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Coronary artery calcium assessed years before was positively associated with subtle white-matter injury of the brain in asymptomatic middle-aged men: the Framingham Heart Study

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Abstract

Background: Using magnetic resonance diffusion tensor imaging (DTI), we previously showed a cross-sectional association between carotid-femoral pulse wave velocity, a measure of aortic stiffness, and subtle white-matter injury in clinically asymptomatic middle-age adults. While

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Disclosures:
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coronary artery calcium (CAC) is a robust measure of atherosclerosis, and a predictor of stroke and dementia, whether it predicts DTI-based subtle white-matter injury in the brain remains unknown.

Methods: In Framingham Heart Study, an observational study, third-generation participants were assessed for CAC (2002–2005) and brain magnetic resonance imaging (2009–2014). Outcomes were DTI-based measures; free water, fractional anisotropy (FA), and peak width of mean diffusivity. After excluding the participants with neurological conditions and missing covariates, we categorized participants into three groups according to CAC score (0, 0 < to 100, and > 100), and calculated a linear trend across the CAC groups. In secondary analyses treating CAC score as continuous, we computed slope of the outcomes per 20–80th percentiles higher log-transformed CAC score using linear regression.

Results: In a total of 1052 individuals analyzed (mean age 45.4 years, 45.4 % women), 71.6, 22.4, and 6.0 % had CAC score of 0, 0 < to 100, and > 100, respectively. We observed a significant linear trend of FA, but not other measures, across the CAC groups after multivariable adjustment. In the secondary analyses, CAC was associated with lower FA in men, but not in women.

Conclusions: CAC may be a promising tool to predict prevalent subtle white-matter injury of the brain in asymptomatic middle-aged men.

Keywords

white matter disease; brain imaging; coronary artery calcium; Epidemiology

INTRODUCTION

Coronary artery calcium (CAC) is a well-established marker of atherosclerosis[1] and is known to predict non-cardiac outcomes[2] including stroke[3] and low cognition[4] and/or dementia[5,6]. The speculated mechanism for CAC to predict those brain diseases is the coexistence of CAC and subclinical cerebrovascular diseases (SCVDs)[7] given the systematic nature of atherosclerosis. Similarly, arterial stiffness measured as carotid-femoral pulse wave velocity (CFPWV), among many tonometer measures, has been considered a promising predictor of brain health as it predicted cognitive decline/dementia and SCVDs in some, but not all[8], populations[9].

Many previous studies relied on conventional magnetic resonance imaging (MRI) techniques in assessing SCVDs. In recent years, however, more subtle white-matter injury can be detected using diffusion tensor imaging (DTI)[10,11]. Detecting subtle white-matter injury with the new technique in otherwise asymptomatic individuals has a great potential for early intervention and prevention for brain health. Using the new technique in the Framingham Heart Study, we reported that hypertension[12] and high CFPWV[13] were associated with subtle white-matter injury among young to middle aged adults who were likely years before white-mater hyperintensities detection by conventional MRI. Yet, it remains unknown whether CAC can predict subtle brain injury in adults of those ages. Furthermore, the magnitude of association between CAC and brain injury may not be as strong as that of CFPWV. Since CAC is currently one of the few “extra” modalities recommended by the 2019 ACC/AHA guidelines for primary prevention of cardiovascular diseases[14], we are

interested in CAC as a potential candidate marker for detecting subtle brain injury that may be influenced by systematic atherosclerosis[15].

The primary aim of the study was to examine an association between CAC and measures of white-matter injury in the young to middle aged adults who are free of brain diseases. We assess usefulness of CAC in predicting the overall level of subtle white-matter injury using averages of DTI-based measures in the entire white-matter of the brain. The secondary aim was to compare the strength of association of CAC with white-matter injury and that of CFPWV by standardizing them in a regression model. CAC and CFPWV are non-invasive modalities that are commonly used and suitable for screening for primary prevention. The results will have a potential impact on selecting a clinically useful marker in predicting subtle brain injury.

METHODS

Study participants

Among the third-generation cohort of the Framingham Heart Study (FHS)[16], a subgroup of participants underwent multi-detector row computed tomography (MDCT) for CAC assessment in 2002–2005 (n=2,087)[17]. Of the total of 3,519 participants who attended the 2nd examination, 2,034 individuals had successful arterial tonometry measures including CFPWV in 2008–2011, and further underwent brain MRI in 2009–2014[13]. A total of 1,107 participants completed those exams and imaging. For the current study, we excluded those participants who had prevalent stroke (n = 4) and other neurological conditions (n = 41) based on the information available at the time of brain MRI. None of the participants were diagnosed with dementia by the Diagnostic and Statistical Manual of Mental Disorders IV[18] at the MRI examination. Additionally, we excluded those with missing pertinent data (n =10) leaving 1,052 individuals for analysis. The institutional review board of Boston University Medical Center approved this study protocols, and participants provided written informed consent. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to FHS at dipersio@bu.edu, website https://framinghamheartstudy.org/fhs-for-researchers/data-available-overview/.

Clinical examination and definition

All the participants' information used in the study other than age, CFPWV, and DTI-based measures were assessed at second clinical examination (2008–2011). We used age assessed at CT scan. The standard clinical examination included a physician interview, physical examination and laboratory tests. Information on age, sex, height and weight were assessed at physical examination. Smoking status, medication, history of cardiovascular diseases and diabetes were obtained at the interview. Any treatment information was from participants' prescription lists. Systolic blood pressure (SBP) was measured using a mercury column sphygmomanometer on the left arm of seated participants by two physicians separately and the average of these values were used. Fasting serum cholesterol was measured enzymatically. Fasting plasma glucose was measured with hexokinase regent. Participants

were considered to be current smokers if they reported smoking at least one cigarette per day for the last year. Diabetes was defined as a fasting glucose ≥ 126 mg/dL or treatment with either insulin or a hypoglycemic agent at the second-round exam. Body mass index (BMI) was calculated as weight (kilogram) divided by the square of height (meter), and obesity was defined as BMI ≥ 30 kg/m^2.

Imaging and tonometry

Participants were imaged on an eight-slice MDCT scanner (LightSpeed Ultra, General Electric, Milwaukee, WI)[17]. All CT scans were read independently by an experienced reader for the presence and amount of CAC. The amount of CAC was defined by the Agatston score multiplying the area of each lesion with a weighted attenuation score dependent on the maximal attenuation within the lesion[19]. CFPWV values were calculated from tonometry waveforms and body surface transit distance[20]. MRI of the brain was performed with a 1.5T Siemens Avanto scanner (version syngo MR B15). All the participants were acquired on the same machine, using the same protocol (see Supplemental material for details).

We utilized three DTI-based measures as our outcome of interest: free water (FW)[21], fractional anisotropy (FA), and peak width of skeletonized mean diffusivity (PSMD)[22]. FW refers to the fraction of extracellular water content contained in a voxel of the white matte tissue, and reflects the amount of water molecules that are relatively unrestricted by their local microenvironment. FA reflects how water directionality is constrained along white matter tracts. When the white matter tissue is healthy, molecules are hampered by axons and their myelin sheaths and diffusion becomes anisotropic (FA close to 1). Inversely, when the tissue is injured, diffusion becomes isotropic (i.e. FA close to 0). PSMD was designed to eliminate the contaminating signal of cerebrospinal fluid from DTI-derived mean diffusivity (MD; a mean of all three axes of the diffusion) maps [22]. PSMD is calculated as the difference between the 95th and 5th percentiles of MD values within a white matter tract skeleton, taking a value around 0.245 $\times 10^{-3}$ mm^2 /s calculated on the basis of previous report (age range from 38 to 58) (see Supplemental Table I for more details). Recent studies on those biomarkers showed associations between white-matter integrity and vascular risk factors, even in the younger adult population, decades before white matter hyperintensities appear or cognitive function declines[12,23,24].We had no *a priori* hypothesis about which of the three DTI-based measures would be most important because each of the measures has unique feature as described above.

Statistical analysis

For the primary aim, we divided participants into three groups according to their CAC scores (0, 0 < to 100, and >100). Then we computed adjusted difference of DTI-based measures in the higher CAC groups in reference to no CAC group (CAC score = 0) using linear regression. Of the three DTI-based outcomes, we used natural log-transformed values for mean FW (lnFW), and PSMD (lnPSMD) to reduce heteroscedasticity. In Model 1, we adjusted for sex, age at CT, age at CT squared (to allow non-linear association between age and DTI-based measures), and time between at CT and MRI because those measurements differed in time point. In Model 2, we further adjusted for conventional vascular risk factors: current smoker (yes/no), SBP (mmHg), total cholesterol (mg/dL), diabetes (yes/no),

medications for hypertension (yes/no) and for dyslipidemia (yes/no), and total cranial volume (TCV, mL). The adjustment for TCV is conventional in the research field[25,26] because TCV is shown to determine DTI-based measure[25], although we repeated the analysis without adjustment for TCV as a sensitivity analysis. P-value for linear trend (P_{trend}) across the CAC categories was obtained treating each group as rank (0, 1, 2).

In the secondary aim of comparison between CAC and CFPWV, we treated CAC score and CFPWV as continuous and transformed each variable as follows owing to their highly skewed distributions: natural log transformed CAC score +0.1 (lnCAC), and negative inverse CFPWV (niCFPWV). Then we expressed a slope of regression coefficient as an estimated outcome value at 80^{th} versus 20^{th} percentile of lnCAC or niCFPWV in our regression model for each of three DTI-based outcomes. In other words, we compare the regression coefficient after standardization of exposure variables of our interest, CAC and CFPWV. Such standardization using 20^{th}-80^{th} percentile in regression analysis has been conducted in previous studies [27,28]. Otherwise, the set of adjusting covariates was the same as the main analyses. For clinical interpretability of effect size in DTI-measures, we computed one-year difference in the DTI-measures regressing them on age of the participants.

Interaction by sex was tested by adding a product term in the models. P-value < 0.05 was considered to be significant. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Among 1,052 participants (mean age at CT scan, 45.4 years; 45.4 % women), 753 (71.6%), 236 (22.4%), and 63 (6.0%) individuals had CAC score of 0 (i.e. no CAC), ≤ 100, and >100, respectively (Table 1). Medication users for hypertension and dyslipidemia were 20.7% (n = 218) and 21.9% (n = 230), respectively. Average time intervals from CT for CAC to MRI and from CFPWV to MRI were 7.7 years, and 1.7 years, respectively. The mean SBP was 118 mmHg and the mean serum total cholesterol concentration was 190 mg/dL. Thirty percent of the participants were obese. Compared to women, men were slightly younger but tended to have more unfavorable risk factors including higher average SBP, more likely to be obese and diabetics and on treatment for hypertension and dyslipidemia.

For the primary aim, higher CAC groups were associated with lower mean FA, higher lnFW, and higher lnPSMD in a graded fashion in Model 1 (P_{trend} was 0.010, 0.016, and 0.029, respectively)(Table 2). Compared to no CAC, CAC score of > 100 was significantly associated with 0.268 lower FA (P=0.04), 0.295 higher lnFW (P=0.02), and 0.325 higher lnPSMD in the model (P=0.01). Each magnitude of association can be interpreted that individuals with CAC score of > 100, compared to no CAC, had a 5.15 (0.268/0.052), 5.78 (0.295/0.051), and 6.37 (0.325/0.051) years of aging in the brain by the measure of FA, lnFW, and lnPSMD, respectively, based on regressed estimates on age (Table 2). In Model 2, the graded relationship seemed to remain by point estimates, but largely became attenuated in all the outcome measures such that FA remained statistically significant, and lnFW became marginal for linear trend across the CAC group (P_{trend} for FA, lnFW and lnPSMD were 0.029, 0.098, and 0.137, respectively). Model 2 without TCV adjustment yielded

similar results to the main ones (Supplemental Table II). There was no evidence of interaction by sex in the CAC-group model (P-values for sex-interaction were 0.176, 0.260, and 0.977 for FA, lnFW, and lnPSMD, respectively).

In analyses for the secondary aim using continuous lnCAC or niCFPWV, we observed a significant association between lnCAC and all the three DTI-based outcomes in Model 1. Among them, however, only mean FA remained significant in Model 2 (Table 3). Likewise, niCFPWV was significantly associated with lnFW and with lnPSMD in Model 1 but all of them were attenuated to non-significant in Model 2. We observed a significant interaction by sex on the association between lnCAC and mean FA, and on the association of niCFPWV with FA and with lnFW in Model 1. In Model 2, the sex-interactions remained significant for the association between lnCAC and mean FA ($P_{interaction}$=0.043), or became marginally significant for the association of niCFPWV with FA, and with lnFW ($P_{interaction}$ = 0.053, and 0.084, respectively). The corresponding sex-stratified analyses in Model 2 showed that lnCAC was significantly associated with lower mean FA in men (P = 0.03), but not in women (P = 0.91), and that a significant association between niCFPWV and lnFW was seen only in men (P = 0.03) but not in women (P = 0.73), and no association between niCFPWV and FA in either sexes (Supplemental Table III).

DISCUSSION

In this population-based study of young to middle-aged adults, we observed CAC, assessed average of 7.7 years prior to the brain imaging, had a graded association with mean FA of the entire white matter after adjustment for risk factors and TCV. In continuous model, the inverse association between CAC and FA was significant only in men but not in women according to Model 2.

This is the first community-based study that showed a significant and graded association between CAC and subtle white-matter injury of the brain, measured with DTI. The finding suggests that the heart-brain connection[29] can be observed even at an early subclinical stage in middle-aged apparently healthy individuals, and that CAC may identify an individual at elevated risk of early white-matter injury.

Mechanism for CAC to predict white-matter injury is likely due to the shared common risk factors between coronary and brain arteries. We have previously shown a direct association between blood pressure and white-matter injury in the same cohort (i.e. the third-generation cohort of the Framingham Study)[12]. In addition, other cardiovascular risk factors such as cigarette smoking[30] and diabetes[31] have been shown as probable attributes to early/subclinical microstructural injury of the white-matter. In asymptomatic elderly populations, graded relationship between CAC and subclinical cerebral vascular disease has been reported both from the West[32] and the East[7,33]. Adding to the literature, our study further suggests usefulness of CAC in middle-age adults as a predictor for subtle brain injury that is difficult to identify with a conventional MRI technique.

Based on regressed DTI-measures on age of our cohort, we interpreted that individuals with CAC score of >100, compared to no CAC, had a 5 to 6 years of “aging in the brain” by the

DTI-measures in Model 1. Aside from such interpretation, a long-term clinical implication of those DTI-measures remain to be determined since we are unaware of any threshold for DTI-measures that are applicable to middle-age adults to predict clinical outcome. From pathological point, studies suggested that decreased FA, elevated FW and PSMD reflect axonal injury, mild vascular injury and neuroinflammation (microglia activation, edema), and small vessel disease, respectively[22,34–36]. In addition, population-based studies on older individuals suggested that the relationship between baseline FA or FW and subsequent cognition decline over years was graded/continuous[37,38]. Furthermore, those with cognitive impairment tended to have decreased FA and elevated FW than healthy controls[39,40], and the patients with vascular dementia were reported to have elevated PSMD[22,41].

Combined with those existing literature, our results suggest that young to middle-aged adult with high CAC score may benefit from tight risk-factor control with regard to prevention of atherosclerotic diseases but also prevention of long-term cognitive decline. For example, a randomized trial of multi-domain intervention including vascular risk monitoring reported better cognition in the intervention group than control group[42]. Nevertheless, it is premature to recommend screening with CAC for such purpose because there is no established evidence to prevent cognitive decline by vascular risk control and usefulness of CAC for that purpose warrants further study.

It is noteworthy that analytical method in this study differs from the previous Framingham Heart Study reports[12,13,21]. In the present study, we focused on global measures of subtle white-matter injury in the entire brain because our aim in this study was to assess overall usefulness of CAC in predicting subtle white matter injury. The previous studies, in contrast, employed lesion specific analyses as well as voxel-based morphometry, which is likely to be more sensitive for detecting localized injury. In fact, the previous study showed significant regional association of CFPWV with lower FA and higher FW[21]. Use of the global measures in the present study may limit our ability to identify a small, localized change.

Although CAC has been shown to be a better predictor for cardiovascular diseases than other novel biomarkers such as carotid intima-media thickness or C-reactive protein[1], there is only one community-based study showing superiority of CAC over PWV in predicting risk of coronary heart disease[43]. To our knowledge, no study has compared CAC and CFPWV in the association with DTI-based measures of white-matter injury. With our results, however, it remained inconclusive which of them performed better. The sex-combined results showed a significant, or a marginally significant association between CAC and FA, and between CFPWV and FW, respectively, and the corresponding sex-stratified analyses showed that CAC was associated with FA, and that CFPWV was associated with FW, both only in men, but not in women. Therefore, CAC and CFPWV may be complimentary to each other, at least for men, in predicting subclinical white-matter injury.

Sex-difference

We observed statistically significant association only in men but not in women according to continuous models. One possible explanation is because men of our participants on average had a worse cardiovascular risk profile than women, likely leading to more advanced stages in CAC, CFPWV, and DTI-based outcomes. In line with this finding, a recent population-

based study reported a less burden of brain aging in those who have more ideal cardiovascular risk profile[44].

Implication

Our study suggests that CAC may be a useful screening tool to predict prevalent subtle changes of the brain, particularly white-matter injury, in an asymptomatic middle-aged man. High CAC score may be taken not only as a sign of coronary disease but also a predictor for subclinical white-matter injury of the brain. Further study using voxel-based morphometry is clearly needed to elucidate an extent and specific locations in the brain CAC can predict. Additionally, a further study is needed which marker, CAC vs CFPWV, performs better in predicting subclinical brain disease.

Strengths of the study include use of DTI-based measure allowing us to identify subtle white-matter change that may be overlooked but later progress to overt white-matter lesions with conventional MRI[10,11]. Other strength includes community-based recruitment of relatively young men and women enhancing the generalizability of the findings. The following limitations should be considered in interpreting our results. First, among three DTI-based measures, CAC was significantly associated only with FA, and we had no *a priori* hypothesis about which of the three measures would be most important. Therefore, we are unable to refute the possibility that the observed association was due to chance given the multiple outcomes we tested, although we attempted to minimize the problem of multiple testing by limiting our outcomes to three DTI-measures, and by not looking at location-specific associations. Furthermore, the reason we observed only one out of three measures significant may be because the population we studied was relatively young and healthy without much of subclinical brain injury. Second, average time intervals from CT to MRI and from CFPWV to MRI differed by 6 years, which may have obscured a fair comparison between CAC and CFPWV although adjustment for time interval was made to overcome this limitation.

Conclusion

Our study suggests that CAC may be a promising screening tool to predict subclinical vascular burden, particularly subtle white-matter injury, in asymptomatic middle-aged men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Clinical Perspective:

Using recent modality, diffusion tensor imaging, this study showed a significant association between CAC and a measure of subtle white-matter injury of the brain in community dwelling individuals without neurological deficits, especially for men. CAC may be a potentially useful tool to predict prevalent subtle white matter injury of the brain in apparently healthy middle-aged men. Although CAC is currently one of the few “extra” modalities recommended by the 2019 ACC/AHA guidelines for primary prevention of cardiovascular diseases, further study is clearly needed to confirm the role of CAC for brain health.

Table 1.

Characteristics of study participants: Framingham Heart Study third-generation cohort (N = 1052).

	Total (N=1052)	Women (n=478)	Men (n=574)	P-value
Age at CT scan, years	45.4 (6.0)	46.7 (5.5)	44.3 (6.2)	< 0.01
Interval between CT scan and MRI, years	7.69 (1.05)	7.62 (1.10)	7.75 (1.01)	< 0.05
Interval between CFPWV and MRI, years	1.70 (0.94)	1.67 (0.93)	1.73 (0.95)	0.31
Systolic blood pressure, mmHg	118 (13)	114 (13)	121 (12)	< 0.01
Hypertension treatment, n (%)	218 (20.7)	79 (16.5)	139 (24.2)	< 0.01
Diabetes, n (%)	63 (6.0)	22 (4.6)	41 (7.1)	0.08
Total cholesterol, mg/dL	190 (35)	193 (37)	187 (33)	< 0.01
Dyslipidemia treatment, n (%)	230 (21.9)	71 (14.9)	159 (27.7)	< 0.01
Current smoker, n (%)	82 (7.8)	35 (7.3)	47 (8.2)	0.60
Total cranial volume, mL	1274 (124)	1189 (96)	1345 (98)	< 0.01
Obesity *, n (%)	316 (30.0)	119 (24.9)	197 (34.3)	< 0.01
CAC score (75^{th}, 90^{th} percentile)	(1.2, 36.0)	(0, 4.3)	(10.7, 94.8)	< 0.01
CAC group, n (%)				
CAC score 0	753 (71.6)	413 (86.4)	340 (59.2)	< 0.01
0< to 100	236 (22.4)	58 (12.1)	178 (31.0)	
> 100	63 (6.0)	7 (1.5)	56 (9.8)	
CFPWV (median [Q1, Q3]), m/s	7.2 [6.5, 8.1]	6.9 [6.3, 7.7]	7.5 [6.7, 8.4]	< 0.01
Mean FA	0.538 (0.011)	0.536 (0.010)	0.539 (0.011)	< 0.01
Mean FW (median [Q1, Q3])	0.192 [0.182, 0.204]	0.191 [0.181, 0.202]	0.194 [0.183, 0.206]	< 0.01
PSMD (median [Q1, Q3]), ×1000	0.220 [0.207, 0.241]	0.217 [0.203, 0.236]	0.224 [0.211, 0.246]	< 0.01

Values were mean and standard deviation in parenthesis unless otherwise specified. Abbreviations: CAC, coronary artery calcium; CFPWV, carotid-femoral pulse wave velocity; CT, computed tomography; FA, fractional anisotropy; FW, free water; MRI, magnetic resonance imaging; PSMD, peak width of skeletonized mean diffusivity; SBP, systolic blood pressure; SD, standard deviation; Q, quartiles of each variable.

*Obesity was defined as body mass index ≥ 30 kg/m^2

Table 2.

The association between CAC and subtle white-matter injury: Framingham Heart Study third-generation cohort (N = 1052)

			Mean FA				lnFW				lnPSMD			
	One year of aging*		−0.052				0.051				0.051			
Method	**Group**	**n**	**Estimate**	**95%CI**	***P*-value**	***P* for trend**	**Estimate**	**95%CI**	***P*-value**	***P* for trend**	**Estimate**	**95%CI**	***P*-value**	***P* for trend**
Model 1	CAC=0	753		Reference				Reference				Reference		
	0 < CAC ≤100	236	−0.147	(−0.292, −0.002)	0.05	0.010	0.106	(−0.041, 0.253)	0.16	0.016	0.050	(−0.094, 0.195)	0.50	0.029
	CAC>100	63	−0.268	(−0.520, −0.017)	0.04		0.295	(0.041, 0.549)	0.02		0.325	(0.075, 0.575)	0.01	
Model 2	CAC=0	753		Reference				Reference				Reference		
	0 < CAC ≤100	236	−0.124	(−0.267, 0.018)	0.09	0.029	0.066	(−0.080, 0.212)	0.38	0.098	0.008	(−0.137, 0.153)	0.91	0.137
	CAC>100	63	−0.220	(−0.466, 0.026)	0.08		0.213	(−0.040, 0.466)	0.10		0.259	(0.008, 0.510)	0.04	

Abbreviations: CAC, coronary artery calcium; CFPWV, carotid-femoral pulse wave velocity; FA, fractional anisotropy; FW, free water; PSMD, peak width of skeletonized mean diffusivity, SE, standard error.

Mean FW and PSMD were log-transformed since they have skewed distributions, which represent lnFW and lnPSMD respectively.

Model 1:sex, age at CT, age at CT squared, and time between at CT and MRI, Model 2:current smoker (yes/no), SBP (mmHg), diabetes (yes/no), total cholesterol (mg/dL), medications for hypertension (yes/no) and dyslipidemia (yes/no), and total cranial volume (mL)

*: One year of ageing naturally has changed three outcomes above. Interpretation of the CAC results was that those with CAC>100 had an adjusted mean FA 0.268 lower than those with CAC=0, equivalent to (0.268/0.052)=5.2 years of ageing.

Table 3.

The association between continuous CAC/CFPWV and subtle white-matter injury including sex interaction tests: Framingham Heart Study third-generation cohort (N = 1052)

	Mean FA				lnFW				lnPSMD			
Methods	Estimate	95%CI	P value	P value for sex interaction	Estimate	95%CI	P value	P value for sex interaction	Estimate	95%CI	P value	P value for sex interaction
20^{th}–80^{th} percentile of lnCAC												
Model 1	−0.139	(−0.237, −0.041)	< 0.01	0.020	0.123	(0.023, 0.185)	0.02	0.285	0.130	(0.033, 0.228)	< 0.01	0.756
Model 2	−0.114	(−0.211, −0.018)	0.02	0.043	0.086	(−0.013, 0.185)	0.09	0.326	0.097	(−0.002, 0.196)	0.054	0.628
20^{th}–80^{th} percentile of niCFPWV												
Model 1	−0.009	(−0.122, 0.104)	0.88	0.045	0.152	(0.038, 0.266)	< 0.05	< 0.05	0.132	(0.019, 0.244)	0.02	0.756
Model 2	−0.003	(−0.126, 0.120)	0.96	0.053	0.124	(−0.002, 0.251)	0.06	0.084	0.102	(−0.024, 0.227)	0.11	0.666

The values were expressed as adjusted mean per 20th-80th percentile higher coronary artery calcium (CAC) in Agatston score (log-transformed), or negative inverse carotid-femoral pulse wave velocity (CFPWV) in meter/sec.

The set of adjusting covariates were sex, age at CT/tonometry, age at CT/tonometry squared, and time between at CT/tonometry and MRI, current smoker (yes/no), SBP (mmHg), diabetes (yes/no), total cholesterol (mg/dL), medications for hypertension (yes/no) and dyslipidemia (yes/no), and total cranial volume (mL) (Model 2)