

Carotid Intima-Media Thickness Is Associated With White Matter Hyperintensities

The Northern Manhattan Study

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Background and Purpose—Brain white matter hyperintensities (WMH) have been associated with increased risk of stroke, cognitive decline, and dementia. WMH can be a manifestation of small vessel disease, although the total microvascular contribution to multifactorial WMH pathophysiology remains unknown. We hypothesized a possible relationship between carotid intima-media thickness (cIMT), an ultrasound imaging marker of subclinical vascular disease, and brain WMH in a multiethnic, elderly stroke-free community-based cohort.

Methods—We evaluated the relationship between cIMT and WMH in the population-based Northern Manhattan Study, among individuals free of stroke. We used linear regression to examine the association of continuous measures of cIMT with quantitatively derived WMH volume, as a proportion of cranial volume, measured from fluid-attenuated inversion recovery magnetic resonance imaging while adjusting for sociodemographics, lifestyle, and vascular risk factors.

Results—In a cohort of 1229 participants (mean age, 71±9 years; 60% women, 15% White; 18% Black; 65% Hispanics), the mean cIMT was 0.71±0.08 mm and the median log-transformed WMH volume was 0.36 (interquartile range, 0.21–0.76). In a multivariable model, larger cIMT was significantly associated with greater WMH volume ($\beta=0.046$ per SD cIMT; $P=0.04$). Age and race/ethnicity were significant modifiers (P for age, 0.02; and P for race/ethnicity, 0.04). cIMT was associated with WMH volume in participants 70 years or older ($\beta=0.088$ per SD cIMT; $P=0.01$) and among Hispanics ($\beta=0.084$ per SD cIMT; $P=0.003$).

Conclusions—Larger cIMT was associated with greater burden of cerebral WM lesions independently of demographics and traditional vascular risk factors, particularly among elderly and Hispanic participants, who are at high risk for stroke and cognitive decline. (*Stroke*. 2018;49:304-311. DOI: 10.1161/STROKEAHA.117.018943.)

Key Words: carotid arteries ■ carotid intima-media thickness ■ dementia ■ risk factors ■ white matter

Cerebral white matter hyperintensities (WMH) are lesions detected on magnetic resonance imaging (MRI) based on their bright, increased signal appearance on T2-weighted and fluid-attenuated inversion recovery MRI.¹ Fixed pathology specimens that correspond to WMH on MRI show a pathological continuum, from no change to perivascular myelin loss with gliosis and areas of infarction.^{1,2} WMH are suggested to be a manifestation of small vessel disease^{2,3} although real pathophysiology of WMH is likely heterogeneous and largely remains unknown.

Although WMH were once thought to be asymptomatic, incidental findings,⁴ WMH are highly prevalent in subjects

with cognitive impairment, vascular dementia, and Alzheimer disease.^{5–7} WMH are also more prevalent in patients with stroke.⁸ Aging,⁹ hypertension,¹⁰ homocysteine,¹¹ and several genetic factors¹² have been identified as significant contributors to WMH burden.

The association of systemic subclinical atherosclerotic changes with cerebral small vessel disease and increased burden of WMH has been suggested.¹³ Carotid intima-media thickness (cIMT) is a marker of subclinical atherosclerosis and a predictor of stroke and cardiovascular disease.¹⁴ cIMT has also been associated with subjective memory complaints,¹⁵ vascular dementia,⁷ and increased risk of neurodegenerative

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disease including Alzheimer¹⁶ and Parkinson diseases.¹⁷ However, most of these studies were conducted in Caucasians or in small samples of participants.

Based on the hypothesis that increased cIMT would be associated with greater burden of WMH, the aims of this analysis, therefore, were to determine the relationship between cIMT and WMH in an elderly, stroke-free, community dwelling cohort consisting of men and women from Hispanic, non-Hispanic black and non-Hispanic white race/ethnic backgrounds.

Materials and Methods

Study Population

All data analytic methods and study materials are not available to other researchers because eligible patients did not give consent to share personal information. The NOMAS (Northern Manhattan Study) is an ongoing prospective cohort study of incident stroke and cognitive decline. Study design, methods, and determination of risk factors used in this study have been described previously.¹⁸ Briefly, race/ethnicity was based on self-identification through interview questions modeled after the US census.¹⁹ In 2003, NOMAS participants who remained stroke-free and who were 50 years or older were offered to participate in the NOMAS MRI substudy. The final NOMAS MRI substudy sample consists of 1290 subjects. Of these, 1229 individuals had both MRI and carotid ultrasound measurements performed and represented the final sample for these analyses. Carotid ultrasound was performed on the same day (39%) or within a mean of 2±2 years of MRI.

The study was approved by the Institutional Review Boards of Columbia University Medical Center and the University of Miami Miller School of Medicine. All participants provided written informed consent.

Carotid Ultrasound

Carotid ultrasound was performed according to the standard scanning and reading protocols by a trained and certified sonologist and published previously.²⁰ cIMT measurements were performed outside the areas of plaque as recommended by the consensus statement.²¹ cIMT was measured using an automated computerized edge tracking software M'Ath (Intelligence in Medical Technologies, Inc, Paris, France), which improved precision and reduced variance of the measurements.²² The carotid artery segments were defined as follows: (1) near and far wall of the segment extending from 10 to 20 mm proximal to the tip of the flow divider into the common carotid artery; (2) near and far wall of the carotid bifurcation beginning at the tip of the flow divider and extending 10 mm proximal to the flow divider tip; and (3) near and far wall of the proximal 10 mm of the internal carotid artery. The composite IMT was calculated as the means of near and far wall IMT of all carotid segments. We previously reported excellent reliability in our measures of cIMT.²⁰

Measurement of WMH Volume

Participants were enrolled in the MRI substudy between 2003 and 2008. Brain images were obtained with a 1.5 T MRI (Philips Medical Systems, Best, the Netherlands). Quantitative analyses of WMH volume (WMHV) were obtained with the Quantum 6.2 package run on a Sun Microsystems Ultra 5 workstation.¹ Fluid-attenuated inversion recovery images were quantified for WMHV as described previously.^{23,24} Briefly, after image segmentation of the brain from the cerebral spinal fluid was performed, the pixel intensity histogram of the brain-only fluid-attenuated inversion recovery image was modeled as a log normal distribution, and pixel intensities 3.5 SDs above the mean were considered as WMH.²⁵ To correct for head size, we expressed WMHV as percent total intracranial volume, intracranial volume [WMHV=(WMH/intracranial volume)×100] and log transformed this measure (log-WMHV) to normalize the distribution.²⁶

Risk Factors

The associations of composite IMT with demographics (age, sex, race/ethnicity, and education), traditional vascular risk factors, and lifestyle factors have been extensively analyzed in NOMAS.²⁷ Standard techniques were used to measure height, weight, and cholesterol levels, and their continuous measures were used in the analyses.²⁷ Hypertension was defined as a blood pressure ≥140/90 mm Hg (based on the average of 2 measurements during), the patient's self-reported hypertension, or use of antihypertensive medications. Diabetes mellitus was defined as a fasting blood glucose ≥126 mg/dL, self-reported diagnosis, or self-reported use of insulin or hypoglycemic medications. Education was self-reported and categorized as completed high school or not. We defined leisure-time physical activity categorically as no exercise to light exercise less than weekly versus moderate to heavy weekly exercise. Reported alcohol use was categorized as moderate consumption (>1 drink per month up to 2 drinks per day) in the past year compared with other amounts (heavy drinkers [>5 drinks per week] constituted <4% of total subjects). Smoking was categorized as never, former, and current smoking (within the past year).

Statistical Analysis

For participant characteristics, we summarized continuous variables as means with SD and presented categorical variables as frequencies with percentages. For each categorical covariate, we used a *t*-test or *F*-test to assess the mean differences in composite IMT and WMHV. We performed multivariable linear regression to evaluate the association between composite IMT (continuously) and WMHV (natural log transformed) with 3 sequential models. We first examined the association adjusting for age, sex, race/ethnicity, and education in model 1, and then additionally adjusted for health behaviors (smoking, moderate alcohol drinking, leisure-time exercise) and body mass index in model 2, and further adjusted for vascular risk factors (hypertension, diabetes mellitus, and hypercholesterolemia) in model 3. In model 4, we further adjusted for carotid diastolic diameter. We also tested for potential effect modification by demographic and vascular factors by including interaction terms for each covariate in the full model and conducted stratified analyses for those variables with significant interactions. Age was a significant effect modifier and we stratified age into 2 strata, <70 years of age, and >70 years. This age cutoff was close to the mean of the age distribution in our cohort. As the secondary analyses, we examined the association of IMT at the specific carotid segment with WMHV and further adjusted for intraluminal common carotid artery (CCA) diastolic diameter in the regression model to test if the IMT association was attenuated. We performed all the analyses using SAS (version 9.4, SAS Institute, NC). A *P* value <0.05 was considered statistically significant for all analyses.

Results

Demographic characteristics for the study population (n=1229) are included in Table 1. Overall, the mean age was 71±9 years and 60% of the subjects were women; 65% were Hispanic, 18% non-Hispanic black, and 15% non-Hispanic white. Overall, the median WMHV was 0.36 (range, 0.21–0.76) and the mean of composite IMT was 0.71±0.08 mm. In univariate analyses, risk factors significantly associated with WMHV and composite IMT were age, race/ethnicity, smoking, moderate alcohol drinking, and hypertension (Table 1). Sex and diabetes mellitus were associated only with composite IMT, whereas body mass index only associated with WMHV (Table 1).

Table 2 shows the association between composite IMT and WMHV after adjusting for demographics (model 1: β=0.042 per SD composite IMT; *P*=0.079), added behaviors (model 2: β=0.050 per SD composite IMT; *P*=0.034), and added

Table 1. Sample Characteristics

	n	%	WMHV (% TIV)		Composite IMT	
			Median (IQR)	P Value	Mean±SD	P Value
All	1229	100.0	0.36 (0.21–0.76)		0.71±0.08	
Age at MRI (mean±SD, 71±9)				<0.0001		<0.0001
<70	588	47.8	0.25 (0.17–0.43)		0.70±0.08	
≥70	641	52.2	0.56 (0.30–1.15)		0.73±0.09	
Sex				0.18		<0.0001
Female	737	60.0	0.38 (0.22–0.77)		0.70±0.08	
Male	492	40.0	0.35 (0.19–0.72)		0.72±0.09	
Race/ethnicity				<0.0001		0.01
Non-Hispanic white	184	15.0	0.38 (0.20–0.67)		0.72±0.09	
Non-Hispanic black	217	17.7	0.54 (0.28–1.19)		0.72±0.08	
Hispanic	799	65.0	0.33 (0.20–0.68)		0.71±0.08	
Other	29	2.4	0.41 (0.22–0.79)		0.69±0.05	
Smoking				0.002		0.01
Never	584	47.5	0.36 (0.22–0.74)		0.71±0.08	
Former	529	43.0	0.34 (0.20–0.71)		0.72±0.09	
Current	116	9.4	0.54 (0.25–1.04)		0.71±0.08	
Moderate alcohol drinking				<0.0001		0.02
No	815	66.3	0.39 (0.23–0.81)		0.71±0.08	
Yes	414	33.7	0.32 (0.18–0.62)		0.72±0.09	
Leisure-time exercise				0.10		0.66
No	535	43.5	0.34 (0.20–0.70)		0.71±0.08	
Yes	694	56.5	0.38 (0.22–0.80)		0.71±0.08	
BMI (mean±SD, 28±5)				0.003		0.97
<25	298	24.2	0.45 (0.23–0.95)		0.71±0.09	
25–<30	519	42.2	0.36 (0.22–0.77)		0.71±0.08	
≥30	412	33.5	0.33 (0.19–0.64)		0.71±0.08	
Hypertension				<0.0001		0.01
No	343	27.9	0.29 (0.17–0.51)		0.70±0.08	
Yes	886	72.1	0.40 (0.23–0.82)		0.72±0.08	
Diabetes mellitus				0.06		0.04
No	957	77.9	0.35 (0.20–0.72)		0.71±0.08	
Yes	272	22.1	0.42 (0.24–0.84)		0.72±0.09	
Hypocholesteremia				0.59		0.10
No	751	61.1	0.35 (0.21–0.82)		0.71±0.08	
Yes	478	38.9	0.38 (0.22–0.69)		0.72±0.09	

BMI indicates body mass index; IMT, intima-media thickness; IQR, interquartile range; MRI, magnetic resonance imaging; TIV, total intracranial volume; and WMHV, white matter hyperintensity volume.

vascular risk factors (model 3: $\beta=0.046$ per SD composite IMT; $P=0.049$); sequential adjustment of covariates did not significantly affect the association.

Age was strongly associated with WMHV in all models ($\beta\geq 0.046$; $P<0.0001$ for all 3 models). Compared with non-Hispanic whites, both non-Hispanic blacks and Hispanics had greater WMHV in all models. In fully adjusted model

3, smoking, body mass index, and hypertension were significantly associated with WMHV (Table 2).

Table 3 reports the association between composite IMT and WMHV stratified by age (P for interaction 0.02) and race/ethnicity (P for interaction 0.04). The association was significant among individuals age ≥ 70 years ($\beta=0.088$ per SD composite IMT; $P=0.01$) and among Hispanics ($\beta=0.084$ per SD

Table 2. Association Between Composite IMT and WMHV After Adjusting for Demographics, Behaviors, and Vascular Factors

	Model 1			Model 2			Model 3			Model 4		
	β	SE	PValue	β	SE	PValue	β	SE	PValue	β	SE	PValue
Composite IMT, per SD*	0.042	0.024	0.079	0.050	0.024	0.034*	0.046	0.024	0.049*	0.028	0.025	0.276
Age (>70 vs <70)	0.049	0.003	<0.0001*	0.048	0.003	<0.0001*	0.046	0.003	<0.0001*	0.044	0.003	<0.0001*
Female vs male	-0.046	0.049	0.353	-0.040	0.052	0.433	-0.040	0.051	0.439	-0.080	0.054	0.139
Black vs white	0.390	0.084	<0.0001*	0.335	0.085	<0.0001*	0.294	0.085	0.001*	0.324	0.087	0.0002*
Hispanic vs white	0.217	0.070	0.002*	0.192	0.072	0.007*	0.150	0.072	0.038*	0.160	0.075	0.032*
Current smoking vs never				0.305	0.086	0.0004*	0.302	0.086	0.0004*	0.286	0.087	0.001*
Former smoking vs never				-0.046	0.051	0.364	-0.043	0.051	0.402	-0.038	0.052	0.460
Moderate drinking				-0.109	0.053	0.040*	-0.101	0.053	0.055	-0.088	0.054	0.103
Leisure-time exercise				0.022	0.049	0.653	0.018	0.049	0.706	0.043	0.050	0.389
BMI, kg/m ²				-0.008	0.005	0.104	-0.012	0.005	0.020*	-0.013	0.005	0.010*
Hypertension							0.172	0.056	0.002*	0.144	0.057	0.012*
Diabetes mellitus							0.077	0.058	0.189	0.044	0.060	0.459
Hypercholesterolemia							-0.081	0.049	0.100	-0.065	0.050	0.195
Diastolic CCA diameter										0.095	0.027	0.001*

BMI indicates body mass index; CCA, common carotid artery; IMT, intima-media thickness; and WMHV, white matter hyperintensity volume.

*Most significant associations.

composite IMT; $P=0.003$) but not among those younger than 70 years of age, non-Hispanic blacks or non-Hispanic whites (Figure [A] and [B]). We did not observe significant interactions between composite IMT and hypertension, diabetes mellitus, or other vascular risk factors on WMHV.

In the secondary analyses, increased IMT was associated with greater WMHV across all carotid segments. The association was significant for IMT at bifurcation ($P<0.05$), marginally significant at CCA ($0.05<P<0.1$), and not significant at internal carotid artery ($P>0.05$; Table I in the [online-only Data Supplement](#)). We have also additionally adjusted for the intraluminal CCA diameter. In this model (model 4; Table 2), CCA diameter was a significant contributor to WMHV, whereas composite IMT (Table 2) or segment specific IMT (Table I in the [online-only Data Supplement](#)) were no longer significantly associated with WMHV.

Discussion

In this multiethnic community study, we report a significant association between cIMT and brain WMH that is independent of hypertension and other vascular and lifestyle factors. The effect of increased composite IMT on greater burden of WMH was particularly prominent among those 70 years of age or older and among Hispanics. Our findings suggest the possible role of subclinical atherosclerosis in the pathophysiology of WMH among the elderly that may not be fully mediated by hypertension and other traditional vascular risk pathways. Among vascular risk factors, a significant association with increase in WMH was present for age, hypertension, and smoking. We also expand the importance of the relationship among subclinical phenotypes of atherosclerosis, as markers for vascular accidents, and Hispanics, the fastest growing population in the United States, who are particularly vulnerable to vascular brain damage, stroke, and cognitive decline.²⁸

cIMT has been associated with brain MRI changes and cognitive impairment in several prior studies.^{29,30} The Cardiovascular Health Study reported a strong and consistent relationship between increased cIMT and MRI abnormalities such as ventricular enlargement, sulcal widening, and increased WM signal intensity.³¹ Similar findings were observed in the Framingham Offspring Cohort, composed of a relatively younger population with a mean age of 58 years.³² Other studies conducted in elderly hypertensive patients with subjective memory complaints,¹⁵ and more recently in elderly patients with Alzheimer disease and vascular dementia,⁷ demonstrated the positive association between cIMT and leukoaraiosis on MRI. These studies suggested that increased cIMT may be a marker of intracranial arterial small vessel disease or

Table 3. Association Between Composite IMT and WMHV Stratified by Age and Race/Ethnicity

	β (per SD Composite IMT)	SE	PValue*	PValue for Interaction*
Age<70 y	-0.001	0.033	0.977	0.022
Age≥70 y	0.088	0.034	0.010†	
White	-0.040	0.057	0.478	0.043
Black	0.000	0.066	0.994	
Hispanic	0.084	0.028	0.003†	
Other	0.076	0.391	0.849	

IMT indicates intima-media thickness; and WMHV, white matter hyperintensity volume.

*Adjusted for sex, smoking status, moderate drinking, leisure-time exercise, body mass index, hypertension, diabetes mellitus, hypercholesterolemia, age and race/ethnicity if applicable.

†Most significant associations.

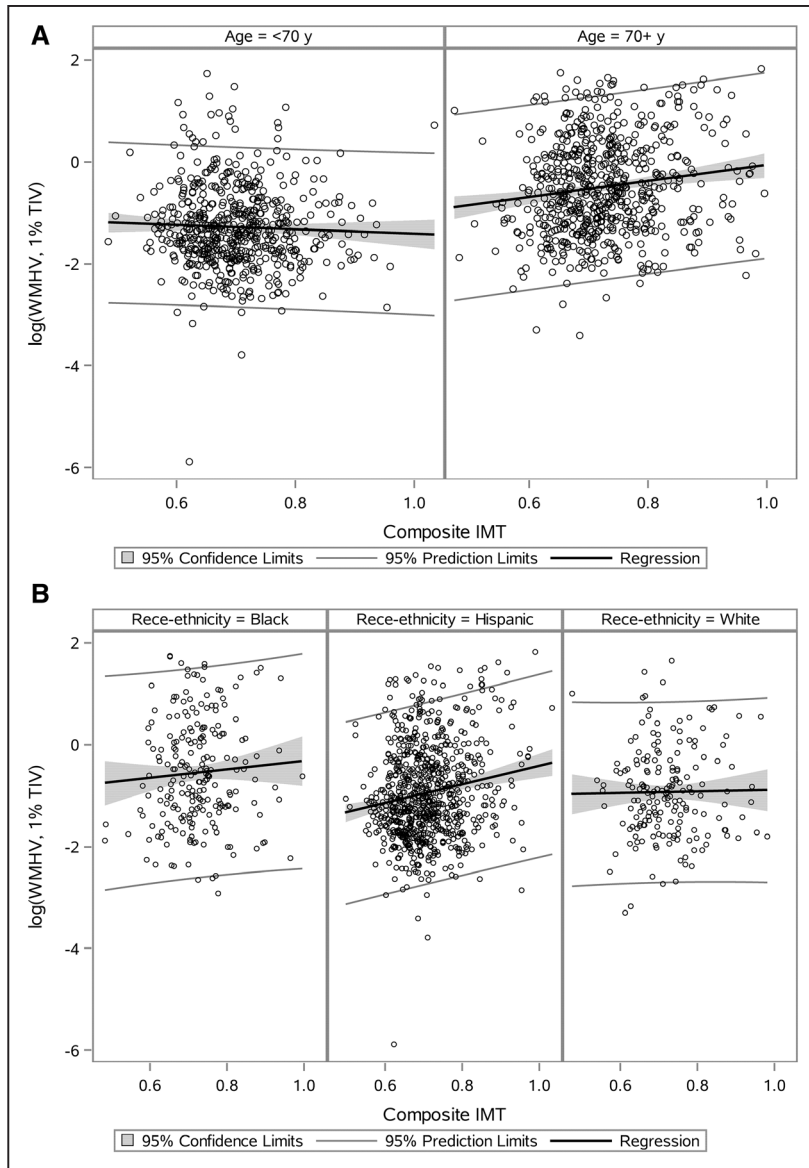


Figure. Regression plot for logarithm-transformed white matter hyperintensity volume (WMHV; as % of total cranial volume [TCV]) against carotid intima-media thickness (cIMT; mm): **(A)** by age (<70 y, ≥70 y), **(B)** by race/ethnicity (Hispanic, non-Hispanic black, and non-Hispanic white).

large arterial wall changes that alter the cerebral microcirculation and produce diffuse hypoperfusion with chronic brain hypoxia, that in turn ultimately trigger neurodegenerative changes. Further supporting this evidence, increase in cIMT has been demonstrated in a cohort of hypertensive patients as a significant predisposing factor for lacunar infarction in comparison to intracerebral hemorrhage.³³ Lacunar infarction has been in turn associated with increase in WMH,³¹ suggesting a common underlying cerebral vasculopathy that could be related to increased cIMT. Moreover, increased cIMT has been strongly associated with recurrent ischemic stroke independent of traditional vascular risk factors.^{34,35} This suggests a potentially important role of cIMT in neurodegenerative diseases, most likely through small vessel arteriopathy and chronic brain hypoperfusion.

Lower cerebral blood flow is associated with subcortical brain atrophy leading to WM lesions³⁶ and increasing in cIMT has been associated with lower cerebral blood flow velocity.³⁷ The link between cIMT and cerebral blood flow may explain, at least in part, the atherosclerotic mediated damage leading to WMH.

The relation between cIMT and WMHV in our study was age dependent. Increased cIMT was significantly associated with increased burden of WM disease among individuals 70 years of age but not among those younger than 70 years of age. This age-related association may be dependent on pathophysiological processes that characteristically increase with age.³⁸ WMH seen on MRI correspond primarily to areas of ischemic demyelination, gliosis, and to clinically silent infarcts often seen in elderly people.² Atherosclerotic changes in large and small vessels are also age dependent.³⁹ Several molecular mechanisms are proposed to link atherosclerosis with WM abnormalities, although the exact pathophysiological causation is unclear.² Postmortem studies have indicated that WMH seen on MRI scans are associated with degenerative changes in arterioles, such as hyalinization and cellular wall thickening, suggesting that cerebral arteriosclerosis may be among major factors in the pathogenesis of WMH.⁴⁰ Cerebral arteries may be affected by endothelial shear stress locally but also by the age-related stiffness of

systemic arteries that convey reduced wave reflection and facilitate transmission of excessive pulsatile energy into the cerebral microcirculation.¹³ The cerebral microcirculation is particularly sensitive to increased pulsatile wave energy that ultimately leads to microvascular damage and WMH.⁴¹ The molecular basis of this process is likely mediated by the upregulation of proinflammatory factors (eg, angiotensin II, platelet-derived growth factor, and endothelin-1) causing increased intima-medial thickness, especially in the carotid bifurcation and in the cerebral arteries susceptible to turbulent flow.⁴² These processes are associated with degenerative neuropathology and reactive astrogliosis from the resulting hypoperfusion in the periventricular WM that may correspond to WMH on MRI.⁴³

We found significant positive and independent associations between current smoking and hypertension and WMH. Although these vascular risk factors are also associated with increased cIMT^{44,45} they did not attenuate the association between cIMT and WMH. The mechanism linking increased cIMT to WM burden, according to our results, therefore is not directly dependent on presence of hypertension and smoking, although it may be potentiated by their presence.^{10,46,47}

We report novel associations between cIMT and WMH among Hispanics. This may be explained by a different predisposition for vascular risk factors among ethnicities⁴⁸ including different genetic susceptibility to cIMT and WMH.^{12,49} Previous studies conducted in the Washington Heights-Inwood Columbia Aging Project⁵⁰ and in NOMAS⁵¹ reported that Hispanic and black participants had more severe WMH burden than white participants. In addition, the anatomy of the carotid segments in Hispanics may differ in comparison to whites and blacks, with Hispanics having larger internal carotid arteries suggestive of dilatative arteriopathy.⁵² In the present analysis, CCA diameter was a significant and independent contributor to WMHV, whereas composite IMT or segment specific IMT were no longer significantly associated with WMHV in the same model. This observation may suggest diverse mechanisms of vasculopathy that contributes to WMHV; one associated with increase arterial wall thickness and another associated with arterial dilatation that seems more prominent. Further studies are needed to elucidate these potential mechanisms.

Some strengths of our study include the use of a large multiethnic population-based sample of stroke-free individuals, the use of standardized ultrasound scanning and reading protocols, and a MRI quantitative measurement technique.³¹ The potential relevance of our results may be to use cIMT as readily available and low cost ultrasound imaging to serve as an additional tool in the prediction of cerebral white matter burden and subsequent increased risk of cognitive decline, dementia, and other neurodegenerative disorders. Testing the medium magnitude effect of cIMT on WMHV may be also more useful compared with the powerful effect of vascular risk factors on WMHV, such as age, hypertension, and smoking, in terms of time of prediction for neurodegenerative diseases.

A limitation of this study is that the time between MRI and carotid ultrasound measurements was up to 4 years and this may have led to an underestimation of the investigated associations. In addition, statistical power may be limited for stratified analyses by race/ethnicity. This is a cross-sectional study so causation cannot be inferred.

Summary

In summary, we found a significant association between increased carotid intima-medial thickness and increased brain WM disease, particularly in the elderly and in Hispanics. Our results also strengthen some of these previously reported associations and extend them to an understudied Hispanic population.

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Disclosures

None.

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Carotid Intima-Media Thickness Is Associated With White Matter Hyperintensities: The Northern Manhattan Study

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Supplemental Table I. Site-specific association between IMT and WMHV after adjustment for demographics, behaviors and vascular factors

Model*	CCA			ICA			BIF		
	β	SE	P	β	SE	P	β	SE	P
1	0.039	0.025	0.121	0.023	0.024	0.333	0.048	0.024	0.046
2	0.049	0.025	0.052	0.030	0.024	0.210	0.052	0.024	0.030
3	0.044	0.025	0.083	0.030	0.024	0.218	0.048	0.024	0.044
4	0.019	0.026	0.461	0.019	0.024	0.429	0.034	0.025	0.164

Model was adjusted for age, sex, race/ethnicity, and education in Model 1, additionally adjusted for health behaviors (smoking, moderate alcohol drinking, leisure-time exercise) and body mass index in Model 2, and further adjusted for vascular risk factors (hypertension, diabetes, and hypercholesterolemia) in Model 3, and further adjusted for diastolic diameter in Model 4.