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Carotid Artery Atherosclerosis, MRI Indices of Brain Ischemia and Aging and Cognitive Impairment: The Framingham Study

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Abstract

Background and Purpose—Carotid atherosclerosis has been associated with increased risk of stroke, and poorer cognitive performance in older adults. The relation of carotid atherosclerosis to cognitive impairment and MRI indices of ischemia and aging in midlife is less clear.

Methods—We studied 1,975 Framingham Offspring Study participants free of stroke and dementia with available carotid ultrasound, brain MRI and neuropsychological testing. We related common and internal carotid artery intima-media thickness (ICA-IMT and CCA-IMT respectively) and internal carotid stenosis (CAS) to large white matter hyperintensity (>1-SD above age-specific mean; LWMH), total brain volume (TCBV), hippocampal volume, silent cerebral infarcts (SCI) and neuropsychological measures of verbal memory, executive function and non-verbal memory measures.

Results—We observed that ICA-IMT, but not CCA-IMT, was associated with higher prevalence of SCI (OR 1.21, 95% CI 1.03–1.43, $p<0.05$), LWMH (OR 1.19, 95% CI 1.03–1.38, $p<0.05$), lower TCBV (−0.05 per SD, $p<0.05$) and poorer performance in verbal memory (−0.06 per SD; $p<0.05$) and non-verbal memory measures (−0.08 per SD; $p<0.01$), but not with hippocampal volume. CAS ≥25% was associated with a higher prevalence of LWMH (adjusted OR 1.77, 95% CI 1.25–2.53) and lower TCBV (−0.11 per SD, $p=0.042$) but not with SCI or hippocampal volume. CAS ≥50% was associated with higher prevalence of SCI (OR 2.53, 95% CI 1.17 – 5.44), LWMH (OR 2.35, 95% CI 1.08–5.13) and poorer performance on executive function (−0.39 per SD; $p<0.05$) but not with TCBV or hippocampal volume.

Conclusions—Carotid atherosclerosis markers were associated with MRI indices of brain ischemia and aging and with cognitive impairment in a community-based sample of middle-aged adults. Our data suggest that ICA-IMT may be a better marker for cognitive impairment than CCA-IMT.

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The authors report no conflicts of interest.

Keywords

Carotid atherosclerosis; brain MRI; cognitive performance

Introduction

Atherosclerosis of the carotid artery is an important mechanism underlying cerebrovascular disease, and has been associated with stroke, cognitive impairment[1,2] and dementia.[3] Whereas the majority of studies evaluating the relation of carotid atherosclerosis and cognitive function have been done in symptomatic patients,[4,5] with severe stenosis, recent population-based studies also have suggested that asymptomatic carotid atherosclerosis is related to poorer neuropsychological performance,[1,2,6] even with mild degrees of stenosis.[1] Traditional vascular risk factors have been associated with both, carotid atherosclerosis[7] and cognitive impairment,[8,9] but the pathophysiology of these processes remains unclear and understanding of their relation is limited.

Carotid stenosis and carotid intima-media thickness (IMT) reflect different stages and severity of the atherosclerotic process. Although IMT is considered a marker of subclinical atherosclerosis, the relations between hypertension, atherosclerosis and measures of carotid IMT are complex and likely reflect the interaction of both processes, whereas carotid stenosis more accurately reflects the atherosclerotic process. Both, carotid stenosis and IMT are related to cardiovascular events within and outside the brain, such as stroke and myocardial infarction.[10] IMT studies, however, have also found strong associations with magnetic resonance imaging (MRI) findings and neuropsychological measures, particularly among older individuals.[2,11]

Site-specific differences in carotid measures of atherosclerosis may be important in their role in cerebrovascular disease, brain injury and cognitive impairment. Prior studies have shown differences in severity of these measures depending on the site of evaluation.[12] In addition, other studies suggest that carotid site-specific differences may relate differentially to vascular risk factors,[13,14] and progression rates of carotid measures differ depending on the arterial site studied.[15,16]

The atherosclerotic process as measured by carotid IMT or mild stenosis may relate to decreased cognitive performance via structural changes measurable at MRI, such as large white matter hyperintensities (LWMH), silent cerebral infarcts (SCI) and decreased total brain volume, decreased cognitive performance via atherosclerotic vascular disease even in the absence of demonstrable structural change, the independent impact of vascular risk factors such as increasing levels of systolic blood pressure on cognition, or through all three mechanisms.

We hypothesize that carotid atherosclerosis as reflected by IMT and stenosis, relates to MRI markers of brain ischemia and aging, and also to poorer cognitive performance. This relation may vary depending on the site of IMT measurement (i.e. common versus internal carotid artery) and the measure used (stenosis or IMT).

Methods

Study Sample

The Framingham Offspring Cohort was recruited in 1971, and has been examined periodically approximately every 4 to 8 years.[19] Carotid duplex ultrasound was conducted during the 6th examination cycle (1995 – 1998) and brain MRI and cognition were assessed during the 7th examination cycle (1999–2001). Of the 3,380 participants who underwent carotid ultrasound, 2,028 also underwent brain MRI, and neuropsychological (NP) testing; 57 were excluded due to prevalent clinical stroke, dementia, multiple sclerosis, or other neurological conditions that could affect MRI measures, yielding a study sample of n=1,971. The Institutional Review Board of Boston University Medical Center approved the study protocol and informed consent was obtained from all subjects.

Carotid Ultrasound

Carotid ultrasound was acquired by a certified sonographer, following a standard protocol.[20] Ultrasound studies were conducted on 3377 of 3532 (96%) of examination cycle 6 participants. An ultrasound 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) was used. Common carotid arteries were imaged with a 7.5MHz transducer while a 5 MHz transducer (-3dB point 6.2 MHz) was used to image the carotid bulb and the internal carotid arteries. Images were gated to an electrocardiogram and taken at end-diastole (peak of the R-wave).

Determination of carotid stenosis

One image was taken 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). The images were analyzed by one operator and over-read by an experienced radiologist (J.F.P.). Hemodynamically significant stenosis (≥50%) was defined by peak-systolic velocities ≥150 cm/s. If peak systolic velocities were lower than 150cm/sec, the degree of stenosis was divided in 3 groups by an experienced sonographer: 0 (no stenosis), 1–24%, and 25–49%. The side with more severe degree of ICA stenosis was used. The Framingham Heart Study intra-reader reproducibility of carotid stenosis ≥25% has been previously reported (Kappa value = 0.69).[21]

Measurements of IMT

IMT was measured bilaterally at 3 sites of the carotid arteries, CCA, carotid bulb and ICA. The mean of the maximal IMT measurements of the near and far walls (maximum 4 artery walls was used 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. Good intraclass correlation coefficients for the mean and maximum ICA and CCA IMT have been reported (0.74, 0.74, 0.86, and 0.90, respectively, based on 25 readings by two separate readers).[22]

Brain MRI Measurements

MRI scans were processed and analyzed by a neuroradiologist (CD) who was blinded to the subjects' demographic and clinical information, and to the carotid ultrasound measures. The acquisition and data processing of MRI scans has been described previously in detail.[23,24] In brief, the analyses were done using semi-automated measurements of pixel distributions based on mathematical modeling of MRI pixel intensity histograms. This was done for cerebral spinal fluid and brain (white matter and gray matter) to determine the optimal pixel intensity threshold to best distinguish cerebral spinal fluid from brain matter. All analyses were performed using a custom-designed image analysis package, QUANTA 6.2, operating on a Sun Microsystems (Santa Clara, CA) Ultra 5 workstation.

Determination of brain volume was done manually in coronal sections by outlining the intracranial cavity above the tentorium to determine the total cranial volume. Next, the skull and other non-brain tissues were removed from the image, and mathematical modeling was done to measure total brain volume. Of note, total brain volume excludes cerebrospinal fluid, and includes the supratentorial gray and white matter. The ratio of total brain volume to total cranial volume (TCBV) was used as a measure of brain volume to correct for head size differences.

Hippocampal volume was determined manually in coronal sections. The hippocampus was defined to include fields CA1 – CA4, in addition to the dentate gyrus and the subicular complex. The coronal 3D MR dataset was first resliced for alignment perpendicular to the long axis of the hippocampal formation in the left side, followed by manual outline of the hippocampus borders in the anterior to posterior direction, on 1.5mm thickness coronal slices, verifying the boundaries in the corresponding sagittal and axial views. Hippocampal volume was also analyzed as percent of total cranial volume.

The method used to determine abnormal white matter hyperintensities volume also has been published previously. The inter-rater reliabilities range between 0.90 and 0.94 for TCV, TCBV, and white matter hyperintensities, and intra-rater reliabilities average 0.98 across all measures.[25,26] The intra-rater reliability for both right and left hippocampus using the method described above is 0.98 for the right and 0.96 for the left hippocampus. LWMH was defined as log white matter hyperintensity areas >1 SD above the age-specific mean.[25,26] The presence or absence of SCI was determined manually by the operator based on the size (≥3 mm), location and imaging characteristics of the lesion (cerebrospinal fluid signal intensity on subtraction images (Proton density-T2) and hyperintense on T2-weighted images) and using previously described methods.[26]

Neuropsychological tests

Trained examiners administered a comprehensive NP test battery during a single 50-minute session using standard protocols. To reduce the number of individual test comparisons, individual tests were grouped in factors, using factor analysis.[27] This approach identified factors related to specific cognitive domains including verbal memory factor (Wechsler Memory Scale Logical Memory, Paragraph A subtest, Immediate and Delayed Recall), executive function factor (Halstead Reitan Trail Making Tests A & B) and non-verbal memory factor (Boston Naming Test, Wechsler Adult Intelligence Scale Similarities subtest and Hooper Visual Orientation Test). We selected these three factors as outcome measures to evaluate the relation with carotid atherosclerosis measures as prior studies suggest that in subjects with high vascular risk factor burden the pattern of cognitive impairment predominantly involves attention and psychomotor speed whereas verbal memory is affected mostly in subjects with amnestic cognitive impairment (such as seen in Alzheimer's disease). The non-verbal memory factor provides assessment of additional cognitive functions including language, abstract reasoning and visuoperceptual skills.

Covariates

Stroke risk factors, measured at the 6th examination cycle, were defined as follows: systolic blood pressure, recorded as the average of two physician measurements; use of an antihypertensive drug; current cigarette smoking; diabetes mellitus, defined as a random blood glucose of ≥126mg/dl, a previous diagnosis of diabetes or being on hypoglycemic medication or insulin; history of atrial fibrillation; and prior cardiovascular disease, including coronary heart disease, heart failure and peripheral arterial disease.[28]

Statistical Analysis

Multivariable regression analyses were used to determine the associations of carotid atherosclerosis measures with brain MRI markers and with NP factors. Separate analyses were performed to investigate each of the four measures of carotid atherosclerosis. Two cut points of carotid stenosis were evaluated. The cut point of 25% for carotid stenosis has been related to several vascular risk factors in previous carotid ultrasound studies in Framingham and other cohorts,[29] and the 50% threshold represents hemodynamically significant stenosis used in clinical practice. ICA IMT and CCA IMT were each log-transformed to normalize their skewed distributions and were standardized using z-scores, so that the regression analyses provide estimates of the effect of change in IMT of 1 SD.

Logistic regression analyses were performed for dichotomous outcomes (SCI, LWMH) and results are given as odds ratios with 95% confidence intervals. Linear regression analyses were used for continuous outcomes (TCBV, hippocampal volume, NP factors) and results are given as standardized beta coefficients (and their standard errors), reflecting, in standard deviation units, the effect of each measure of carotid atherosclerosis. All analyses were adjusted for age and sex, for stroke risk factors and the time interval between carotid ultrasound and acquisition of brain MRI and neuropsychological testing. In order to address possible confounding by the MRI markers, we performed additional analyses of NP outcomes adjusted for LWMH, TCBV and SCI. The effect of side of carotid atherosclerosis measures on NP performance was also evaluated (left versus right). All analyses were determined a priori and performed using Statistical Analyses System software version 9.1 (SAS Institute, Cary, NC). A two-sided p-value <0.05 was considered statistically significant.

Results

Baseline demographic data for the study participants at the 6th examination cycle are shown in Table 1. There were no significant differences in clinical characteristics of subjects included and excluded from the present analysis. Hippocampal volume measurements were available in a subset of 787 participants (mean age 64years, 52% women) who were significantly older than those without hippocampal volume measurements, but did not differ in any of the other stroke risk factors. Carotid artery stenosis ≥25% was observed in 289 participants (14.7%) and carotid stenosis ≥50% in 35 participants (1.8%). In brain MRI we observed LWMH in 306 participants (15.5%), and SCI in 206 participants (11%). Mean TCBV (SD) was 0.78 (0.03) and the mean hippocampal volume (SD) was 0.31 (0.04). Performance in neuropsychological testing according to carotid atherosclerosis measures is shown in Table 2.

Relation of carotid atherosclerosis measures and brain MRI markers (Table 2)

Carotid stenosis ≥25% and ≥50% were both related to SCI and LWMH and inversely related to TCBV. Participants with ≥25% stenosis had a higher prevalence of SCI (Odds Ratio [OR] 1.64, 95% confidence interval [CI] 1.14–2.36, p=0.007), a higher prevalence of LWMH (OR 1.76, 95% CI 1.27–2.45, p <0.001) and lower brain volume (β −0.21 ± SE 0.05, p <0.001). After adjusting for vascular risk factors and the time between acquisition of carotid ultrasound and MRI and NP testing, the associations remained significant with LWMH (OR 1.77, 95% CI 1.25–2.53, p=0.001) and brain volume (β β − 0.11 ± SE 0.06, p=0.04), but not with SCI.

Carotid stenosis ≥50% was also associated with an increased prevalence of SCI (OR 3.07, 95% CI 1.46–6.42, p=0.003), and of LWMH (OR 2.26, 95% CI 1.06–4.80, p=0.03), and with lower brain volume (β −0.28 ± SE 0.14, p=0.047). After the full multivariable adjustment, carotid stenosis ≥50% was associated with SCI (OR 2.53, 95% CI 1.17 – 5.44, p=0.02), and with LWMH (OR 2.35, 95% CI 1.08–5.13, p=0.03).

We observed that ICA IMT was significantly associated with a higher prevalence of SCI (OR 1.33, 95% CI 1.14 – 1.55, p<0.001), and LWMH (OR 1.23, 95% CI 1.07 – 1.42, p=0.003) and with lower brain volume (β −0.10± SE 0.02, p<0.001). All of the associations above remained significant when using the full multivariable adjusted model, with the increase in odds of having LWMH for each increase of 1 SD age in log-transformed baseline ICA IMT value, OR=1.19 (95% CI 1.03 – 1.38) and with brain volume decreasing by 0.05 per 1SD increase in log-transformed baseline ICA IMT value (SE 0.02, p=0.02). Common carotid artery IMT was also associated with higher prevalence of SCI (OR 1.20, 95% CI 1.03 –1.41, p=0.02) and with lower brain volume (β −0.06 ± SE 0.02, p=0.003), but these associations were no longer significant in the full multivariable adjusted model.

Neither carotid stenosis, nor IMT were associated with hippocampal volume, possibly due to the smaller sample size (N=787) with available hippocampal volume measurements.

Relation of carotid atherosclerosis measures and NP Factors (Table 2 and Table 3)

Carotid stenosis ≥25% was associated with poorer performance on the executive function factor (β −0.08 ± SE 0.03, p=0.002) and non-verbal memory factor (β −09 ± SE 0.03, p=0.001) but not with the verbal memory factor. After full multivariable adjustment there was a trend for association with poorer performance on verbal memory and non-verbal memory factors, but the associations did not reach statistical significance. Carotid stenosis ≥ 50% was associated with poorer performance only on the executive function factor (β −0.42 ± SE 0.18, p=0.02). After the full multivariable adjustment, the association remained significant with persons with carotid stenosis ≥50% scoring a mean of 0.39 SD lower as compared to those with stenosis <50% (p<0.03). There was no significant association of carotid stenosis ≥ 50% with performance on verbal memory and non-verbal memory factors.

Higher ICA IMT was associated with poorer performance on the executive function factor (β −0.08 ± SE 0.03, p=0.002) and the non-verbal memory factor (β −0.09 ± SE 0.03, p=0.001). After full multivariable adjustment, the association became significant for the verbal memory factor (β −0.06± SE 0.03, p=0.047), remained significant for the non-verbal memory factor (β −0.08 ± SE 0.03, p=0.005), and was borderline for the executive function factor (β −0.05 ± SE 0.03; p=0.053). CCA IMT was not associated with any of the cognitive measures.

Additional adjustment for the MRI markers (SCI, LWMH, TCBV and hippocampal volume), which have been associated with cognitive impairment, did not alter the results (data not shown). We did not observe an effect of side (left versus right) in the association of carotid atherosclerosis measures and cognitive performance.

Discussion

Carotid atherosclerosis considered clinically asymptomatic was significantly related to poorer cognitive performance and to subclinical brain MRI indices of ischemia. These associations were significant even after adjusting for contemporaneously measured vascular risk factors, suggesting that carotid atherosclerosis measures provide additional information over vascular risk factors in the relation to cognitive performance. MRI markers did not explain the association, suggesting that the association of carotid atherosclerosis with cognitive function was not confounded by structural brain changes. Carotid stenosis and IMT may represent past exposure to vascular risk factors, and therefore provide valuable information over vascular risk factors.

Relation of carotid atherosclerosis and MRI markers

Although it may be argued that carotid atherosclerosis measures and MRI indices of brain injury each reflect the effects of exposure to vascular risk factors and systemic atherosclerosis, the results of our study suggest that carotid ultrasound measures of atherosclerosis are independent markers of brain MRI changes.

Our data adds to findings of prior studies such as the Cardiovascular Health Study (CHS) (mean age 75 years), by using highly reliable techniques to quantitatively measure brain and white matter hyperintensity volumes. We expand previous results to a younger cohort (mean age 58 years), including men and women, with lower prevalence of vascular risk factors, in addition to using milder degrees of carotid stenosis. Investigators of the CHS evaluated the relation of carotid stenosis and IMT to MRI markers including SCI, WMH, sulcal and ventricular enlargement.[30] Using subjective grading scales of brain MRI the authors found that carotid IMT and stenosis related to the MRI markers after adjusting for vascular risk factors. The findings in our study are in agreement, suggesting that carotid atherosclerosis is likely a marker of morphometric brain changes assessed by MRI.

SCI were more common in association with more severe degrees of atherosclerosis as reflected by a stronger association with stenosis ≥50% than with stenosis ≥25%. This is similar to findings in the CHS, in which subjects with stenosis had more MRI infarcts than those without.[30] Although the associations of CCA and ICA IMT with SCI were significant after adjusting for age and sex, only the association with ICA IMT remained significant after adjustment for vascular risk factors. This finding contrasts with the observations in the CHS, and suggests that vascular risk factors play a more important role in the relation of CCA IMT and SCI, as our cohort had lower prevalence of vascular risk factors than in the CHS.

The association of carotid atherosclerosis with decreased brain volume as measured in our study is a novel observation. Although it had been indirectly suggested by measures of sulcal widening and ventricular enlargement in the CHS,[30] we used volumetric quantitative measurement of brain volume, not reported previously in association with carotid atherosclerosis. We observed a 5% decrease in total brain volume per 1SD increase in log transformed ICA IMT after full multivariable adjustment. Given that few participants had hemodynamically significant stenosis ≥50% it is unlikely that significant hemodynamic reduction in cerebral flow was responsible; carotid atherosclerosis may be a marker of brain atrophy related to involvement of microcirculation, systemic atherosclerosis or other factors such as inflammation.[31]

IMT has been considered a subclinical marker of early atherosclerosis, although the relation with hypertension is complex, and increased IMT likely reflects effects of both processes. The observed association of increased ICA IMT with SCI, LWMH and decreased total brain volume suggests that the process of atherosclerosis is not “silent” in subclinical stages and the brain is affected during those phases. Whether aggressive evaluation and treatment of carotid atherosclerosis is useful to prevent the development of brain MRI changes or cognitive impairment is a question that cannot be answered with this study and deserves further attention. This is particularly relevant because of available therapies that may affect the atherosclerotic process in subclinical stages such as statins, which have been shown to reduce progression of IMT.[32,33] Our data suggests that IMT measured at the ICA may be a better marker of brain MRI changes than CCA IMT.

Relation of carotid atherosclerosis measures and cognitive performance

Carotid atherosclerosis was related to lower cognitive performance. Our data is supportive of findings in previous studies such as the CHS,[2] which found high grade (>75%) left but not right sided ICA stenosis and IMT related to poorer cognitive performance after adjusting for right side stenosis, vascular risk factors and demographic characteristics. Increased CCA IMT (fourth versus first quartiles) also was associated with lower cognitive performance, but no difference was found between the left and right sides. Similar to the results in the CHS cohort, we found that carotid stenosis and IMT were associated with poorer cognitive performance. More severe stenosis (≥50%) was associated with poorer performance, while milder stenosis (≥25%) did not reach statistical significance. We did not observe a different relation between left and right-sided measures and cognitive performance, even though there was an effect of side in the relation of carotid stenosis and LWMH.

In addition, data from our study suggest that site of IMT measurement is important and that ICA IMT may be a better marker of poorer cognitive performance than CCA IMT. In contrast to prior studies, including the CHS[2], ARIC[9], Tromsø[1] and Rotterdam[3] studies, we separately evaluated the relation of IMT measured in the CCA and ICA to cognitive performance. Increased ICA IMT was associated with poorer performance but not CCA IMT, after adjusting for vascular risk factors. Prior studies have shown that site of measurement of IMT may be relevant as associations with cardiovascular events and vascular risk factors may vary depending on the site of measurement.[10] Atherosclerosis develops earlier in vessel bifurcations and origins such as the carotid bulb and proximal ICA. As opposed to the CHS results, the association of increased IMT with poorer cognitive performance in our study persisted after adjustment for vascular risk factors. As noted earlier the Framingham Offspring cohort had a lower prevalence of vascular risk factors, thus it may be possible that vascular risk factors explain the relation of CCA IMT but not ICA IMT with cognitive performance.

Since it may be argued that the association of carotid atherosclerosis with poorer cognitive performance is mediated by brain structural changes such as those assessed with brain MRI we also evaluated the effect of MRI markers on the association of carotid atherosclerosis and cognitive performance. The associations remained significant after adjusting for the MRI measures, which supports that carotid atherosclerosis, is an independent marker of poor cognitive performance.

We confirm the findings of prior studies, expanding the results by using a larger sample, and quantitative assessment of MRI markers. The CHS,[2] found an association of high grade left ICA stenosis and poorer cognitive performance in a subset of subjects without brain infarct demonstrated by MRI, but did not evaluate the presence of white matter hyperintensities or brain volume. The Tromsø Study[1] was limited by small sample of subjects with brain MRI.

The precise underlying mechanism explaining the relation of carotid atherosclerosis and cognitive performance in our study is unclear, but as in the case of MRI markers, it is unlikely that hemodynamic effects explain the findings as most of the participants had lower grades of stenosis. Our results suggest that carotid IMT and stenosis may have different effects in cognitive performance.

Strengths and Limitations

The present study has several strengths including: a large sample size; inclusion of both men and women; a middle aged population; the community-based sample, use of reproducible quantitative carotid ultrasound techniques, as well as quantitative brain MRI techniques and interpretation of ultrasound and brain MRI imaging data by separate experienced readers, independent of one another and blinded to all clinical data. Our data expands the results of prior studies, and support previous observations.

One of the limitations of our study is the assessment of carotid, MRI and NP measures at single time-points. As a result, we cannot draw conclusions regarding the cause effect relationship between carotid atherosclerosis measures, brain MRI markers and cognitive performance. In addition, carotid measures were assessed an average of 4 years prior to brain MRI and NP measures, and hence, may have changed in the interim. We attempted to address the non-contemporaneous assessment by adjusting for the interval, and the results were largely unchanged. Another limitation is the fact that Framingham Heart Study participants are of predominantly white, European descent; thus, generalization of our findings to other ethnic and racial groups is limited and requires additional study. We acknowledge that we did not account for multiple statistical testing, but derive some reassurance from the consistency of the findings across correlated phenotypes and with the prior literature. Obviously, the results of this study should not be taken as justification for surgical intervention in patients with asymptomatic carotid stenosis.

Conclusion

Carotid atherosclerosis markers are associated with subclinical indices of brain ischemia and aging assessed via volumetric brain MRI, and with poorer cognitive performance after adjusting for standard vascular risk factors in a community-based sample of middle-aged adults, free of clinical stroke and dementia. Further analysis of our data suggests that carotid atherosclerosis may have effects on cognition independent of MRI changes. Our findings are consistent with regional variation in the relation of carotid atherosclerosis measures, brain MRI markers of ischemia and cognitive performance and support the notion that carotid atherosclerosis in subclinical stages is not truly silent.

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TABLE 1

Characteristics of study sample, sex-specific subsamples and excluded subjects

	Included Men and Women (n=1971)	Excluded Men and Women (n=1561)
Clinical Characteristics		
Women, %	53%	53%
Age at Exam 6, yrs, mean [SD]	58±10	61±10
Age at MRI, yrs, mean [SD]	62±9	
Systolic blood pressure, mm Hg, mean [SD]	126±18	131±19
Diabetes mellitus, %	8.7%	12.3%
Atrial fibrillation, %	2.2%	4.5%
Electrocardiographic LVH, %	0.3%	1.2%
Current smokers, %	13.6%	17.4%
Hypertension treatment, %	24.1%	33.8%
Prevalent cardiovascular disease, %	7.5%	13.9%
Carotid Ultrasound Measures		
Carotid stenosis ≥25% (%)	14.7%	
Carotid stenosis ≥50% (%)	1.8%	
MRI measures		
Silent Cerebral Infarcts, %	11%	
Large White Matter Hyperintensity volume, %	15.5%	
Total Cerebral Brain Volume (mean ± SD)	0.78 ± 0.03	
Hippocampal Volume, N=787 (mean ± SD)	0.31 ± 0.04	

TABLE 2

Relation of carotid atherosclerosis measures, and MRI measures and Neuropsychological Factors performance

	Carotid Stenosis*		Log (IMT)*		Carotid Stenosis†		Log (IMT)†	
	≥25%	≥50%	CCA	ICA	≥25%	≥50%	CCA	ICA
MRI measures								
SCI	**1.64 [1.14–2.36]** ‡	**3.07 [1.46–6.42]** ‡	**1.20 [1.03–1.41]** §	**1.33 [1.14–1.55]** //	1.35 [0.92–1.98]	**2.53 [1.17–5.44]** §	1.09 [0.93–1.29]	**1.21 [1.03–1.43]** §
LWMH	**1.76 [1.27–2.45]** //	**2.26 [1.06–4.80]** §	1.10 [0.95–1.26]	**1.23 [1.07–1.42]** ‡	**1.77 [1.25–2.53]** //	**2.35 [1.08–5.13]** §	1.09 [0.94–1.27]	**1.19 [1.03–1.38]** §
TCBV	**−0.21±0.05** //	**−0.28±0.14** §	**−0.06±0.02** ‡	**−0.10±0.02** //	**−0.11±0.06** §	−0.18±0.14	−0.02±0.02	**−0.05±0.02** §
Hippocampal volume	−0.01±0.10	0.01±0.23	−0.05±0.04	−0.01±0.04	0.09±0.1	0.11±0.28	−0.02±0.04	0.03±0.04
Neuropsychological Factors								
Verbal memory	−0.08±0.07	0.03±0.17	0.02±0.03	−0.03±0.03	−0.12±0.07	−0.02±0.18	0.01±0.03	**−0.06±0.03** §
Executive function	**−0.16±0.07** §	**−0.42±0.17** §	−0.01±0.03	**−0.08±0.03** ‡	−0.09±0.07	**−0.39±0.18** §	0.02±0.03	−0.05±0.03
Non-verbal memory	**−0.14±0.07** §	−0.15±0.17	−0.02±0.03	**−0.09±0.03** //	−0.12±0.07	−0.13±0.18	−0.01±0.03	**−0.08±0.03** ‡

* Adjusted for age and sex

† Additionally adjusted for time to MRI/NP, diabetes, smoking, hypertension treatment, systolic blood pressure and cardiovascular disease. P value shown when significant

§ p<.05

‡ p<.01

// p<.001.

SCI= Silent cerebral infarcts; LWMH= Large white matter hyperintensities (>1 SD age specific); TCBV= total brain volume (cranial to brain volume ratio). Effects on SCI and LWMH are Odds Ratio [95 % Confidence Interval] and on TCBV, Hippocampal volume and Neuropsychological factors Standardized Beta correlation coefficient [Standard Error]. IMT=Intima-media thickness. ICA=Internal carotid artery. CCA=common carotid artery.

TABLE 3

Carotid atherosclerosis measures and Neuropsychological Factors performance adjusted for MRI measures

	Carotid Stenosis*		Log (IMT)*		Carotid Stenosis †		Log (IMT) †	
	≥ 25%	≥ 50%	CCA	ICA	≥ 25%	≥ 50%	CCA	ICA
Verbal memory	−0.09±0.07	0.01±0.17	0.01±0.03	−0.04±0.03	−0.12±0.07	−0.03±0.18	0.01±0.03	**−0.06±0.03** §
Executive function	−0.11±0.07	**−0.35±0.17** §	0.001±0.03	**−0.06±0.03** §	−0.06±0.07	**−0.34±0.17** §	0.02±0.03	−0.04±0.03
Non-verbal memory	−0.12±0.07	−0.13±0.17	−0.02±0.03	**−0.08±0.03** ‡	−0.10±0.07	−0.12±0.18	−0.01±0.03	**−0.08±0.03** ‡

*Adjusted for age and sex

†Additionally adjusted for time to MRI/Neuropsychological testing, diabetes, smoking, hypertension treatment, systolic blood pressure and cardiovascular disease. Effects on neuropsychological factors are Standardized beta correlation coefficient [Standard Error]. IMT=Intima-media thickness. ICA=Internal carotid artery. CCA=common carotid artery. P value shown when significant.

§ $p<.05$

‡ $p<.01$.