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Association of Carotid Intima Media Thickening with Future Brain Region Specific Amyloid-β Burden

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Abstract

Background: Carotid atherosclerosis is associated with cognitive impairment and dementia, though there is limited evidence of a direct link between carotid disease and amyloid-β (Aβ) burden.

Objective: We studied the association of baseline and progressive carotid intima media thickness (CIMT) with Aβ on ^{11}C-Pittsburgh Compound B (PiB) to determine if those with carotid atherosclerosis would have higher Aβ burden.

Methods: We studied 47 participants from the Framingham Offspring cohort with carotid ultrasounds measuring CIMT at their 6th clinic examination (aged 49.5 ± 5.7 years) and an average of 9.6 years later, and PiB imaging measuring Aβ on average 22.1 years post baseline. We

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SUPPLEMENTARY MATERIAL

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used multivariate linear regression analyses to relate baseline, follow-up, mean, and progression of internal carotid artery (ICA) and common carotid artery (CCA) CIMT to Aβ in brain regions associated with Alzheimer's disease (AD) and related dementias (ADRD), adjusting for age, sex, and other vascular risk factors.

Results: Participants with higher mean ICA IMT had more Aβ in the precuneus (beta ± standard error [β ± SE]: 0.466 ± 0.171 mm, $p = 0.01$) and the frontal, lateral, and retrosplenial regions (β ± SE: 0.392 ± 0.164 mm, $p = 0.022$) after adjusting for age, sex, vascular risk factors, and medication use. We did not find an association between any CCA IMT measures and Aβ or progression of ICA or CCA IMT and Aβ.

Conclusion: Carotid atherosclerosis, as measured by ICA IMT, is associated with increased Aβ burden later in life. These findings support a link between vascular disease and AD/ADRD pathophysiology.

Keywords

Alzheimer's disease; amyloid; carotid atherosclerosis; carotid ultrasound

INTRODUCTION

With a paucity of prevention and treatment techniques, there has been increased attention to the search for potentially modifiable early risk factors for the development of dementia and cognitive impairment [1, 2]. Carotid artery atherosclerosis is emerging as a potential contributor to not only vascular dementia, but also all-cause dementia and Alzheimer's disease (AD) [2–4]. Carotid artery intima-media thickness (CIMT), as measured on ultrasound, is an early marker of carotid atherosclerosis and is considered a marker of subclinical atherosclerosis [5]. CIMT has been associated with cardiovascular events including stroke and myocardial infarction, and with impaired cognitive function, lower hippocampal volumes, and increased risk of dementia [6–10].

Though there seems to be evidence of an association between CIMT and dementia, the exact pathophysiologic mechanism underpinning this relation is not clearly established. Some potential explanations include the possibility that cerebral hypoperfusion from carotid artery disease may lead to decreased amyloid-β (Aβ) clearance from the brain with a net increase in deposition [11]. Though the exact relationship between CIMT and amyloid deposition is unknown, evidence from animals suggest that sequelae of vascular disease and hypertension may potentiate the impacts of aging and lead to increased Aβ deposition [12]. Increased brain deposition of Aβ can be seen years before a clinical diagnosis of dementia and are associated with progressive cognitive impairment and incident AD [13]. PET imaging using ^{11}C-Pittsburgh Compound B (PiB) Aβ allows assessment of Aβ burden *in vivo*, and has been related to AD and mild cognitive impairment because PiB binds to amyloid plaques within the brain [14].

Despite the potential pathophysiologic associations, there has been limited community-based investigation into the relation of early carotid artery atherosclerotic disease and Aβ deposition in the brain. We sought to investigate this potential link between CIMT and future

presence of Aβ with the hypothesis that those with higher CIMT would have increased presence of Aβ on future PiB examinations. We evaluated the association of both baseline and progression of carotid artery disease, as measured by CIMT, to Aβ deposition in the community-based Framingham Heart Study (FHS) Offspring Cohort. Since carrying the apolipoprotein (*APOE*) ε4 allele is associated with Aβ accumulation and with carotid artery disease, we examined the interactions with *APOE* ε4 carrier status.

MATERIALS AND METHODS

Sample

The FHS Offspring cohort, consisting of the offspring of the original FHS cohort and their spouses, were recruited in 1971 and have been followed prospectively for nearly 5 decades, with periodic examinations approximately every 4 years. We included FHS Offspring Cohort participants who had carotid duplex ultrasound (US) at their sixth examination cycle (1995–1998) and their eighth exam cycle (2005–2008). Among participants who underwent at least one carotid ultrasound and also had information on vascular risk factors at each examination, a total of 47 participants also had brain PiB Aβ imaging. Participants with known diagnosis of dementia or stroke were excluded. The final sample included 47 participants. Figure 1 shows a flow diagram of sample selection. The institutional review board of Boston University Medical Center approved the study protocol. Informed consent was obtained from all participants.

Carotid ultrasound

Carotid US examinations were obtained using a standard protocol that has been previously described in detail [15, 16]. Briefly, a certified sonographer used an US device equipped with a high-resolution linear array transducer with color Doppler and Doppler spectral analyzer (Model SSH-140A; Toshiba America Medical Systems, Tustin, CA). A 7.5 MHz transducer was used to image the common carotid arteries and a 5 MHz transducer (–3 dB point 6.2 MHz) was used to image the carotid bulb and internal carotid arteries. Images were gated to an electrocardiogram and taken at end-diastole (peak of the R-wave).

One image of the distal common carotid artery (CCA), two of the carotid artery bulb, and two of the proximal 2 cm of the internal carotid artery (ICA) were analyzed by one operator and over-read by an experienced radiologist (JFP). Hemodynamically significant stenosis (≥50%) was defined by peaksystolic velocities ≥150 cm/s and lower velocities were divided in three groups by the same operator: 0 (no stenosis), 1–24%, and 25–49%. Because of the low numbers of hemodynamically significant stenosis, we categorized stenosis as 0% and > 0%. Intra-reader reproducibility of carotid stenosis ≥25% has been previously reported (Kappa value = 0.69) [15].

Carotid IMT

IMT was measured at the CCA, carotid bulb, and ICA bilaterally and the mean of the maximal IMT measurements of the near and far walls was used (maximum 4 artery walls for the common carotid artery). The internal carotid/bulb IMT was defined as the mean of the 4 maximal IMT measurements made in the carotid artery bulb and the ICA on both

sides for a maximum of 16 wall segments. The examinations were analyzed by a single laboratory, side-by-side both longitudinally and circumferentially. Reproducibility of IMT measurements has been reported previously [17]. Pearson's correlation coefficient for this cohort was 0.82 for the mean intima–media thickness of the common carotid artery and 0.80 for the maximum intima–media thickness of the internal carotid artery when re-interpreted to compensate for temporal effects.

Carotid site IMT rate of change (mm/year) was defined as the difference between site specific IMT (ICA and CCA) measured in the second ultrasound minus same site specific IMT measured in the first carotid ultrasound, divided by the time interval between the two studies [9].

11*C-Pittsburgh Compound B (PiB) Aβ imaging*

Details of the PiB Aβ imaging have been previously described. Briefly, imaging was performed on a Siemens ECAT HR + scanner (3D mode; 63 image planes; 15.2 cm axial FOV 5.6 mm transaxial resolution; 2.4 mm slice interval) [18]. The PiB images were coregistered to a T1-weighted structural brain MRI using SPM8 and FreeSurfer v6.0 was used to derive regions of interest. PiB retention was expressed as the distribution volume ratio (DVR) with the cerebellar cortex used as a reference region [19]. Frontal, lateral, and retrosplenial (FLR) PiB was used as a summary measure derived from the mean of the superior frontal, inferior frontal, rostral middle frontal, rostral anterior cingulate, medial orbitofrontal, inferior and middle temporal, inferior parietal, and precuneus regions. Regional precuneus PiB was also specifically assessed given this region's susceptibility to early Aβ accumulation [20]. For all ROIs, values from both the right and left hemisphere were averaged.

Vascular risk factors

Vascular risk factors were assessed at both exam cycles 6 and 8. Systolic blood pressures were each taken as the average of the Framingham clinic physician's two measurements. Current cigarette smoking was defined as self-reported use in the year prior to the examination. Fasting glucose was considered as a continuous variable in mg/dL. Total cholesterol levels were included as continuous variables. Prevalent cardiovascular disease included coronary heart disease, heart failure and peripheral arterial disease.

APOE genotype

APOE genotype was determined by PCR from leukocyte DNA acquired from whole blood, as previously described [21]. Participants with at least one copy of the $\varepsilon 4$ allele were classified as *APOE* $\varepsilon 4$ carriers.

Statistical analysis

Descriptive statistics are provided for the sample characteristics for both exam 6 and 8 (Table 1). The ICA and CCA IMT, and the Aβ retention in the FLR and precuneus were standardized (subtracting the mean and dividing by standard deviation of the sample) for analysis. Multivariable linear regression was used to assess the association between site-specific CIMT measurements (i.e., measured at the common and ICA sites) with burden of

Aβ in the precuneus and FLR (summary measure as previously described). We analyzed site-specific CIMT at exam 6, exam 8, the average CIMT across both exams, and the change between exams. We utilized the mean ICA across exams 6 and 8 as a variable in order to minimize technical inaccuracies in measurement and to better reflect the cumulative effects of vascular risk throughout midlife. Primary analysis was performed adjusting for age, sex, and time interval between CIMT measurement and the PiB exam. A second model was performed to additionally adjust for levels of systolic blood pressure, current smoking, fasting glucose, and total cholesterol levels at the time of the CIMT measurement. These variables were included to account for vascular risk factors which may affect development of cognitive impairment [22–24]. A third model was performed additionally adjusting for use of anti-hypertensives and statins. We adjusted for these medications as they can affect cognitive impairment and carotid vascular disease, respectively [25, 26]. When evaluating the average CIMT across both exams, we adjusted for the mean of the covariates across the two exams. We also evaluated the interaction between carrying an *APOE ε*4 allele and CIMT on Aβ burden using linear regression. We evaluated variance inflation factors with a cut-off of 5 in our regression models. All statistical tests were 2-sided and the criterion for significance was set at p-value < 0.05. Analyses were performed using SAS version 9.4.

RESULTS

Descriptive statistics of the sample included are shown in Table 1. The mean ICA and CCA CIMT measurements were 1.29 (0.45) and 0.58 (0.10) at exam 6, respectively, and 1.77 (0.7) and 0.63 (0.1) at exam 8, respectively, and 60% of the participants had 0% carotid stenosis. The mean time interval from CIMT measurements to the PiB Aβ examination was 22.1 (20.1–24.5) years from exam 6 and 12.5 (11.2–13.8) years from exam 8. Our sample was generally healthy, including middle aged adults, with a low prevalence of cardiovascular risk factors. Nearly 20% were *APOE ε*4 carriers.

In our primary multivariable adjusted analyses, we found that participants with higher mean ICA CIMT across exam cycles (mean of exams 6 and 8) had significantly more Aβ in the precuneus (standardized beta±standard error [β±SE]: ±SE]: 0.466±0.171, $p = 0.01$) and in the FLR regions (β±SE: 0.392±0.164, $p = 0.022$) after adjusting for age, sex, vascular risk factors, anti-hypertensive, and statin use (Table 2). We found that participants with higher follow-up ICA CIMT (exam 8, closest to PiB exam) had significantly more Aβ in the precuneus (standardized beta±standard error [β±SE]: ±SE]: 0.403±0.18, $p = 0.0321$) and in the FLR regions (β±SE: 0.358±0.172, $p = 0.0454$) after adjusting for age, sex, vascular risk factors, anti-hypertensive, and statin use. We did not find a significant interaction with *APOE ε*4 carrier status.

We did not find similarly significant findings with IMT measurements in the CCA. Specifically, we did not find a significant association with baseline, follow-up, or mean CCA CIMT with Aβ burden (Table 2). Further, we found no significant association between change in either ICA or CCA CIMT and Aβ deposition (Table 3). To see if carotid stenosis may play a role in an association, we also tested for an association between carotid stenosis and Aβ burden and found no significant association in our cohort, which had relatively low levels of stenosis (Table 4). For all analyses, variance inflation factors were less than 5.

DISCUSSION

In our study in a community-based cohort, we found that early carotid atherosclerosis, as measured by ICA CIMT on US, was associated with increased amyloid burden in the precuneus and FLR over 10 years later. This significant association persisted after adjusting for other vascular risk factors and anti-hypertensive and statin use. We found a similar association with borderline statistical significance with baseline (exam 6) ICA CIMT and amyloid deposition, but not with CCA CIMT. This study is one of few studies which has shown an association between a marker of carotid atherosclerosis and future Aβ deposition. Our results point to a potential pathophysiologic mechanism by which vascular disease may contribute to or accelerate the development of dementia, including AD and related dementias (ADRD).

Prior studies have shown that other markers of cardiovascular disease are associated with Aβ burden, specifically carotid or central arterial stiffness. These studies include one study which demonstrated an association between carotid stiffness and amyloid burden in patients with amnestic mild cognitive impairment [27] and another which showed that amyloid deposition increased with age and was associated with higher central arterial stiffness [28]. Our study differs from the previously published reports in that we evaluated CIMT, a specific early biomarker of systemic atherosclerosis, rather than central or arterial stiffness. Further, due to the nature of the longitudinal cohort study, we were able to compare CIMT over 10 years prior to evaluating amyloid burden in participants who were free of dementia at baseline. Most of the existing studies evaluating similar associations have been cross-sectional or in patients with known dementia or cognitive impairment [20].

Thus far, several epidemiologic cohort studies have demonstrated an association between atherosclerosis and future cognitive impairment [29–31]. CIMT is thought to be a surrogate marker for systemic atherosclerosis and is used as a marker for generalized cardiovascular risk. We found that having an increased mean ICA IMT is associated with higher burden of Aβ in regions associated with ADRD and with progression of dementia. Though we found a statistically significant association between ICA IMT and Aβ burden, we did not find a similar robust association with CCA IMT. This finding is not unexpected as there is strong evidence that ICA IMT may better reflect vascular risk factors than CCA IMT [9, 10, 32, 33].

CIMT and other markers of atherosclerosis have long been thought to contribute to primarily vascular dementia; however, our findings suggest a potential link between carotid atherosclerosis and other dementia subtypes, including ADRD. There are a number of potential mechanisms underlying this association, including that carotid atherosclerosis may contribute to cerebral hypoperfusion which limits clearance of Aβ [11, 34]. In our study, we found that carotid stenosis was not significantly associated with amyloid burden, so flow-limiting stenosis leading to hypoperfusion was likely not the driving force. Another consideration would be that CIMT is a surrogate marker of generalized vascular disease and may indicate that smaller cerebral microvasculature may also be diseased, leading to amyloid clearance impairment. Further investigation into the association between CIMT

and amyloid clearance and deposition is needed to determine the exact role of carotid atherosclerosis in the development of cognitive impairment.

PiB imaging is one of the few examinations which allows *in vivo* imaging of amyloid burden for the imaging diagnosis of AD [20]. The presence of Aβ on PiB in a specific pattern, including the precuneus, is associated with symptomatic AD and preclinical AD [20]. While the participants in our cohort were cognitively-intact and in middle age, the differences in Aβ burden may indicate early changes that may predate the onset of cognitive impairment. Continued follow-up to determine which participants ultimately develop clinically evident cognitive impairment is critical in assessing the utility of ICA IMT as a risk factor in the development of dementia.

Our study had several strengths. First, we were able to follow a cohort of participants longitudinally for over 10 years to determine if past CIMT was associated with future amyloid burden. This long lag time allowed us to assess how the midlife exposure of a vascular risk factor (increased IMT) is associated to later life deposition of Aβ accumulation. The large temporal difference in carotid US and PiB exam makes it difficult to definitively conclude increased ICA IMT is the main driver of increased Aβ on PiB, though the association did persist despite adjustment for multiple variables. Additionally, the participants in our sample are younger than those in many other studies evaluating the link between carotid disease and amyloid burden and have relatively low levels of vascular risk at baseline. Despite this relatively young sample, we were able to detect a significant association, even independent of other confounders and contributors to amyloid burden. This younger participant population allowed us to assess for early changes to Aβ accumulation before the onset of clinical dementia.

We did encounter several limitations. One is that we were unable to assess for a change in amyloid deposition overtime because we only evaluated amyloid burden at a single time point. Further, the FHS cohort is relatively homogenous with the majority of the participants of European, white descent which limits our ability to generalize the findings to all ethnic and racial groups. Also, our study is limited by a relatively small sample size with potential for selection bias given that only a subset of FHS participants underwent PiB imaging. Because of the limited power from our relatively small sample size, our study did not adjust for multiple testing and our results would not survive familywise error rate or false discovery rate correction. Further, because of the small sample size, our analyses were limited by the non-normal distribution of data, however, linear regression is robust to the normality assumption. We did not perform a non-parametric approach as it would not allow for adjustment of covariates and would be more conservative. Our results should be viewed as hypothesis generating and require replication in larger sample sizes for confirmation. Further, our small sample size and large number of variables limit our ability to truly evaluate for interaction effects with *APOE4*. Because there is a strong effect of *APOE4* on cognition, we have included the results of this interaction analysis though the results should be considered exploratory. An additional limitation is the inherent difficulties in IMT measurement on US. We utilized mean IMT measurements over two exams in order to minimize technical inaccuracies in measurement.

In summary, our study detected a significant association between ICA CIMT, a marker of atherosclerosis, and amyloid burden in brain regions associated with ADRD over 10 years later. This significant association persisted despite adjusting for other potential confounders, including vascular risk factors and medication use. While future longitudinal studies with more participants are necessary to confirm this association, our findings indicate a potential risk factor for the development of dementia pathophysiology and may be helpful in identifying those who may benefit most from targeted preventative strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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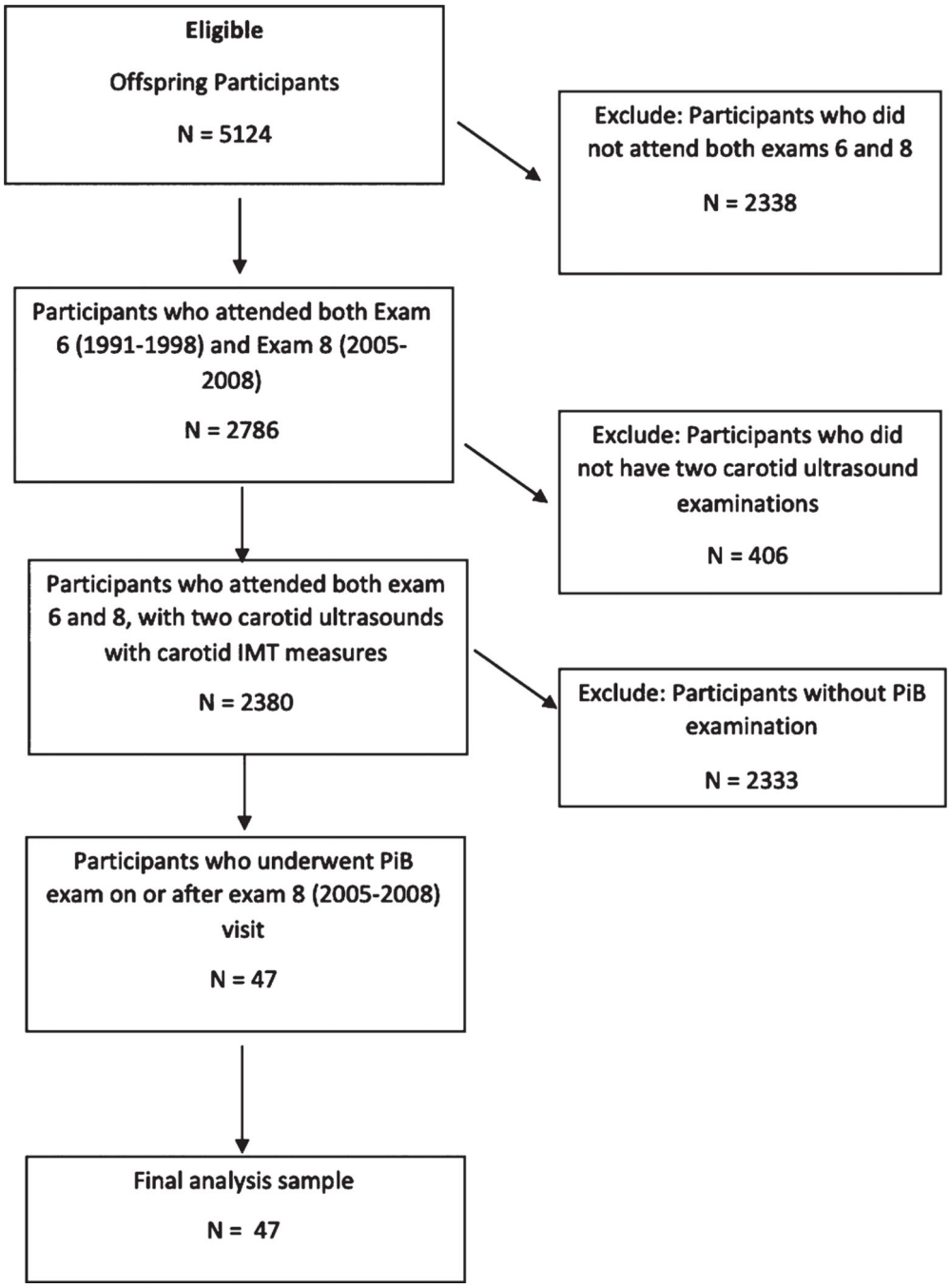

Fig. 1.
Flowchart of participant inclusion.

Table 1

Demographics and clinical characteristics of the included participants

	N	Exam 6	Exam 8
Age, y (SD)	47	49.5 (5.7)	59.1 (5.7)
Female, *n* (%)	47	21 (45%)	
Education, *n*, %	47		
<High school degree		0 (0%)	
High school degree		6 (12.8%)	
Some college		11 (23.4%)	
≥college degree		30 (63.8%)	
Body mass index, m/kg^2	47	28.0 (5.0)	28.4 (4.9)
Hypertension, *n* (%)	47	13 (28%)	21 (45%)
Current smoking status	47	4 (8.5%)	1 (2.1%)
SBP, mmHg	47	120.0 (16.1)	121.3 (12.3)
DBP, mmHg	47	76.2 (10.1)	75.7 (8.0)
Heart rate, BPM	47	61.17 (9.0)	61.1 (9.3)
Diabetes, *n* (%)	47	2 (4%)	2 (4%)
Fasting glucose, md/dL	47	97.3 (10.1)	102.7 (10.3)
Prevalent cardiovascular disease	47	4 (8.5%)	7 (14.9%)
Total Cholesterol, mg/dL	47	200.5 (27.0)	186.6 (31.7)
APOE ε4 status, (%)	47	9 (19%)	
Anti-hypertensive use	47	8 (17%)	
Statin use	47	8 (17%)	
ICA CIMT	46	1.29 (0.45)	1.77 (0.7)
CCA CIMT	46	0.58 (0.10)	0.63 (0.1)
Change in ICA CIMT	46	0.05 (0.06)	
Change in CCA CIMT	46	0.006 (0.005)	
Carotid Stenosis	47		
0%		28 (60%)	N/A
>0% (0–24%)		19 (40%)	
Log(FLR amyloid-β)	47	0.13 (0.15)	

	N	Exam 6	Exam 8
Precuneus amyloid-β	47	1.21 (0.24)	

Table 2

Associations of standardized CIMT at baseline (exam 6) and follow-up (exam 8) with amyloid-β burden

	Model 1		Interaction with *APOE4*	Model 2		Model 3	
	β **(SE)**	***p***	***p***	***β*** **(SE)**	***p***	***β*** **(SE)**	***p***
			Baseline ICA CIMT				
Amyloid-β FLR	0.286 (0.139)	0.045	0.182	0.286 (0.155)	0.073	0.222 (0.171)	0.202
Amyloid-β precuneus	0.343 (0.143)	0.021	0.237	0.332 (0.157)	0.042	0.285 (0.174)	0.111
			Follow-up ICA CIMT				
Amyloid-β FLR	0.296 (0.159)	0.071	0.121	0.348 (0.168)	0.046	0.358 (0.172)	0.045
Amyloid-β precuneus	0.332 (0.164)	0.049	0.056	0.374 (0.175)	0.040	0.403 (0.18)	0.032
			Mean ICA CIMT				
Amyloid β FLR	0.346 (0.145)	0.022	0.094	0.406 (0.157)	0.014	0.392 (0.164)	0.022
Amyloid-β precuneus	0.392 (0.15)	0.013	0.064	0.442 (0.163)	0.010	0.466 (0.171)	0.010
			Baseline CCA CIMT				
Amyloid-β FLR	–0.164 (0.147)	0.271	0.916	–0.186 (0.158)	0.246	–0.317 (0.162)	0.058
Amyloid-β precuneus	–0.050 (0.156)	0.751	0.927	–0.068 (0.166)	0.684	–0.184 (0.173)	0.295
			Follow-up CCA CIMT				
Amyloid-β FLR	–0.166 (0.159)	0.303	0.887	–0.187 (0.171)	0.282	–0.193 (0.172)	0.270
Amyloid-β precuneus	–0.058 (0.167)	0.730	0.707	–0.099 (0.181)	0.588	–0.096 (0.185)	0.607
			Mean CCA CIMT				
Amyloid-β FLR	–0.148 (0.150)	0.330	0.903	–0.153 (0.161)	0.351	–0.153 (0.162)	0.352
Amyloid β precuneus	–0.04 (0.159)	0.804	0.749	–0.047 (0.17)	0.783	–0.042 (0.174)	0.810

Model 1 adjusted for age, sex, and time interval between CIMT measurement and the PiB exam. Model 2 additionally adjusted for levels of systolic blood pressure, current smoking, fasting glucose, and total cholesterol levels at the time of the CIMT measurement. Model 3 additionally adjusted for use of anti-hypertensives and statins.

Table 3

Associations between change in CIMT and amyloid-β burden

	Model 1		Interaction with *APOE4*	Model 2		Model 3	
	β **(SE)**	***p***	***p***	***β*** **(SE)**	***p***	***β*** **(SE)**	***p***
			ICA CIMT change				
Amyloid-β FLR	0.068 (0.15)	0.654	0.480	0.064 (0.213)	0.767	0.175 (0.218)	0.428
Amyloid-β precuneus	0.070 (0.157)	0.657	0.219	0.046 (0.219)	0.834	0.162 (0.226)	0.478
			CCA CIMT change				
Amyloid-β FLR	–0.039 (0.159)	0.807	0.511	–0.102 (0.182)	0.578	–0.126 (0.186)	0.502
Amyloid-β precuneus	–0.021 (0.166)	0.898	0.421	–0.137 (0.187)	0.468	–0.154 (0.191)	0.425

Model 1 adjusted for age, sex, and time interval between CIMT measurement and the PiB exam. Model 2 additionally adjusted for levels of systolic blood pressure, current smoking, fasting glucose, and total cholesterol levels at the time of the CIMT measurement. Model 3 additionally adjusted for use of anti-hypertensives and statins.

Table 4

Association between carotid stenosis and amyloid-β deposition

	Model 1		Interaction with *APOE4*	Model 2		Model 3	
	β **(SE)**	***p***	***p***	***β*** **(SE)**	***p***	***β*** **(SE)**	***p***
			Stenosis > 0% versus stenosis = 0 *				
Amyloid-β FLR	0.222 (0.303)	0.467	0.213	0.208 (0.335)	0.538	0.076 (0.344)	0.827
Amyloid-β precuneus	0.209 (0.317)	0.513	0.209	0.161 (0.346)	0.643	0.03 (0.354)	0.933

* Stenosis values (stenosis >0% or 0 stenosis) at the time of exam 6 due to unavailability of stenosis measures at exam 8. Model 1 adjusted for age, sex, and time interval between carotid stenosis measurement and the PiB exam. Model 2 additionally adjusted for levels of systolic blood pressure, current smoking, fasting glucose, and total cholesterol levels at the time of the carotid stenosis measurement. Model 3 additionally adjusted for use of anti-hypertensives and statins.