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Review

Breast arterial calcifications: A systematic review and meta-analysis of their determinants and their association with cardiovascular events

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ABSTRACT

Objective: Breast arterial calcifications (BAC), regularly observed at mammography, are medial calcifications and as such an expression of arteriosclerosis. Our objective was to evaluate and summarize the available evidence on the associations of BAC with cardiovascular risk factors and cardiovascular risk.
Methods: A systematic literature review and meta-analysis were conducted. Embase and PubMed databases were searched. After critical appraisal, odds ratios were extracted from studies of moderate or good quality that examined risk factors for BAC or associations of BAC with cardiovascular disease. Random effects model meta-analyses were used to calculate pooled odds ratios and 95% confidence intervals (95%CIs).
Results: BAC prevalence is around 12.7% among women in breast cancer screening programs. Increasing age (pooled OR 2.98 [95%CI 2.31–3.85] for every 10 years), diabetes (pooled OR: 1.88 [95%CI 1.36–2.59]) and parity as opposed to nulliparity (pooled OR 3.43 [95%CI 2.23–5.27]) are associated with higher BAC prevalence. Smoking is associated with lower BAC prevalence (pooled OR 0.48 [95%CI 0.39–0.60]). No associations were found with hypertension, obesity or dyslipidemia. Although longitudinal studies (n = 3) were scarce, BAC appear to be associated with an increased risk of cardiovascular disease events (adjusted hazard ratios for coronary heart disease ranging from 1.32 [95%CI 1.08–1.60] to 1.44 [95%CI1.02–2.05]).
Conclusion: BAC appear to be associated with an increased risk of cardiovascular disease events, while only being associated with some of the known cardiovascular risk factors, illustrating that medial arterial calcification might contribute to cardiovascular disease through a pathway distinct from the intimal atherosclerotic process.

Contents

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1. Introduction

Arterial pathology can occur in all three layers of the arterial wall. In the intima, calcification occurs within plaques and is associated with the well-known atherosclerotic process [1]. In the deeper layers, especially in the media, circular calcifications are fairly common, generally considered innocent, though a scarcely studied phenomenon [2]. The formation of bone tissue in the media is part of a process called arteriosclerosis. Media calcifications could contribute to cardiovascular disease through a different mechanism than atherosclerosis, supposedly by increasing arterial stiffness [3]. If so, this could have important therapeutic and prognostic consequences.

A limited number of articles have been published on the topic of medial calcification. Pathologic studies convincingly demonstrated the presence of medial calcification in the aorta, and in the arteries of the lower extremity, with prevalence increasing with age [4,5]. Furthermore, some studies investigated associations of radiographical medial arterial calcification in the lower extremity with cardiovascular disease outcomes. These studies were mostly performed in highly selected subgroups, such as diabetes patients and renal disease patients [6,7]. Large prospective studies in the general population are lacking, in part because intimal and medial calcification cannot be easily distinguished with non-invasive methods.

An exception is breast arterial calcification (BAC), which is a type of medial calcification that is regularly observed on screening mammography [8]. BAC is a potential women-specific risk factor for cardiovascular disease risk [9–13]. Several studies have suggested that BAC is associated with traditional cardiovascular risk factors, such as hypertension, diabetes and chronic kidney disease [8,14–17]. In 2013, two reviews addressing the relation between cardiovascular risk factors and BAC as well as its association with cardiovascular disease outcomes were published. However, a quantitative pooling of the results was lacking, nor was the potential for confounding systematically addressed [18,19].

Therefore, our objective was to systematically review and critically appraise the literature on the determinants of BAC and its associations with cardiovascular events and to summarize these findings in a meta-analysis, taking into account the potential for confounding and other types of bias.

2. Methods

This review was conducted in concordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [20]. A review protocol outlining the methods was agreed upon before the start of the study and provided in the Supplementary Materials.

2.1. Eligibility criteria

Inclusion criteria were: original research reported in English, German, Dutch or Spanish on women who had undergone mammography that addressed BAC in association with cardiovascular disease, cardiovascular risk factors or reproductive factors; or that reported BAC prevalence in the general population, diabetes patients or renal disease patients. For risk factors or reproductive factors, articles had to present odds ratios (ORs) or data from which these could be calculated for one of the following determinants: age, diabetes, hypertension, dyslipidemia, obesity, renal disease, menopausal status and use of hormone replacement therapy, smoking, parity, and lactation history. Conference abstracts were excluded, as they do not provide sufficient information to make an informed decision on risk of bias.

2.2. Information sources and search strategies

PubMed and EMBASE were searched using a predefined search string provided in the supplement including “breast artery calcification” and its synonyms (Table S1). Our search was updated until the 24th of June 2014. References of all relevant articles were screened to identify potential missing articles.

2.3. Study selection and assessing risk of bias in individual studies

Titles and abstracts were screened by one reviewer (EJEH) to determine whether they reported on the topic of BAC. Two authors assessed all possibly relevant articles independently (EJEH and JWJB), and applied the eligibility criteria to the full text article. Non-concordant judgments were discussed with a third author (PAdJ) and resolved by consensus.

As no universally recommended tool for assessing the quality of observational epidemiological studies exists [21], we used predefined criteria. We assessed articles on the following items: selecting representative study population, selecting appropriate controls (when applicable), methods for measuring BAC, methods for measuring (other) outcomes, dealing with missing data/non-response, statistical methods and controlling for confounding. Every item was rated “unknown/unreported”, “poor”, “moderate” or “adequate” and assigned 0, 0, 1 or 2 points, respectively. Overall quality was calculated by summing all scores and dividing by the number of applicable items (6 or 7). Studies scoring below 1.0 were rated “poor quality”, studies scoring $\geq$1.0 but <1.5 were rated “moderate quality” and studies scoring $\geq$1.5 were rated “good quality”.

2.4. Data extraction

For the extraction of general population prevalences, studies that scored at least "moderate" on both the items "Selecting representative study population" and "Methods for measuring BAC" were included. Only studies of "moderate" to "good" quality were used to extract association measures (ORs). ORs or hazard ratios describing the association between BAC and cardiovascular disease were extracted for the following outcomes: cardiovascular mortality, coronary heart disease, stroke, and peripheral artery disease. For these outcomes, we chose only to include longitudinal (cohort or case control) studies.

As age is consistently reported as a determinant of BAC and an important determinant of cardiovascular disease and its risk factors, we used age-adjustment as a minimum requirement in the controlling for confounding for the following variables: diabetes, hypertension, dyslipidemia, obesity, renal disease, menopausal status, the use of hormone replacement therapy and cardiovascular disease outcomes. Age-adjustment was considered adequate if age was incorporated in a regression model as a continuous variable or if stratified analyses were performed across at least 3 age strata. When no age-adjusted ORs were given but prevalence rates among groups were provided stratified by age across at least 3 strata, a Mantel–Haenszel pooled OR was calculated. We did not impose the requirement of age-adjustment to the extraction or calculation of ORs for smoking, parity and lactation history as these do not change (much) with age among older women. Also, for age itself, no minimum requirement for controlling for confounding was set.

2.5. Data analysis

We conducted meta-analyses for specified outcomes when at least three moderate to good quality studies provided effect sizes across similar levels of a specific outcome. Random effects meta-analysis models were fitted to the natural logarithms of the odds ratios, as effects were expected to be heterogeneous due to the variety of study populations and study designs included in the analyses. Heterogeneity was tested and reported using I^2. Sensitivity analyses were performed stratifying by quality and including different degrees of adjusting for confounding. The presence of small study effects and the possibility of publication bias were assessed using funnel plots. Funnel plot asymmetry was formally tested using the random/mixed-effects version of Egger's test [22] when at least 10 studies were included in one analysis. Analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria), version 2.15.2 and the 'metafor' package, version 1.8–0.

3. Results

We identified 1658 unique articles through our PubMed and Embase database searches. After screening of titles and abstracts, 116 articles were found to be relevant and were assessed full text (Fig. 1). Quality assessment was performed on 63 relevant articles. We found 30 articles to be of "good quality" [8–11,17,23–47], 18 articles of "moderate quality" [12–16,48–60] and 15 articles of "poor quality" [61–75]. The full critical appraisal is provided in the Supplementary Material (Table S2).

No data was extracted from 11 articles, because they did not fulfill criteria of quality and adjustment for confounders as described in the methods section [15,35,51,55,59,63–65,70,71,74]. Data was extracted from 52 articles; their characteristics are summarized in Table 1. About half of all studies included women from the general population, recruited through breast cancer screening programs. A wide range of populations was included in the remainder of selected studies. Articles were fairly consistent in

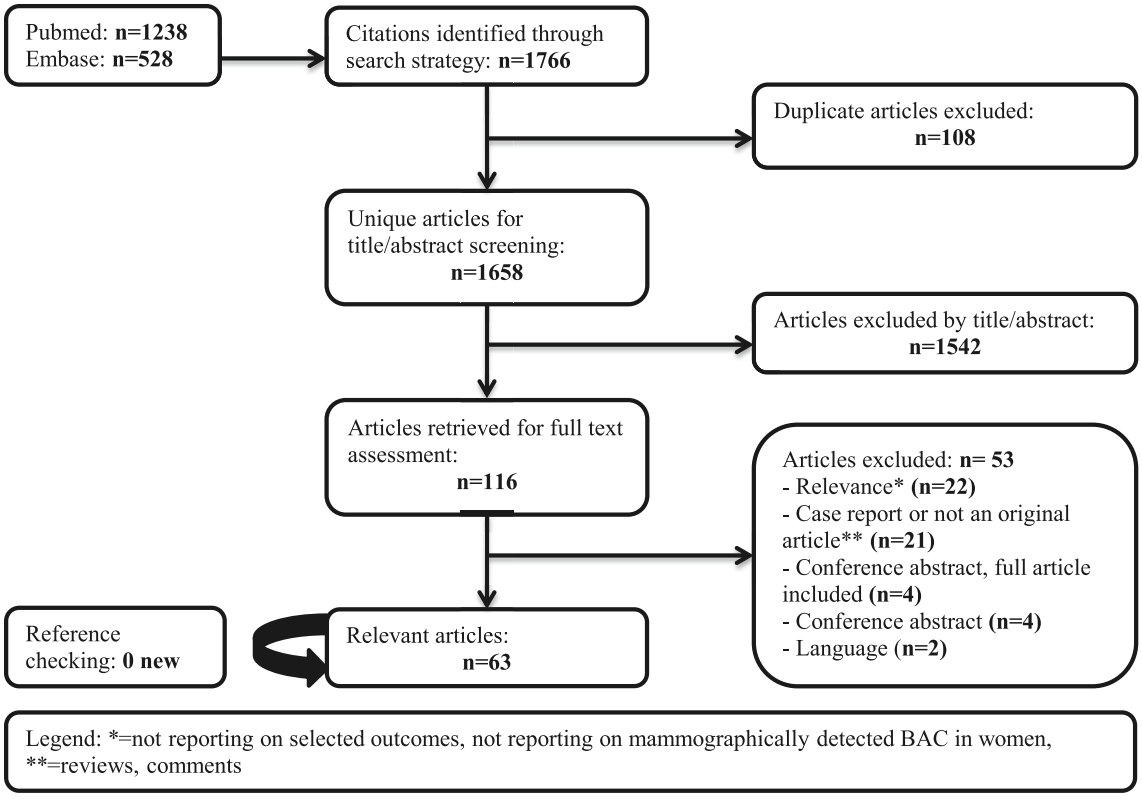

Fig. 1. Search strategy flowchart.

Table 1
Overview of all included studies.

Author	Year	Design	N	Mean age (years)	Overall quality	BAC prevalence[a]
Population: general						
Bae	2013	CaCo	959	? r. > 40	±	10.5%
Cetin	2004 (I)	CS	2400	? r. 32–75	±	9.1%
Cetin	2004 (II)	CS	2400	? r. 32–75	±	9.1%
Cox	2002	CS	4400	? r. 49–66	±	12.0%
Crystal	2000	CS	865	56	+	17.6%
Dale	2008 (II)	CS	1000	58	±	16.1%
Ilica	2011	CaCo	6118	? r.40–95	±	11.5%
Iribarren	2004	Cohort	12,761	56	+	3.0%[b]
Kemmeren	1996&1998	Cohort	12,239	57.7	+	9.0%
Loberant	2014	CS	1786	? r. 40–93	+	14.4%
Maas	2006 (I)	CS	1699	57	+	11.4%
Maas	2007 (II)	CS	1689	57.2	+	11.0%
Markopoulos	2004	CS	420	? r. 41–75	–	11.0%
Pidal	2009	CaCo	1759	? r. 45–65	±	8.4%
Reddy	2005	CS	1905	57.6	+	29.4%
Rotter	2008	CS	1919	55.9	+	14.0%
Sanchez Vidal	2000	CS	600	52.7	–	8.2%
Schnatz	2007	CS	1919	55.9	+	14.0%
Schnatz	2011	Cohort	1454	56.3	+	16.3%
Sedighi	2011	CaCo	537	52.3	+	14.7%
Taskin	2006	CaCo	6156	? r. >40	±	7.9%
van Noord	1996	CS	12,239	57.7	+	9.0%
Xue	2008	CS	1139	39.7	–	11.7%
Zafar	2013	CS	200	46	–	13.5%
Population: general, postmenopausal						
Bielak	2010	CS	240	62.1	+	43.8%
Ferreira	2009	CS	307	55.2	±	8.5%
Kataoka	2006	CS	1590	63.2	+	16.0%
Maas	2007 (I)	Cohort	499	57.9	+	11.6%
Nasser	2014	CS	211	62.1	±	18.0%
Yildiz	2008	CaCo	636	?	+	10.2%
Population: chronic kidney disease						
Abou-Hassan	2014	Cohort	202	58.3	+	58.4%
Canabal	2008	CS	61	?	–	55.7%
Duhn	2011	CaCo	106,71	61.3	+	47.2%
Evans	1992	CS	16	56.6	–	56.3%
Hassan	2012	CaCo	292, 292	62.2	+	39.7%
Nieto	2005	CaCo	26, 492	?. ±64	–	34.6%
Sommer	1987	CaCo	15, 100	? r. 37–74	–	45.1%
Population: diabetes						
Dale	2010	CaCo	790, 819	? r. 24–93	±	36.5%
Fuster	2004	CS	230	59.8	+	40.0%
Fuster	2005	CS	230	59.8	±	40.0%
Schmitt	1984 (II)	CS	169	?	–	16.0%
Schmitt	1985	CaCo	150, 300	? r. 35–74	±	8.7%
Population: miscellaneous						
Fiuza Ferreira	2007	CS	131	61.1	+	39.7%
Hekimoglu	2012	CS	55	63	+	41.8%
Henkin	2003	CaCo	319	61.8	+	41.1%
Maas	2004	CS	600	67.4	+	23.0%
Matsumura	2013	CS	202	58.8	+	?
Penugonda	2010	CS	94	66.7	+	60.6%
Reddy	2008	CS	228	64	+	39.0%
Sickles	1985	CS	5000	?	±	9.6%
Zgheib	2010	CS	172	64.3	+	33.1%

CaCo = case control, CS = cross sectional, ? = not mentioned in paper (when mean age is not provided, we report r. = range if available), + = good quality, ± = moderate quality, – = poor quality.

[a] In case of case control studies of diabetic and renal disease patients, stated prevalences are of the patients, not of the controls.

[b] Mammograms were not read specifically for breast arterial calcification.

their definition of BAC, describing it as “parallel lines along the course of vessels”, “railroad track configuration” or a description of a similar nature. The vast majority of articles described BAC only as present (in at least one breast) or absent. Articles that did attempt to quantify BAC did so in a variety of ways. We chose to use only results from analyses using present/absent scoring. All articles but one specifically (re-) assessed mammograms for BAC, which screened the original mammography reports for mention of BAC [11].

3.1. The prevalence of BAC

BAC prevalences reported by studies including women in breast cancer screening programs, as an approximation of the general population of women in their fifth to seventh decade of life are shown in Fig. 2 (top). A random effects model yielded a prevalence estimate of 12.7% with a 95%CI (95% confidence interval) of 10.4–15.1%. Seven of the general population studies reported prevalences for different age groups, summarized in Fig. 2 (bottom),

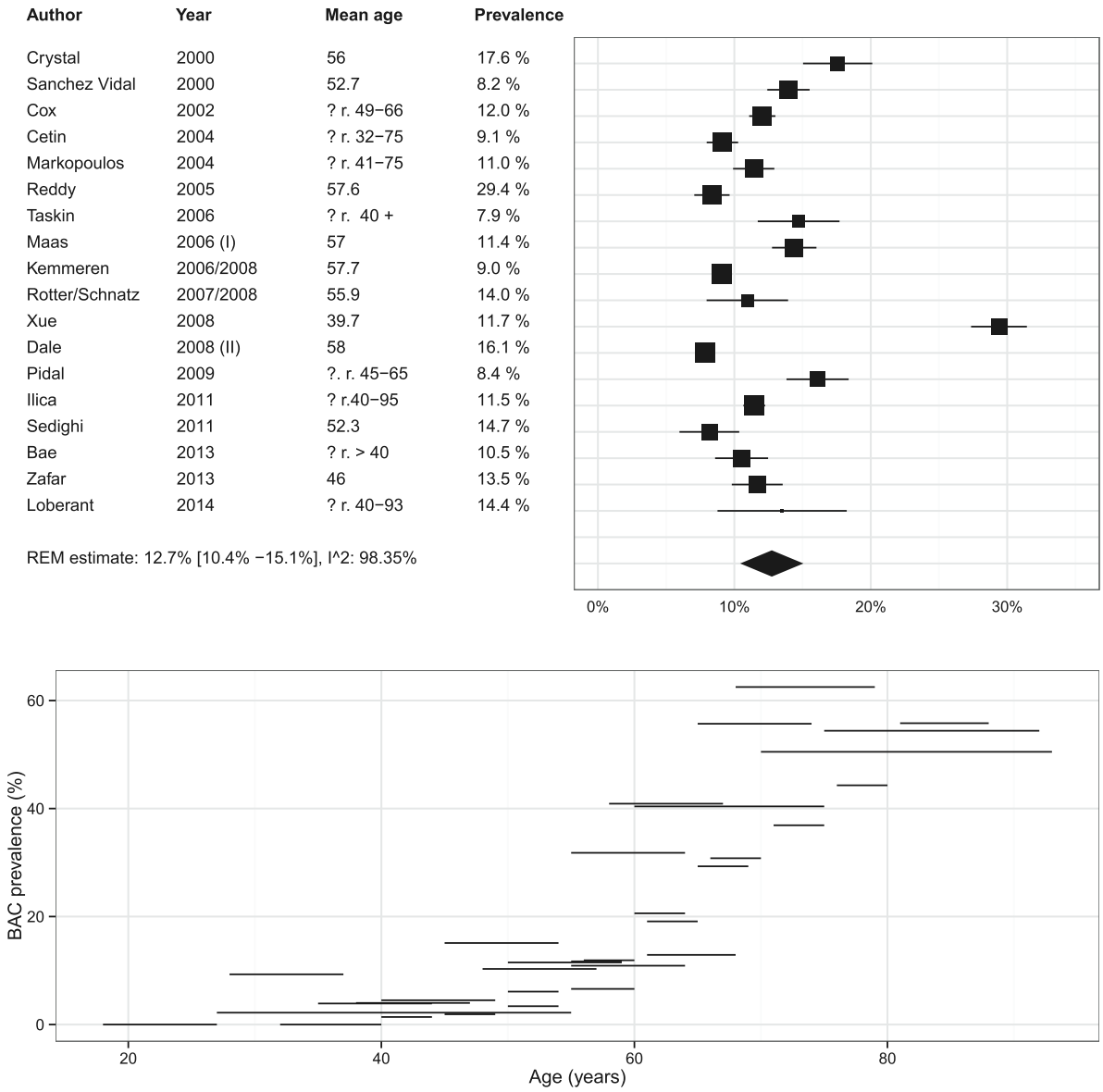

Fig. 2. BAC prevalence in the general population – Top: BAC prevalences reported in general population studies. ? = not mentioned in paper (when mean age is not provided, we report r. = range if available). Bottom: BAC prevalence among different age groups, from 7 studies [12,25,27,29,45,49,73].

which shows that BAC prevalence increases from around 10% in 40-year-old women to around 50% in 80-year-old women [12,25,27,29,45,49,73].

Increasing age was almost universally found to be an important determinant for BAC prevalence. Including all 10 studies reporting ORs for the presence of BAC, we found a pooled OR of 2.98 [95%CI 2.31–3.85] for every 10 years of increasing age (Fig. 3A) [8,11,24,26,30,33,37,38,50,57]. Effects were heterogeneous ($I^2 = 87.02\%$). Sensitivity analyses did not affect the results, nor was the heterogeneity reduced (see Supplement 3 for all sensitivity analyses).

3.2. Reproductive factors

Women with children were found to have a higher prevalence of BAC than women without children (OR 3.43; [95%CI 2.23–5.27], Fig. 3B) [11,28,47,52,53,57,76]. Effects were homogenous (I^2: 0.00%) and sensitivity analyses did not materially change results. The number of children was also positively associated with BAC, indicating a dose–response relation [30,37,73]. Two studies reported significantly higher prevalences of BAC in women who reported to have breastfed at least one of their children, compared to women with children who did not breastfeed [24,47]. All studies providing age- or multivariable adjusted ORs for the use of hormone replacement therapy pointed towards a reduced prevalence of BAC among users (OR 0.56; [95%CI 0.37–0.84], Fig. 3C), despite variation in the effect sizes (I^2: 88.23%) [11,24,26,50,53,76]. Heterogeneity could not be explained by degree of adjustment, but was diminished when including good quality studies only. No meta-analysis on the association of menopausal status with BAC was performed as we found only 2 articles reporting age-adjusted ORs. Both studies reported increased rates of BAC prevalence in menopausal women, irrespective of age [28,38].

3.3. Cardiovascular risk factors

From studies that presented age- or multivariable adjusted ORs for BAC according to the presence or absence of hypertension, we

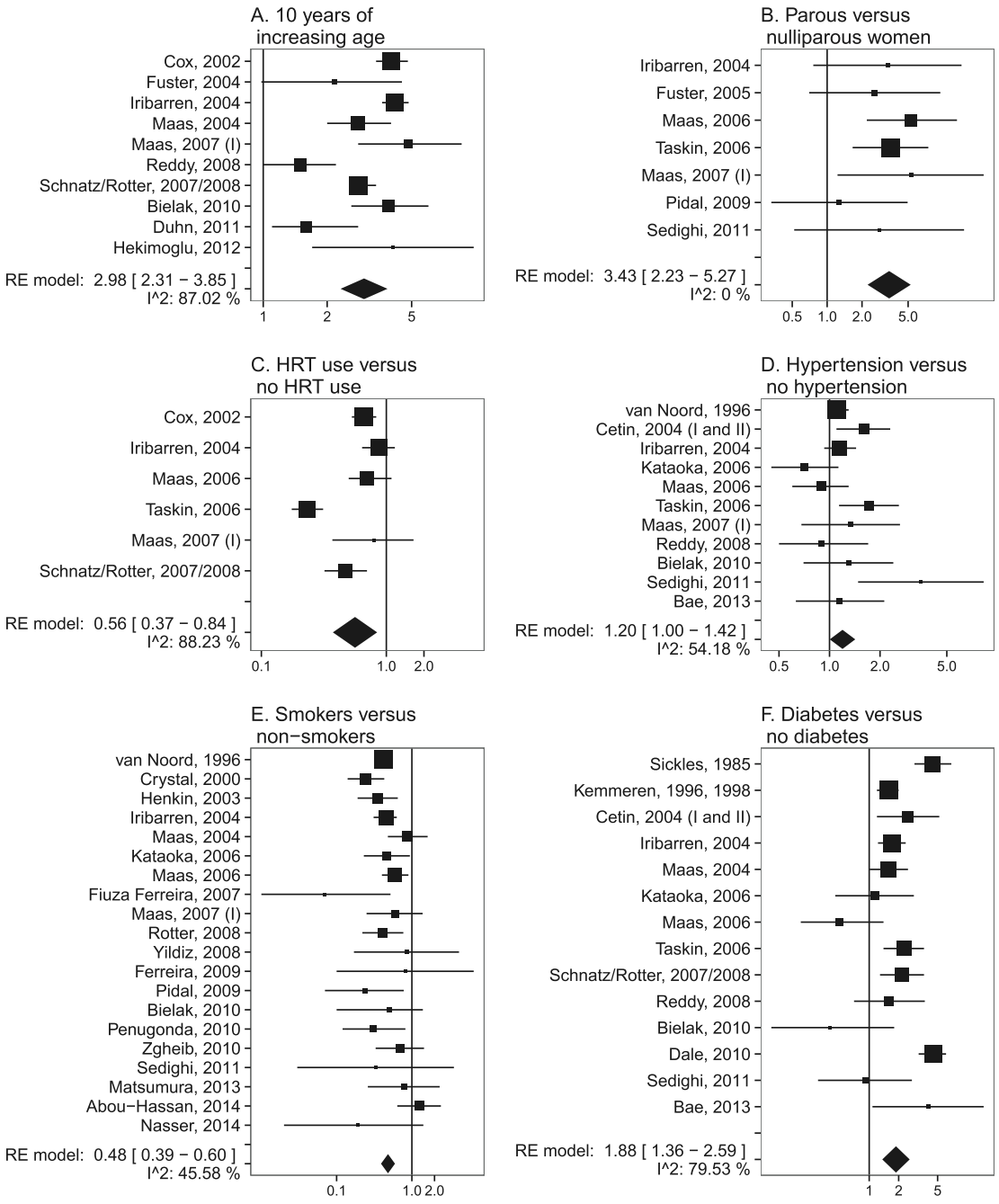

Fig. 3. Forest plots – Forest plots of the ORs and 95%CIs of the risk factors and reproductive factors as determinants of BAC. RE model: random effects model.

calculated a borderline significant overall OR estimate of 1.20 [95% CI 1.00–1.42] (Fig. 3D) [11,14,28–31,38,47–49,53,77]. Heterogeneity (I^2: 54.18%) was reduced to non-significant levels (I^2: 0.00%) when including good quality studies only, with a comparable OR of 1.08 [95%CI 0.98–1.19]. Studies consistently reported ORs below 1 for smokers versus non-smokers, indicating that the prevalence of BAC is lower among smokers (OR of 0.48 [95%CI 0.39–0.60], Fig. 3E) [10,11,13,23,26,28,30–32,34,37,40,41,43,44,46,47,52,60,77]. The estimated OR did not change substantially in any of the sensitivity analyses, but heterogeneity (I^2: 45.58%) was reduced to non-significant levels in the analyses limited to current smoking or age- or multivariable adjusted ORs. We found a combined OR of 1.72 [95%CI 0.95–3.09] for BAC for women diagnosed with hyperlipidemia versus women without this condition [24,28,48,53], with marked heterogeneity (I^2: 63.87). We did not find an association between BMI and BAC; the pooled adjusted OR for BAC per unit increase in body mass index (BMI) was 0.99 [95%CI 0.95–1.04] [24,30,36]. Effect sizes were homogeneous (I^2: 27.50%). Two other studies compared BMI categories and also found ORs with confidence intervals comprising unity [11,28].

Pooling 14 studies reporting age-adjusted or multivariable adjusted ORs, we found that there is an increased rate of BAC among diabetes patients (OR: 1.88; [95%CI 1.36–2.59], Fig. 2F), but with marked heterogeneity in effect sizes (I^2: 79.53%). The pooled

Table 2
Longitudinal studies reporting on the association between BAC and cardiovascular disease.

Study	Outcome	HR (age-adjusted)	95%CI	HR (RF adjusted[a])	95%CI
Kemmeren, 1996, 1998					
	All-cause mortality	1.11	0.95–1.28	1.29	1.06–1.58
	Cardiovascular mortality	1.35	1.07–1.70	1.29	1.01–1.66
	CHD mortality	1.47	1.06–2.03	1.44	1.02–2.05
	Cerebrovascular mortality	0.98	0.56–1.71	0.88	0.49–1.61
	Other cardiovascular mortality	1.45	0.96–2.19	1.38	0.89–2.16
	Cardiovascular mortality among DM patients			1.71	1.00–2.94
Iribarren, 2004					
	Coronary heart disease	1.29	1.07–1.57	1.32	1.08–1.60
	Ischemic stroke	1.40	1.11–1.76	1.41	1.11–1.78
	Transient ischemic attack	1.44	0.77–2.70	1.42	0.75–2.67
	Hemorrhagic stroke	1.43	0.79–2.60	1.54	0.84–2.83
	Heart failure	1.52	1.18–1.96	1.52	1.18–1.98
Schnatz, 2011					
	Incident cardiovascular disease	3.54 (OR)	2.28–5.50		
Abou-Hassan, 2014					
	Coronary artery disease			1.06 (OR)	0.48–2.38
	Peripheral arterial disease			4.56 (OR)	1.20–17.3

HR= Hazard ratio, 95%CI = 95% confidence interval, CHD = coronary heart disease, DM = diabetes mellitus, RF = risk factor.
[a] Kemmeren: adjusted for age, DM, hypertension, parity, body mass index and smoking, Iribarren: adjusted for age, race, education level, body mass index, total serum cholesterol, smoking, alcohol, hypertension, diabetes, family history of myocardial infarction, parity, early menarche and hormone replacement therapy, Abou-Hassan: adjusted for age, ESRD duration, diabetes, smoking.

OR was attenuated when only good quality studies were included or when only multivariable adjusted studies were included. Resulting ORs were 1.56 [95%CI 1.32–1.83] and 1.73 [95%CI 1.39–2.15], respectively, but still statistically significant. Seven papers assessed BAC prevalence among renal disease patients, reporting considerably higher prevalences than those found in the general population, ranging from 25% among patients with chronic kidney disease stage 3, to 63% among patients with end-stage renal disease (in need of dialysis or transplantation) [8,17,44,66–69]. No meta-analysis incorporating ORs comparing kidney patients to healthy controls could be performed as only 2 studies of moderate to good quality compared these groups [8,17].

There was no funnel plot asymmetry for age, smoking and hypertension. For diabetes, the funnel plot was asymmetrical ($p = 0.0354$), including more small studies that showed relatively small effect sizes compared to larger studies (see Fig. S1).

3.4. BAC as a risk factor for CVD

Only 5 articles reported prospectively on cardiovascular disease [9,11,23,42]. As outcomes were not similarly defined, no pooled effect size could be calculated. The first cohort study, reporting on mortality, found an age-adjusted hazard ratio of 1.35 [95%CI 1.07–1.70] for cardiovascular death for women with BAC, which did not change considerably after additionally adjusting for known risk factors and parity [9,23]. The second cohort study found comparable results, with BAC being associated with a 1.32 [95%CI 1.08–1.60]-fold increased rate of coronary heart disease, and a 1.52 [95%CI 1.18–1.98]-fold increased rate of heart failure after adjusting for several cardiovascular risk factors as well as age and parity [11]. The third cohort study found a much larger effect size with an OR of 3.54 [95%CI 2.28–5.50] for incident cardiovascular disease [42]. The most recent study did not recruit from the general population as the previous cohorts did, but included women with end stage renal disease. As a secondary analysis, they studied the association of coronary artery disease and peripheral artery disease that occurred after the time of the mammography, in women who did not have clinical events before. They found a significantly increased risk for peripheral artery disease (OR 4.56, 95%CI 1.20–17.3) but not for coronary artery disease (OR 1.06, 95%CI 0.48–2.38) (See Table 2).

4. Discussion

This review systematically summarized the evidence on the associations of cardiovascular risk factors and reproductive factors with BAC, and its association with cardiovascular disease risk. Our data show that BAC appear to be associated with an increased risk of cardiovascular disease events, while only being associated with some of the known cardiovascular risk factors.

4.1. Risk factors for BAC

A strong and consistent association is found between increasing age and presence of BAC. Although a strongly age-related phenomenon, it is not an omnipresent finding among elderly women nor to be too eagerly accepted as part of healthy aging. An interesting finding is the reduced prevalence of BAC among women who smoke. This is in line with Shah et al., replicated in a larger number of studies, and found to be robust to several sensitivity analyses [78]. Although it may seem surprising at first, an inverse relationship of smoking with BAC is not unthinkable, as BAC is a type of medial calcification, a pathophysiological process distinct from intimal calcification [79]. Limited data on other arterial beds support that smoking is associated with less medial calcification [80,81], or not associated with medial calcification, while intimal calcification is [7]. Explanations proposed in literature include effects of smoking on weight and estrogen metabolism and the selective survival of smokers without BAC after the age of 50 [29,30]. The latter explanation appears unlikely for such a big effect in this age group. A satisfactory explanation is not available.

Clear associations were also found for reproductive variables, with higher rates of BAC among parous versus nulliparous women, among those with a history of lactation and lower rates with hormone replacement therapy. Although no meta-analyses could be performed, menopause appeared to be associated with BAC presence, independently of age. A proposed mechanism behind the associations of parity and lactation with BAC is the transient hypercalcemia and over-distension and micro-trauma during pregnancy and lactation [47]. However, as BAC tends to appear decades after the fertile age, this cannot be a direct effect but rather changes induced to the vascular wall that persist long-term. For example, smooth muscle cells could be triggered to up-regulate

mineralization by hormonal influences more directly.

A clear and consistent association was found between diabetes and BAC presence, an association that persists after age-adjustment. Renal disease also appears to be associated with a higher BAC prevalence. However, other cardiovascular risk factors were not associated with BAC. Heterogeneous effects were found in the associations reported of hyperlipidemia and hypertension with BAC. This could in part be due to different outcome definitions ranging from direct measurements to a self-reported diagnosis. Confidence intervals comprise unity, providing insufficient evidence to confirm or reject an association between these risk factors and BAC. However, if present, the effect size is likely to be small.

4.2. BAC and cardiovascular risk

Longitudinal studies investigating the associations between BAC and cardiovascular disease risk were scarce, but results were consistent in showing increased hazards for cardiovascular disease among BAC-positive women after adjusting for age and traditional cardiovascular risk factors [9,11,23,42]. The review by Shah et al. [78] included all studies regardless of study design, population under study, or degree of adjustment for confounding and reached the same conclusion. In any case, the certainty of the conclusions on different subtypes of cardiovascular disease is premature given the scarcity of high quality evidence. Whether BAC can aid in risk stratification and risk management for cardiovascular disease needs to be further investigated.

4.3. BAC and medial arterial calcification

BAC is generally considered to be a type of medial arterial calcification, also called Mönckeberg's medial calcific sclerosis or medial elastocalcinosis. Only one study directly assessed the correlation between the presence of BAC on mammography and medial arterial calcification in radiographs of the extremities in renal patients and they reported a high correlation [8]. Further research is needed to establish whether this finding is generalizable to other vascular beds and populations. Although not much is known about the risk factors for medial calcification, at first impression our findings appear to correspond to those published, as medial arterial calcification is reported to be associated with older age, diabetes and renal disease [2,7].

4.4. Strengths and limitations

The strength of our study is that we systematically reviewed, critically appraised and meta-analyzed the literature on the determinants of BAC and on the associations with cardiovascular risk.

As in any meta-analysis, the validity of the summary measures relies on the validity of the original research. Although we have applied certain quality criteria, the diversity in study designs made critical appraisal a hard and somewhat subjective process. The heterogeneity encountered for many of the associations warrants cautious interpretation and reported ORs should therefore not be interpreted as exact effect size estimates, but rather as an indication of the direction and magnitude of effects. The possibility of publication bias can never be completely discarded although we have only observed clear funnel plot asymmetry once, analyzing ORs for BAC by diabetes status. The analysis included more small studies that showed relatively small effect sizes (nearest to 1), compared to bigger studies, which is not the normal direction of asymmetry found in publication bias.

4.5. Conclusion

Although longitudinal studies are scarce, BAC, an expression of arteriosclerosis, appear to be associated with an increased risk of cardiovascular disease events, while only being associated with some of the known cardiovascular risk factors. This illustrates that medial arterial calcification might contribute to cardiovascular disease through a pathway distinct from the intimal atherosclerotic process. Although our understanding of medial arterial calcifications is still limited, these calcifications may provide a novel route to an improved understanding and treatment of cardiovascular disease.

Disclosures

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2014.12.035.

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