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Authors

Wright, Clinton B
Dong, Chuanhui
Caunca, Michelle R
et al.

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MRI markers predict cognitive decline assessed by telephone interview: the Northern Manhattan Study

Clinton B. Wright, M.D., M.S.[1,2], **Chuanhui Dong, Ph.D.**[1], **Michelle R. Caunca, B.S.**[1], **Janet DeRosa, M.P.H.**[3], **Ying Kuen Cheng, Ph.D.**[4], **Tatjana Rundek, M.D., Ph.D.**[1,2], **Mitchell S. V. Elkind, M.D., M.S.**[3,5], **Charles DeCarli, M.D.**[6], and **Ralph L. Sacco, M.D., M.S.**[1,2]

[1]Evelyn F. McKnight Brain Institute, Department of Neurology, Leonard M. Miller School of Medicine, University of Miami, Miami, FL

[2]Department of Public Health Sciences, Leonard M. Miller School of Medicine, University of Miami, Miami, FL

[3]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY

[4]Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY

[5]Department of Neurology, College of Physicians and Surgeons of Columbia University, New York, NY

[6]Department of Neurology and Center for Neuroscience, University of California, Davis, Sacramento, CA

Abstract

Background—Brain MRI allows researchers to observe structural pathology that may predict cognitive decline. Some populations are less accessible through traditional in-person visits, and may be under-represented in the literature.

Corresponding author: Clinton Wright, MD, MS, Evelyn F. McKnight Brain Institute, Miller School of Medicine, University of Miami, 1120 NW 14th Street, CRB 1349, Miami, FL 33136, c.wright21@med.miami.edu, Tel: 305-243-1664, Fax: 305-243-7081.

Conflicts of Interest:

For the remaining authors, no conflicts of interest were declared.

Author Contributions:

Clinton Wright: Study concept and design; Study supervision; Acquisition of data; Analysis and interpretation of data; Critical revision of the manuscript for important intellectual content.

Chuanhui Dong: Study concept and design; Statistical analysis; Analysis and interpretation of data; Drafting of the manuscript; Critical revision of the manuscript for important intellectual content.

Michelle Caunca: Analysis and interpretation of data; Drafting of the manuscript; Critical revision of the manuscript for important intellectual content.

Janet DeRosa: Analysis and interpretation of data; Drafting of the manuscript; Critical revision of the manuscript for important intellectual content.

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Methods—We examined white matter hyperintensity volume (WMHV) and cerebral parenchymal fraction (CPF) as predictors of cognitive decline measured by a modified Telephone Interview for Cognitive Status (TICS-m) in Northern Manhattan Study (NOMAS), a racially and ethnically diverse cohort study. Participants were stroke-free, >50 years old, and had no contraindications to MRI. 1,143 participants had MRI and TICS-m data available (mean age 70 (SD=9), 61% women, 66% Hispanic, 17% black, 15% white).

Results—Those in the third and fourth quartiles of WMHV had significantly greater decline in TICS-m over time as compared to those in the first quartile (Q3: −0.17 points/year, Q4: −0.30 points/year). Those in the bottom two quartiles of CPF had significantly greater decline in TICS-m than those in the top quartile (Q1: −0.3 points/year, Q2: −0.2 points/year). APOE e4 allele carriers had greater cognitive decline per unit of CPF. Those with greater CPF preserve TICS-m performance better despite greater WMHV.

Conclusions—Telephone cognitive assessments can detect decline due to white matter lesions and smaller brain volumes.

Keywords

brain volume; white matter hyperintensities; cognition

INTRODUCTION

The number of people with vascular cognitive impairment (VCI) and neurodegenerative disease is expected to increase as the population of older people expands during this century.[1] Blacks and Hispanics/Latinos carry a disproportionate burden of vascular risk factors and may suffer a greater risk of both stroke and dementia than non-Hispanic whites.[2,3] Understanding the effects of modifiable vascular risk factors on cognitive performance and identifying practical methods to remotely detect cognitive changes related to vascular or neurodegenerative damage may aid in preventing cognitive impairment in these at-risk groups. We hypothesized that the modified Telephone Interview for Cognitive Status (TICS-m) would provide such a tool.

Epidemiological studies show that white matter hyperintensities (WMH), an MRI marker of cerebral small vessel disease (SVD), are associated with cognitive decline.[4–6] Cerebral atrophy has also been associated with cognitive decline[7] and may synergize with WMH to affect cognition[8]. Most studies are limited to non-Hispanic white populations or have relied on semi-quantitative measures of WMH burden that lack reliability and do not provide quantitative measurements of WMH volume.[5,6,9–11] Additionally, studies relating the TICS-m to WMH lesion load are limited, though the TICS-m has been shown to effectively identify dementia in a race/ethnically diverse cohort of older adults[12].

The purpose of this study was to examine WMH lesion load and cerebral parenchymal fraction (CPF) as predictors of cognitive decline on the TICS-m among stroke-free Hispanic, black, and white people older than age 50 from an urban community-based sample. We also explored the contribution of WMHV and the APOE4 allele as potential effect modifiers of

any association between CPF and cognitive decline to understand their potential contribution to age-related losses in cerebral volume.

METHODS

Cohort

The Northern Manhattan Study (NOMAS), a racially and ethnically diverse, stroke-free prospective cohort study, included 3,298 participants at baseline who were identified through random digit dialing using dual-frame sampling to identify published and unpublished numbers in Northern Manhattan.[13] People were eligible if never diagnosed with stroke, >40 years of age, and residents of Northern Manhattan >3 months in a household with a telephone. Participants were recruited for in-person assessments (overall response rate of 68%) and underwent complete neurological examinations between 1993 and 2001 by trained bilingual research assistants, and underwent complete neurological examinations, medical histories and risk factor interviews using standardized instruments, and fasting blood samples for glucose and lipids.

MRI sub-study

Between 2003 and 2008, NOMAS participants were recruited for a brain MRI during annual telephone follow-up using the following criteria: 1) still clinically stroke-free; 2) >50 years; and 3) no contraindications to MRI. To supplement the sample, original cohort subjects were asked if there were other individuals, 50 years or older and stroke free, living in their household, that might wish to participate. An additional 199 stroke-free people were thus added to the prospective cohort from 2006–2008 (Figure 1). All participants provided written IRB-approved informed consent.

Imaging was performed on a 1.5T MRI system (Philips Medical Systems, Best, the Netherlands) at the Columbia University Medical Center. Quantification of WMH has been previously described.[13] Briefly, we removed non-brain elements manually using operator-guided tracing of the dura matter within the cranial vault, including the middle cranial fossa but above the posterior fossa and cerebellum, to define the total intracranial volume (TIV). Segmentation of WMH required the identification of brain matter (total cerebral volume), removal of image intensity non-uniformities, and modeling of a mixture of two Gaussian probability functions with the segmentation threshold determined at the minimum probability between these distributions. A single Gaussian distribution was then fitted to image data and a segmentation threshold for WMH volume was determined a priori as 3.5 standard deviations (SDs) in pixel intensity above the mean of the fitted distribution of brain parenchyma, with morphometric erosion of two exterior image pixels to remove the effects of partial volume cerebrospinal fluid pixels on WMH determination. We used a custom-designed image analysis package (QUANTA 6.2 using a Sun Microsystems Ultra 5 workstation).[13] All analyses were performed blind to participant identifying or risk factor information.

Determination of the presence or absence of subclinical brain infarcts (SBIs) has been previously published[14]. In brief, a superimposed image of the subtraction, proton density,

and T2-weighted images at three times magnified view was used to assist in the interpretation of lesion characteristics. Vessels were indicated via signal void, best seen on T2-weighted images. Other imaging characteristics required for interpretation included CSF density on the subtraction image, and if stroke was in the basal ganglia area, distinct separation from the circle of Willis and perivascular spaces. Infarcts were counted for total number, and characterized by location (cortical, subcortical, and specific region) and size (small: <1 cm or large: >1cm). Two raters were used to determine the presence of infarcts, and agreement among them has been generally good (previously published kappa values: 0.73 to 0.90)[15].

Cognitive Assessment

Beginning in 2001, we assessed cognition during our annual telephone follow-up with the modified Telephone Interview for Cognitive Status (TICS-m). As a global measure, the TICS-m was designed to assess a variety of cognitive domains including attention, language, calculation, and immediate recall of ten words.[16] The TICS-m includes a delayed recall of the ten words, and has been validated in clinical and research settings.[16–18] Only TICS-m assessments done at or after MRI were included. Among 1,290 MRI subjects, 135 participants did not complete TICS-m evaluations at or after MRI. We excluded incomplete TICS-m exams since the total score is not valid.

Baseline Evaluation

Study definitions for race/ethnicity, diabetes, cardiac disease and other risk factors have been previously described.[19] Briefly, trained bilingual research assistants and study physicians collected demographic, medical, and laboratory data at enrollment using standardized data collection techniques and risk factor questions based on the Centers for Disease Control and the Prevention Behavioral Risk Factor Surveillance System. Race-ethnicity was based on self-identification. Smoking status was categorized as never smoked verse ever smoker. Moderate alcohol usage was defined as current drinking between one drink per month and two drinks per day versus other.[20] Physical activity was defined as any recreational physical activity in the prior two weeks versus none[21]. Body mass index (BMI) was calculated as kg/m^2. Hypertension was defined as blood pressures ≥ 140/90 mm Hg (based on the average of two measurements with a mercury sphygmomanometer), the patient's self-reported history of hypertension, or antihypertensive medication use at time of MRI. Diabetes mellitus was defined by the subject's self-reported medical history, usage of hypoglycemic medications, or fasting blood sugar ≥126 mg/dL at time of MRI. Hypercholesterolemia was defined as total cholesterol ≥240 mg/dL or use of lipid-lowering medication use at time of MRI. Peripheral vascular disease was defined as any history of pain or arterial disease in the legs. Past history of heart disease included any history of angina, myocardial infarction, congestive heart failure, coronary artery disease, atrial fibrillation, or valvular heart disease. Subjects were contacted annually via telephone after enrollment to gather information regarding illnesses, hospitalizations, vital status, and cardiovascular events.

Statistical Analyses

Established risk factors and potential confounders of the association between WMHV and cognitive performance were selected as covariates for multivariable analysis. Each

participant's WMHV and total cerebral volume (TCV) was divided by TIV to correct for differences in head size, and WMHV was natural log transformed to create a normal distribution. Cerebral parenchymal fraction (CPF) is used to refer to TCV as a fraction of TIV. We used mixed effects models with random intercepts to examine the association between WMHV and performance on the TICS-m. The time variable was calculated based on the TICS-m examination date and MRI date, and was used as a continuous variable. We examined the effect of WMHV on change in cognition over time by entering an interaction term between WMHV and time in the model and adjusted for sociodemographic variables (model 1: age, sex, education, race-ethnicity), vascular risk factors (model 2; smoking status, reported alcohol intake, physical activity, body mass index, hypertension, diabetes mellitus, hypercholesterolemia, peripheral vascular disease, and a history of heart disease), and finally, SBI, and APOE genotype (model 3). We tested for effect modifiers of the association between TICS-m and WMHV by including interaction terms in the models.

RESULTS

The characteristics of the 1,143 stroke-free NOMAS participants with WMHV, CPF, TICS-m, and other covariate data available for this analysis are presented in Table 1. The sample had a mean age of 70.1 (8.7) years and was made up of 61% women, 66% Hispanics/Latinos, 17% non-Hispanic blacks, and 15% non-Hispanic whites. The mean age TICS-m score at MRI was 32 (6.1), and participants had an average of 4.6 (2.5) TICS-m assessments since MRI. Compared to those without complete data, there were more Hispanics (66% versus 63%), and fewer blacks (17% versus 20%) and whites (15% versus 16%). The sample was younger on average than those not included (70 years vs. 75 years). This sample had smaller WMHV (n=1143, median: 0.3, IQR: 0.2–0.7; p value<0.001) when compared to those not included (n=147, median: 0.5, IQR: 0.3–1.1), and brain volume was significantly larger in the included group (p value<0.001) (Supplemental Table 1).

The adjusted mean of TICS-m at year of MRI and 5 years since MRI for quartiles of WMHV and CPF are shown in Figure 2. TICS-m scores at year of MRI were similar across levels of WMHV when comparing the top to the bottom quartile (Supplemental Table 2). Participants with the greatest white matter lesion load (i.e. quartile 4) at MRI performed significantly worse on the TICS-m at year 5 of follow-up compared to those with the lowest white matter lesion load at MRI (i.e. quartile 1, P=0.002). Additionally, CPF was similar among participants at year of MRI, though participants in the third quartile of CPF performed slightly better than those in the fourth quartile (P=0.03). Those with the lowest cerebral volume at MRI (i.e. quartile 1 of CPF) performed significantly worse on the TICS-m at year 5 of follow-up, compared to those with the greatest brain volume (P=0.01) (Supplemental Table 2).

Per 1 SD larger WMHV, participants exhibited worse performance on the TICS-m over an average of 4.6 years in a model adjusted for sociodemographic factors, and this effect remained significant in models further adjusted for vascular risk factors, MRI variables, and APOE genotype (Table 2). We also divided the participants into quartiles of WMHV to observe any dose-dependent effects of WMHV on TICS-m performance. There was a significant trend across increasing quartiles of WMHV of having worse TICS-m scores over

time. When compared to those in quartile 1, those in the third and fourth quartiles, i.e. those with greater WMHV, performed significantly worse over time when compared to those in quartile 1. This pattern remained significant in models further adjusted for vascular risk factors, MRI variables, and APOE genotype. There was a trend for worse TICS-m performance over time for those in the second quartile in the models adjusted for sociodemographics and then further adjusted for vascular risk factors (Table 2).

We examined the association of CPF on TICS-m performance over time (Table 2). Per 1 SD smaller CPF, participants performed significantly worse on the TICS-m in models adjusted for sociodemographics, as well as for models further adjusted for vascular risk factors, MRI variables, and APOE genotype. We examined the dose-dependent relationship of cerebral volume on TICS-m performance over time by dividing participants into quartiles. There was a significant trend across quartiles for those with smaller CPF to have worse TICS-m scores over time (Table 2). When compared to the fourth quartile, or those with the largest cerebral volumes, those in the first and second quartiles performed significantly worse on the TICS-m over time. This remained significant in models further adjusted for vascular risk factors, MRI variables, and APOE genotype. Those in the third quartile also performed worse on the TICS-m over time as compared to those in the fourth quartile, but this association did not reach significance in any models. The presence of SBIs or an APOE e4 allele did not independently predict TICS-m performance in any models (Table 2).

Finally, we observed effect modification by APOE e4 allele and WMHV on the association between CPF and change in TICS-m scores over time, after adjustment for sociodemographics, modifiable vascular risk factors, cardiovascular disease history, and APOE e4 genotype. For those with an APOE e4 allele, smaller CPF was significantly associated with worse TICS-m scores over time as compared to those without an APOE e4 allele (interaction term beta=−0.11, P=0.02). Also, those with greater WMHV performed better on the TICS-m over time with larger CPF (beta=0.17, P<0.01). There was no significant modification affect by race-ethnicity in the association of cognitive decline with WMHV (p=0.69) or with brain volume (p=0.62).

DISCUSSION

In this prospective study of an urban, community-based, stroke-free sample, we found more cerebral small vessel disease and smaller cerebral volumes were associated with greater decline in general cognition over time in a dose-dependent manner as measured by a telephone assessment tool, independent of vascular risk factors, APOE genotype, or other MRI markers. APOE e4 carriers, who are at high risk for developing Alzheimer Disease, were more likely to exhibit greater cognitive decline with smaller cerebral volumes when compared to APOE e4 non-carriers. Larger brain volumes seemed to preserve cognition in those with the greatest cerebral small vessel disease.

Other population-based studies have observed worse cognition with increased WMHV[7,22–25], but few studies have investigated the association between MRI markers of cerebral small vessel disease and general cognition as measured by a practical, validated, telephone interview. Our data suggests such a tool is able to measure cognitive variability

due to such brain changes. The TICS-m is a valuable instrument for testing cognition in populations that may be unable to accommodate a regular in-person visit, providing more flexibility in both research and clinical settings.

Since WMH burden has been associated with the risk of stroke, dementia, and mortality[26–28], identification of small vessel disease in older adults becomes a target for prevention of these outcomes. Recent data indicate that vascular risk factors in mid-life, such as hypertension, smoking, diabetes mellitus, and obesity, predict cerebrovascular damage, brain atrophy, and poorer executive function.[29] In particular, WMH may mediate the relationship between hypertension and cognition.[30] Most of these studies are performed in non-Hispanic white populations, despite race/ethnic disparities in cardiovascular health.[31] In the NOMAS cohort, hypertension is particularly prevalent,[32] and higher diastolic blood pressure has been associated with larger WMH lesion load[33]. When examined in quartiles, only those with the greatest WM lesion load exhibited significant cognitive decline, despite similar cognitive performance at initial assessment across quartiles of WMH load, suggesting that accumulation of a certain amount of damage from vascular risk factors is required to reach a critical level before cognitive decline occurs. However, the TICS-m is not as sensitive as detailed neuropsychological tests and may not detect decline in those with less disease.

The presence of an APOE e4 allele and greater WM lesion load modified the effect of cerebral volume on cognitive decline over time. Brain volume is heterogeneous in etiology, but aging, neurodegenerative processes, and vascular damage are important contributors, and may have a synergistic effect with cerebral small vessel disease on cognitive decline. Data from cognitively normal older adult samples show that WM lesion load and brain atrophy are associated with each other[34], and that more atrophy and WM lesion load are associated with worse cognition[35]. Several studies in cognitively normal older adults have also found that measures of brain atrophy and cerebral small vessel disease interact to accelerate cognitive decline[36,37].

Other studies have shown an interaction between cerebral atrophy and WML load in Alzheimer's patients[38] and their future decline[39], suggesting a synergistic effect between neurodegeneration and cerebral small vessel disease on the pathophysiology of AD. Our finding that APOE e4 carriers had greater cognitive decline than APOE e4 non-carriers with smaller cerebral volumes supports a synergistic relationship. In addition, those with greater cerebral volumes were more likely to preserve cognition with greater WM burden. This finding supports theories of brain reserve, which posit that clinical symptoms associated with pathological changes occur after a certain amount of pathological damage has occurred, and individuals with greater cerebral volumes may be able to withstand more damage compared to those with smaller cerebral volumes before clinical symptoms present[24]. Overall, those who are affected by both neurodegenerative disease and small vessel damage are at greater risk for cognitive impairment than those who suffer from either pathology independent of the other. None of the aforementioned studies assess cognition with a brief telephone interview. Therefore, the interaction between brain atrophy and measures of cerebral small vessel disease on cognitive performance as measured by the TICS-m

emphasizes the potential for this tool to detect cognitive deficits due to underlying brain changes detectable with MRI.

There are important limitations to this study. First, the TICS-m is a test of global cognition, and while it has been used in a number of other large studies, the test does not allow examination of specific cognitive domains that may be preferentially affected in different disease processes. In addition, TICS-m was not administered on the same day as the MRI, but our analysis shows that scores did not differ by the time interval between the initial TICS-m assessment and MRI. Since participants were enrolled in the original study an average of eight years prior to the MRI visit (Figure 1), and had to be healthy enough to undergo an MRI, survivor bias is an issue, though this would most likely have reduced the apparent effect of WMHV on cognitive decline. Finally, unmeasured confounding is likely in this observational study and our results must be interpreted with caution. The strengths of this study include its prospective design, and race/ethnically diverse cohort. We assessed cognition using the modified TICS, which is a tool that is not constrained by ceiling effects and has been used in other large studies where in-person examination is not practical.[17,40]

We found that that greater white matter lesion load and smaller cerebral volume were associated with decline on a global test of cognitive performance in dose-dependent manner in a clinically stroke-free race/ethnically diverse urban sample. Our findings have implications for detecting vascular contributions to cognitive impairment in populations where telephone follow-up is the preferred means of contact.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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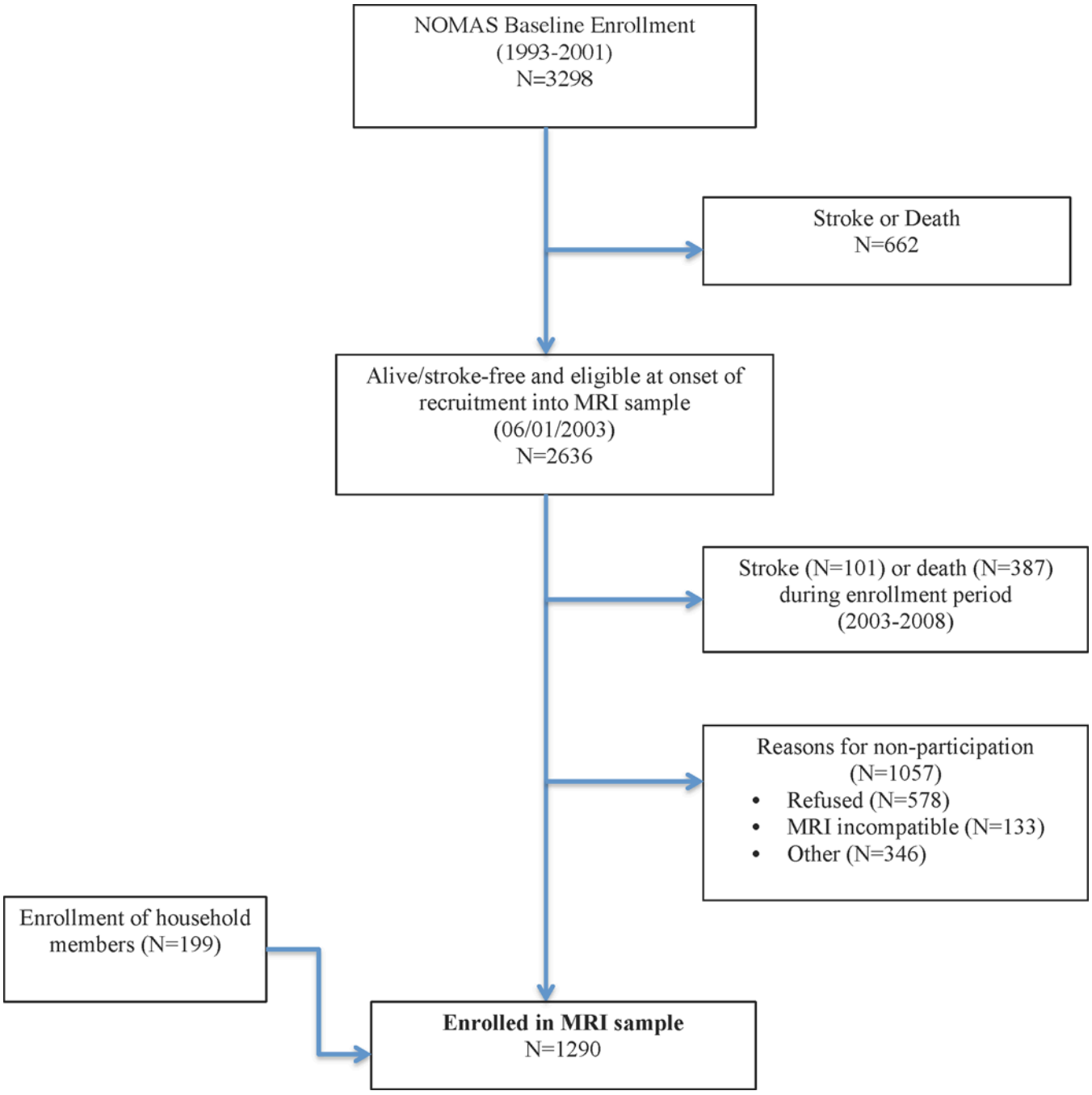

Figure 1.
Recruitment of the Northern Manhattan Study.

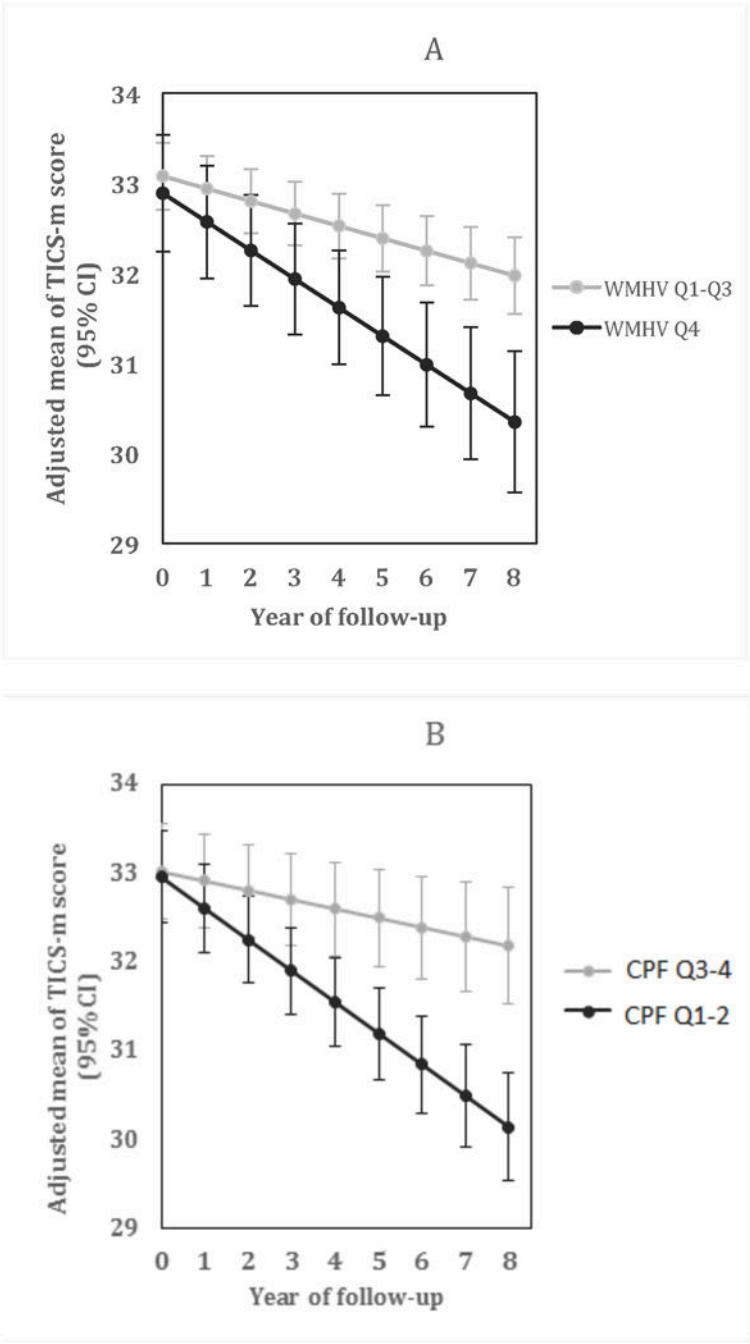

Figure 2.

a) Trajectory of TICS-m score over time, stratified by WML lesion load quartiles. b) Trajectory of TICS-m score over time, stratified by CPF quartiles.

Table 1

Sample Characteristics (N=1,143)

	N (%)	
Women	698 (61)	
Less than high school education	617 (54)	
Non-Hispanic, White	168 (15)	
Non-Hispanic-Black	193 (17)	
Hispanics	755 (66)	
Non-Hispanic other	27 (2)	
Medicaid/no insurance	539 (47)	
Former smoker	487 (43)	
Current smoker	101 (9)	
Moderate alcohol intake	389 (34)	
Leisure-time physical activity	648 (57)	
Heart disease	175 (15)	
Hypertension	831 (73)	
Diabetes	263 (23)	
Hypercholesterolemia	462 (40)	
SBI *	161 (15)	
APOE 4 allele carriers	277 (24)	
	Mean (SD)	**Median (IQR)**
TICS-m score at MRI	32 (6.1)	32 (28–36)
White matter hyperintensity volume (WMHV)#	0.66 (0.8)	0.35 (0.20–0.75)
Age, years	70.1 (8.7)	69 (64–76)
Body mass index (BMI, kg/m^2)	28.6 (5.1)	28 (25–32)
Brain volume (CPF)#	72.6 (4.2)	72 (70–75)
Intracranial volume (TIV) (cm^3)	1154.4 (124)	1143(1066–1237)
Numbers of TICS-m assessments since MRI	4.6 (2.5)	4 (2–6)

* 43 with missing data.

presented as %TIV

Table 2

Effects of WMHV and CPF on change in TICS-m scores over time

	Model 1		Model 2		Model 3	
	Estimate (95% CI)	**P**	**Estimate (95% CI)**	**P**	**Estimate (95% CI)**	**P**
WMHV (%TIV)						
Per SD increase[#]	−0.11 (−0.15, −0.07)	<.001	−0.11 (−0.15, −0.07)	<.001	−0.10 (−0.15, −0.06)	<.001
Quartile 1 (<0.20)	Ref.		Ref.		Ref.	
Quartile 2 (0.20-<0.35)	−0.10 (−0.21, 0.01)	0.07	−0.10 (−0.20, 0.01)	0.07	−0.09 (−0.19, 0.02)	0.11
Quartile 3 (0.35–0.72)	−0.17 (−0.28, −0.06)	0.002	−0.17 (−0.28, −0.06)	0.002	−0.13 (−0.24, −0.02)	0.02
Quartile 4 (>0.72)	−0.30 (−0.41, −0.19)	<.001	−0.30 (−0.41, −0.19)	<.001	−0.27 (−0.39, −0.16)	<.001
Trend		<.001		<.001		<.001
CPF (%TIV)						
Per SD decrease	−0.09 (−0.14, −0.05)	<.001	−0.09 (−0.14, −0.05)	<.001	−0.08 (−0.12, −0.04)	<.001
Quartile 1 (<70.0)	−0.31 (−0.43, −0.20)	<.001	−0.31 (−0.43, −0.20)	<.001	−0.28 (−0.40, −0.16)	<.001
Quartile 2 (70.0–<72.8)	−0.19 (−0.30, −0.08)	<.001	−0.19 (−0.30, −0.08)	<.001	−0.14 (−0.25, −0.04)	0.01
Quartile 3 (72.8–75.3)	−0.08 (−0.19, 0.03)	0.14	−0.08 (−0.18, 0.03)	0.15	−0.05 (−0.16, 0.06)	0.35
Quartile 4 (>75.3)	Ref.		Ref.		Ref	
Trend		<.001		<.001		<.001
SBI (yes vs. no)	−0.02 (−0.13, 0.1)	0.79	−0.01 (−0.13, 0.1)	0.824	0.09 (−0.03, 0.21)	0.14
APOE4 (yes vs. no)	−0.01 (−0.10, 0.08)	0.83	−0.01 (−0.10, 0.08)	0.812	−0.02 (−0.12, 0.07)	0.59

[#]log-transformed.

Model 1: Adjusted for age, age2, sex, race-ethnicity, education and medical health insurance status.

Model 2: Adjusted for age, age2, sex, race-ethnicity, education and health insurance status, smoking, moderate alcohol intake, physical activity, BMI, hypertension, diabetes, hypercholesterolemia, history of heart disease.

Model 3: Full model: including all covariates in Model 2 and WMHV, CPF, SBI and APOE genotype.