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Breast Arterial Calcification Is Not Associated with Mild Cognitive Impairment or Incident All-Cause Dementia Among Postmenopausal Women: The MINERVA Study

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Abstract

Background: Since vascular risk factors are implicated in cognitive decline, and breast arterial calcification (BAC) is related to vascular risk, we postulated that BAC may be associated with cognitive impairment and dementia.
Methods: We used a multiethnic cohort of 3,913 asymptomatic women 60–79 years of age recruited after mammography screening at a large health plan in 2012–2015. A BAC mass score (mg) was derived from digital mammograms. Cognitive function was measured at baseline using the Montreal Cognitive Assessment (MoCA) and incident all-cause dementia ($n = 49$ events; median follow-up = 5.6 years) were ascertained with validated ICD-9 and ICD-10 codes. We used cross-sectional linear regression of MoCA scores on BAC, then multinomial logistic regression predicting mild cognitive impairment not progressing to dementia and incident all-cause dementia and, finally, Cox regression of incident all-cause dementia.
Results: No association by linear regression was found between MoCA scores and BAC presence in unadjusted or adjusted analysis. Women with severe (upper tertile) BAC had a MoCA score lower by 0.58 points (standard error [SE] = 0.18) relative to women with no BAC. However, this difference disappeared after multivariate adjustment. No significant associations were found in multinomial logistic regression for either BAC presence or gradation in unadjusted or adjusted analysis. No significant associations were found between BAC presence with incident all-cause dementia (fully adjusted hazard ratio = 0.74; 95% confidence interval: 0.39–1.39). Likewise, no significant association with incident all-cause dementia was noted for BAC gradation.
Conclusions: Our results do not support the hypothesis that BAC presence or gradation may contribute to cognitive impairment or development of all-cause dementia.

Keywords: breast arterial calcification, cognitive impairment, Alzheimer's disease, dementia, women's health, cohort study

Background

Breast arterial calcification (BAC) is a common incidental finding in mammography assessments that has been associated with angiographically-defined coronary artery disease[1–8] and risk of incident clinical cardiovascular disease (CVD).[9–15] Emerging evidence also supports associations of BAC with subclinical CVD measures, including carotid intimal-media thickness (c-IMT)[16,17] and coronary artery calcified plaque.[6,18–23]

It is well established that both subclinical and clinical CVD are associated with cognitive impairment and risk of both vascular dementia and Alzheimer disease, supporting the notion that vascular health is an important determinant of

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cognitive function.[24–30] Since BAC may be a novel CVD imaging biomarker, we reasoned that is pertinent and timely to test the hypothesis that BAC may be a contributor to the risk of cognitive impairment and dementia. This will fill a knowledge gap since no studies to date have examined the relationship of BAC presence or its severity with cognitive function or incident dementia.

The aims of this study in a large cohort of postmenopausal women were therefore to: (1) Examine the cross-sectional association of BAC presence and gradation with demographic, behavioral, and clinical vascular risk factors and (2) Ascertain the independent associations of BAC presence and gradation with mild cognitive impairment (MCI) at baseline and with incident all-cause dementia.

Methods

Cohort description

MINERVA (MultIethNic study of brEast aRterial calcium gradation and cardioVAscular disease) is a large cohort of postmenopausal women with adequate representation of those with Caucasian, African American, Asian, and Hispanic ethnicity. Details of recruitment, study procedures and baseline characteristics are published elsewhere.[31] In brief, eligible participants were female active members of Kaiser Permanente of Northern California (KPNC) between the ages of 60 and 79 when they attended regular mammography screening at one of nine KPNC facilities (Oakland, Richmond, Pleasanton, Antioch, Walnut Creek, San Francisco, Santa Clara, Campbell, and Mountain View) between October 24, 2012 and February 13, 2015. Women attending mammography for diagnostic purposes were not invited to participate. Those with a prior history of myocardial infarction, coronary revascularization, stroke, heart failure, peripheral vascular disease, breast cancer, mastectomy or breast implants, Alzheimer's disease/dementia, chronic dialysis/renal transplant, or not having an assigned primary care provider were not eligible. A total of 201,830 women underwent screening mammography at the study centers, and 46,112 met eligibility criteria. The derivation of the eligible cohort is described in detail in a prior publication.[31] Of those, 5,145 women with available digital, uncompressed mammograms were recruited into the study. Of the 5,145 women, 86% ($n=4,425$) attended a clinic visit and completed the full questionnaire, and 14% ($n=720$) completed an abbreviated version of the questionnaire administered over the phone and did not attend clinic visits. The study was approved by the Institutional Review Boards of the participating institutions and all participants signed an informed consent. The analytical sample for the current analysis ($n=3,913$) consisted of attendees to the clinic visit who had complete information on main covariates of interest, although we retained in the analysis (using a dummy variable representing missing values) 1,071 participants with missing data on breast feeding history and 93 participants with missing data on the Center for Epidemiological Studies Depression (CES-D) scale (a CONSORT diagram of study sample derivation is provided as Supplementary Appendix SA1).

Study procedures

BAC assessment. All images were acquired using full-field digital mammography units (Senographe 2000D, General Electric Medical Systems, Milwaukee, WI or Selenia Hologic, Hologic, Inc., Malborough, MA). Standard full-field digital mammograms were acquired from mediolateral oblique and craniocaudal projections. A new, but rigorously validated densitometry method was used to estimate a continuous BAC mass (in milligrams [mg]) score using raw (uncompressed) digital mammograms prospectively acquired and transmitted to the BAC Reading Center at UC Irvine Department of Radiological Sciences.[32,33] In the analytical sample of 3,913, 1,102 women (28%) had a BAC score >0 mg. The minimum, median, interquartile range, and maximum BAC score among those with BAC score >0 mg were 0.0005, 3.0, 10.1, and 341.6 mg, respectively.

Cognitive function and incident all-cause dementia outcomes. Cognitive performance was measured only once (at the baseline clinic visit) using the Montreal Cognitive Assessment (MoCA),[34] a screening instrument with components of visuoconstructional, executive function, memory, orientation, attention, verbal fluency, and abstraction. It takes about 10–15 minutes to complete, and the maximum number of points is 30 and 26 or above is considered normal. One point was added for women who had 12 years or fewer of formal education (*i.e.*, to those who self-reported completing high school or less educational attainment), making the potential maximum 31 points. The MoCA has been shown to be a useful screening tool for the detection of mild dementia and MCI,[35] with better sensitivity than the Mini-Mental State Examination (MMSE).[36] It has been extensively validated in non-European populations.[37–40] We defined MCI as MoCA scores <25. Incident all-cause dementia was ascertained through December 31, 2019 using standard validated ICD-9 and ICD-10 inpatient and outpatient codes (Supplementary Appendix SA2). This method of dementia ascertainment is consistent with previous studies in the KPNC population.[41–43] A similar battery of ICD-9 codes was reported to have a sensitivity of 77% and a specificity of 95% compared with a consensus diagnosis of dementia in a health care system in Seattle, Washington.[44] In Medicare claims data, this method of identifying cases had a sensitivity of 87% in a sample of Alzheimer's disease patients who participated in the Consortium to Establish a Registry for Alzheimer's Disease.[45] A 3-level categorical variable was created to define cognitive status, as follows: normal cognition, MCI at baseline not progressing to all-cause dementia, and incident all-cause dementia.

Covariate assessment. Age, race/ethnicity, education attainment, smoking, menopausal hormone therapy, reproductive history (menarche, menopausal hormone therapy, number of live births, breast feeding), aspirin use, and omega-3 supplementation were ascertained with a self-administered questionnaire. Blood pressure was measured, by standard procedure, three times (with a 1-minute rest between assessments) in seated position in the right arm using an automated blood pressure device (Welch Allyn model 5200, Skaneateles Falls, NY) after 5 minutes of rest. The blood pressure cuff size was customized to the individual's arm circumference, and the average of second and third readings were used in analysis. Weight was measured to the nearest 0.5 kg using a standard balance beam scale with participants wearing light clothing and without shoes.

Standing height was measured in centimeters to the nearest 0.5 cm with a standard generic wall-mounted stadiometer. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Laboratory analyses were performed for a selected panel of blood analytes in nonfasting state at a Clinical Laboratory Improvement Amendments-approved regional health plan laboratory. Analytes included total cholesterol, direct low-density lipoprotein cholesterol and high-density lipoprotein (HDL) cholesterol (Sekisui Diagnostics LLC, Lexington, MA), hemoglobin A1C (HbA1c) (by immunoturbidimetric assay; Roche Diagnostics, Indianapolis, IN), and high-sensitive C-reactive protein (by chemiluminescent assay; Siemens-Immulite 2000XPi, Tarrytown, NY). Glycemic status was defined as normoglycemia (no self-report and HbA1c ≤5.7% and no self-report of treatment and fasting glucose <100 mg/dL); prediabetes (no self-report and HbA1c >5.7 but ≤6.5% and no self-report of treatment and fasting glucose ≥100 and <126 mg/dL); and diabetes diagnosis or treatment (self-report or HbA1c >6.5% or fasting glucose ≥126 or self-report of treatment for diabetes). Hypertension was defined as self-report of hypertension and/or self-report of treatment for hypertension and/or systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, and we further subclassify the cohort into normotensives, untreated hypertension, treatment for hypertension without self-report of diagnosis, and treated hypertension. We defined pulse pressure (a surrogate measure of large artery stiffening and pulsatile load) as SBP minus DBP. We obtained the most recent outpatient, nonemergency department serum creatinine measurement within 1 year before the study visit and estimated glomerular filtration rates (e-GFR) using the CKD-EPI equation.[46] Depressive symptoms were assessed with the Center for Epidemiological Studies (CES-D) scale.[47] We use the standard 16 points or greater for the CES-D as an indicator of risk for clinical depression.[48]

Statistical methods

BAC and risk factors. We first assessed the association of BAC presence and BAC severity with baseline demographics, reproductive history, and vascular risk factors. Differences in continuous variables between groups with BAC absence (BAC = 0 mg) and BAC presence (BAC >0 mg) were tested using the *t*-test for those normally distributed, the Wilcoxon–Mann–Whitney test for those non-normally distributed (high-sensitive C-reactive protein [hs-CRP]), and the chi-square test for categorical variables. For BAC severity, we divided those with BAC presence into tertiles of BAC mass calcium score (denoted as minimal to mild, moderate, and severe BAC) and tested differences across continuous, normally distributed variables using analysis of variance (the Kruskal–Wallis test was used for hs-CRP) and tested differences across categorical variables with the chi-square test.

Bivariate association of BAC and BAC severity with cognitive function assessment at baseline. To assess the bivariate cross-sectional association between BAC and cognitive function, we estimated the Pearson coefficient between Log(BAC +1) and MoCA scores.[49] We then examined the proportion of participants falling into each cognitive status category by levels of BAC and tested differences in proportions with the Chi-Square test. We then considered linear models predicting MoCA score as a function of BAC presence/absence and BAC gradation before and after adjusting for relevant confounders, namely age, race, educational attainment, breast feeding history, CES-D, and pulse pressure. These were ascertained using a stepwise multivariate linear regression[50] with forward selection and retaining variables with *p*-values <0.05.

Multivariate association of BAC and BAC severity with 3-level cognitive status. The independent association of BAC presence and gradation with the 3-level dependent variable representing cognitive status was assessed using multinomial logistic regression. This approach generates two sets of odds ratios (ORs), one for the comparison of MCI not progressing to dementia versus normal cognition, and another set comparing incident all-cause dementia with normal cognition.

Analysis of time to all-cause dementia. To complement the latter analysis, we also ran Cox proportional hazards models[51] predicting incident all-cause dementia (using age as the time scale) with main exposures being BAC presence versus absence and the same BAC gradation groups as before. We also run a sensitivity model considering a linear effect [*i.e.*, Log(BAC +1)]. No violations of the proportionality assumption were detected with either parameterization of BAC (*p* for Schoenfeld Residuals test all >0.53). To determine which variables were true confounders of the BAC-cognitive status relation, we also examined the association of baseline demographics, reproductive history, and vascular risk factors with the 3-level cognitive status variable. Age, race/ethnicity, menopausal hormone therapy, breast feeding, parity, hs-CRP, hypertension status, and pulse pressure, all significantly associated with both BAC presence and cognitive status, thus qualifying as confounders. We therefore considered two levels of adjustment in the logistic and Cox models: age and race/ethnicity only, and then adding all identified confounders. The mean ± standard deviation (SD) follow-up time was 5.6 ± 1.3 years (minimum = 0.1, maximum = 7.2 years). All statistical analyses were done using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Participant's characteristics

Baseline cohort characteristics according to BAC presence versus absence are given in Table 1. Compared with women with BAC = 0 mg, those with BAC >0 mg were older, more likely to be white or Hispanic, less likely to be black or Asian, and less likely to have pursued graduate studies or a professional degree. Participants with BAC >0 mg self-reported significantly lower use of menopausal hormone therapy, had a higher likelihood of history of breast feeding and of having had three or more children. BAC presence was also associated with higher levels of hs-CRP, lower e-GFR, hypertension, and higher pulse pressure. No significant differences by BAC presence were noted for age at menarche, smoking status, BMI, total cholesterol/HDL ratio, nonfasting triglycerides, glycemic status, aspirin use, omega-3 supplementation, depressive symptoms, and MoCA score.

The cohort characteristics by severity of BAC among those with BAC >0 mg are shown in Supplementary Table S1. The factors that differed significantly across tertiles of BAC mass

Table 1. Cohort Characteristics by BAC Presence ($n = 3{,}913$)

Baseline cohort characteristics	*BAC = 0* n = *2,811* *(71.8%)*	*BAC >0* n = *1,102* *(28.2%)*	p[a]
Age (years), mean ± SD	65.3 (4.2)	67.3 (4.9)	<0.01
Race, *n* (%)			<0.01
White	1,783 (63.4)	741 (67.2)	
Black	345 (12.3)	117 (10.6)	
Hispanic	249 (8.9)	119 (10.8)	
Asian	434 (15.4)	125 (11.3)	
Educational attainment, *n* (%)			<0.01
Less than completed high school or GED	49 (1.7)	32 (2.9)	
Completed high school or GED	425 (15.1)	214 (19.4)	
At least some college or completed college	1,407 (50.1)	561 (50.9)	
Graduate school or professional degree	930 (33.1)	295 (26.8)	
Menarche (years), *n* (%)			0.36
<12	581 (20.7)	256 (23.2)	
12–13	1,505 (53.5)	569 (51.6)	
≥14	682 (24.3)	259 (23.5)	
Unknown/never had	43 (1.5)	18 (1.6)	
Currently on menopausal hormone therapy, *n* (%)			0.02
No	2,440 (86.8)	986 (89.5)	
Yes	371 (13.2)	116 (10.5)	
History of breast feeding, *n* (%)			0.40
No	463 (16.5)	219 (19.9)	
Yes	1,503 (53.5)	657 (59.6)	
Missing	845 (30.1)	226 (20.5)	
Number of live births, *n* (%)			<0.01
0	1,177 (41.9)	367 (33.3)	
1–2	1,170 (41.6)	405 (36.8)	
≥3	464 (16.5)	330 (30.0)	
Smoking status, *n* (%)			0.78
Never	1,705 (60.6)	667 (60.5)	
Former	1,002 (35.7)	399 (36.2)	
Current	104 (3.7)	36 (3.3)	
BMI (kg/m^2), mean ± SD	27.6 (6.0)	27.7 (5.8)	0.59
Total cholesterol/HDL ratio, mean ± SD	3.3 (0.8)	3.3 (0.9)	0.40
Non-fasting triglycerides (mg/dL), median ± IQR	130 (85)	129 (88)	0.46
hs-CRP (mg/dL), median ± IQR	1.4 (3.0)	1.6 (3.3)	0.02
e-GFR (mL/min/1.73 m^2), mean ± SD	80.7 (13.1)	79.1 (13.1)	<0.01
Glycemic status[b], *n* (%)			0.54
Normoglycemia	1,202 (42.8)	476 (43.2)	
Prediabetes	1,248 (44.4)	472 (42.8)	
Diabetes diagnosis or treatment	361 (12.8)	154 (14.0)	
Hypertension status[c], *n* (%)			0.02
Normotensive	1,484 (52.8)	525 (47.6)	
Untreated hypertension	312 (11.1)	124 (11.3)	
Treatment for hypertension without diagnosis	40 (1.4)	19 (1.7)	
Treated hypertension	975 (34.7)	434 (39.4)	
Pulse pressure (mmHg)[d], mean ± SD	54.2 (12.2)	56.0 (11.6)	<0.01
Aspirin use, *n* (%)	826 (29.0)	327 (29.7)	0.69
Omega-3 supplementation, *n* (%)	966 (34.4)	358 (32.5)	0.26
Depressive symptoms scale			
mean ± SD	6.9 (5.7)	6.5 (5.6)	0.09
CES-D <16	2,539 (90.3)	992 (90.0)	0.82
CES-D ≥16	206 (7.3)	83 (7.5)	
Missing	66 (2.4)	27 (2.5)	
MoCA score (mg), mean ± SD	25.3 (3.2)	25.1 (3.4)	0.07

[a] *t*-Test or chi square tests.

[b] Normoglycemia: No self-report and HbA1c ≤5.7% and no self-report of treatment and fasting glucose <100.
Prediabetes: No self-report and HbA1c >5.7 but ≤6.5% and no self-report of treatment and fasting glucose ≥100 and <126.
Diabetes diagnosis or treatment: Self-report or HbA1c >6.5% or fasting glucose ≥126 or self-report of treatment

[c] Normotensive: no self-report and SBP <140 and DBP <90 and no self-report of treatment.
Untreated hypertension: (Self-report or SBP ≥140 or DBP ≥90) and no self-report of treatment.
Treatment for hypertension without diagnosis: No self-report and SBP <140 and DBP <90 and self-report of hypertension.
Treated hypertension: self-report or SBP ≥140 or DBP ≥90 and self-report of treatment.

[d] SBP-DBP.

BAC, breast arterial calcification; BMI, body mass index; CES-D, Center for Epidemiological Studies Depression; DBP, diastolic blood pressure; e-GFR, estimated glomerular filtration rates; HbA1c, hemoglobin A1C; HDL, high-density lipoprotein; IQR, interquartile range; MoCA, Montreal Cognitive Assessment; SBP, systolic blood pressure; SD, standard deviation.

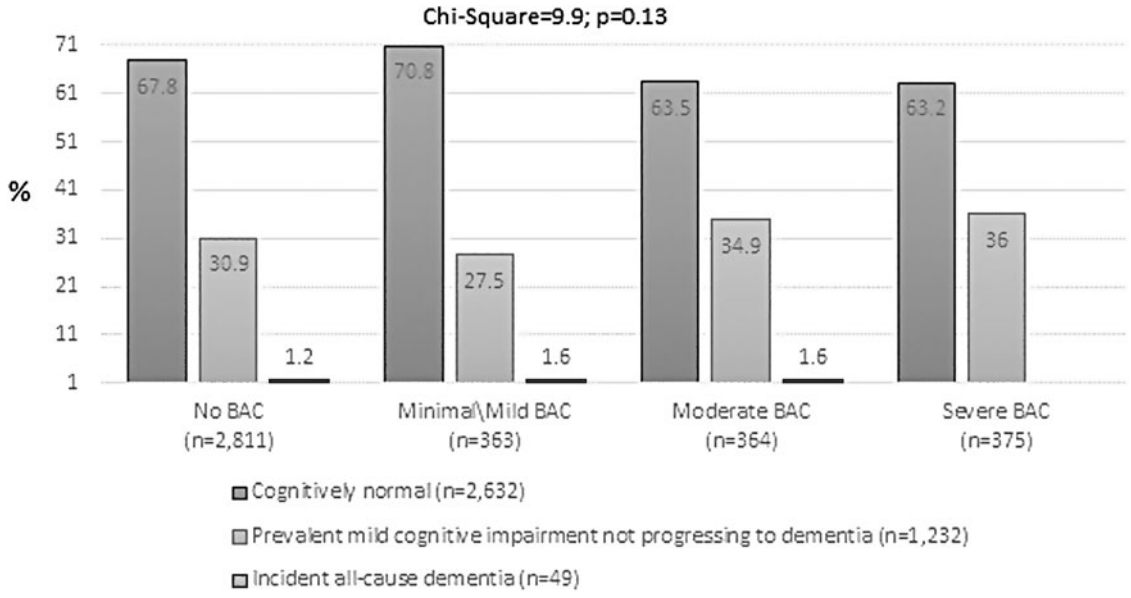

FIG. 1. Histogram of cognitive status according to BAC severity groups in the MINERVA cohort with MoCA at baseline ($n = 3{,}913$). BAC, breast arterial calcification; MoCA, Montreal Cognitive Assessment.

score were age, race/ethnicity, education level, menopausal hormone therapy, breast feeding, parity, BMI, hs-CRP, pulse pressure, and MoCA score. The association of study variables with cognitive status is shown in Supplementary Table S2. All variables, except total cholesterol/HDL ratio, aspirin use, or omega-3 supplementation, were significantly associated with cognitive status (all $p < 0.01$).

Bivariate association of BAC and BAC severity with cognitive function assessment at baseline

The Pearson correlation between Log(BAC +1) and MoCA score was −0.05 ($p < 0.01$). Figure 1 shows the proportion of women in each cognitive status category by level of BAC. There were no overall significant differences in proportions (chi-square[6 df] = 9.9; $p = 0.13$), although there was a trend toward more MCI not progressing to dementia with more severe BAC. The linear models predicting MoCA score from BAC presence/absence indicate no significant association in either unadjusted or adjusted models (Supplementary Table S3). On the other hand, women with severe BAC had, on average, a lower MoCA score by 0.58 points (standard error [SE] = 0.18) relative to women with BAC = 0 mg. However, this difference in MoCA scores disappeared after multivariate adjustment ($\beta = -0.009$; SE = 0.16; $p = 0.95$).

Analysis of 3-level cognitive status outcome

The results of multinomial logistic regression predicting MCI not progressing to dementia and incident all-cause dementia (both vs. normal cognition) from BAC presence versus absence and BAC gradation are summarized in Table 2. In either comparison, no significant associations were found for either BAC presence versus absence or for BAC gradation groups in unadjusted analysis or after adding covariates. As an example, the OR of 0.85 in the unadjusted model for women with minimal/mild BAC (defined as BAC in the first tertile of those with any BAC) means that the likelihood of MCI is expected to decrease by a factor of 0.85 (or 15% lower) compared with women with no BAC. On the other hand, the likelihood of mild cognitive function in women having severe BAC (upper tertile) is expected to increase by a factor of 1.25 (or 25% higher) compared with women with no BAC. However, in the fully adjusted Model 3 holding all the covariates constant, this increased likelihood was completely obliterated (OR = 0.99).

Analysis of time to all-cause dementia

After a mean follow-up of 5.6 years, 49 women (34 in the BAC = 0 mg group [1.2%], 15 in the BAC >0 mg group [1.4%]) were diagnosed with all-cause dementia. Dementia type was 42% nonspecific, 29% dementia in other diseases, 24% Alzheimer's disease, 3% dementia with Lewy bodies, and 2% vascular dementia. The mean (SD) MoCA score at baseline for those subjects who were identified with incident all-cause dementia by ICD-9/10 coding ($n = 49$) was 22.4 (4.0), and the median was 24.0. As shown in Table 3, no significant associations were found between BAC presence versus absence with incident all-cause dementia (fully adjusted Hazard ratio [HR] = 0.74; 95% confidence interval: 0.39–1.39). Likewise, no significant association with incident all-cause dementia was noted for BAC gradation: the fully adjusted HR were 1.00 (0.42–2.40), 0.94 (0.39–2.26), and 0.36 (0.11–1.21) for minimal/mild, moderate, and severe BAC, respectively. Results for the models using continuous effects of standardized Log(BAC +1) instead of categories of BAC presence or severity yielded no statistically significant results (data not shown).

Discussion

Our results confirm previously reported associations of BAC presence with older age,[52,53] white and Hispanic ethnicities,[54] history of breast feeding,[55] high parity,[55] menopausal hormone therapy,[56] hypertension,[2,14,16] and

Table 2. Multinomial Odds Ratios of Mild Cognitive Impairment Not Progressing to All-Cause Dementia and of Incident All-Cause Dementia Relative to Normal Cognition Associated with BAC Presence Versus Absence and with Gradation of BAC

Mild cognitive impairment not progressing to all-cause dementia vs. normal cognition						
BAC presence vs. absence models	*Model 1 OR (95% CI)*	p	*Model 2 OR (95% CI)*	p	*Model 3 OR (95% CI)*	p
BAC >0 mg vs. BAC = 0 mg	1.09 (0.94–1.27)	0.23	1.04 (0.88–1.22)	0.66	0.99 (0.84–1.18)	0.96
Severity of BAC models[a]						
Minimal/mild BAC	0.85 (0.67–1.09)	0.20	0.87 (0.67–1.14)	0.31	0.84 (0.65–1.10)	0.21
Moderate BAC	1.20 (0.96–1.52)	0.11	1.22 (0.95–1.57)	0.11	1.17 (0.91–1.50)	0.22
Severe BAC	1.25 (0.99–1.56)	0.05	1.03 (0.80–1.32)	0.80	0.99 (0.77–1.28)	0.94
Incident all-cause dementia vs. normal cognition						
BAC presence vs. absence models						
BAC >0 mg vs. BAC = 0 mg	1.16 (0.63–2.14)	0.63	0.79 (0.42–1.49)	0.47	0.76 (0.40–1.46)	0.42
Severity of BAC models[a]						
Minimal/mild BAC	1.31 (0.54–3.15)	0.54	1.08 (0.44–2.62)	0.87	1.02 (0.42–2.49)	0.96
Moderate BAC	1.46 (0.60–3.51)	0.40	1.07 (0.43–2.61)	0.88	1.03 (0.42–2.53)	0.95
Severe BAC	0.71 (0.22–2.33)	0.57	0.38 (0.11–1.27)	0.11	0.35 (0.10–1.22)	0.10

[a]Defined as tertiles of Log(BAC) among those with BAC >0 mg. BAC = 0 mg is the reference group.
Model 1: unadjusted.
Model 2: age, race.
Model 3: age, race, menopausal hormone therapy, breast feeding, parity, hs-CRP, hypertension status and pulse pressure.
CI, confidence interval; hs-CRP, high-sensitive C-reactive protein; OR, odds ratio.

hs-CRP.[2,14,16,57] Novel correlates of BAC presence in our analysis were pulse pressure (indicating that BAC may be a marker of arterial stiffness), and e-GFR (although in prior work we have demonstrated that renal function is not independently related to BAC).[58]

To our knowledge, this is the first report examining the association of BAC presence and gradation with MCI and incident all-case dementia in a large, ethnically diverse cohort of postmenopausal women. We observed, in unadjusted analysis, an association of severe BAC with lower MoCA scores. However, this association was completely explained by relevant confounders, including age, race, educational attainment, breast feeding, CES-D, and pulse pressure. We failed to detect significant associations of BAC presence versus absence or gradation with incident all-cause dementia.

The relationship between vascular risk factors and cognitive performance is well established.[59–64] Moreover, measures of subclinical atherosclerosis such as c-IMT,[29,30,65] calcified coronary plaque,[26–28,66] aortic stiffness,[25] and a composite index of subclinical CVD[24] have been implicated in cognitive decline. BAC is mostly medial or Mönckeberg-type calcification,[67,68] and it is generally construed as a marker of vascular stiffness rather than of atherosclerosis, which is a phenomenon localized in the intimal layer of the arterial wall. Vascular stiffness appears to be relevant for neurodegeneration and vascular-driven decline in cognitive function.[69–71] However, our findings are not consistent with this assertion and suggest that BAC may not be implicated in neurobiological processes leading to MCI or dementia.

This study has several strengths. Our cohort was large, and with representation of postmenopausal women from all four major ethnicities in the United States. We had extensive, rigorously obtained phenotypic information on risk factors for both BAC and cognitive function. We recognized several important limitations in our study. Since the cohort is insured, findings may not generalize to uninsured populations. Because we focused on women over age 60, our analysis does not address the BAC-cognitive function association at an

Table 3. Hazard Ratios of Incident All-Cause Dementia Associated with BAC Presence Versus Absence and with BAC Gradation Using Age as the Time-to-Event Variable

BAC presence vs. absence models	*Model 1 OR (95% CI)*	p	*Model 2 OR (95% CI)*	p	*Model 3 OR (95% CI)*	p
BAC >0 mg vs. BAC = 0 mg	0.74 (0.40–1.39)	0.35	0.75 (0.40–1.39)	0.35	0.74 (0.39–1.39)	0.35
Severity of BAC models[a]						
Minimal/mild BAC	1.00 (0.42–2.38)	1.00	1.03 (0.43–2.46)	0.96	1.00 (0.42–2.40)	0.99
Moderate BAC	0.95 (0.39–2.26)	0.95	0.95 (0.40–2.29)	0.91	0.94 (0.39–2.26)	0.89
Severe BAC	0.38 (0.11–1.24)	0.38	0.37 (0.11–1.23)	0.11	0.36 (0.11–1.21)	0.10

Model 1: unadjusted.
Model 2: race.
Model 3: race, menopausal hormone therapy, breast feeding, parity.
[a]Defined as tertiles of Log(BAC) among those with BAC >0 mg. BAC = 0 mg is the reference group, hs-CRP, hypertension status and pulse pressure.

earlier age. The power for the analysis of BAC and incident all-cause dementia was limited by the small number of events that occurred over 5.6 years of follow-up. Larger cohorts with longer follow-up are warranted to corroborate or refute our results. Also because of small number of dementia events we were unable to pursue analysis of separate types of dementia. We recognize that having a single MoCA score at baseline and no follow-up MoCA scores is a significant limitation. It should be pointed out, however, that the results of the MoCA testing at baseline did not become part of the electronic health record, nor the results provided to participants, so the likelihood of the testing influencing future dementia diagnosis is negligible. We further recognize that our densitometry method used for determination of BAC is not in standard clinical use now, but publishing these results is the first step toward dissemination and adoption of the densitometry approach.

In conclusion, the presence and/or gradation of BAC were not associated with either MCI not progressing to dementia or incident all-cause dementia in our cohort of asymptomatic postmenopausal women. Additional prospective studies are required to investigate the association of medial-type calcification phenotypes with cognitive decline and with clinical dementia across the lifespan.

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Author Disclosure Statement

No competing financial interests exist

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Supplementary Material

Supplementary Appendix SA1
Supplementary Appendix SA2
Supplementary Table S1
Supplementary Table S2
Supplementary Table S3

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