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Associations between vascular risk factors, carotid atherosclerosis and cortical volume and thickness in older adults

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Abstract

Background and Purpose—To investigate whether the Framingham Cardiovascular Risk Profile (FCRP) and carotid artery intima-media thickness (CIMT) are associated with cortical volume and thickness.

Methods—Consecutive subjects participating in a prospective cohort study of aging and mild cognitive impairment enriched for vascular risk factors for atherosclerosis underwent structural MRI scans at 3T and 4T MRI at three sites. Freesurfer (v5.1) was used to obtain regional measures of neocortical volumes (mm³) and thickness (mm). Multiple linear regression was used to determine the association of FCRP and CIMT with cortical volume and thickness

Results—152 subjects (82 men) were aged 78 (±7) years old, 94 had a CDR of 0, 58 had a clinical dementia rating (CDR) of 0.5 and the mean mini-mental status examination (MMSE) was 28 ± 2. FCRP score was inversely associated with total gray matter (GM) volume, parietal and temporal GM volume (adjusted p<0.04). FCRP was inversely associated with parietal and total cerebral GM thickness (adjusted p<0.03). CIMT was inversely associated with thickness of parietal GM only (adjusted p=0.04). Including history of myocardial infarction or stroke and radiologic evidence of brain infarction, or apoE genotype did not alter relationships with FCRP or CIMT.

Conclusions—Increased cardiovascular risk was associated with reduced GM volume and thickness in regions also affected by Alzheimer’s disease (AD), independent of infarcts and apoE genotype. These results suggest a “double hit” toward developing dementia when someone with incipient AD also has high cardiovascular risk.

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Disclosures
None.

Keywords

Framingham cardiovascular risk profile; carotid intima media thickness; gray matter; cortical volume; cortical thickness; atrophy

Introduction

We have previously reported in an autopsy sample that cerebral atherosclerosis contributes to brain atrophy independent of Alzheimer pathology and cerebral infarcts¹. Atrophy is a non-specific finding associated with normal aging², Alzheimer's disease (AD)³, stroke⁴, myocardial infarction (MI)⁵, and other neurodegenerative disorders⁶. Regional patterns of atrophy may differ by etiology such as in AD³, where atrophy is most prominent in the medial, inferior and lateral temporal lobes, followed by multi-modal association areas. Epidemiologic studies have shown that risk factors for atherosclerosis (e.g., hypertension, diabetes mellitus, and hyperlipidemia) increase the risk for cognitive impairment associated with both stroke and AD⁷⁻⁹.

Brain atrophy is associated with cognitive impairment¹⁰. The $\epsilon 4$ allele of the apolipoprotein E (apoE) gene, a genetic risk factor for cognitive decline in the elderly¹¹, has demonstrated a particular phenotype of atrophy of medial temporal lobe structures¹². Global brain atrophy is also seen in survivors of myocardial infarction⁵ and in the presence of cerebrovascular disease^{4, 13}. Previous work focusing on the relationships between FCRP or CIMT and brain volumes in healthy older adults¹⁴ or patients with cardiovascular disease¹⁵ did not account for cognitive status, cerebrovascular disease, and cardiovascular disease. Moreover, the regional pattern of atrophy associated with atherosclerosis is relatively unknown.

The primary objective of the present study was to determine whether Framingham Cardiovascular Risk Profile (FCRP) and subclinical atherosclerosis measured as carotid artery intima media thickness (CIMT) are associated with brain atrophy independent of vascular injury and apoE. A secondary goal was to determine whether FCRP and CIMT are associated with regional patterns of brain atrophy.

In this study, FCRP¹⁶ was used to assess vascular risk and CIMT was used as a measure of subclinical atherosclerosis. If cardiovascular risk factors contribute to atherosclerosis then brain atrophy, we hypothesize that both FCRP and CIMT will be inversely associated with brain volume and cortical thickness, globally and regionally.

Methods

Subjects

Consecutive subjects were identified from an ongoing, longitudinal, multi-institutional Aging Brain program project that recruits subjects with normal cognition to mild cognitive impairment, representing a spectrum of low to high vascular risk¹⁷. Most participants were acquired through community-based recruitment using a protocol designed to obtain a demographically diverse cohort, or through sources such as stroke clinics and support groups attended by people with high vascular risk factors. All participants gave written informed consent in accordance with the policies of each institutional review board. Inclusion criteria include age 60 or older, with cognitive function in the normal to mild cognitive impairment range (Clinical Dementia Rating [CDR] score of 0 or 0.5)¹⁸. Persons with history of multiple vascular risk factors, coronary or carotid disease, myocardial infarction, or ischemic stroke were targeted for inclusion, although patients with very large strokes that interfered with estimation of cortical volume and thickness were excluded.

Exclusion criteria included evidence of alcohol or substance abuse, head trauma with loss of consciousness lasting longer than 15 minutes, factors contraindicating MRI, and severe medical illness, neurologic or psychiatric disorders unrelated to AD or vascular dementia that could significantly affect brain structure (e.g., schizophrenia and other psychotic disorders, bipolar disorder, current major depression, post-traumatic stress disorder, obsessive-compulsive disorder, liver disease, multiple sclerosis, amyotrophic lateral sclerosis). Participant demographics by CDR are shown in Table 1.

Measures of cardiovascular risk and carotid atherosclerosis

The FCRP uses empirically-derived age- and gender-adjusted weighting of categorical variables to predict the 10-year risk of coronary heart disease and is a weighted sum of: age, gender, active smoking, diabetes, systolic blood pressure (and/or use of hypertensive medications) and total cholesterol and high-density lipoprotein cholesterol levels¹⁶. Higher scores indicate greater coronary risk.

CIMT was used as a measure of subclinical atherosclerosis. CIMT is a measure of the thickness of the inner two layers of the carotid artery; higher CIMT indicates greater atherosclerosis burden. High-resolution B-mode ultrasound images of the right and left common carotid arteries were obtained with a 7.5-MHz linear array transducer attached to an ATL Apogee ultrasound system (Bothell, WA). CIMT was determined as the average of 70 to 100 measurements between the intima-lumen and media-adventitia interfaces along a 1 cm length just proximal to the carotid artery bulb at the same point of the cardiac cycle using computerized automated edge detection. Right and left CIMT were measured in each individual whenever possible. For individuals with CIMT measurements from both sides, the maximum of these two quantities was used in subsequent statistical analyses.

Measure of AD risk

Blood was drawn with the subject's consent for apolipoprotein E genotyping. Genotyping was completed for 102 participants. Subjects with 3/4 or 4/4 combined alleles were classified as apoE ϵ 4 positive, and those with 3/3 alleles as apoE ϵ 4 negative. Because the 2/4 combined allele is associated with a lower risk of AD¹⁹, these subjects were not included in the APOE ϵ 4 positive group.

MRI: acquisition

Structural T1-weighted MRI scans for participants were collected on 3T and 4T MRI systems. Forty-three participants were scanned at the University of Southern California using a 3T General Electric Signal HDx system with an 8-channel head coil. Acquired images included a T1-weighted volumetric SPGR (TR = 7 ms, TE = 2.9 ms, TI = 650 ms, 1 mm³ isotropic resolution). Fifty-four participants were scanned at the University of California, Davis research center. Nine participants were scanned using a 3T Siemens Magnetom Trio Syngo System with an 8-channel head coil. Forty-five were scanned using a 3T Siemens Magnetom TrioTim system with an 8-channel head coil. Acquired images for all 54 participants included a T1-weighted volumetric MP-RAGE (TR = 2500, TE = 2.98, TI = 1100, 1 mm³ isotropic resolution). Thirty-three participants were scanned at the San Francisco Veterans Administration Medical Center using a 4T Siemens MedSpec Syngo System with an 8-channel head coil. A T1-weighted volumetric MP-RAGE scan (TR = 2300, TE = 2.84, TI = 950, 1 mm³ isotropic resolution) was acquired. Twenty-two participants were scanned at the University of California, San Francisco Neuroscience Imaging Center using a 3T Siemens Magnetom TrioTim system with a 12-channel head coil. Acquired images included a T1-weighted volumetric MP-RAGE (TR = 2500, TE = 2.98, TI = 1100, 1 mm³ isotropic resolution).

MRI: processing

The publicly available Freesurfer v5.1 (<http://surfer.nmr.mgh.harvard.edu/>) volumetric segmentation and cortical surface reconstruction methods were used to obtain regional measures of neocortical volumes (mm³) and thickness (mm). The reconstructed cortical surface models for each participant were manually inspected to ensure segmentation accuracy; regions with poor segmentation accuracy due to poor image quality or misregistration were excluded from further statistical analyses. Cortical surfaces were automatically parcellated²⁰ and combined to create average cortical thickness and volume for total GM and for frontal, temporal, parietal, and occipital lobar regions. Region of interest volumes and thicknesses by cognitive status are shown in Table 2.

Vascular injury

History of vascular injury—Data regarding clinical history of stroke or myocardial infarction were obtained from medical history.

Radiologic evidence of vascular brain injury—Infarcts were identified by an experienced neurologist (NS) blind to any other participant data using the T1-weighted and FLAIR MRI images. Infarcts were categorized according to structures involved, size (small: 3-10mm, large: >10mm), and severity (cystic, not cystic). For the current analysis, infarcts were then labeled: *cortical gray matter* (affecting any cortical region), *white matter* (affecting any subcortical white matter region, internal capsule, corpus callosum), *subcortical gray matter* (affecting basal ganglia, thalamus, amygdala, or hippocampus), and *other* (affecting midbrain, pons, medulla, or cerebellum). The number of infarcts for each participant (range 0-4) was used in subsequent statistical models.

Statistical analysis

Multiple linear regressions were used to test the association of cardiovascular risk or atherosclerosis with measures of brain volume and cortical thickness. Analyses were adjusted for age, sex, magnet strength (3T vs. 4T), CDR, and intracranial volume (volume analyses only). For volume and thickness models, P-values for FCRP or CIMT were adjusted for multiple comparisons according to the number of ROIs (5 ROIs: total GM, frontal, temporal, parietal and occipital GM) and the average intercorrelations among the ROIs²¹. Average intercorrelations were $r = 0.813$ for volumes, $r = 0.713$ for thickness. A 2-sided adjusted $P < 0.05$ was considered statistically significant.

Results

There were 152 consecutive subjects with mean age 78 (range 62-92), 45% women, mean years of education 15.7 (range 9-24), and mean MMSE 28.3 (range 20-30). The cognitive status groups were very similar, with CDR=0.5 having significantly lower MMSE score and thinner cortex in all regions. All other measures were equivalent, as shown in Table S1 (please see <http://stroke.ahajournals.org>).

Thirty-four participants had radiologically identified brain infarcts. Of these participants, 3 had cortical, 15 had subcortical gray, 14 had white matter, and 9 had an infarct in another location. These numbers do not sum to 34 because eight individuals had more than one infarct and many infarcts affected multiple regions. Cortical infarcts were located in the frontal and occipital lobes. Of the 34 people with MRI-identified infarct, 18 (53%) had a clinical history of stroke. Of the 118 with no MRI-identified infarct, 18 (15%) had a clinical history of stroke. Fifty-one participants had a clinical history of stroke or myocardial infarction.

Table 2 shows the relationships between FCRP and measures of cortical volume and thickness. All fits were significant (all model $p < 0.0001$, $0.19 < R^2 < 0.42$). Significant inverse relationships we observed between FCRP and total GM volume and volume of the parietal and temporal lobes. FCRP was significantly inversely associated with total and temporal GM thickness, with a trend for parietal and occipital thickness.

Table 3 shows the relationships between CIMT and measures of cortical volume and thickness. All fits were significant (all model $p < 0.0002$, $0.19 < R^2 < 0.50$). There were no significant associations between CIMT and brain volume. CIMT was inversely associated with thickness of the parietal lobe. GM volume and thickness relationships are illustrated in Figures S1 and S2 (please see <http://stroke.ahajournals.org>).

Models were re-run with two additional independent variables adjusting for history and evidence of vascular injury. The number of brain infarcts had a negative effect on frontal and parietal volumes (adjusted $p < 0.05$), and history of vascular injury had a negative effect on frontal, parietal, and occipital volume (adjusted $p < 0.04$). The number of brain infarcts did not affect cortical thickness, and history of vascular injury had a negative effect on occipital thickness only (adjusted $p = 0.02$). The inverse relationship of FCRP or CIMT with volume and thickness were preserved in models accounting for history and evidence of vascular injury, and the regression coefficients were essentially unchanged. There was no evidence for a mediating effect of vascular injury on either volume or thickness. Moreover, as FCRP and infarcts were uncorrelated ($r = -0.05$, $p = 0.57$), there was no evidence that the presence of infarcts was obscuring a relationship between FCRP and frontal volume or thickness. Figure 1 illustrates these results, demonstrating that the FCRP/volume relationships were preserved even when history and/or evidence of vascular injury significantly affected GM volume.

Models with significant relationships between FCRP or CIMT and brain measures were also rerun adjusting for the presence of apoE4 genotype, to determine whether the associations were independent of the genetic risk for AD. In these models our sample size was substantially reduced, because apoE genotyping was only available in 68% of the participants. No volume or thickness measure was associated with apoE4 genotype. All FCRS and CIMT regression coefficients were of similar magnitude and direction as in the model without apoE.

Tables 2 and 3 also show the association of the other covariates on brain volume and cortical thickness. Higher age was significantly associated with decreased brain volume and thickness in all regions, even in the very restricted age range studied. Men had significantly thinner cortex in all regions. CDR=0.5 participants had thinner cortices in all regions compared to CDR=0 participants.

Discussion

Greater cardiovascular risk was associated with global and regional cortical atrophy and thinning. CIMT was associated with cortical thinning of the parietal lobe. History of vascular cardiac or brain injury affected total and parietal GM volume and occipital GM volume and thickness. Radiologic evidence of vascular brain injury (i.e., number of infarcts) was associated with lower frontal and parietal GM volume. However, the FCRP and CIMT effects were independent of those of vascular injury. Together the findings suggest that cardiovascular risk and atherosclerosis may lead to cortical loss via mechanisms other than, or in addition to, frank vascular brain injury, and that FCRP and CIMT are measuring different aspects of vascular injury.

Given the well-established association between cardiovascular risk factors and atherosclerosis, it is perhaps surprising that we found no relationship between CIMT and

most measures of brain volume and cortical thickness. One consideration is that CIMT is an imperfect measure of atherosclerosis. CIMT is essentially a point measure of a widely distributed process that varies from location to location. Changes in the thickness of the carotid wall reflect both hypertrophic and inflammatory processes, and because CIMT avoids areas of significant atherosclerotic plaque it is not a measure of stenosis. Thus, the lack of association we observed does not rule out the possibility that atherosclerosis has an effect on brain structure.

The pattern of associations with regional atrophy measures may be informative. The hypothesis that cardiovascular risk leads to cortical changes via subclinical small vessel cerebrovascular disease would suggest that relationships between FCRP and atrophy would be especially strong in frontal lobe. In fact, correlations with frontal lobe were notably absent. Instead, temporal and parietal lobe measures were consistently associated with both FCRP and CIMT.

The number of infarcts was related to frontal and parietal GM volume, independent of the effects of FCRP or CIMT. Moreover, cortical infarctions were located in the frontal and occipital lobes, and the vast majority (12/15) of white matter infarcts were located in the frontal lobe. Therefore, although infarct was related to GM atrophy, particularly in the frontal lobe, it does not appear to be the mechanism by which risk leads to GM atrophy in the temporal and parietal regions. The temporal and parietal regions are selectively vulnerable to Alzheimer's disease. A recent report, based on a subset of these same subjects, found that elevated levels of cerebral amyloid deposition, as measured by [11C]Pittsburgh compound B positron emission tomography (PIB PET), was correlated with greater FCRP¹⁷ but not with greater burden of abnormal white matter²². This is consistent with previous findings reporting that atherosclerosis may be associated with the pathology of AD^{23, 24}. However, in the current study, we found no association between GM volume or thickness with the apoE ϵ 4 allele. Cross-sectional MRI studies of individuals with apoE- ϵ 4 compared with non- ϵ 4 subjects have reported smaller bilateral hippocampus in AD patients and healthy elderly¹². Given these reports, the lack of significant volume or thickness reductions in the apoE ϵ 4 carriers for the temporal lobe was surprising. Segmentation inaccuracies may contribute to our failure to detect an effect of apoE in the temporal lobe²⁵. We also had relatively few subjects with apoE4 ϵ 4 allele (overall 23%) suggesting that our sample was relatively enriched for cerebrovascular disease, rather than AD. Limitations of this study include the relatively small number of participants with high FCRP scores. In this study, 41% of participants were low risk (FCRP <10%), 41% were intermediate risk (10% <FCRP <20%), and 18% were high risk (FCRP >20%). Most participants took medication to control their blood pressure (73%) and cholesterol (65%). This may have reduced the number of participants with FCRP scores >20%, despite the fact that a substantial number have already experienced stroke or myocardial infarction and have relatively high CIMT measures. Hypertensive and statin therapy may also reduce CIMT and confound the relationship between CIMT and GM volume or thickness. In addition, we did not control for carotid stenosis, which is reportedly associated with cortical atrophy^{26, 27}, the possible presence of which may have confounded relationships between cardiovascular risk and brain measures.

The study included images acquired from five different MRI scanners and two different magnetic field strengths, introducing a significant technical issue. In our examination of images, we ascertained that the images from all 3T magnets were comparable, but that the 4T images showed greater magnetic field inhomogeneity. To address this, all image processing outputs were manually inspected and we statistically covaried for magnet strength in analyses. A potential limitation is that carotid atherosclerosis was assessed using common carotid artery IMT. A previous report suggests that internal carotid artery IMT is a

better marker for cognitive impairment than the common carotid²⁸, and by extension might also be a better marker of brain volume and thickness to the degree that these underlie cognition. Lastly, apoE genotyping was only available on a subset of participants, so our interpretations that the associations between brain volume and cardiovascular risk are independent of a genetic marker for AD should be viewed with caution.

Conclusions

Increased cardiovascular risk as measured by the FCRP was associated with reduced volumes of total, parietal and temporal GM. Increased FCRP scores were also significantly associated with reduced thickness for temporal and total GM. Notably, FCRP was not associated with frontal GM volume or thickness. Increased carotid atherosclerosis, indexed by CIMT, was associated with reduced parietal cortical thickness. These results suggest that FCRP and CIMT are measuring different aspects of vascular brain injury. The brain regions associated with increased cardiovascular risk are also affected by AD, and this may partially explain why hypertension and diabetes were found to be risk factors for clinically-diagnosed AD in epidemiological studies^{7, 8}. GM atrophy of the temporal lobe, especially the hippocampus and ERC, is a structural hallmark of AD and its clinical precursor, mild cognitive impairment^{10, 29}. With AD progression, atrophy in the parietal regions, particularly the posterior cingulate and precuneus regions, is also observed^{30, 31}. These results suggest a “double hit” toward developing dementia when someone with incipient AD also has high cardiovascular risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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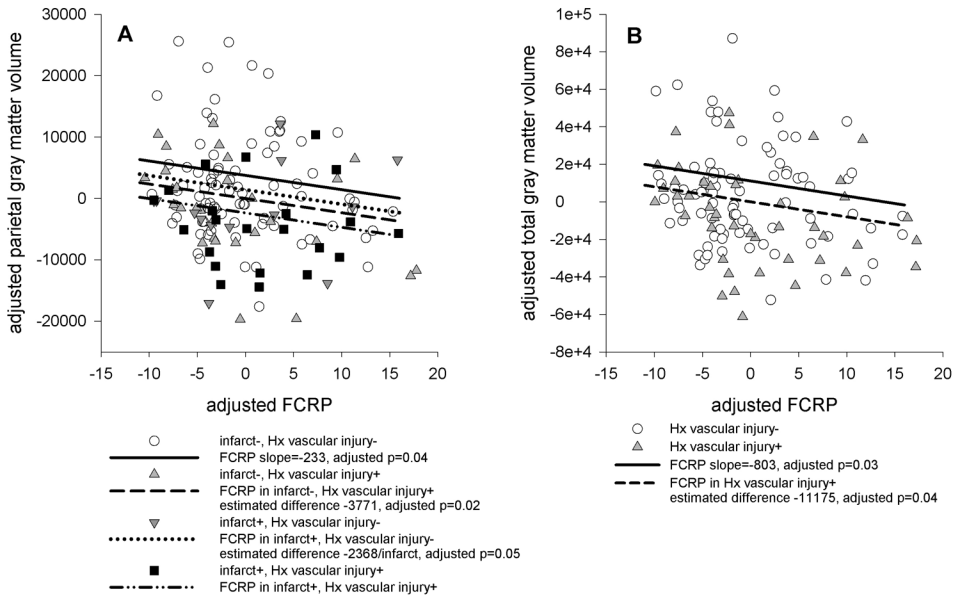


Figure 1. Scatterplots showing the relationships between Freesurfer regional volumes and FCRP. FCRP and volumes were regressed on age, gender, magnet strength, intracranial volume, and cognitive status, and the residuals were plotted against each other. The slope of the line of best fit is the same as the regression coefficient for FCRP in the linear models that included history and evidence of vascular injury. When there are significant differences due to evidence and/or history of vascular injury, regression lines offset by the estimated difference are plotted. A: FCRP and parietal gray matter volume, illustrating effect of history of vascular injury, evidence of vascular injury, and combined effect of history and evidence of vascular injury. B: FCRP and total gray matter volume, illustrating effect of history of vascular injury.

Table 1

Participant demographics by cognitive status.

	CDR=0	CDR=0.5
	N=94	N=58
Age (yrs)	77±7	79±7
Education (yrs)	16±3	16±3
MMSE	29.0±1.3	27.6±2.3*
% men	50	62
% stroke history	19	31
% radiologically identified brain infarcts	19	33
% myocardial infarction	12	16
% coronary artery bypass or angioplasty	17	17
% carotid endarterectomy	2	5
% coronary, carotid or other artery stent	12	17
% taking medication to reduce blood pressure	76	67
% taking medication to reduce cholesterol	64	67
apoE4 allele (pos, neg)	17, 55	6, 24
%apoE4 allele	24	20
FCRP (% risk)	12 ± 7	14 ± 8
CIMT (mm)	0.92 ± 0.14	0.95 ± 0.14

*
p<0.05

continuous variables are summarized as mean ± SD

continuous variables compared with t-test, proportions compared with Fisher's exact test

CDR=clinical dementia rating; MMSE=mini-mental status examination; apoE4=apolipoprotein E epsilon 4; FCRP=Framingham cardiovascular risk profile; CIMT=common carotid artery intima-media thickness

Table 2

Relationships of FCRP to measures of cortical volume and thickness, reported as B (SE); B=unstandardized regression coefficient, SE=standard error.

Measure	Region	Intercept B	FCRP B	Age B	Male Gender B	3T Field strength B	CDR=0 B	ICV B
Volume (mm ³)	Total gray matter	368694 (32485)	-836 (360)	-1388 (372)	1749 (6897)	4262 (4262)	4203 (4944)	0.088 (0.015)
	Frontal	138026 (13393)	-225 (155)	-337 (152)	2609 (2854)	1584 (2522)	473 (2083)	0.035 (0.006)
	Parietal	100417 (9502)	-236 (109)	-307 (105)	1664 (1995)	-538 (1747)	1773 (1474)	0.020 (0.004)
	Temporal	114547 (9770)	-304 (108)	-589 (110)	666 (2021)	4422 (1786)	2627* (1466)	0.026 (0.004)
Average Thickness (mm)	Occipital	30424 (3849)	-67 (44)	-130 (42)	421 (806)	75 (707)	898 (589)	0.007 (0.002)
	Total gray matter	2.596 (0.086)	-0.003 (0.001)	-0.003 (0.001)	-0.062 (0.017)	0.130 (0.018)	0.048 (0.015)	NA
	Frontal	2.349 (0.092)	-0.001 (0.001)	-0.0001 (0.001)	-0.049 (0.018)	0.139 (0.020)	0.041 (0.016)	NA
	Parietal	2.467 (0.093)	-0.003* (0.001)	-0.004 (0.001)	-0.063 (0.018)	0.080 (0.020)	0.059 (0.017)	NA
	Temporal	3.159 (0.114)	-0.004 (0.001)	-0.008 (0.001)	-0.066 (0.022)	0.172 (0.024)	0.072 (0.020)	NA
	Occipital	2.040 (0.099)	-0.003* (0.001)	-0.003 (0.001)	-0.045 (0.020)	0.029 (0.021)	0.044 (0.018)	NA

Bold: adjusted p<0.05;

* 0.05<adjusted p<0.10.

CDR=clinical dementia rating; FCRP=Framingham cardiovascular risk profile; ICV=intracranial volume

Table 3

Relationships of common carotid artery intima-media thickness (CIMT) to measures of cortical volume and thickness, reported as B (SE); B=unstandardized regression coefficient, SE=standard error.

Measure	Region	Intercept B	cIMT B	Age B	Male Gender B	3T Field strength B	CDR=0 B	ICV B
Volume (mm ³)	Total gray matter	361903 (38012)	-14216 (20095)	-1488 (435)	-8245 (6947)	8675 (6421)	5988 (5545)	0.100 (0.016)
	Frontal	136575 (15246)	-12561 (7885)	-306* (166)	633 (2779)	2690 (2604)	2394 (2238)	0.040 (0.007)
	Parietal	104097 (11285)	-10782* (5840)	-305 (121)	136 (2032)	492 (1906)	1935 (1655)	0.023 (0.005)
Average Thickness (mm)	Temporal	111427 (11220)	1296 (5930)	-672 (127)	-3146 (2027)	6163 (1893)	3162* (1613)	0.029 (0.005)
	Occipital	29937 (4345)	-1578 (2234)	-128 (46)	-307 (786)	552 (738)	1178* (628)	0.007 (0.002)
	Total gray matter	2.584 (0.099)	-0.041 (0.059)	-0.003 (0.001)	-0.084 (0.016)	0.145 (0.016)	0.039 (0.019)	NA
Average Thickness (mm)	Frontal	2.345 (0.106)	-0.049 (0.061)	0.0003 (0.001)	-0.061 (0.017)	0.149 (0.017)	0.037 (0.020)	NA
	Parietal	2.534 (0.108)	-0.144 (0.063)	-0.003 (0.001)	-0.075 (0.018)	0.093 (0.018)	0.051 (0.021)	NA
	Temporal	3.110 (0.136)	-0.002 (0.082)	-0.008 (0.002)	-0.099 (0.023)	0.190 (0.022)	0.067 (0.026)	NA
	Occipital	2.034 (0.117)	-0.077 (0.069)	-0.002 (0.001)	-0.065 (0.019)	0.050* (0.019)	0.037* (0.023)	NA

Bold: adjusted p<0.05;

* 0.05<adjusted p<0.10.

CDR=clinical dementia rating; FCRP=Framingham cardiovascular risk profile; ICV=intracranial volume