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Authors

Willey, Joshua Z
Gardener, Hannah
Moon, Yeseon P
et al.

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Lipid profile components and subclinical cerebrovascular disease in the Northern Manhattan Study

Joshua Z. Willey[1], **Hannah Gardener**[2], **Yeseon P. Moon**[1], **Mitsuhiro Yoshita**[3], **Charles DeCarli**[4], **Ying Kuen Cheung**[5], **Ralph L. Sacco**[2], **Mitchell S. V. Elkind**[1,6], and **Clinton B. Wright**[2]

[1]Department of Neurology, Columbia University, New York, NY

[2]Evelyn F. McKnight Brain Institute and the Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL

[3]Department of Neurology, Hokuriku National Hospital, Nanto, Japan

[4]Department of Neurology, University of California at Davis, Davis, CA

[5]Department of Biostatistics, Columbia University, New York, NY

[6]Department of Epidemiology, Columbia University, New York, NY

Abstract

Background—Subclinical cerebrovascular disease has been associated with multiple adverse events related to aging, including stroke and dementia. The modifiable risk factors for subclinical cerebrovascular disease beyond hypertension have not been well characterized. Our objective was to examine the association between baseline, and changes over time, in lipid profile components and subclinical cerebrovascular disease on magnetic resonance imaging (MRI).

Methods—Fasting plasma lipids were collected on participants in the Northern Manhattan Study, a prospective cohort study examining risk factors for cardiovascular disease in a multi-ethnic elderly urban dwelling population. A subsample of the cohort underwent brain MRI between 2003 and 2008 (a median of 6.2 (range=0–14) years after enrollment, when repeat fasting lipids were obtained. We used lipid profile components at the time of initial enrollment (n=1256 with lipids available) as categorical variables, as well as change in clinical categories over the 2 measures (n=1029). The main outcome measures were (1)total white matter hyperintensity volume (WMHV) using linear regression, and (2)silent brain infarcts (SBI) using logistic regression.

Address for correspondence: Joshua Z Willey, MD, Neurological Institute, 710 West 168th Street, New York, NY 10032, Tel: 212 305-1710, Fax: 212 305-1658, jzw2@columbia.edu.

Disclosures

The first author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The others report no other financial conflicts of interest.

Author contributions:

Study concept and design: all authors

Acquisition of data: Drs. Willey, Elkind, Sacco, and Wright

Analysis and interpretations: Drs. Willey, Gardener, Cheung, Elkind, Wright and Ms. Moon

Critical revision of the manuscript for important intellectual content: Drs. Elkind, Sacco, Wright, Cheung

Study supervision: Drs. Elkind, Sacco, Wright

Results—None of the plasma lipid profile components at the time of enrollment were associated with WMHV. The association between baseline lipids and WMHV was however modified by apoE status (chi-squared with 2 degrees of freedom, p=0.03), such that among apoE4 carriers those with total cholesterol (TC) ≥200mg/dl had a trend towards smaller WMHV than those with TC<200mg/dl (difference in log WMHV − 0.19, p=0.07) while there was no difference among apoE3 carriers. When examining the association between WMHV and change in lipid profile components we noted an association with change in high-density lipoprotein cholesterol (HDL-C) (>50 mg/dl for women,>40 mg/dl for men) and TC. A transition from low risk high-density lipoprotein cholesterol (HDL-C)(>50 mg/dl for women,>40 mg/dl for men) at baseline to high risk HDL-C at the time of MRI (versus starting and remaining low risk) was associated with greater WMHV (difference in logWMHV 0.34, p-value 0.03). We noted a similar association with transitioning to a TC≥200mg/dl at the time of MRI (difference in logWMHV 0.25, p-value 0.006). There were no associations with baseline or change in lipid profile components with SBI.

Conclusions—The association of plasma lipid profile components with greater WMHV may depend on apoE genotype and worsening HDL and TC risk levels over time.

Introduction

As the population ages, chronic diseases of aging will have a greater public health impact. Subclinical cerebrovascular disease, observed on magnetic resonance imaging (MRI) as white matter hyperintensities (WMH) and silent brain infarcts (SBI), increases the risk of important diseases of aging such as cognitive impairment, reduced mobility, and ischemic stroke[1, 2]. The increased recognition of SBI and WMH highlights the importance of identifying modifiable risk factors so as to then allow for trials aimed at preventing diseases of aging associated with cerebrovascular injury. Plasma lipids are a major determinant of coronary artery disease, though the association with stroke remains less well established[3]. Total cholesterol and low density lipoprotein cholesterol (LDL-C) levels tend to decline with age, though the plasma lipid profile components remain associated with cardiovascular disease across all age groups[4]. Lowering LDL-C with statins is recommended as a coronary risk reduction strategy, and treatment with statins also reduces the risk of first and recurrent stroke[5, 6]. The data on the role of dyslipidemia as a risk factor for ischemic stroke is more mixed with most studies showing neutral results, or an association with only large artery atherosclerotic subtypes[7].

Several gaps exist in our understanding of the determinants of SBI and WMH. Recognized cerebrovascular risk factors associate with WMH suggesting a vascular etiology, though non-ischemic etiologies have also been proposed[8]. The latter may be supported by studies showing no association between WMH and established stroke risk factors such as physical activity[9]. Few studies, however, have examined the association of lipid profile components with subclinical measures of cerebrovascular brain injury such as WMH and SBI, with one prior study showing an inverse association between WMH volumes and dyslipidemia[10]. However current literature is limited on the role of changes in plasma lipid profile components over time and the association with subclinical cerebrovascular disease, and few studies have included multi-ethnic populations with a high proportion of Hispanics. Furthermore there has been little work on whether the association of lipid profile

components with SBI and WMH could be modified by genetic risk factors, particularly apolipoprotein E (apoE) isoforms that are implicated in both lipid metabolism and neurodegenerative diseases[11].

The purpose of this analysis was to examine the association of lipid profile components of SBI and WMH in a cohort of Northern Manhattan residents, and whether these effects would be modified by apoE status. We hypothesized that baseline higher levels, as well increases over time, in total cholesterol, triglycerides, and LDL-C, would be associated with a greater prevalence of SBI and larger WMH volumes (WMHV), with an inverse association with high-density lipoprotein cholesterol (HDL-C).

Methods

Recruitment of the Cohort

The Northern Manhattan Study (NOMAS) (n = 3298) is a population-based prospective cohort study designed to evaluate the effects of medical, socio-economic, and other risk factors on the incidence of vascular disease. Details regarding initial recruitment are available in prior publications[9]. Between 2003 and 2008 participants in NOMAS were invited to participate in an MRI substudy if they were older than 55 years of age, had not had a clinical stroke, and did not have a contra-indication to MRI. In order to increase recruitment an additional 199 participants who were household members, but not blood relations, were invited to participate in the MRI substudy for a total of 1290 participants. Compared to the overall cohort, the MRI substudy sample was younger and had a lower proportion of diabetes, hypertension, and cardiac disease[12] The study was approved by the Institutional Review Boards at Columbia University Medical Center (CUMC) and the University of Miami. All participants gave informed consent to participate in the study. The authors report no conflicts of interest.

Cohort Evaluation and Follow up—Data regarding risk factors were collected through interviews of participants by trained bilingual research assistants at enrollment in the NOMAS cohort, as previously described[13]. In-person measurements and collection of fasting blood specimens were carried out by study physicians. Race-ethnicity was determined by self-identification. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control and Prevention regarding the following conditions: hypertension, diabetes mellitus (DM), hypercholesterolemia, peripheral vascular disease, cigarette smoking, and cardiac conditions. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg based on the average of the two measurements 5 minutes apart in a seated position with a manual sphygmomanometer, or a patient's self-report of a history of hypertension or anti-hypertensive use. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dl or the patient's self-report of such a history, or insulin or hypoglycemic use. These same in-person measurements were repeated at the time of enrollment into the MRI sub-study.

We included only individuals for whom fasting lipids were available. A total of 1256 participants enrolled in the MRI cohort had fasting blood samples with total cholesterol

available from their time of initial enrollment into NOMAS. Of these, we have repeat lipid profiles collected at both baseline and the time of MRI with collection dates over 1 year apart among 1029 participants. Lipids were measured as previously described[14]. Briefly, total cholesterol and triglyceride levels were determined using standard enzymatic procedures in an automated spectrometer (Hitachi 705; Boehringer, Mannheim, Germany). Plasma HDL-C cholesterol levels were measured after precipitation of apolipoprotein B-containing lipoproteins by phosphotungstic acid. LDL-C cholesterol was calculated using the Friedewald formula[15]; the LDL-C was listed as missing when the TG was greater than 400 mg/dl (n = 15 at baseline, n =13 on follow up)[16].

ApoE alleles were determined by *Hha*I digestion of PCR products amplified from genomic DNA as described by Hixson et al[17] using fasting blood samples at the time of the MRI. We considered apoE 3/3 as the reference group, while carriers of one or two alleles of apoE 4 were collapsed into the same category (i.e. apoE 4/2, apoE 4/3, apoE 4/4); carriers of one or two alleles of apoE2 carriers were also collapsed into the same group (i.e. apoE 2/2, apoE 2/3)[11].

MRI data acquisition—Imaging was performed on a 1.5-T MRI system (Philips Medical Systems) at the Hatch Research Center at Columbia University. The processing of MRI scans in NOMAS has been previously described[12]. The presence or absence of brain infarction was determined from the size, location, and imaging characteristics of the lesion[18]. SBI was defined as a cavitation on the FLAIR sequence of at least 3mm in size, and distinct from a vessel due to the lack of signal void on T2 sequence, and of equal intensity to cerebrospinal fluid without associated focal neurological complaints. Analyses for WMHV were performed using semi-automated measurements of pixel distributions and mathematical modeling of pixel-intensity histograms for cerebrospinal fluid and brain (white and gray matter) to identify the optimal pixel-intensity threshold to distinguish cerebrospinal fluid from brain matter. Analyses were performed using a custom-designed image analysis package (QUANTA 6.2 using a Sun Microsystems Ultra 5 workstation). WMHV was calculated as a proportion of total cranial volume to correct for differences in head size[19], and log-transformed to achieve a normal distribution (log-WMHV) for analysis. All analyses were performed blind to participant identifying information.

Statistical Analysis—The primary predictors of interest were: 1) total cholesterol (TC), HDL-C, LDL-C, and triglycerides (TG) at the time of initial enrollment as binary variables using National Cholesterol Education Program-defined cut-offs for high risk categories (TC > 200 mg/dl, LDL-C > 130 mg/dl, HDL-C < 40 mg/dl for men and < 50 mg/dl for women, and TG > 200 mg/dl)[20] and their low risk counterparts as the reference; and 2) change from the initial enrollment into NOMAS to the time of MRI in clinical categories defined as (a) low risk to high risk, (b) remaining high risk, (c) high risk to low risk and (d) remaining low risk as the reference. The primary outcomes of this analysis were total WMHV and SBI. We fitted linear regression models to examine the associations with total WMHV and logistic regression models with the outcome of SBI, unadjusted and adjusting for all lipid profile components, demographics (age, sex, race-ethnicity, and time interval between enrollment and MRI), and additional confounders (hypertension, diabetes mellitus, smoking,

coronary artery disease, moderate alcohol consumption, physical activity, education, medical insurance status, body mass index, estimated glomerular filtration rate, apoE, and any use of cholesterol lowering medications). Age, sex, race-ethnicity, treatment with any cholesterol lowering medications (at enrollment and in follow up), and apoE isoforms were considered in all models as possible effect modifiers. The improvement of model fit for models with multiple levels of categories was tested using a likelihood ratio test (LRT) with appropriate degrees of freedom; stratified models were fitted when the p-value for the LRT was < 0.05. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Baseline characteristics of the cohort available for this analysis (N=1,282) are shown in table 1. Briefly, the mean age of the cohort was 64±8.4 years; 61% were women. The majority were Hispanic, with a similar proportion of non-Hispanic blacks and whites making up the rest of the cohort. ApoE genotyping was available in 95% of the MRI cohort. Plasma lipid profile components were obtained a mean of 6.1 years before enrollment into the MRI cohort (median=6.2 years, range=0–14 years), and repeated at the time of the MRI. Means (± standard deviations) of annual changes in the plasma lipid profile values were TC (−1.2±6.3 mg/dl), HDL-C (1.2±1.8 mg/dl), LDL-C (−2.2±5.7 mg/dl), and TG (−1.3±13.0 mg/dl). Table 2 outlines the distribution of categorical lipid profile change over time.

Association between baseline plasma lipid profile components and WMH volumes

The association between lipid profile components and WMHV are presented in table 3. In summary, none of the plasma lipid profile components at the time of enrollment were associated with WMH volumes. We found, however, that the effect of TC differed by apoE4 isoform (LRT with 2 d.f., p =0.03). In stratified models high risk TC (> 200 mg/dl) versus low risk TC (<200 mg/dl) revealed a trend toward an association with smaller WMHV among those who were apoE4 positive (difference in logWMHV −0.19, p=0.07), whereas there was no association in those with other apoE isoforms (data not shown). We found no interactions with baseline demographics or treatment with cholesterol lowering medications.

Association between categorical change over time in plasma lipid profile components and WMH volumes

We examined the association between categorical change in lipids between enrollment and MRI (table 4). In fully adjusted models we found that a transition from a low risk HDL-C category (>50mg/dl in women, >40mg/dl in men) at baseline to a high risk category at follow up was associated with greater WMHV (difference in logWMHV 0.34, p-value 0.03), using those who remained at low risk as the reference group. Compared to those with low risk TG levels (<200mg/dl) at both time points, those with a transition from a high risk TG category (>200 mg/dl) to a low risk category had a lower WMHV (difference in logWMHV −0.23, p-value 0.03). For TC a transition from low risk of TC to high risk (difference in logWMHV 0.25, p-value 0.006) or remaining in a high risk of TC (difference in logWMHV 0.14, p-value 0.04) was associated with a greater WMHV, using those remaining at low risk as the reference group. We found no associations of change in LDL-C with WMHV.

Association between plasma lipid profile components and SBI

We found no association between any of the plasma lipid profile components at baseline or with change over time and SBI (table 5), and there were no interactions for treatment with cholesterol lowering medications, apoE isoforms, or baseline socio-demographic factors.

Discussion

In our analyses we found that plasma lipids at initial enrollment were not associated with total WMH volumes or SBI. However, the associations between TC and total WMH volumes differed by apoE isoform status, with a trend towards an association of TC with WMH volumes only among those with an apoE4 genotype. Unlike other studies[21] we did not find that higher levels of HDL-C were associated with larger WMH volumes. Furthermore we found no association of any lipid components with subclinical infarction. We did however find that increases in plasma lipids over an average of 6 years between baseline enrollment and the time of MRI were associated with greater WMH volumes, notably with a transition from low risk categories to high risk for HDL-C and TC. We further found that treatment with cholesterol medications did not modify the associations with the plasma lipid profile components.

There are few published studies examining the association between plasma lipid profile components and subclinical cerebrovascular disease. Two recent studies showed a an association between dyslipidemia and lower WMH volumes, one study being a community cohort referred for clinical MRI[22] and another an analysis of acute ischemic stroke patients[10]. The largest study to date has been the Cardiovascular Health Study (CHS), which demonstrated increased WMH volumes over time among participants with high HDL-C and low LDL-C[21]. These studies, however, did not consider more than one lipid measure over time, or an interaction with genetic risk factors. The genetic determinants of WMH volumes are an area of controversy, with a recent meta-analysis showing no clear association with apoE isoforms[23]. Previous studies have examined the role of the interaction between the plasma lipid profile components and apoE isoforms (especially apoE4) in informing the risk of Alzheimer’s disease, as well as coronary artery disease[11], but subclinical cerebrovascular disease is not well reported.

There are several possible explanations for our findings. The lack of association with SBI may be similar to the findings seen in other studies for ischemic stroke[24], particularly among the non-atherosclerotic subtypes[7]. The pathology of most SBI is similar to lacunar infarction due to lipohyalinosis in small cerebral penetrating arteries that may not be related to dyslipidemia[25]. On the other hand we may be underpowered to detect more subtle effects of plasma lipid profile components on SBI given the binary nature of this variable and the low prevalence of SBI given the young age of our cohort at the time of MRI. The pathology of WMH remains an area of active investigation, and though ischemic etiologies are frequently invoked, other pathological features have also been postulated including neuro-degeneration, demyelination, gliosis, edema, and inflammation[26]. The lack of an association in our study between LDL-C, the principal target of treatment with statins for stroke prevention, and WMHV supports these non-ischemic etiologies. In non-ischemic etiologies, dyslipidemia may play a limited or seemingly paradoxical role suggesting a

degenerative process. The association of plasma lipid profile components with WMH parallels that of the findings with intra-cerebral hemorrhage[27] and symptomatic intra-cranial hemorrhage after thrombolysis[28, 29], further raising the possibility of an association with non-ischemic etiologies such as cerebral amyloid angiopathy or disruption in vascular endothelium[30]. Similarly the role of dyslipidemia with ischemic stroke, which is more likely to share pathological features with SBI, remains controversial[3]. Apolipoprotein E4 isoforms are associated with increased levels of TC and LDL-C, as well as a greater affinity for binding to the LDL receptor, which have both been implicated in the increased association with atherosclerotic disease. In the central nervous system the apo E4 isoform has also been implicated in reduced glial cell repair in response to amyloid beta and reactive oxygen species damage. This effect may be in part due to reduced transport of cholesterol moieties across the blood brain barrier and into the intracellular domains[11], in keeping with the important role cholesterol plays in synaptogenesis and neural repair[31]. Our results showing an independent effect of a worsening plasma lipid profile, however, also suggest that atherosclerosis may play a role in the formation of WMH, and highlights the importance of considering temporal trends in risk factors.

Our findings could also be due to non-biological mechanisms stemming from study design. The MRI cohort was enrolled several years after the initial lipid profile was obtained, and survival bias may therefore have led to enrollment of only those who had a genetic predisposition to a reduced effect from dyslipidemia on stroke or death. This is an unlikely explanation for our findings since in previous analyses we have not shown significant differences in baseline modifiable stroke risk factors, including lipid panel, between those enrolled in the MRI cohort and the rest of the cohort. We did not collect information on the size of the SBI which in a recent study was found to lead to an association of plasma lipids with SBI larger than 8 mm (where there may be micro-atheromatous disease), rather than in smaller SBI where lipohyalinosis may be more important[25]. The results for WMH volumes and SBI are nonetheless in keeping with other cohort studies failing to show an association between ischemic stroke and dyslipidemia[9, 32, 33]. Low HDL-C and high triglycerides are components of the metabolic syndrome, which is associated with risk of ischemic stroke[34, 35], as well subclinical cerebrovascular disease[36]. It is thus possible that lipid profile parameters in themselves are not risk factors for subclinical cerebrovascular disease, but instead act in combination with other components of the metabolic syndrome.

Our study has several strengths, including a representative sample of three different race/ethnic groups, repeated measurement of plasma lipid profile components, capture of treatment with cholesterol lowering medications, and consideration of the interaction with apoE isoforms. There are several limitations of the findings in our study. Participants had only one MRI and we therefore lack information on progression of WMH or incident SBI, and we are unable to determine cause and effect. In addition, it is possible that the lipid profile may have a different impact on progression of MRI findings compared to these cross-sectional associations. The number of SBIs may have been too small to examine more subtle associations with dyslipidemia. We may have been underpowered to detect an interaction by sex, age, race-ethnicity, or medication use, and thus we are not able to comment on differences by these important baseline factors. Lastly, we examined for interactions between several lipid profile components and apoE isoforms and it is possible

that our findings of differential effects may have been due to chance. Nonetheless, our findings are in keeping with other studies that have shown either a paradoxical[10, 21, 22], or no, association[37] between plasma lipid profile components and subclinical cerebrovascular disease.

In conclusion our study showed that the association of lipid profile components with WMH was modified by apoE genotype, as well as changes of lipid profile components over time. As the population continues to age the clinical manifestations of subclinical cerebrovascular disease will take on a greater role, and so will the importance of identifying risk factors and potential treatment targets. At this time the data has been inconclusive on the utility of statins in preventing an increase in WMH volumes[38, 39], or SBI[40], though the efficacy in preventing clinical stroke is clear[6]. Further research is needed in identifying risk factors for subclinical cerebrovascular disease, and how these modifiable diseases are influenced by an individual's genetic profile.

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Table 1

Characteristics of the Northern Manhattan magnetic resonance imaging cohort (n =1282) with baseline lipids

Age (Mean +/− standard deviation)	64.0±8.4
Men, n(%)	506 (39)
Race-Ethnicity, n(%)	
Hispanic	842 (66)
Non-Hispanic Black	220 (17)
Non- Hispanic White	191 (15)
Education, completed high school, n (proportion %)	588 (46)
Risk factors, n(proportion %)	
Hypertension	873 (68)
Diabetes Mellitus	248 (19)
Coronary Artery Disease	209 (16)
Current Smoking	201 (16)
Waist circumference, mean± s.d	36.74±4.56
Physically inactive	701 (56)
Moderate alcohol intake	527 (41)
Total cholesterol, mean± s.d in mg/dl (proportion > 200 mg/dl)	201.3±38.9 (51%)
High-density lipoprotein cholesterol, mean± s.d in mg/dl (proportion < 40 mg/dl for men, < 50 mg/dl for women)	47.0±14.6 (54%)
Low-density lipoprotein cholesterol, mean± s.d in mg/dl (proportion > 130 mg/dl)	128.1±35.2 (47%)
Triglycerides, mean± s.d in mg/dl (proportion > 200 mg/dl)	134.6±81.8 (14%)
Treated with a statin before enrollment into the magnetic resonance imaging cohort, n (proportion %)	194 (15.0%)
ApoE genotype, n(proportion %)	
ApoE 4/4, 4/3, 4/2	299 (25)
ApoE 3/3	782 (65)
ApoE 2/2, 2/3	130 (11)

Table 2

Plasma lipid panel components in the Northern Manhattan Study magnetic resonance imaging (MRI) cohort from initial enrollment to the time of imaging (n = 1026).

	High risk at baseline and at the time of MRI (n, proportion) *	**High risk at baseline and low risk at the time of MRI (n, proportion)** *	**Low risk at baseline and high risk at the time of MRI (n, proportion)** *	**Low risk at baseline and at time of MRI (n, proportion)** *
High density lipoprotein cholesterol	330 (32.2%)	245 (23.9%)	35 (3.4%)	415 (40.5%)
Low density lipoprotein cholesterol	255 (25.1%)	235 (23.1%)	73 (7.2%)	452 (44.6%)
Total cholesterol	323 (31.5%)	206 (20.0%)	119 (11.6%)	378 (36.8%)
Triglyceride	69 (6.7%)	78 (7.6%)	60 (5.9%)	819 (79.8%)

*High Risk Categories: High total cholesterol (> 200 mg/dl), High low density lipoprotein cholesterol (> 130 mg/dl), High triglycerides (> 200 mg/dl), Low high density lipoprotein cholesterol (< 40 mg/dl for men, < 50 mg/dl for women).

Table 3

Parameter estimates for the association between plasma lipid profile components at baseline and total white matter hyperintensity volumes in the Northern Manhattan magnetic resonance imaging cohort (linear regression)

Lipid profile component	Unadjusted parameter estimate (p-value)	Model 1: Adjusted parameter estimate (p- value)	Model 2: Adjusted parameter estimate (p-value)	Model 3: Adjusted parameter estimate (p-value)
Baseline HDL-C (men < 40 mg/dl, women < 50 mg/dl)	− 0.11 (0.05)	− 0.073 (0.2)	− 0.084 (0.1)	−0.067 (0.3)
Baseline LDL-C > 130 mg/dl	0.006 (0.9)	0.005 (0.9)	0.009 (0.9)	0.016 (0.8)
Baseline TG > 200 mg/dl	− 0.066 (0.4)	− 0.031 (0.7)	− 0.08 (0.3)	− 0.093 (0.3)
Baseline Total cholesterol > 200 mg/dl	0.025 (0.6)	0.017 (0.7)	0.027 (0.6)	0.041 (0.5)

Model 1: Controlling for age at magenetic resonance image, time from baseline to magnetic resonance image, sex, race/ethnicity

Model 2: Controlling for variables in Model 1 and high school education, insurance, smoking, hypertension, diabetes, body mass index, moderate alcohol use, any physical activity, estimated glomerular filtration rate, apoE, and cholesterol-lowering medication use at baseline

Model 3: Controlling for variables in model 2 and cholesterol-lowering medication use ever during follow-up before magnetic resonance image

Legend: HDL-C (high density lipoprotein cholesterol); LDL-C (low density lipoprotein cholesterol); TG (triglyecerides)

Table 4

Parameter estimates for change in plasma lipid profile components and total white matter hyperintensity volumes in the Northern Manhattan magnetic resonance image (MRI)cohort (linear regression)

Lipid profile component changes*: baseline category to MRI category		Unadjusted parameter estimate (p- value)	Model 1: Adjusted parameter estimate (p- value)	Model 2: Adjusted parameter estimate (p-value)	Model 3: Adjusted parameter estimate (p-value)
Total cholesterol (reference: low risk → low risk)					
	Low risk → high risk	0.21 (0.03)	0.24 (0.006)	0.25 (0.006)	0.25 (0.006)
	High risk → high risk	0.10 (0.2)	0.11 (0.09)	0.12 (0.07)	0.14 (0.04)
	High risk → low risk	0.14 (0.08)	0.07 (0.3)	0.04 (0.6)	0.07 (0.4)
High-density lipoprotein cholesterol (reference: low risk → low risk)					
	low risk → high risk	0.18 (0.3)	0.32 (0.03)	0.34 (0.03)	0.34 (0.03)
	high risk → low risk	−0.04 (0.6)	0.002 (1.0)	−0.04 (0.6)	−0.04 (0.6)
	high risk → high risk	−0.15 (0.03)	−0.04 (0.5)	−0.07 (0.3)	−0.07 (0.3)
Low density lipoprotein cholesterol (reference: low risk → low risk)					
	Low risk → high risk	0.03 (0.8)	0.10 (0.3)	0.05 (0.7)	0.11 (0.6)
	High risk → low risk	0.08 (0.3)	0.03 (0.6)	0.01 (0.9)	0.08 (0.6)
	High risk → high risk	−0.09 (0.2)	-1×10^{-4} (1.0)	0.006 (0.9)	0.07 (0.7)
Triglycerides (reference: low risk → low risk)					
	Low risk → high risk	−0.04 (0.7)	0.02 (0.9)	0.02 (0.9)	0.02 (0.8)
	High risk → low risk	−0.20 (0.08)	−0.16 (0.1)	−0.24 (0.02)	−0.23 (0.03)
	High risk → high risk	−0.08 (0.5)	0.06 (0.6)	0.007 (0.9)	0.01 (0.9)

*High risk categories: High total cholesterol (> 200 mg/dl), High low density lipoprotein cholesterol (> 130 mg/dl), High triglycerides (> 200 mg/dl), Low high density lipoprotein cholesterol (< 40 mg/dl for men, < 50 mg/dl for women).

Model 1: Controlling for age at magnetic resonance image, time from baseline to MRI, sex, race/ethnicity

Model 2: Controlling for variables in Model 1 and high school education, insurance, smoking, hypertension, diabetes, body mass index, moderate alcohol use, any physical activity, estimated glomerular filtration rate, apoE, and cholesterol-lowering medication use at baseline

Model 3: Controlling for variables in model 2 and cholesterol-lowering medication use ever during follow-up before magnetic resonance image

Table 5

Odds ratios (OR) and 95% confidence intervals for association of plasma lipid profile components and silent brain infarcts (n = 114) in the Northern Manhattan magnetic resonance imagecohort

Lipid profile component	Unadjusted Odds Ratio and 95 % confidence interval	Model 1: Adjusted Odds Ratio and 95 % confidence interval	Model 2: Adjusted Odds Ratio and 95 % confidence interval	Model 3: Adjusted Odds Ratio and 95 % confidence interval
Baseline HDL-C (men < 40 mg/dl, women < 50 mg/dl)	0.94 (0.63–1.40)	1.04 (0.68–1.59)	0.95 (0.60–1.52)	0.84 (0.52–1.37)
Baseline LDL-C > 130 mg/dl	0.96 (0.65–1.42)	1.03 (0.69–1.55)	1.05 (0.66–1.65)	0.99 (0.60–1.62)
Baseline TG > 200 mg/dl	0.95 (0.51–1.77)	1.03 (0.54–1.94)	0.95 (0.47–1.91)	0.84 (0.40–1.77)
Baseline Total cholesterol > 200 mg/dl	0.81 (0.55–1.20)	0.87 (0.58–1.32)	0.86 (0.55–1.35)	0.82 (0.50–1.35)

Model 1: Controlling for age at magnetic resonance image, time from baseline to magnetic resonance image, sex, race/ethnicity

Model 2: Controlling for variables in Model 1 and high school education, insurance, smoking, hypertension, diabetes, body mass index, moderate alcohol use, any physical activity, estimated glomerular filtration rate, apoE, and cholesterol-lowering medication use at baseline

Model 3: Controlling for variables in model 2 and cholesterol-lowering medication use ever during follow-up before magnetic resonance image

Legend: HDL-C (high density lipoprotein cholesterol); LDL-C (low density lipoprotein cholesterol); TG (triglyecerides)