assays, ECG, or further diagnostic imaging (ie, coronary artery calcification scores).

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AAC** | abdominal aortic calcification |
| **ARD** | absolute risk difference |
| **sROC** | summary receiver operator characteristic |

often preceding the development of coronary artery calcification.[3,4] Population-based studies have found abdominal aortic calcification (AAC) occurs in ≈1 in 3 people aged 45 to 54 years and up to 9 in 10 people aged over 75 years.[5] For older patients with type 2 diabetes mellitus or CKD requiring dialysis, the prevalence ranges between 84% and 97%.[6–8] AAC can be assessed by computed tomography (CT) or lateral spine images from standard radiographs or dual-energy x-ray absorptiometry (DXA) machines. Associations between AAC and cardiovascular events were reported in a wide range of clinical settings such as middle-aged to older men and women from the general population,[9–11] individuals with type 2 diabetes mellitus,[12] and patients with CKD.[6] Some, but not all, reports have suggested that the magnitude of risk for cardiovascular events, fatal cardiovascular events, and all-cause mortality depends on the amount of AAC visible on imaging tests, with the greatest risk found in patients with the most advanced calcification.[9,13,14]

However, these studies are relatively small and report on a limited number of clinically meaningful outcomes. To date, most systematic reviews and meta-analyses have focused on a single clinical population,[15,16] and few attempts have been made to summarize and integrate data from all published studies to identify clinically important differences among studies, identify subsets of patients where AAC is more or less clinically important, and identify areas where more research is needed. As such, we undertook this systematic review and meta-analysis.

We hypothesized that people with AAC would have a greater risk of cardiovascular events, fatal cardiovascular events, and poorer prognosis. Additionally, we sought to determine the strength of this association and whether this varied across different clinical settings using different imaging modalities and in populations with varying comorbid factors such as older age, sex, diabetes mellitus, smoking, hypertension, and dyslipidemia.

## METHODS

This systematic review and meta-analysis was written and reported in adherence to the Meta-analysis of Observational Studies in Epidemiology[17] reporting criteria. All data relevant to this study are available from the corresponding author upon reasonable request.

### Inclusion and Exclusion Criteria

We included any cohort or case-control study that reported the association between AAC and any cardiovascular outcomes such as coronary heart disease, cerebrovascular disease, heart failure, peripheral arterial disease and the like, or all-cause mortality. We excluded cross-sectional studies and reviews of existing literature.

### Search Strategy and Process for Selecting Studies

A comprehensive literature search within MEDLINE and Embase databases was conducted to source all possibly relevant studies for review, without language restriction, until March 2018. Conference proceedings and abstracts were evaluated, and a hand search of reference lists was undertaken. The search terms were combined with the Boolean "AND" to find all potentially relevant studies. When >1 publication for a study was retrieved, articles with the most up-to-date and complete information were included, although additional unique data from all sources were considered and included when relevant. Examples of the search strategy are shown in Table S1. At least 2 investigators independently retrieved and assessed citations for eligibility, assessed the risk of bias, and extracted the data (K.L., P.S., H.S., or M.S.), and another investigator was sought when agreement could not be reached (J.R.L.).

### Risk of Bias and Level of Evidence Assessment

The risk of bias was assessed using the Newcastle-Ottawa Scale for case-control and cohort studies

and included the following domains: representativeness of the exposed population, appropriate selection and comparison of the study groups, adequate ascertainment of exposure, and whether the comparability of the cohorts was evaluated appropriately with detailed assessment of all outcomes within an appropriate follow-up time. At least 2 investigators independently assessed risk of bias (K.L., M.S., H.S., or J.R.L.). Summary estimates of the confidence placed on the evidence were evaluated using the Grading of Recommendations Assessment Development and Evaluation of evidence about prognosis. Unlike Grading of Recommendations Assessment Development and Evaluation for clinical practice guidelines where observational evidence starts at low-quality evidence and can then be rated up or down, the Grading of Recommendations Assessment Development and Evaluation for evidence about prognosis for observational studies starts with high-quality evidence. These criteria are based on (1) 5 domains diminishing confidence (–1 for risk of bias, inconsistency, imprecision, indirectness, and publication bias) and (2) 2 situations increasing confidence (+1 or +2 for large–very large effect size and a +1 for a dose-response gradient [increasing pooled relative risks for cardiovascular events and all-cause mortality with increasing severity of AAC]).[18] Details of how the Grading of Recommendations Assessment Development and Evaluation assessments were performed are provided in Tables S2 and S3.

## AAC Reporting

AAC was reported either quantitatively (computed tomography) or semiquantitatively (x-ray and DXA). We used the group with the lowest reported AAC as the referent and combined all other reported groups (any or more advanced AAC) to calculate the absolute risk difference (ARD) and relative risk for any cardiovascular outcomes or all-cause mortality. This approach was required because of different severity or distribution thresholds used to define categories of AAC (Tables S4 and S5). In secondary analyses, we analyzed studies that reported AAC by either (1) the absence versus the presence of AAC to determine the association between any AAC and outcomes or (2) studies that reported ≥3 categories of AAC for assessing whether a "dose-response" gradient was evident. Where data for >3 categories of AAC were available, we collapsed the middle groups and assigned them as "moderate AAC." To further address thresholds of AAC we used the R package for the meta-analysis of diagnostic accuracy ("mada") to calculate the bivariate summary receiver operator characteristic (sROC) curves with default parameters.[19,20] sROC converts paired sensitivity and specificity into a single measure of accuracy (diagnostic odds ratio).[20]

## Data Synthesis and Statistical Analysis

Where cardiovascular event data were reported in individual studies, pooled risk differences and risk ratios (RRs) with 95% CIs were calculated, from which a summary estimate was determined using DerSimonian-Laird random-effects models using Comprehensive Meta-Analysis, Version 3.[21] We chose the random-effects model over the fixed-effects as a more conservative approach in the presence of heterogeneity. However, we also performed the main analyses using fixed effects. Heterogeneity was investigated using the $I^2$ statistic.[22,23] We considered the $I^2$ thresholds of <25%, 25% to 49%, 50% to 75%, and >75% to represent low, moderate, high, and very high heterogeneity, respectively. The likelihood of publication bias was evaluated by visual inspection of funnel plots and using the Egger regression test.[24] To understand how adjusting for traditional cardiovascular risk factors may affect the pooled results, we extracted adjusted estimates of risk from individual studies (hazard ratio or odds ratio) of the general population, see Table S6 for adjustments used in each study.

## Subgroup Analysis and Meta-Regression

We used subgroup analysis to investigate clinical heterogeneity (general population, CKD, or other and age of cohort <60, 60–69, and ≥70 years) and methodological heterogeneity (risk of bias of studies, imaging modality [radiograph, DXA, or CT] and duration of follow-up <5, 5–9, ≥10 years). Meta-regression was also conducted using a random effects model in the subgroup categories above and with the variables presented in Table 1 such as mean cohort systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol.

# RESULTS

## Literature Search

Of the 458 potentially eligible publications, 52 studies (50 cohort studies and 2 case-control studies; total number of individuals, 36 092) met the eligibility criteria.[6,8–14,25–68] Details of the individual studies are provided in Table 2. The interreviewer level of agreement regarding eligibility of included studies was very good (κ=0.97). Four cohorts had multiple eligible publications (Framingham Heart Study [n=4], Rotterdam Study [n=2], MINOS study [n=2] and PERF (Prospective Epidemiological Risk Factors) study [n=2]) for a total of 46 unique cohorts (Table 1

**Table 1. Characteristics of Included Studies (n=46)**

| Characteristic | n (%) |
|---|---|
| Year of publication | |
| Pre-2011 | 15 (33) |
| 2011–2012 | 6 (13) |
| 2013–current | 25 (54) |
| Setting | |
| Chronic kidney disease | 26 (57) |
| General population | 12 (26) |
| Other | 8 (17) |
| Region | |
| United States | 8 (17) |
| Europe | 19 (41) |
| Asia | 15 (33) |
| Oceania | 3 (7) |
| Middle East | 1 (2) |
| Number of subjects | |
| <100 | 7 (15) |
| 100–500 | 24 (52) |
| ≥500 | 15 (33) |
| Years of follow-up | |
| 1–3 | 19 (41) |
| >3–5 | 13 (28) |
| >5–10 | 10 (22) |
| >10 | 3 (7) |
| Not specified | 1 (2) |
| Test characteristics | |
| Modality of assessing abdominal aortic calcification | |
| X-ray | 22 (48) |
| Quantitative computed tomography | 17 (37) |
| Dual energy X-ray absorptiometry | 5 (11) |
| Ultrasound | 2 (4) |
| Demographic | |
| Mean age, y | |
| <60 | 18 (39) |
| 60–70 | 20 (43) |
| >70 | 6 (13) |
| Not specified | 2 (4) |
| Sex | |
| All male | 1 (2) |
| All female | 4 (9) |
| Mixed | 39 (85) |
| Not specified | 2 (4) |
| Prevalence of diabetes mellitus | |
| <10% | 13 (28) |
| ≥10% | 30 (65) |
| Not specified | 3 (7) |
| Proportion of current smokers | |
| <15% | 13 (28) |
| ≥15% | 16 (35) |
| Not specified | 17 (37) |
| Prevalence of hypertension | |
| <50% | 16 (35) |
| ≥50% | 17 (37) |
| Not specified | 13 (28) |

and Figure 1). A total of 32 publications (29 cohorts) provided extractable data for quantitative synthesis.

## Newcastle-Ottawa Scale Risk of Bias

For the 52 cohort and case-control studies, the overall risk of bias was considered low to moderate for comparability. For the selection and outcomes domains, the risk of bias was considered moderate to high. Detailed risk of bias assessment and results are presented in Data S1 and Figure S1.

## Characteristics of Included Studies

Most studies were published in 2011 or later and represented cohorts of <500 people. Over half (57%) of the studies were in patients with CKD (estimated glomerular filtration rate <60 mL/min per 1.73 $m^2$ to dialysis) and kidney transplant recipients, 26% were from the general population, 4% patients with diabetes mellitus, and 13% from other clinical settings (Table 1). AAC was evaluated by radiograph in 46% of studies, 37% by CT, 11% DXA, and 6% by ultrasound or 2 separate imaging modalities. Follow-up time in the cohorts ranged from 1 to 22 years, with a median follow-up time of 6.5 years.

## Reporting of AAC

AAC was reported in a number of different ways for x-rays and DXA (presence versus absence, AAC 8 scores, AAC 24 scores, or measured length of calcification). For CT, AAC was reported as presence versus absence, percentiles of the cohort, calcium scores, or AAC index, as outlined in Table 2. Cut points for individual studies that contributed data for incident events—cardiovascular events (n=16), fatal cardiovascular events (n=11), all-cause mortality (n=17), cerebrovascular events (n=5), and coronary heart disease (n=6)—are shown in Table S4 (x-ray and DXA) and Table S5 (CT). There were insufficient studies reporting AAC for all other cardiovascular outcomes. Absolute risk differences and relative risk differences for each individual study are presented in Table 3.

## Clinical Heterogeneity

A priori subgroup analyses (CKD versus general population) identified clinical heterogeneity attributable to the participants recruited (data not shown). This was

**Table 2. Overview of Studies Reporting the Association of AAC With Outcomes**

| Study Reference | Design | End Points | Population | No. at Risk | Follow Up (y) | Imaging Modality | AA Segment | AAC Modeled as |
|---|---|---|---|---|---|---|---|---|
| General population | | | | | | | | |
| Bolland 2010[11] | Two independent longitudinal studies | CVE, MI, CVA, sickle cell disease | W=Healthy postmenopausal women and middle-aged and M=older men | W-1471 M-323 | W-4.4 M-3.3 | DXA | L1-L4 | Present/absent AAC8-continuous |
| Criqui 2014[9]* | Longitudinal | Cardiovascular death, CVE, ACM | Men and women aged 45–84 y | 1974 | 5.5 | EBCT or MDCT | 8-cm segment proximal to the aortic bifurcation (L2–L4) | Agatston score -percentiles- 0–50th/51–75th/76–100th |
| Ganz 2012[25] | Longitudinal | Cardiovascular deaths, ACM | Postmenopausal women aged 45–70 y | 308 | 9.0 | X-ray | L1–L4 | Present/absent AAC24-continous |
| Golestani 2010[26] | Nested case-control | Cardiovascular death, CVE, MI, CVA | Consecutive patients referred for BMD testing between 2005 and 2007 | 489 | 2.6 | DXA | L1–L4 | AAC8—control/low/high |
| Hoffman 2016[27] | Longitudinal | CVE, CHD, ACM | Men aged ≥35 y and women aged ≥40 y | 3217 | 8.0 | MDCT | Above the iliac bifurcation and below the diaphragm (L1–L4) | Agatston score –quartiles and continuous |
| Hollander 2003[28] | Longitudinal | CVA | Men and women aged ≥55 y | 6913 | 6.1 | X-ray | L1–L4 | Length of calcification (cm)—tertiles |
| Lewis 2018[10] | Longitudinal | CVE, cardiovascular death, ACM, CHD, CVA | Healthy women aged >70 | 1052 | 14.5 | DXA | L1–L4 | AAC24- present/absent, low/moderate/severe |
| Rodondi 2007[29] | Longitudinal | Cardiovascular death, ACM | Elderly white women aged ≥65 y | 2056 | 13.0 | X-ray | ns | Present/absent |
| Schousboe 2008[14] | Nested case-control | CVE | White women ≥75 y recruited from general practice registers | 732 | 4.0 | DXA | L1–L4 | AAC24—tertiles |
| Szulc 2008[30] | Longitudinal | ACM | Men aged 51–85 y | 781 | 10 | X-ray | L1–L4 | Present/absent AAC24—tertiles |
| Wilson 2001[13] | Longitudinal | CVE, cardiovascular death, CHD | Framingham Heart Study free of CVD | 2515 | 22.0 | X-ray | L1-L4 | AAC24- tertiles |
| Witteman 1986[31] | Nested case-control | Cardiovascular death | People ≥45 y | 415 | 9.0 | X-ray | ns | Present/absent |
| Chronic kidney disease | | | | | | | | |
| Blacher 2001[32] | Longitudinal | Cardiovascular death, ACM | Hemodialysis ≥3 mo | 110 | 4.4 | Ultrasound and x-ray | 10-cm segment above the iliac bifurcation (L1–L4) | Present/absent |
| Cho 2017[33] | Longitudinal | CVE | Hemodialysis >3 mo | 191 | 1.5 | X-ray | L1–L4 | AAC24–low/high |

(*Continued*)

**Table 2. Continued**

| Study Reference | Design | End Points | Population | No. at Risk | Follow Up (y) | Imaging Modality | AA Segment | AAC Modeled as |
|---|---|---|---|---|---|---|---|---|
| Claes 2013[34] | Longitudinal | CVE | Single-kidney transplant recipients (assessed at time of admission for transplant) | 253 | 3.0 | X-ray | L1–L4 | AAC24-none/mild/moderate-severe, continuous |
| Disthabanchong 2018[35] | Longitudinal | ACM | Consecutive nondialysis patients with CKD stage 2–5, maintenance hemodialysis patients on kidney transplant waiting list and long-term kidney transplant recipients | 419 | 5 | X-ray | L1–L4 | AAC24 low/high |
| Djuric 2016[8] | Longitudinal | ACM | Hemodialysis >6 mo | 71 | 3.0 | CT | ns | Agatston score—2 groups selected based on ROC |
| Fusaro 2012[36] | Longitudinal | ACM | Hemodialysis >12 mo | 387 | 2.7 | X-ray | L1–L4 | Present/abse |
| Gorriz 2015[37] | Longitudinal | Cardiovascular death, CVE, ACM | ≥18 y nondialysis patients with CKD stages 3–5 | 568 | 3.0 | X-ray | L1–L4 | AAC24—low/high |
| Hanada 2010[38] | Longitudinal | CVE | ≥18 y non-dialysis patients with CKD stage 3–5 | 83 | 4.0 | CT | 10-cm segment above the iliac bifurcation (L1–L4) | AAC index—median AAC index |
| Hong 2013[39] | Retrospective | Cardiovascular death, ACM | Patients on hemodialysis with dialysis ≥3 times/wk for >3 mo | 217 | 2.2 | X-ray | L2–L3 | Present/absent |
| Huang 2014[40] | Longitudinal | CVE, ACM | Peritoneal dialysis >2 mo and aged ≥20 y | 183 | 3.0 | MDCT | 4 consecutive slices above the iliac bifurcation | % calcified—2 groups based on ROC low/high |
| Imanishi 2014[41] | Longitudinal | CVE | Renal transplant recipients (assessed within 12 mo before transplant) | 61 | 5.0 | CT | 10-cm segment above the iliac bifurcation (L1–L4) | AAC index—median AAC index |
| Kato 2003[42] | Longitudinal | Cardiovascular death, ACM | Stable patients on hemodialysis | 219 | 5.0 | CT | L2–L3 | AAC index—median AAC index |
| Kwon 2014[43] | Retrospective | CVE, ACM | Patients on chronic hemodialysis | 112 | 4.0 | X-ray | L1–L4 | AAC24—quartiles, 2 groups based on ROC |
| Li 2016[44] | Longitudinal | Cardiovascular death, ACM | Patients on hemodialysis ≥3 mo | 164 | 4.5 | X-ray | L1–L4 | Present/absent |
| Martino 2013[45] | Longitudinal | Cardiovascular death, ACM, CVE | All patients on peritoneal dialysis from October 2008 -January 2009 | 74 | 2.5 | X-ray | L1–L4 | AAC24—tertiles |
| Munguia 2015[46] | Longitudinal | MACE, MACE or cardiovascular death, ACM | Renal transplant recipients (assessed before transplant) from July 2011 to September 2013 | 119 | 3.8 | X-ray | L1–L4 | AAC24—3 groups |
| NasrAllah 2016[47] | Longitudinal | CVE, ACM | Patients on hemodialysis | 93 | 5.0 | X-ray, CT | L1–L4 (X-ray), | AAC24, upper AAC index, lower AAC index |

(*Continued*)

**Table 2. Continued**

| Study Reference | Design | End Points | Population | No. at Risk | Follow Up (y) | Imaging Modality | AA Segment | AAC Modeled as |
|---|---|---|---|---|---|---|---|---|
| Ohya 2011[48] | Longitudinal | Cardiovascular deaths, ACM | Patients on maintenance hemodialysis | 137 | 7.9 | CT | 10-cm segment above the iliac bifurcation (L1–L4) | AAC index—median AAC index |
| Okuno 2007[49] | Longitudinal | Cardiovascular death, ACM | Patients on maintenance hemodialysis >3 mo | 515 | 4.3 | X-ray | L1–L4 | Present/absent |
| Peeters 2017[50] | Longitudinal | CVE | Nondialysis patients with CKD | 280 | 2.4 | X-ray | L1–L4 | Present/absent AAC24- median |
| Tatami 2015[6] | Longitudinal | CVE, cardiovascular death, HF, MI, CVA, revascularization, ACM | Nondialysis patients with CKD | 347 | 3.5 | CT | Renal artery to iliac bifurcation (L2–L4) | AAC index—tertiles AAC index |
| Verbeke 2011[63] | Longitudinal | CVE/ACM | Patients aged ≥18 y undergoing maintenance hemodialysis or peritoneal dialysis | 1076 | 2.0 | X-ray | L1–L4 | AAC24- |
| Vezzoli 2014[64] | Longitudinal | CVE | Patients with CKD at different stages including dialysis | 92 | 2.0 | DXA | L1–L4 | CVD-2 groups ns why cutoff was chosen |
| Wang 2017[65] | Longitudinal | CVE | Patients with CKD at stages 3–5 | 161 | 1.3 | X-ray | L1–4 | Present/absent |
| Yoon 2012[66] | Longitudinal | CVE/ACM | Patients undergoing maintenance hemodialysis | 128 | 1.4 | CT | ns | AAC index—tertiles AAC index |
| Yoon 2013[67] | Longitudinal | CVE/ACM | Patients undergoing peritoneal dialysis | 92 | 2.9 | CT | ns | AAC index—median AAC index |
| Other populations | | | | | | | | |
| Allison 2012[68]* | Longitudinal | Cardiovascular death, ACM | Individuals presenting for preventive medicine services | 4544 | 7.8 | CT | Diaphragm to the iliac bifurcation (L1–L4) | Present/absent Agatston score-continuous |
| Cox 2014[12]* | Longitudinal | Cardiovascular death, ACM | Patients with type 2 diabetes mellitus | 699 | 8.4 | CT | 2.5-cm proximal of the superior mesenteric artery-2.5-cm below the aortic bifurcation (L1–L5) | Agatston score -continuous |
| Davila 2006[51] | Longitudinal | CVE | Consecutive patients undergoing CT colonographic examinations | 467 | 3.1 | CT | 1 cm above the origin of the celiac axis to 1 cm below the iliac bifurcation (L1–L4/L5) | Agatston score –percentiles ≤75th/<75th |
| Harbaoui 2016[52] | Longitudinal | Cardiac death, CHF, ACM | Patients undergoing transcatheter aortic valve implantation surgery | 155 | 1.5 | CT | Aortic hiatus to the aortic bifurcation (L1–L4) | Total volume delineated calcifications-tertiles |

(*Continued*)

**Table 2. Continued**

| Study Reference | Design | End Points | Population | No. at Risk | Follow Up (y) | Imaging Modality | AA Segment | AAC Modeled as |
|---|---|---|---|---|---|---|---|---|
| Harbaugh 2013[53] | Longitudinal | Cardiovascular death, ACM | Patients who underwent elective general or vascular surgery between 2006 and 2009 | 1180 | 1.0 | CT | L1–L3 | % of the total wall area containing calcification—none/mild/significant |
| Niskanen 1990[54] | Unmatched case-control | MI, peripheral artery disease | Middle-aged patients with newly diagnosed type 2 diabetes mellitus and randomly selected controls | 277 | 5.0 | X-ray | ns | Present/absent |
| Parr 2010[55] | Longitudinal | CVE | Patients from a vascular surgery clinic | 213 | 2.8 | CT | Lowest main renal artery to the iliac bifurcation (L2–L4) | Calcific deposit volume—mild, intermediate and severe |
| Zhang 2010[56] | Longitudinal | Cardiovascular death, ACM | Consecutive patients hospitalized in geriatric departments | 232 | 1.0 | Ultrasound | 10-cm segment above the iliac bifurcation (L1–L4) | Present/absent |
| Levitzky 2008[57] | Framingham cohort, see Wilson for characteristics. | | | | | | | |
| Samelson 2007[58] | Framingham cohort, see Wilson for characteristics. | | | | | | | |
| Walsh 2002[59] | Framingham cohort, see Wilson for characteristics. | | | | | | | |
| Estublier 2015[60] | MINOS cohort, see Szulc for characteristics. | | | | | | | |
| van der Meer 2004[61] | Rotterdam cohort, see Hollander for characteristics. | | | | | | | |
| Nielsen 2010[62] | See Ganz for characteristics. | | | | | | | |

AAC24 indicates abdominal aortic calcification 24 scale scores; AAC8, abdominal aortic calcification 8 scale scores; ACM, all-cause mortality; CHD, coronary heart disease; CHF, congestive heart failure; CT, computed tomography; CVA, cerebrovascular accident; CVE, cardiovascular event; DXA, images captured using a dual X-ray absorptiometry machine; EBCT, electron beam computed tomography; L1–4, lumbar vertebrae 1–4; MACE, major adverse coronary event; MDCT, multidetector row spiral computed tomography; MI, myocardial infarction; ns, not specified; and ROC, receiver operating characteristic.

*Area under the curve significantly larger when adding AAC to Framingham risk factors.

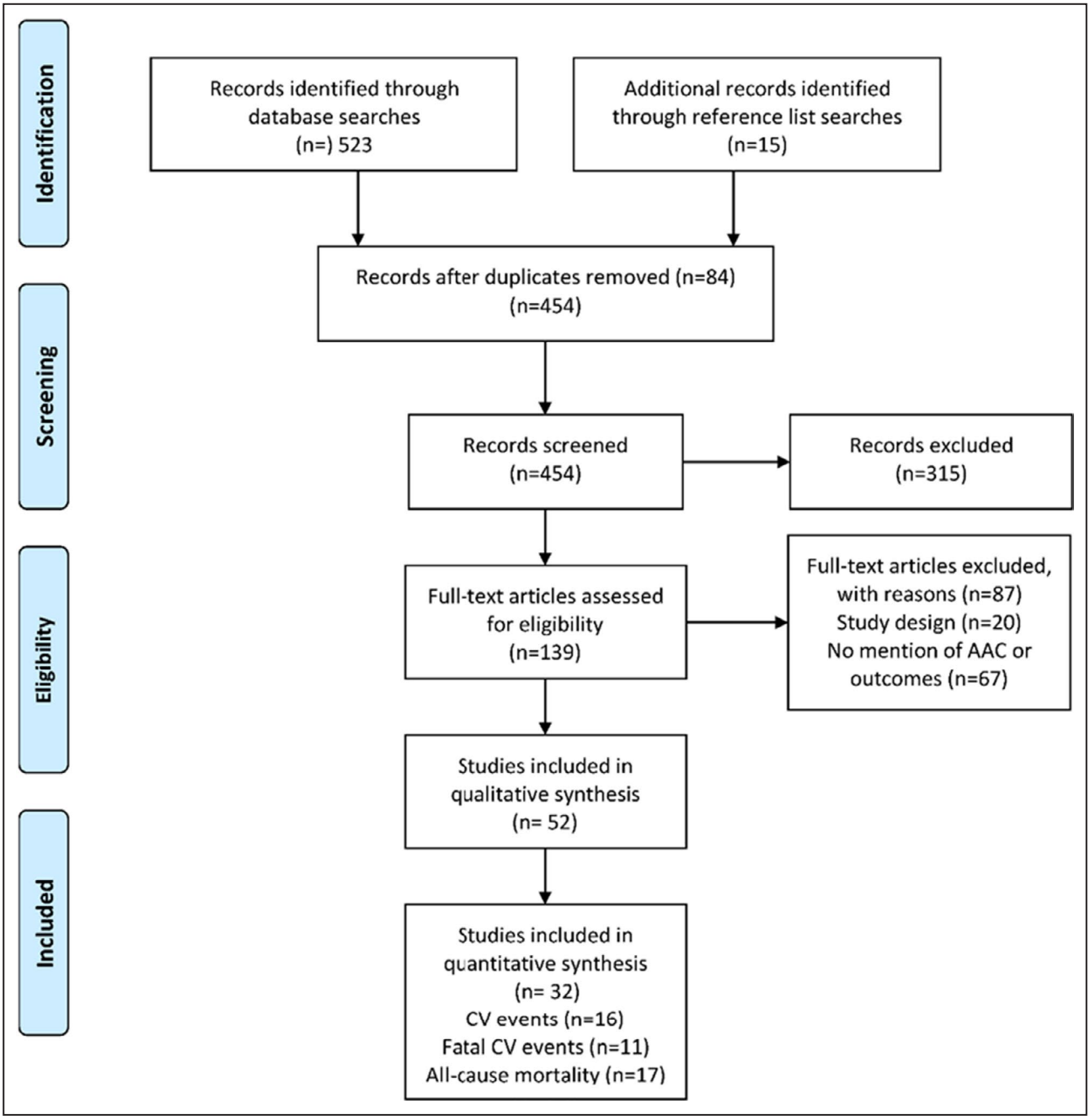


**Figure 1. Study flow.**
AAC indicates abdominal aortic calcification; and CV, cardiovascular.

confirmed in meta-regression analyses where the type of population recruited potentially explained 32% to 50% of the observed between-study heterogeneity for cardiovascular events ($r^2$=50%), fatal cardiovascular events ($r^2$=34%), and all-cause mortality ($r^2$=32%). As there is no recommended approach when clinical heterogeneity is identified,[69] we decided post hoc to undertake all further analyses in studies of patients with CKD and the general population separately. There were insufficient numbers of studies (n=2) to meta-analyze in the "other" populations for any outcome.

## AAC, Cardiovascular Events, Fatal Cardiovascular Events, and All-Cause Mortality in Studies From the General Population

Extractable data were available for 6 studies (n=8498) for cardiovascular events,[9–11,13,14,25] 5 studies (n=8004) for fatal cardiovascular events,[9,10,13,29,31] and 6 studies (n=8662) for all-cause mortality.[9,10,25,29,30,58] Compared with those with no or low AAC, people with any or more advanced AAC had higher pooled

**Table 3. Absolute and Relative Risk in People With Any or More Advanced AAC for All Included Studies**

| Study | Characteristics | | | Cardiovascular Events | | Fatal Cardiovascular Events | | All-Cause Mortality | |
|---|---|---|---|---|---|---|---|---|---|
| | Cohort Age, y | Follow-Up, y | Test | % Events Low vs Mod-High (ARD) | RR (95% CI) | % Events Low vs Mod-High (ARD) | Relative Risk (95% CI) | % Events Low vs Mod-High (ARD) | Relative Risk (95% CI) |
| General population | | | | | | | | | |
| Bolland 2010[11] | 71 | 4 | DXA | 4.2 vs 9.2 (+5.0) | 2.19 (1.51–3.18) | … | … | … | … |
| Criqui 2014[9] | 65 | 6 | CT | 1.6 vs 6.8 (+5.2) | 4.19 (2.45–7.17) | 0.3 vs 2.7 (+2.4) | 9.00 (2.74–29.57) | 2.5 vs 8.1 (+5.6) | 3.20 (2.06–4.97) |
| Ganz 2012[25] | 60 | 9 | X-ray | … | … | … | … | 7.3 vs 28.0 (+20.7) | 3.85 (2.10–7.04) |
| Golestani 2010[26] | 68 | 3 | DXA | 1.5 vs 8.5 (+7.0) | 5.55 (2.03–15.14) | … | … | … | … |
| Lewis 2018[10] | 75 | 15 | DXA | 33.4 vs 42.4 (+8.9) | 1.27 (1.06–1.52) | 13.9 vs 21.7 (+7.8) | 1.56 (1.13–2.14) | 29.6 vs 38.2 (+8.6) | 1.29 (1.06–1.57) |
| Rodondi 2007[29] | 72 | 13 | X-ray | … | … | 10.6 vs 17.7 (+7.1) | 1.67 (1.29–2.15) | 26.8 vs 47.1 (+20.2) | 1.75 (1.52–2.02) |
| Schousboe 2008[14] | 80 | 4 | DXA | 44.1 vs 53.3 (+9.2) | 1.21 (1.02–1.43) | … | … | … | … |
| Szulc 2008[30] | 65 | 10 | X-ray | … | … | … | … | 12.2 vs 34.2 (+22.0) | 2.80 (2.08–3.77) |
| Wilson 2001[13*] | 61 | 22 | X-ray | 36.3 vs 60.7 (+24.5) | 1.68 (1.53–1.84) | 15.2 vs 32.5 (+17.3) | 2.14 (1.81–2.52) | 65.1 vs 92.5 (+27.4) | 1.42 (1.35–1.49) |
| Witteman 1986[31] | 68 | 9 | X-ray | … | … | 16.9 vs 25.3 (+8.5) | 1.50 (1.03–2.20) | … | … |
| Patients with CKD | | | | | | | | | |
| Cho 2017[33] | 60 | 2 | X-ray | 6.4 vs 11.3 (+5.0) | 1.78 (0.69–4.61) | … | … | … | … |
| Claes 2013[34] | 54 | 3 | X-ray | 1.0 vs 20.1 (+19.1) | 19.39 (2.77–143.65) | … | … | | |
| Djuric 2016[8] | 60 | 3 | CT | … | … | … | … | 13.0 vs 50.0 (+37.0) | 3.83 (1.29–11.43) |
| Fusaro 2012[36] | 64 | 3 | X-ray | … | … | … | … | 9.3 vs 22.4 (+13.1) | 2.40 (1.15–5.01) |
| Hanada 2010[38] | 67 | 4 | CT | 14.6 vs 35.7 (+21.1) | 2.44 (1.05–5.67) | … | … | … | … |
| Hong 2013[39] | 60 | 2 | X-ray | … | … | … | … | 5.0 vs 24.1 (+19.1) | 4.82 (1.77–13.10) |
| Munguia 2015[46] | 58 | 3 | X-ray | 5.8 vs 22.0 (+16.2) | 3.83 (1.28–11.23) | … | … | 7.2 vs 14.0 (+6.8) | 1.93 (0.65–5.74) |
| NasrAllah 2017[47] | 43 | 5 | X-ray, CT | … | … | … | … | 28.6 vs 44.4 (+15.9) | 1.56 (0.70–3.48) |
| Imanishi 2014[41] | 44 | 5 | CT | 0 vs 62.5 (+62.5) | 66.00 (3.98–1093.98) | … | … | … | … |
| Li 2016[44] | 59 | 5 | X-ray | … | … | 2.0 vs 18.6 (+16.6) | 9.48 (1.31–68.55) | 7.8 vs 24.8 (+16.9) | 3.16 (1.17–8.54) |
| Ohya 2011[48] | 60 | 8 | CT | … | … | 14.9 vs 51.4 (+36.5) | 3.45 (1.86–6.38) | 37.3 vs 72.9 (+35.5) | 1.95 (1.39–2.75) |
| Okuno 2007[49] | 60 | 4 | X-ray | … | … | 3.1 vs 11.7 (+8.6) | 3.74 (1.69–8.28) | 9.8 vs 27.8 (+18.0) | 2.83 (1.83–4.39) |
| Peeters 2016[50] | 61 | 2 | X-ray | 4.3 vs 14.4 (+10.1) | 3.38 (1.40–8.17) | … | … | … | … |
| Tatami 2015[6] | 67 | 3 | CT | 4.3 vs 16.8 (+12.5) | 3.87 (1.57–9.55) | 0.8 vs 2.2 (+1.3) | 2.48 (0.29–20.97) | 5.2 vs 16.8 (+11.6) | 3.22 (1.41–7.39) |

(*Continued*)

**Table 3. Continued**

| Study | Characteristics | | | Cardiovascular Events | | Fatal Cardiovascular Events | | All-Cause Mortality | |
|---|---|---|---|---|---|---|---|---|---|
| | Cohort Age, y | Follow-Up, y | Test | % Events Low vs Mod-High (ARD) | RR (95% CI) | % Events Low vs Mod-High (ARD) | Relative Risk (95% CI) | % Events Low vs Mod-High (ARD) | Relative Risk (95% CI) |
| Vezzoli 2014[64] | ns | 2 | DXA | 11.5 vs 35.7 (+24.2) | 3.10 (1.22–7.87) | … | … | … | … |
| Other | | | | | | | | | |
| Allison 2012[68] | 57 | 7.8 | CT | … | … | 0.0 vs 1.4 (+1.4) | 15.41 (3.72–63.82) | 1.1 vs 5.8 (+4.7) | 5.49 (3.48–8.64) |
| Davila 2006[51] | 65 | 3.1 | CT | 0.1 vs 5.5 (+5.4) | 10.47 (2.21–49.70) | … | … | … | … |
| Harbaugh 2013[53] | 56 | 1.0 | CT | … | … | 0.5 vs 0.8 (+0.3) | 4.04 (0.58–28.34) | 4.7 vs 9.8 (+5.1) | 2.08 (1.20–3.63) |
| Parr 2010[55] | 69 | 2.8 | CT | 9.2 vs 26.4 (+17.1) | 2.86 (1.27–6.41) | … | … | … | … |

AAC indicates abdominal aortic calcification; ARD, absolute risk difference between no-low and any-advanced AAC; CKD, chronic kidney disease; CT, computed tomography; and DXA, dual X-ray absorptiometry.
*For all–cause mortality in the Framingham study, numbers were derived from Samelson et al.[58]

absolute risk differences for cardiovascular events (+9.9%; 95% CI, +4.1%–15.8%), fatal cardiovascular events (+8.6%; 95% CI, +2.3%–14.8%), and all-cause mortality (+17.4%; 95% CI, +8.1%–26.6%). The summary table of evidence is provided in Table 4. Briefly, the pooled RRs were 1.83 (95% CI, 1.40–2.39) for cardiovascular events, 1.85 (95% CI, 1.44–2.39) for fatal cardiovascular events, and 1.98 (95% CI, 1.56–2.53) for all-cause mortality (moderate-quality evidence, all $P<0.001$). However, high (fatal cardiovascular events, $I^2=69\%$; cerebrovascular events, $I^2=60\%$; and coronary heart disease [CHD] events, $I^2=72\%$) to very high (cardiovascular events, $I^2=87\%$; and all-cause mortality, $I^2=90\%$) between-study heterogeneity was observed (Figure 2). Evidence of small-study publication bias was identified for all-cause mortality ($P=0.044$). The sROC curves generated suggest that AAC alone may provide moderate to good (area under the curve, 0.69–0.75) discriminative ability for cardiovascular events, fatal cardiovascular events, and deaths in this population (Figure 3A, 3C and 3E).

## Studies Reporting by Presence of AAC and Increasing AAC Severity From the General Population

There were 4 studies that reported AAC by the absence and presence of AAC for cardiovascular events,[10,11,13,14] 4 studies for fatal cardiovascular events,[10,13,29,31] and 5 studies for all-cause mortality.[10,25,29,30,58] Increased absolute and relative risks were seen in people with any AAC (Table 5). Studies reporting ≥3 categories of AAC severity (cardiovascular events=5 studies,[9,10,13,14,26] fatal cardiovascular events=3 studies,[2,11,14] and all-cause mortality=3 studies[9,10,13]) had increased absolute and relative risks with increasing severity of AAC (Table 5).

## AAC, CHD, and Cerebrovascular Disease in Studies From the General Population

Extractable data were available for 5 studies (n=7766) for CHD[9–11,13,26] and 4 studies (n=8943) for cerebrovascular disease.[10,11,26,28] People with any or more advanced AAC had higher pooled absolute risk differences for CHD (+7.4%; 95% CI, +2.0 to +12.8%) and cerebrovascular disease (+3.4%; 95% CI, +1.8 to +5.0%), compared with those with no or low AAC. The pooled RRs were 2.22 (95% CI, 1.57–3.15) for CHD events and 2.10 (95% CI, 1.41–3.12) for cerebrovascular events, Figure S2 (high-quality evidence [Tables 2 and 5], both $P<0.001$), with moderate to high between-study heterogeneity (60%–72%). Increasing absolute and relative risk with increasing severity of AAC were seen for CHD events (4 studies) and cerebrovascular events (3 studies) (Table 5).

**Table 4. Summary of Findings Table**

| | Illustrative Comparative Risks | | Relative Risk (95% CI) | No. Studies (No. People) | Quality of the Evidence (GRADE) |
|---|---|---|---|---|---|
| | No or Low AAC | Any or More Advanced AAC | | | |
| General population* | | | | | |
| Cardiovascular events | 2/100 | 4/100 | 1.83 (1.40–2.39) | 6 (8498) | Moderate† |
| Fatal cardiovascular events | 0/100 | 1/100 | 1.85 (1.44–2.39) | 5 (8004) | Moderate† |
| All-cause mortality | 3/100 | 6/100 | 1.98 (1.55–2.53) | 6 (8662) | Moderate† |
| Patients with chronic kidney disease ‡ | | | | | |
| Cardiovascular events | 4/100 | 14/100 | 3.47 (2.21–5.45) | 8 (1426) | Moderate† |
| Fatal cardiovascular events | 1/100 | 4/100 | 3.68 (2.32–5.84) | 4 (1163) | High† |
| All-cause mortality | 5/100 | 12/100 | 2.40 (1.95–2.97) | 9 (2050) | High† |

*Baseline risk calculated from Criqui et al[9] (n=1974), for cardiovascular events, fatal cardiovascular events, and all-cause mortality. AAC assessed by CT in men and women with a mean age of 65 years with a mean follow up of 5.5 years.

†Quality of evidence scoring based on GRADE for prognostic studies[1] for all outcomes presented in Tables S6 and S7.

‡Baseline risk calculated from the Tatami et al[6] (n=347), for cardiovascular events, fatal cardiovascular deaths, and all-cause mortality. AAC assessed by CT in men and women with chronic kidney disease, a mean age of 67 years, and duration of follow-up 3.5 years.

## Pooled Analysis of Adjusted Estimates of Risk

To understand how adjusting for traditional cardiovascular risk factors may affect the pooled results we undertook meta-analyses using the reported adjusted estimates of risk from the individual studies (hazard ratio or odds ratio) interpreted as RR, using weighted random effects with similar results to the unadjusted analyses (Figure 4, Table 6).

## Sources of Methodological and Statistical Heterogeneity

There was not statistically significant between-study heterogeneity attributable to imaging modality (x-ray, DXA, CT), threshold AAC (present/absent, other), mean cohort age (<60, 60–69, ≥70 years), and duration of follow-up (<5, 5–9, ≥10 years; data not shown) (Figures S3, S4, and S5). Heterogeneity for cardiovascular and fatal cardiovascular events was potentially explained by mean cohort systolic blood pressure (42%–45%) and total cholesterol (4% and 13%) with greater RR differences seen in cohorts with lower mean systolic blood pressure and total cholesterol. For fatal cardiovascular events, imaging modality potentially explained 60% of the heterogeneity with no between-group difference for studies using x-rays (2 studies) or DXA (2 studies), while 1 study using CT had the greatest RR. All-cause mortality studies with lower systolic blood pressure (39%) and shorter follow-up time (11%) had higher RR, while 1 study in Oceania had a lower RR than studies in Europe and the United States (36%). Additionally, studies with a higher prevalence of participants with diabetes mellitus at baseline had greater RR differences, potentially explaining 42% of the between-study heterogeneity.

## AAC, Cardiovascular Events, Fatal Cardiovascular Events, and All-Cause Mortality in Patients With Chronic Kidney Disease

Extractable data were available for 8 studies (n=1426) for cardiovascular events,[6,33,34,38,41,46,50,64] 4 studies (n=1163) for fatal cardiovascular events,[6,44,48,49] and 9 studies (n=2050) for all-cause mortality.[6,8,36,39,44,46–49] Compared with those with no or low AAC, people with any or more advanced AAC had higher pooled absolute risk differences for cardiovascular events (+15.1%; 95% CI, +9.1%–21.1%), fatal cardiovascular events (+13.4%; 95% CI, +3.8%–23.0%), and all-cause mortality (+17.1%; 95% CI, +12.2%–22.0%). The pooled RRs were 3.47 (95% CI, 2.21–5.45) for cardiovascular events, 3.69 (95% CI, 2.32–5.85) for fatal cardiovascular events, and 2.41 (95% CI, 1.95–2.97) for all-cause mortality (moderate [cardiovascular events]-high [fatal cardiovascular events and all-cause mortality] quality evidence [Table 2], all $P<0.001$), with no (fatal cardiovascular events and all-cause mortality) to low (cardiovascular events, 29%; $P=0.196$, attributable to a single study[41]) between-study heterogeneity (Figure 2). Evidence of small-study publication bias was identified for cardiovascular events ($P=0.002$). The sROC curves generated suggest that AAC alone may provide moderate to good (area under the curve, 0.64–0.83) discriminative ability for cardiovascular events, fatal cardiovascular events, and deaths in this population (Figure 3B, 3D, and 3F).

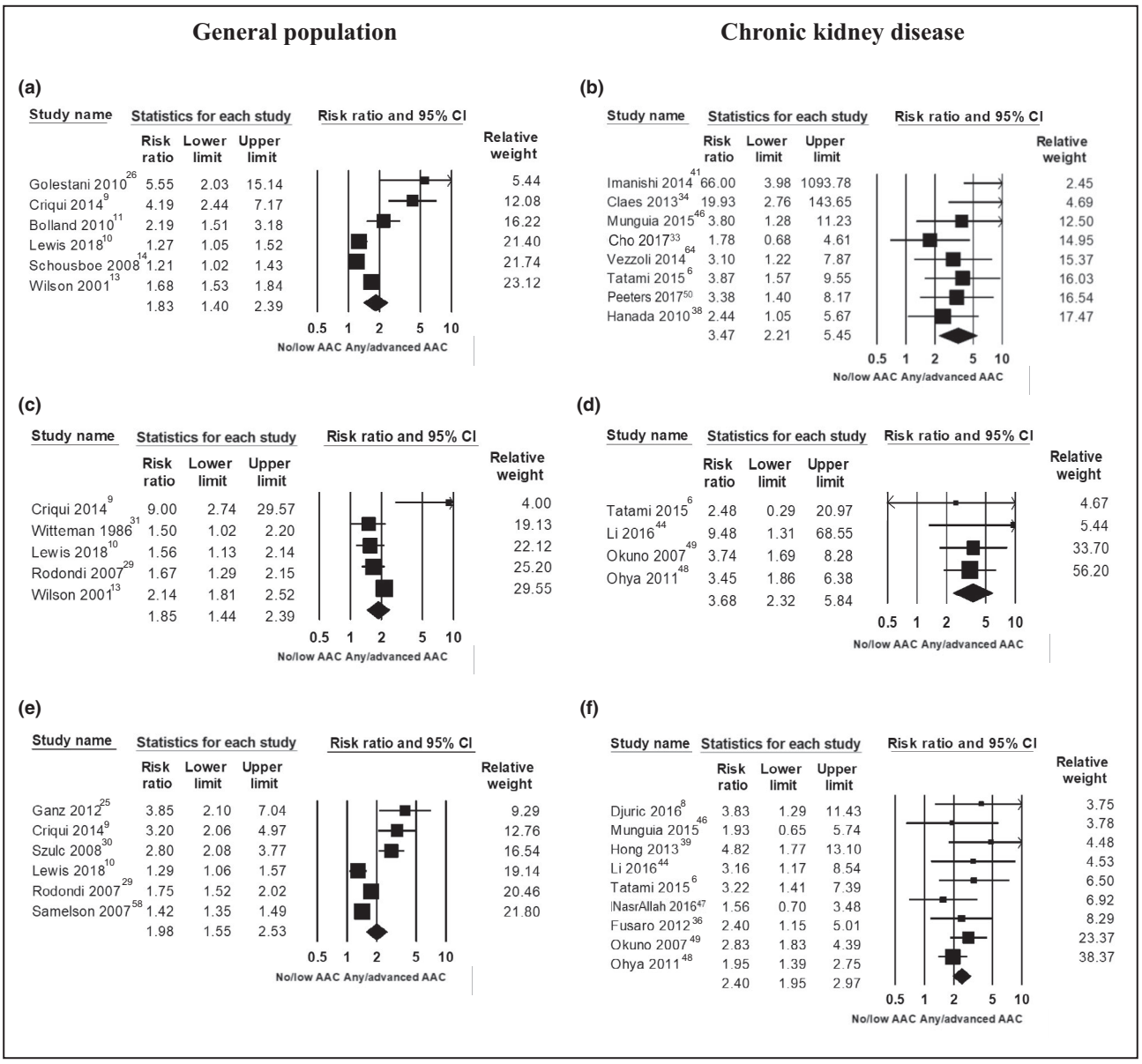


**Figure 2. Association between abdominal aortic calcification (AAC) and cardiovascular disease events (CVD, A and B), fatal cardiovascular events (CV, C and D) and all-cause mortality (E and F) in cohorts from the general population (left panels) or patients with chronic kidney disease (CKD) (right panels).**

## Comparison of Fixed Versus Random Effects

The main analyses were performed using both fixed and random effects for comparative purposes and are presented in Table S7.

# DISCUSSION

In this systematic review and meta-analysis, we observed moderate- to high-quality evidence that people with any or more advanced AAC had substantially higher absolute and relative risk for cardiovascular events, fatal cardiovascular events, and all-cause mortality than people with no or less advanced AAC. The strongest associations were seen in patients with CKD and people from the general population with the most advanced AAC. Importantly, AAC alone had moderate to good discrimination (sROC, 0.6–0.8) for all outcomes, indicating that this may be a clinically useful predictor of future cardiovascular events, fatal cardiovascular events, and prognosis in patients with CKD and the general population. Thus, fortuitous findings of AAC in patients with no known data on cardiovascular risk factors should

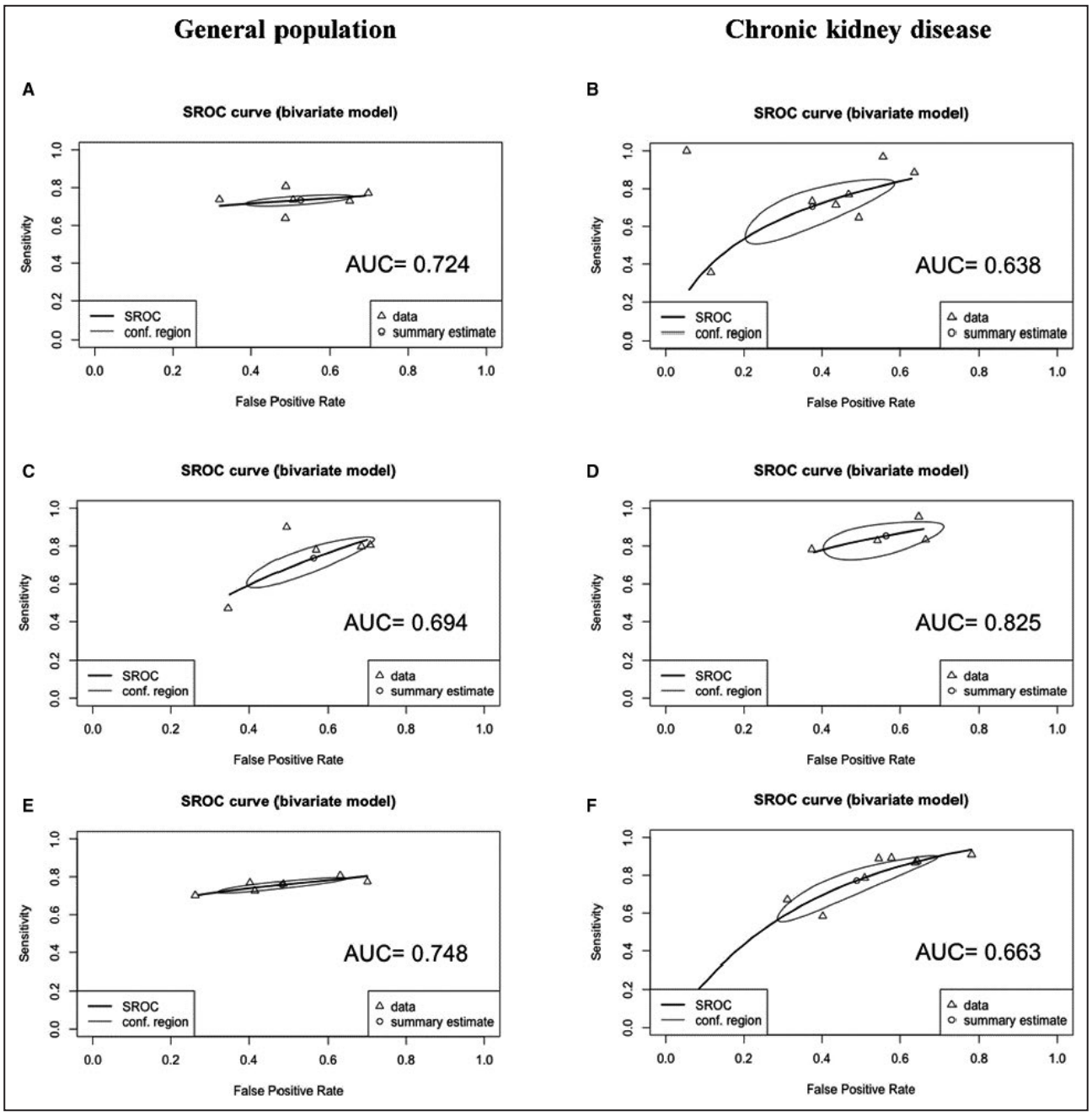


**Figure 3. Summary ROC (sROC) showing the point estimate (area under the curve [AUC]) for the diagnostic accuracy of AAC to identify people at risk of cardiovascular events (A and B), fatal cardiovascular events (C and D) and all-cause mortality (E and F) in cohorts from the general population (left panels) or patients with chronic kidney disease (CKD) (right panels).** Graphs are based on the paired sensitivity and false-positive rates plotted together with a confidence region (circled area). Each triangle represents the summary sensitivity and false positive rate from a single cohort.

be considered to be an indication for further diagnostic testing, such as ECG, lipid assays, and so on.

Both a priori subgroup analysis and meta-regression identified that the risk in people with AAC differed substantially between studies recruiting patients with CKD versus those recruiting from the general population. The strongest and most consistent associations were observed in patients with CKD. These findings may be attributable to a greater burden and progression of AAC in this patient group, differences in drivers of calcification, or higher selected thresholds of AAC, which was particularly evident for cardiovascular events. Irrespective of the reasons, these findings add further support to the current Kidney Disease Improving Global Outcomes clinical practice guidelines suggesting that when AAC is seen in patients with

**Table 5. Studies From the General Population With Different Thresholds**

| AAC Group | Number of Cohorts (No. Events/ No. Group) | Absolute Risk Difference (95% CI) | Relative Risk (95% CI) | $I^2$ |
|---|---|---|---|---|
| Any detectable AAC | | | | |
| Cardiovascular events | | | | |
| No detectable AAC | 4 (485/2538) | 1 (referent) | 1 (referent) | |
| Any AAC | 4 (1361/3262) | +11.4 (+1.7 to +21.0) | 1.76 (1.32 to 2.34) | 81% |
| Fatal cardiovascular events | | | | |
| No detectable AAC | 4 (293/2105) | 1 (referent) | 1 (referent) | |
| Any AAC | 4 (971/3933) | +10.4 (+4.4 to +16.3) | 1.77 (1.47 to 2.13) | 48% |
| All-cause mortality | | | | |
| No detectable AAC | 5 (899/2225) | 1 (referent) | 1 (referent) | |
| Any AAC | 5 (2606/4471) | +18.8 (+12.3 to +25.4) | 1.72 (1.40 to 2.11) | 84% |
| Increasing severity of AAC categories | | | | |
| Cardiovascular events | | | | |
| Lowest reported AAC group | 5 (638/2952) | 1 (referent) | 1 (referent) | |
| Middle/combined AAC group(s) | 5 (735/2029) | +6.5 (−0.2 to +13.3) | 1.40 (1.06 to 1.84) | 84% |
| Highest reported AAC group | 5 (814/1773) | +15.3 (+4.9 to +25.6) | 2.06 (1.48 to 2.88) | 90% |
| Fatal cardiovascular events | | | | |
| Lowest reported AAC group | 3 (219/2400) | 1 (referent) | 1 (referent) | |
| Middle/combined AAC group(s) | 3 (314/1661) | +6.7 (−1.3 to +14.8) | 1.77 (1.24 to 2.52) | 66% |
| Highest reported AAC group | 3 (357/1472) | +12.0 (−0.5 to +24.5) | 2.61 (1.57 to 4.32) | 81% |
| All-cause mortality | | | | |
| Lowest reported AAC group | 3 (193/1674) | 1 (referent) | 1 (referent) | |
| Middle/combined AAC group(s) | 3 (244/1247) | +5.5 (+0.5 to +10.5) | 1.44 (1.13 to 1.84) | 32% |
| Highest reported AAC group | 3 (224/878) | +17.5 (+5.1 to +29.8) | 2.86 (1.30 to 6.28) | 93% |
| Coronary heart disease | | | | |
| Lowest reported AAC | 4 (299/2725) | 1 (referent) | 1 (referent) | |
| Middle AAC group(s) | 4 (382/1576) | 5.6 (−0.4 to 11.6) | 1.58 (1.16 to 2.16) | 60% |
| Highest reported AAC | 4 (458/1531) | 10.7 (−1.3 to 22.8) | 2.70 (1.47 to 4.97) | 88% |
| Cerebrovascular disease | | | | |
| Lowest reported AAC | 3 (105/2677) | 1 (referent) | 1 (referent) | |
| Middle AAC group(s) | 3 (163/2524) | 2.5 (1.4 to 3.5) | 1.72 (1.04 to 2.85) | 65% |
| Highest reported AAC | 3 (183/1971) | 6.0 (3.8 to 8.2) | 2.91 (1.51 to 5.62) | 79% |

AAC indicates abdominal aortic calcification.

CKD stages G3a–G5D (estimated glomerular filtration rate <60 mL/min per 1.73 $m^2$ to dialysis), these patients should be considered at the highest cardiovascular disease risk.[70]

In cohorts recruited from the general population, people with any or more advanced AAC had twice the relative risk and 9% to 17% absolute risk difference for cardiovascular events, fatal cardiovascular events, and all-cause mortality compared with those in the lowest reported AAC category. These very large absolute risk differences are likely attributable to the nature of the included cohorts, for example, elderly who are at high risk of these events. When meta-analyzing the adjusted measures of risk, the pooled RR remained similar, supporting the concept that AAC may provide additional prognostic information to conventional risk factors.[9,27,57]

While our sROC analyses demonstrated that AAC alone had moderate to good discrimination for all outcomes, it did not address whether the addition of AAC to established risk factors improves prognostication. A number of the larger studies from the general population have previously reported that the addition of AAC to conventional risk factors improves measures of discrimination for cardiovascular events, cardiovascular mortality, CHD events, and ischemic strokes.[9,57] In the Framingham offspring cohort, the inclusion of AAC led to a 12% improvement in net reclassification for both

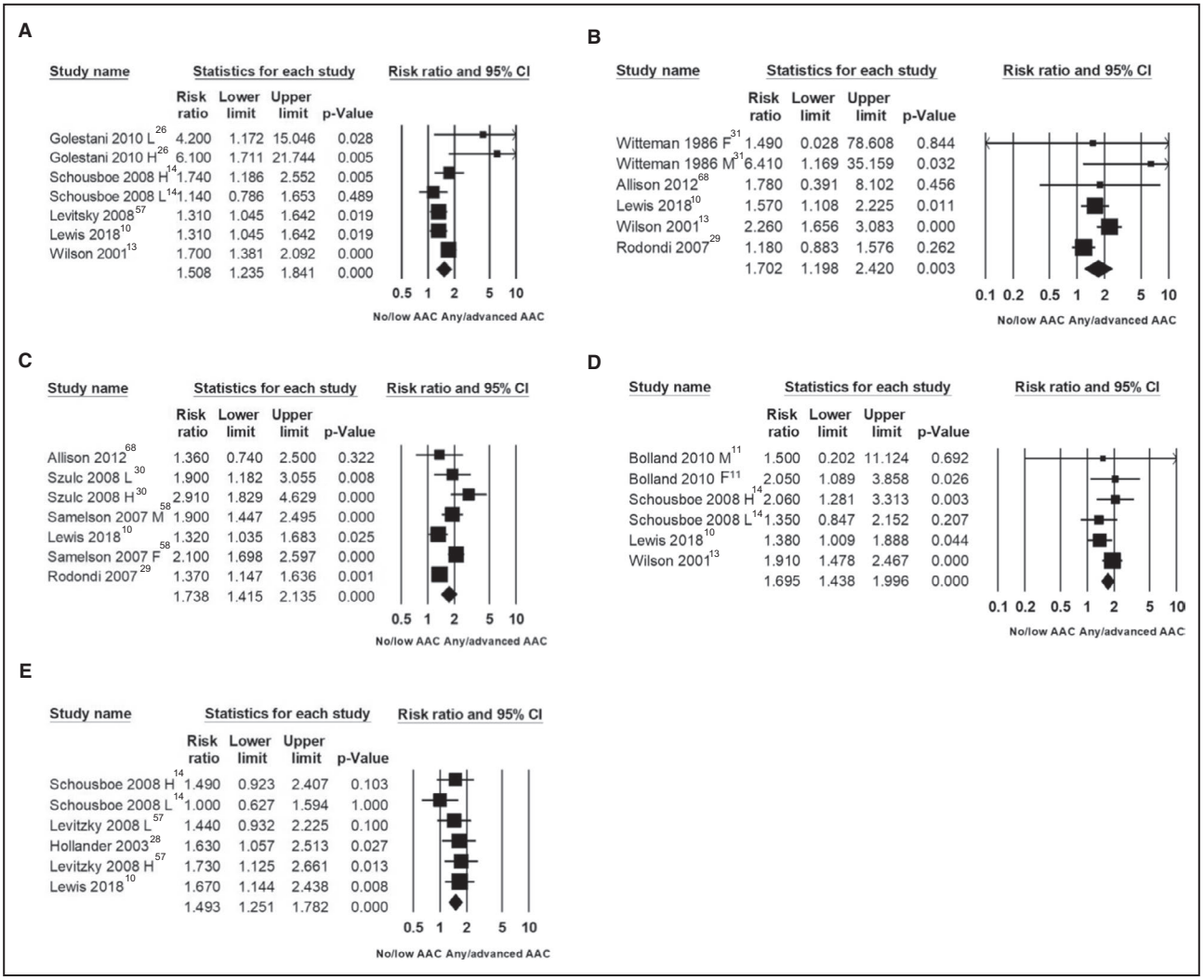


**Figure 4. Cardiovascular risk factor adjusted association between abdominal aortic calcification (AAC) and cardiovascular disease events (CVD) (A), fatal cardiovascular events (B), all-cause mortality (C), coronary heart disease events (D), and cerebrovascular disease events (E) in cohorts from the general population.**
Adjusted measures of risk only presented in; F indicates female only; H, high AAC vs none/less advanced; L, low AAC vs none/less advanced; and M, male only.

CHD and major cardiovascular events.[27] Taken together with the sROC analyses showing moderate to good discrimination, these findings suggest that the addition of AAC measures to Framingham risk factors are likely to improve discrimination for cardiovascular events.

In the general population, there was high between-study heterogeneity for cardiovascular events, fatal cardiovascular events, and all-cause mortality, suggesting that the summary estimates should be interpreted cautiously. This heterogeneity was potentially attributable to cohort differences in systolic blood pressure and total cholesterol, with AAC being more prognostic in people with lower systolic blood pressure and total cholesterol, confirming findings in individual studies.[14,71] This suggests that AAC may identify an as yet underappreciated high-risk group not captured by conventional risk factors. When meta-analyzing the adjusted measures of risk, heterogeneity was reduced for all outcomes.

Surprisingly, AAC imaging using x-ray, DXA, or CT and thresholds of AAC were not a major source of between-study heterogeneity for cardiovascular events or all-cause mortality. However, CT imaging was for cardiovascular death in the general population because of a single study of lower-risk individuals.[9] This suggests that low-cost, widely available imaging modalities can be used to identify people at a clinically significantly increased risk of cardiovascular disease events and mortality. This is an important finding given the likely decline of standard radiographs, attributable to improvements in the image quality of DXA images at a fraction of the radiation dose of a standard radiograph and increasing access to CT as the radiation dose becomes lower.

**Table 6. Comparison of Unadjusted and Adjusted Estimates of Studies From the General Population**

| Any Advanced AAC | Pooled Unadjusted Relative Risk (95% CI) | Pooled Adjusted Relative Risk (95% CI) |
|---|---|---|
| Cardiovascular events | 1.83 (1.40–2.39), $I^2$=87% | 1.51 (1.24–1.84), $I^2$=45% |
| Fatal cardiovascular events | 1.85 (1.44–2.39), $I^2$=69% | 1.70 (1.20–2.42), $I^2$=57% |
| All-cause mortality | 1.98 (1.55–2.53), $I^2$=90% | 1.74 (1.42–2.13), $I^2$=70% |
| Coronary heart disease | 2.22 (1.57–3.15), $I^2$=72% | 1.69 (1.44–2.00), $I^2$=0% |
| Cerebrovascular disease | 2.10 (1.41–3.12), $I^2$=60% | 1.49 (1.25–1.78), $I^2$=0% |

AAC indicates abdominal aortic calcification.

There are a number of strengths of this meta-analysis over the previous meta-analysis in 2012.[71] Because of our broad inclusion criteria and more recent search, we identified substantially more studies than the previous meta-analysis (n=4 studies for cardiovascular events and n=3 studies for fatal cardiovascular events).[71] Additionally, we used the number of people with an event within each group (unadjusted estimates) from studies rather than the adjusted estimates of the risk or hazard ratio where the interpretation and validity can be problematic when studies adjust for different baseline confounders. Additionally, we used subgroup analyses and meta-regression to attempt to explain observed heterogeneity and identified a number of confounders that are likely to contribute to the observed heterogeneity. Finally, we undertook sROC analysis to determine the discriminative performance of AAC alone for future cardiovascular events, cardiovascular deaths, and all-cause mortality. As such, this meta-analysis can inform patients and their treating physicians about their likely future cardiovascular risk and prognosis when AAC is observed.

In regards to limitations, considerable differences between cut points of AAC, even within the same imaging modalities, make interpretation of the results challenging. As such, we cannot propose a potentially useful threshold based on the current meta-analysis. Further individual patient level meta-analyses within the same imaging modalities are needed. Second, small-study publication bias was identified for cardiovascular events in the CKD population and all-cause mortality in the general population and may have compromised the validity of our results. As such, the reported estimates should be considered tentatively. Finally, in some cases, study demographics may have influenced the imaging modality used; for example, younger cohorts from the general population were more likely to have CT or standard radiographs (range, 60–68 years), while DXA-based imaging was predominantly in elderly women (range, 68–80 years) captured during bone density testing.

It is now clear that even in populations considered at high risk of cardiovascular disease but sometimes overlooked, such as the elderly and those with CKD, severe AAC identifies those at substantially higher absolute and relative risk. Potential uses for this information include aiding treatment decisions and increased patient awareness of disease risk and symptoms as a motivational tool for lifestyle decisions and changes, improving individual risk prediction and providing novel targets for new treatments.

In conclusion, future studies should focus on standardization of AAC assessment and reporting and investigate whether the knowledge of AAC improves primary prevention and clinical management strategies. Given that AAC can be quickly and easily captured using low to negligible radiation exposure compared with assessing coronary artery calcifications, it may complement existing early detection and primary prevention strategies for clinical cardiovascular disease.

## ARTICLE INFORMATION

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## Disclosures

None.

## Supplementary Material

**Data S1**
**Tables S1–S7**
**Figures S1–S5**

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# SUPPLEMENTAL MATERIAL

**Data S1. Newcastle-Ottawa scoring**

**NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE - CASE CONTROL STUDIES**

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

**Selection**

**1) Is the case definition adequate?**

a) yes, with independent validation *

b) yes, e.g. record linkage or based on self-reports

c) no description

**2) Representativeness of the cases**

a) consecutive or obviously representative series of cases *

b) potential for selection biases or not stated

**3) Selection of Controls**

a) community controls *

b) hospital controls

c) no description

**4) Definition of Controls**

a) no history of disease (endpoint) *

b) no description of source

**Comparability**

1) Comparability of cases and controls on the basis of the design or analysis

a) study controls for CVD risk factors (Select the most important factor.) *

b) study controls for any additional factor * (This criterion could be modified to indicate specific control for a second important factor.)

**Exposure**

1) Ascertainment of exposure

a) secure record (e.g., surgical records) *

b) structured interview where blind to case/control status *

c) interview not blinded to case/control status

d) written self-report or medical record only

e) no description

**2) Same method of ascertainment for cases and controls**

a) yes *

b) no

**3) Non-Response rate**

a) same rate for both groups *

b) non respondents described

c) rate different and no designation

**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 or CKD patients) of that age in the community *

b) somewhat representative of the average population (e.g., general population or CKD patients) 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 of cardiovascular disease *

b) study controls for any additional conventional cardiovascular 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

**Results**

All studies provided a clear description of how exposure (amount of AAC) was ascertained, however there was significant variability in between-study test characteristics and methods of measurement. Scores used to determine AAC varied between the 52 studies, 19 studies (37%) used thresholds based on the Kauppila AAC 8 or 24 score, 14 studies (27%) used the presence vs. the absence of AAC, 7 studies (13%) used thresholds based on the AAC index (ACI), 5 studies (10%) used thresholds based on Agatston score and the remaining 7 studies (13%) used other scoring methods. Only 15 studies (30%) provided evidence that prevalent cardiovascular disease was not present at the beginning of the study. The majority of studies (94%) adjusted for conventional cardiovascular risk factors or additional disease-specific risk factors. However, only 11 studies (21%) provided adjustment for the history of cardiovascular disease. Only 25 studies (48%) reported a complete/near complete follow-up.

**Table S1.** Search strategy.

| Keyword | MEDLINE | Embase |
|---|---|---|
| Population = None | No search strategy | No search strategy |
| Intervention/Test = Abdominal 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/ or aortic.mp. or vascular calcifications.mp. or exp Vascular Calcification/ and abdomin$.mp. and aortic calc$.mp. | vascular calcification.mp. or exp blood vessel calcification/ or artery calcification.mp. or exp artery calcification/ or exp coronary artery disease/ or exp aorta atherosclerosis/ or exp aorta disease/ or exp arteriosclerosis/ or arteriosclerosis.mp. or exp atherosclerosis/ or exp atherosclerotic plaque/ or extracoronary.mp. and abdomin$.mp. and artery calc$.mp. |
| Methodology = observational | prognosis.sh. or diagnosed.tw. or cohort$.mp. or predictor$.tw. or death.tw. or exp models, statistical | prognosis.sh. or diagnosed.tw. or cohort$.mp. or predictor$.tw. or death.tw. or exp models, statistical |
| Comparator = None | No search strategy | No search strategy |
| Outcome = None | No search strategy | No search strategy |
| Additional specific filters | Human | Human |

***The reference lists of recent literature reviews and guidelines were hand-searched for further studies.

**Table S2.** Detailed GRADE assessment for outcomes in people recruited from the general population*.

| | Quality of assessment (Decrease in quality score) | | | | Effect size/dose response | Summary of findings | | |
|---|---|---|---|---|---|---|---|---|
| Studies† (subjects) | Risk of bias | Inconsistency | Indirectness | Imprecision | | Relative risk (95% CI) | Test for heterogeneity | Quality of evidence |
| **Cardiovascular events** | | | | | | | | |
| 6 (8,498) | - | ↓1 between-study heterogeneity | ↓ popn. selection may not be generalizable | no serious imprecision | 0/↑1 | 1.83 (1.40-2.39) | $I^2$=87%, p-value<0.001 | Moderate |
| **Fatal cardiovascular events** | | | | | | | | |
| 5 (8,004) | - | ↓1 between-study heterogeneity | ↓ popn. selection may not be generalizable | no serious imprecision | 0/↑1 | 1.85 (1.44-2.39) | $I^2$=69%, p-value=0.001 | Moderate |
| **All-cause mortality** | | | | | | | | |
| 5 (8,862) | evidence of publication bias (↓1) | ↓1 between-study heterogeneity | ↓ popn. selection may not be generalizable | no serious imprecision | ↑1/ ↑1 | 1.98 (1.55-2.53) | $I^2$=90%, p-value<0.001 | Moderate |
| **Coronary heart disease events** | | | | | | | | |
| 5 (7,766) | - | ↓1 between-study heterogeneity | ↓ popn. selection may not be generalizable | no serious imprecision | ↑1/ ↑1 | 2.22 (1.57-3.15) | $I^2$=72%, p-value<0.001 | High |
| **Cerebrovascular events** | | | | | | | | |
| 4 (8,943) | - | ↓1 between-study heterogeneity | ↓ popn. selection may not be generalizable | no serious imprecision | ↑1/ ↑1 | 2.10 (1.41-3.12) | $I^2$=60%, p-value<0.001 | High |

***** All outcomes are considered clinically important. Scores are based on the GRADE for assessment of evidence about prognosis where the evidence begins as high quality evidence.[18] 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 CV events, fatal CV events, CHD events, cerebrovascular events and all-cause mortality with increasing severity of AAC]).[18]
† Number of studies with suitable data for meta-analysis.

**Table S3.** Detailed GRADE assessment for outcomes in chronic kidney disease patients*

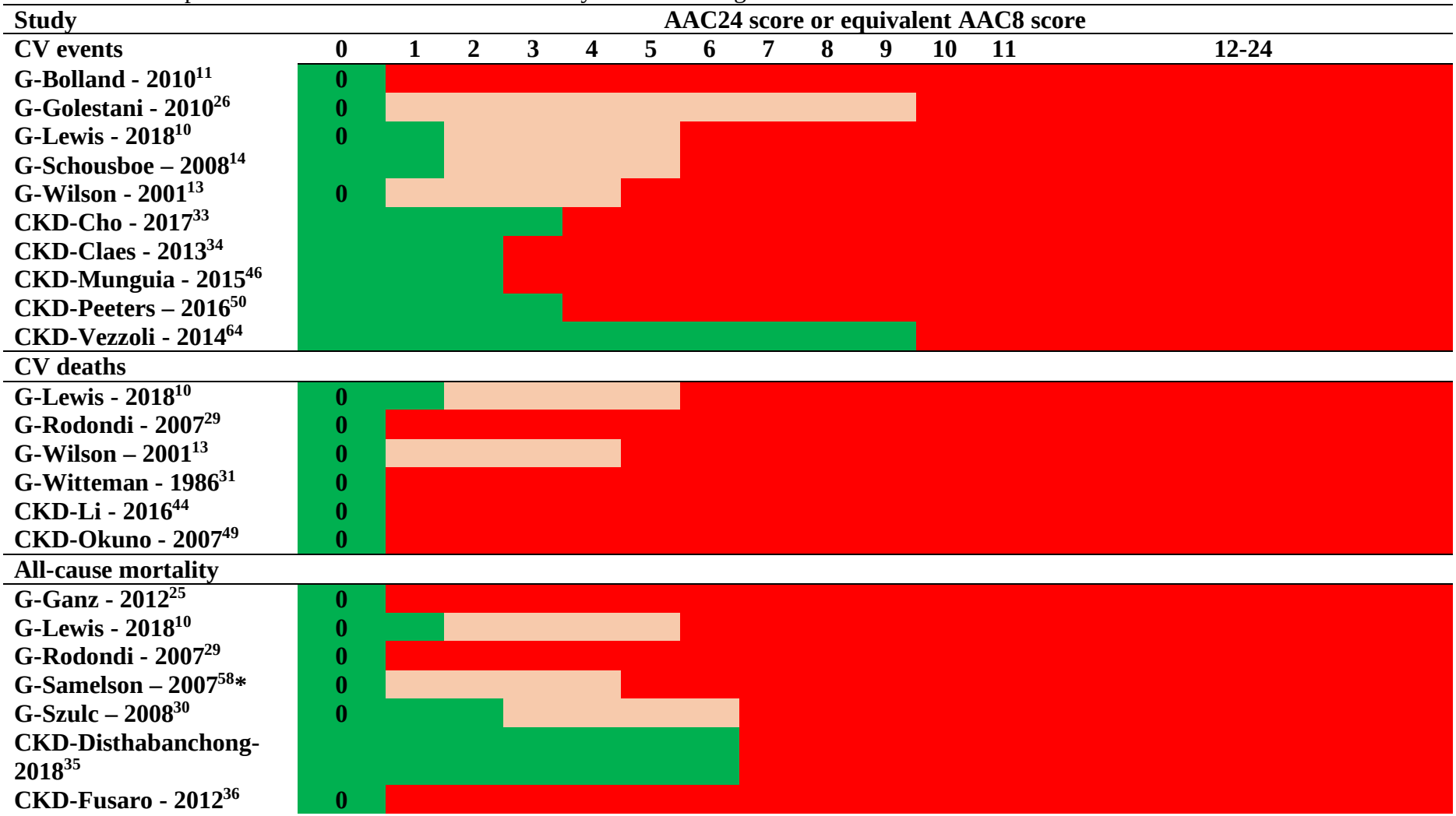
| | Quality of assessment (Decrease in quality score) | | | | Effect size/dose response | Summary of findings | | |
|---|---|---|---|---|---|---|---|---|
| **Studies† (subjects)** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | | **Relative risk (95% CI)** | **Test for heterogeneity** | **Quality of evidence** |
| **Cardiovascular events** | | | | | | | | |
| 8 (1,426) | evidence of publication bias (↓1) | Low/moderate between-study heterogeneity | popn. generalizable | no serious imprecision | ↑1/ insufficient evidence‡ | 3.47 (2.21, 5.45) | $I^2$=29%, p-value=0.196 | Moderate |
| **Fatal cardiovascular events** | | | | | | | | |
| 4 (1,163) | - | Low between-study heterogeneity | popn. generalizable | no serious imprecision | ↑1/ insufficient evidence‡ | 3.68 (2.32, 5.84) | $I^2$=0%, p-value=0.788 | High |
| **All-cause mortality** | | | | | | | | |
| 9 (2,050) | - | Low between-study heterogeneity | popn. generalizable | no serious imprecision | ↑1/ insufficient evidence‡ | 2.40 (1.95-2.97) | $I^2$=0%, p-value=0.584 | High |

***** All outcomes are considered clinically important. Scores are based on the GRADE for assessment of evidence about prognosis where the evidence begins as high quality evidence.[18] 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 CV events and all-cause mortality with increasing severity of AAC]).

† Number of studies with suitable data for meta-analysis

‡Less than 3 studies reported three or more groups.

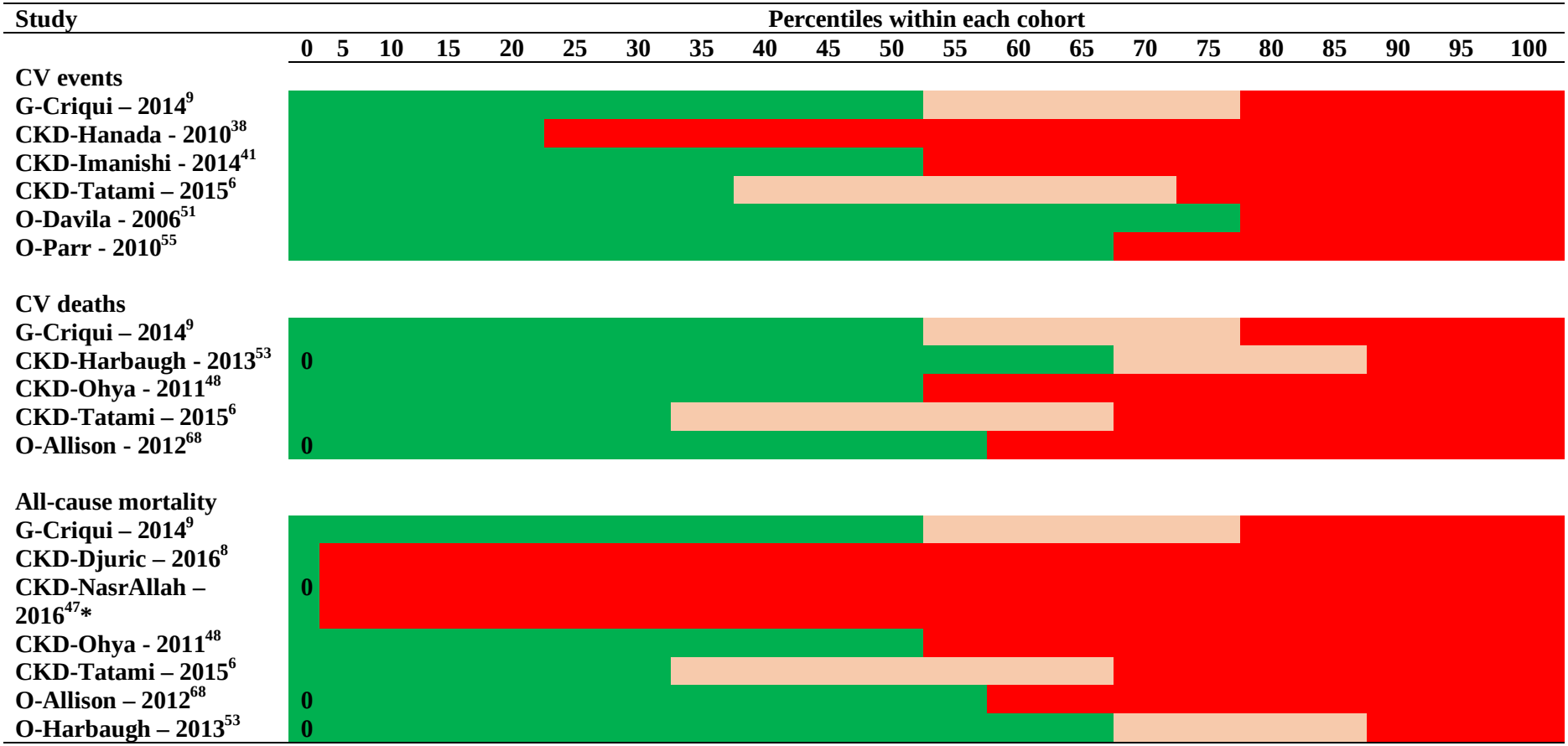
**Table S4.** The reported AAC cut-offs for studies of X-rays or DXA images.



| | |
|---|---|
| **CKD-Hong - 2013[39]** | **0** |
| **CKD-Li - 2016[44]** | **0** |
| **CKD-Munguia - 2015[46]** | |
| **CKD-NasrAllah - 2017[47]** | **0** |
| **CKD-Okuno - 2007[49]** | **0** |

G=recruited from the general population, CKD=recruited from the chronic kidney disease population. Green indicates the lowest reported category of AAC, pink indicates the moderate AAC and red indicates the highest reported category of AAC.
*No extractable data for all-cause mortality in three groups.

**Table S5.** The reported AAC cut-offs for studies using CT.




G=recruited from the general population, O, recruited form other populations, CKD=recruited from the chronic kidney disease population. Zero indicated categorised according to the presence of AAC. Green indicates the lowest reported category of AAC, pink indicates the moderate AAC and red indicates the highest reported category of AAC. * No extractable data for some outcomes.

**Table S6.** Multivariable adjustments used for individual studies of pooled adjusted estimated of risk.

| Study reference | Point estimates (HR or RR) adjusted for |
|---|---|
| **General population** | |
| Allison 2012[68] | age, sex, body mass index, smoking, diabetes, hypertension, dyslipidemia, and family history of CVD. |
| Bolland 2010[11] | age, systolic BP, smoking, status, history of diabetes, history of blood pressure treatment and BMI for women or total cholesterol for men |
| Golestani 2010[26] | age, gender, hypertension, hypercholesterolemia, diabetes mellitus, smoking, and family history of CHD. |
| Hollander 2003[28] | Adjusted for age, sex, diabetes mellitus, smoking, systolic and diastolic BP, cholesterol and HDL cholesterol, and history of CVD. |
| Lewis 2018[10] | Framingham risk model (using BMI) and treatment code |
| Levitzky 2008[57] | age, gender, diabetes, systolic BP, left ventricular hypertrophy on electrocardiogram, BMI, total cholesterol, HDL cholesterol, current cigarette smoking, and hypertension treatment. |
| Rodondi 2007[29] | age, smoking status, diabetes, systolic blood pressure, physical activity, waist girth, and history of angina and myocardial infarction. |
| Schousboe 2008[14] | age, systolic BP, LDL and HDL cholesterol, triglycerides, smoking, renal function, treatment assignment (clodronate or placebo), self-reported diagnoses of diabetes mellitus, hypertension, angina, prior stroke, and health status. |
| Szulc 2008[30] | age, weight, tobacco smoking, diabetes, and medications. |
| Samelson 2007[58] | age, BMI, smoking, systolic BP, total cholesterol, diabetes, CHD, and estrogen use (in women). |
| Wilson 2001[13] | age, cigarettes, diabetes mellitus, systolic BP, left ventricular hypertrophy, BMI, cholesterol, and HDL cholesterol |
| Witteman 1986[31] | Blood pressure, total serum cholesterol, BMI, smoking history (current, past, never) and diabetes |

**Table S7.** Comparison of random and fixed effect estimates of studies from the general population.

| **Any advanced abdominal aortic calcification** | **Random effects RR (95% CI)** | **Fixed effects RR (95% CI)** |
|---|---|---|
| **Chronic kidney diease** | | |
| **Cardiovascular events** | 3.47 (2.21, 5.45) | 3.30 (2.29-4.77) |
| **Fatal cardiovascular events** | 3.69 (2.32-5.85) | 3.69 (2.32-5.85) |
| **All-cause mortality** | 2.41 (1.95-2.97) | 2.41 (1.95-2.97) |
| **General population** | | |
| **Cardiovascular events** | 1.83 (1.40-2.39) | 1.56 (1.45-1.68) |
| **Fatal cardiovascular events** | 1.85 (1.44-2.39) | 1.89 (1.68-2.13) |
| **All-cause mortality** | 1.98 (1.56-2.93) | 1.49 (1.42-1.55) |
| **Coronary heart disease** | 2.23 (1.57-3.15) | 1.98 (1.76-2.28) |
| **Cerebrovascular disease** | 2.10 (1.41-3.12) | 2.11 (1.70-2.62) |

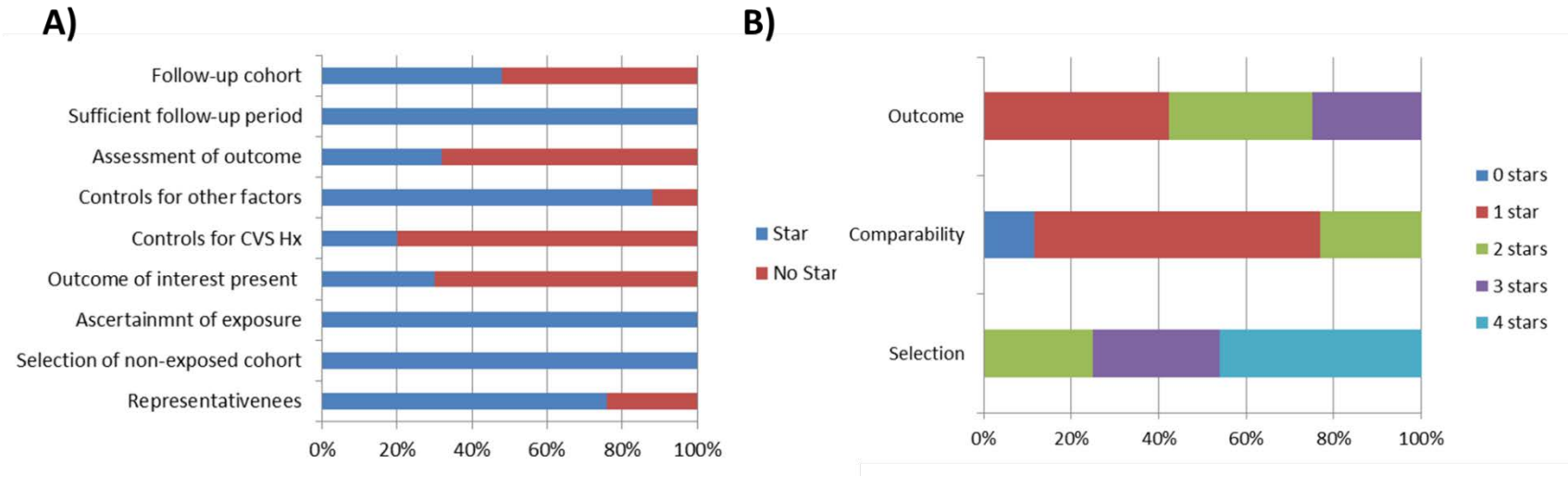



**Figure S1.** Newcastle Ottawa scoring of studies included in the meta-analysis by a) items and b) domains. Maximum number of stars for each domain is 1) outcome maximum of 3 stars 2) comparability maximum of 2 stars, and 3) Selection maximum of 4 stars. CVS Hx = History of cardiovascular disease which was considered the most important factor to be controlled for.

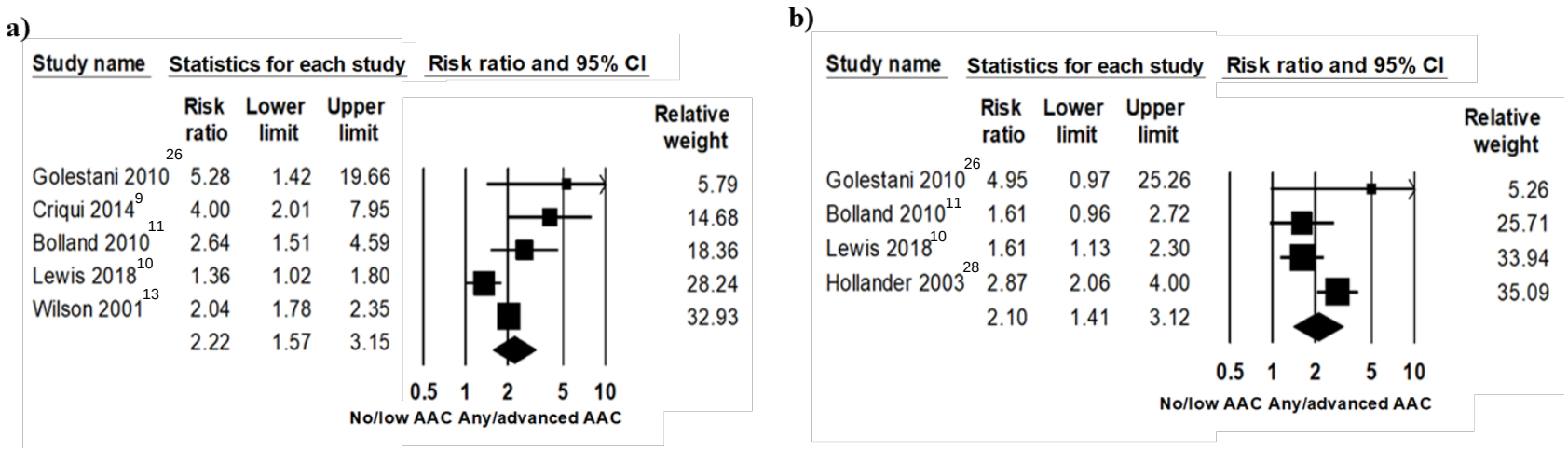



**Figure S2.** Forest plots for the pooled relative risk of a) coronary heart disease events ($I^2$=72%, p-value=0.012) and b) cerebrovascular events ($I^2$=60%, p-value=0.055) in the general population stratified by no or low abdominal aortic calcification (AAC) vs any or more advanced AAC.

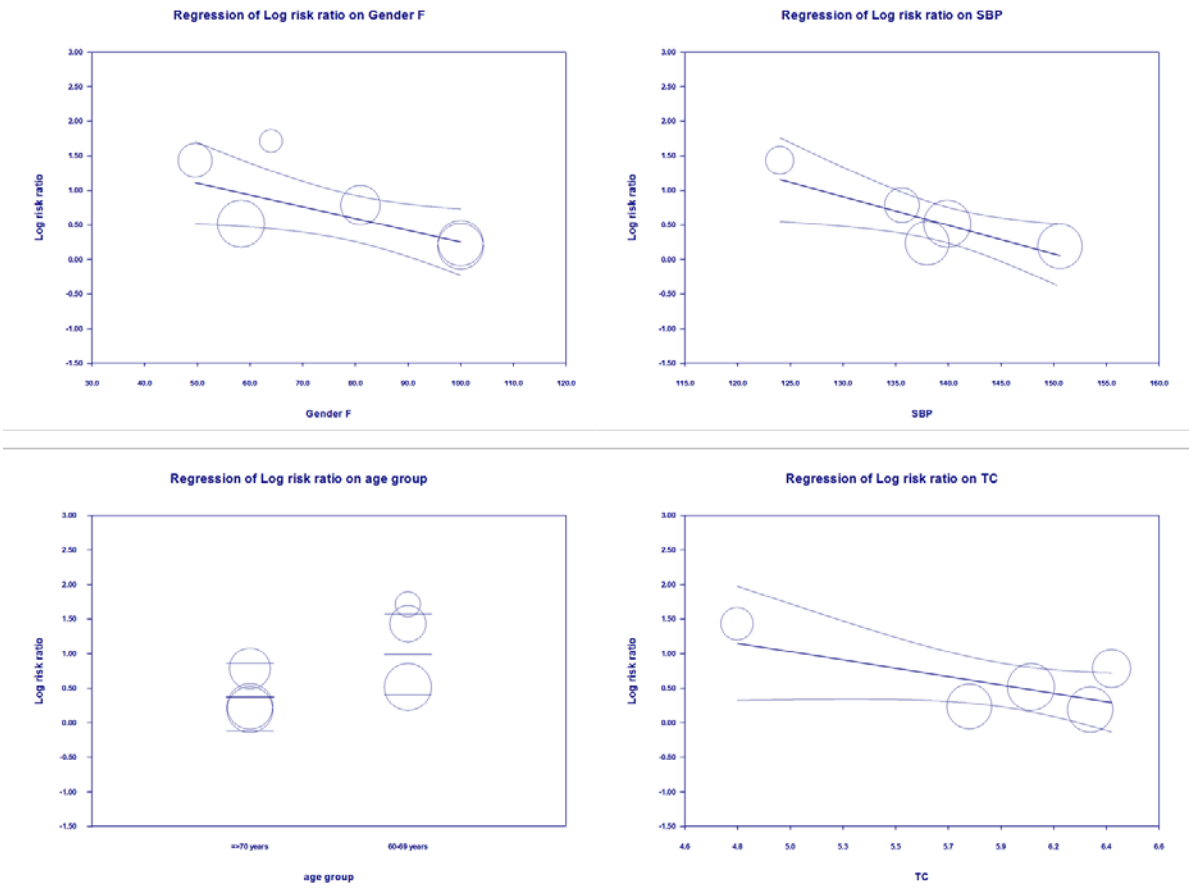



**Figure S3.** Meta-regression – Log RR of any CV event by top left) the proportion of women the study cohort ($r^2$=0.0, p=0.012), top right), baseline systolic blood pressure (SBP) in mmHg ($r^2$=0.42, p=0.003), bottom left) age group ($r^2$=0.0, p=0.048) and bottom right) total cholesterol in mg/dL ($r^2$=0.04, p=0.048). Variables tested (where sufficient studies were available n=3) included: age group, total cholesterol, high density lipoprotein cholesterol, % females, %type 2 diabetics, & current smokers, BMI, SBP, % prescribed anti-hypertensives, % with clinical history of CVD.

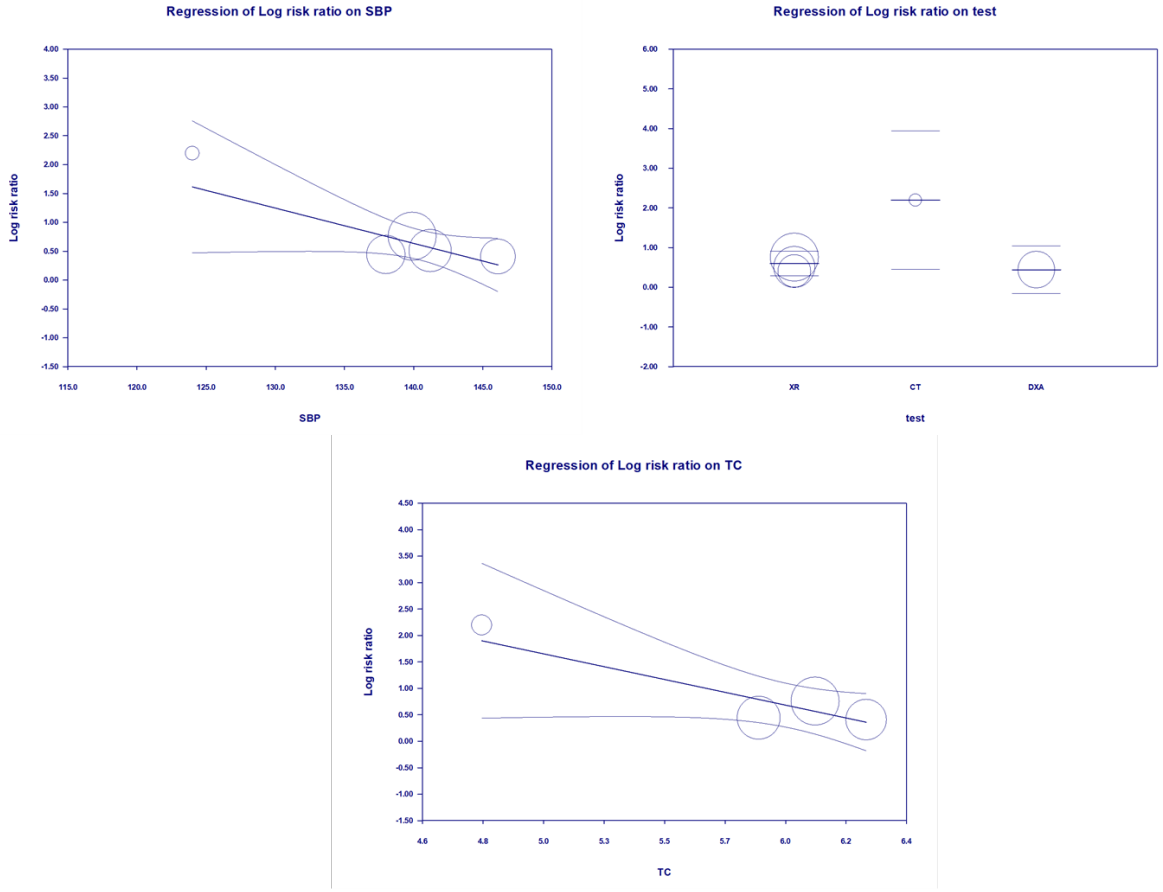



**Figure S4.** Meta-regression – Log RR for fatal CV events top left) imaging modality used in the studies ($r^2$=0.60, p=0.029) and top right) means systolic blood pressure (SBP) in mmHg ($r^2$=0.45, p=0.027) and bottom left) total cholesterol in mg/dL ($r^2$=0.13, p=0.031). Variables tested (where sufficient studies were available n=3) included age group, total cholesterol, high density lipoprotein cholesterol, % females, %type 2 diabetics, & current smokers, BMI, SBP, % prescribed anti-hypertensives, % with clinical history of CVD.

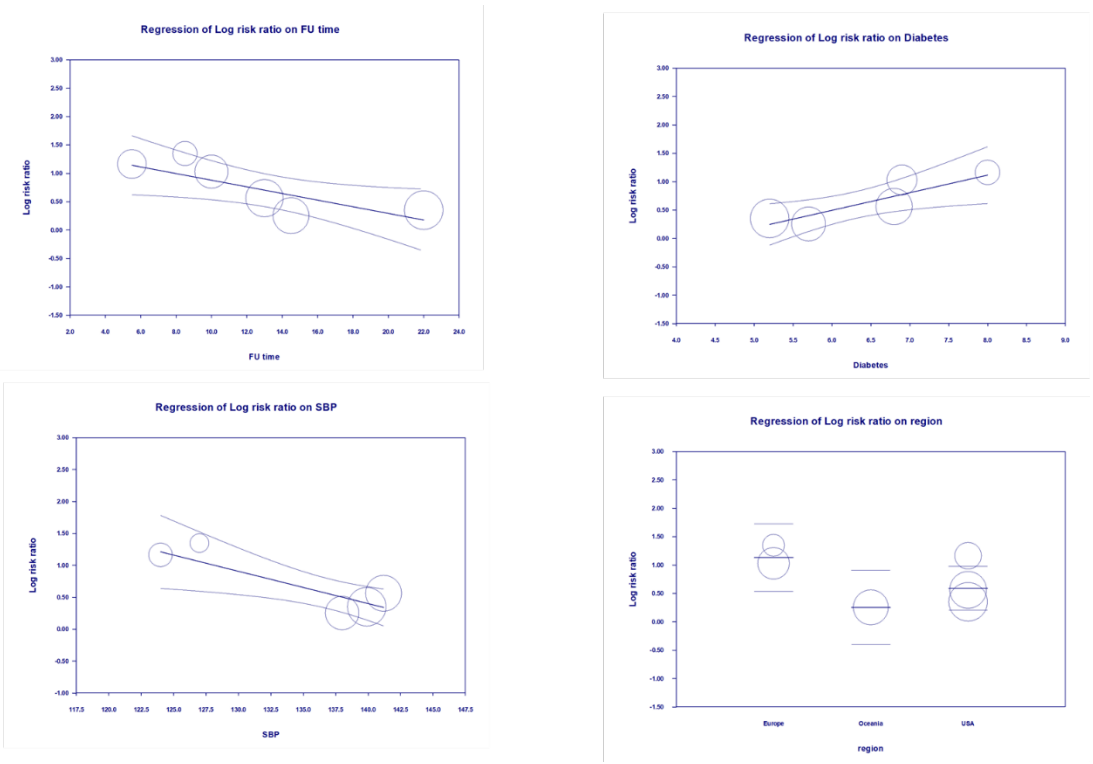



**Figure S5.** Meta-regression – Log RR of any all-cause mortality by top left) follow up time in year ($r^2$=0.11, p=0.008) and top right) % of participants with type 2 diabetes ($r^2$=0.42, p=0.003), bottom left) mean systolic blood pressure (SBP) in mmHg ($r^2$=0.39, p=0.002) and bottom right) region of study ($r^2$=0.36, p=0.017). Variables tested (where sufficient studies were available n=3) included age group, total cholesterol, high density lipoprotein cholesterol, %females, %type 2 diabetics, & current smokers, BMI, SBP, % prescribed anti-hypertensives, % with clinical history of CVD.