Lipid Profile Components and Risk of Ischemic Stroke

The Northern Manhattan Study (NOMAS)

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Objective: To explore the relationship between lipid profile components and incident ischemic stroke in a stroke-free prospective cohort.


Setting: Northern Manhattan, New York.

Patients: Stroke-free community residents.

Intervention: As part of the Northern Manhattan Study, baseline fasting blood samples were collected on stroke-free community residents followed up for a mean of 7.5 years.

Main Outcome Measures: Cox proportional hazard models were used to calculate hazard ratios and 95% confidence intervals for lipid profile components and ischemic stroke after adjusting for demographic and risk factors. In secondary analyses, we used repeated lipid measures over 5 years from a 10% sample of the population to calculate the change per year of each of the lipid parameters and to impute time-dependent lipid parameters for the full cohort.

Results: After excluding those with a history of myocardial infarction, 2940 participants were available for analysis. Baseline high-density lipoprotein cholesterol, triglyceride, and total cholesterol levels were not associated with risk of ischemic stroke. Low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol levels were associated with a paradoxical reduction in risk of stroke. There was an interaction with use of cholesterol-lowering medication on follow-up, such that LDL-C level was only associated with a reduction in stroke risk among those taking medications. An LDL-C level greater than 130 mg/dL as a time-dependent covariate showed an increased risk of ischemic stroke (adjusted hazard ratio, 3.81; 95% confidence interval, 1.53-9.51).

Conclusions: Baseline lipid panel components were not associated with an increased stroke risk in this cohort. Treatment with cholesterol-lowering medications and changes in LDL-C level over time may have attenuated the risk in this population, and lipid measurements at several points may be a better marker of stroke risk.

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STROKE REMAINS A MAJOR CAUSE of death, and the main cause of severe disability, in the United States.1 Stroke is particularly prevalent among elderly individuals, minorities, and those of lower socioeconomic status. Elevated low-density lipoprotein cholesterol (LDL-C) is a risk factor for coronary artery disease, and high levels of high-density lipoprotein cholesterol (HDL-C) are protective.2-4 The Third Report of the National Cholesterol Education Program Adult Treatment Panel recommended that an HDL-C level less than 40 mg/dL (to convert to millimoles per liter, multiply by 0.0259) be considered a risk factor for ischemic heart disease.2

The role of lipids as risk factors for ischemic stroke has been less consistently observed. High-density lipoprotein cholesterol level was associated with stroke risk in a multiethnic, population-based case-control study in northern Manhattan, New York.6 In that study, we found that a higher HDL-C level was protective against ischemic stroke in all racial groups, and especially in those 75 years or older. High-density lipoprotein cholesterol appeared to be particularly protective against the atherosclerotic stroke subtype, an observation that was also noted in a recent meta-analysis.6 Some studies have not confirmed this association.6 The association between LDL-C and stroke risk is simi-
larly uncertain.14 The purpose of this study was to examine the relationship between lipid parameters and ischemic stroke risk in a prospective cohort of stroke-free northern Manhattan residents.

METHODS

RECRUITMENT OF THE COHORT

The Northern Manhattan Study (NOMAS) is a population-based prospective cohort study designed to evaluate the effects of medical, socioeconomic, and other risk factors on the incidence of vascular disease in a stroke-free, multiethnic community cohort. Participants were identified by dual-frame random-digit dialing in the northern Manhattan community, as described in prior publications.2,13 Briefly, participants were eligible if they met the following criteria: (1) had never been diagnosed with a stroke; (2) were older than 39 years; and (3) resided in northern Manhattan for 3 or more months in a household with a telephone. In-person evaluations were performed at the hospital or at home for those who could not come in person (6% were done at home). The study was approved by the institutional review boards at Columbia University Medical Center and the University of Miami. All participants gave informed consent to participate in the study. A total of 3298 participants were recruited between 1993 and 2001.

COHORT EVALUATION AND FOLLOW-UP

Data regarding baseline status and risk factors were collected through interviews of participants by trained research assistants. Physical and neurological examination, in-person measurements, and analysis 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 regarding the following conditions: hypertension, diabetes mellitus, hypercholesterolemia, peripheral vascular disease, transient ischemic attack, cigarette smoking, and cardiac conditions. Hypertension and diabetes were defined based on previously published criteria.12,13

We included individuals without a baseline history of myocardial infarction and for whom fasting lipid levels were available. Two thousand nine hundred forty subjects had available HDL-C and triglyceride (TG) measurements, while 2914 had HDL-C and triglyceride (TG) measurements, while 2914 had available HDL-C measurements. Final analyses were limited to these individuals. Lipids were measured as previously described.13 Briefly, total cholesterol and TG levels were determined using standard enzymatic procedures in an automated spectrophotometer (Hitachi 705; Boehringer, Mannheim, Germany). Plasma HDL-C levels were measured after precipitation of apolipoprotein B–containing lipoproteins by phosphotungstic acid. Non–HDL-C concentrations were calculated by subtracting the HDL-C level from the total cholesterol level. Levels of LDL-C were calculated using the Friedewald formula.

The participants were followed up annually via telephone screening to detect any new neurological symptoms and events. Any participant who responded positively on screening was scheduled for an in-person assessment. Additionally, a 10% sample of the cohort was followed up annually in person for 5 years to evaluate for any telephone screen false-negatives; blood samples for lipid analysis were also taken at these follow-up assessments. The primary outcome of this analysis was ischemic stroke. Neurological events were adjudicated by 2 neurologists independently after review of all data; any disagreements were adjudicated by a third neurologist. Strokes were classified as extracranial atherosclerotic, intracranial atherosclerotic, small vessel (lacunar), cardioembolic, cryptogenic, or other.16

STATISTICAL ANALYSIS

After exploring the distributions of lipid panel components and risk factors, the relationship between total cholesterol, HDL-C, LDL-C, TG, and non–HDL-C levels, total cholesterol:HDL-C and TG:HDL-C ratios, and risk of ischemic stroke was explored. Cox proportional hazard models were constructed using the lipid panel components as continuous variables and with National Cholesterol Education Program–defined cut points using lipid parameters as dichotomous variables (total cholesterol level >240 mg/dL [to convert to millimoles per liter, multiply by 0.0259], LDL-C level >130 mg/dL [to convert to millimoles per liter, multiply by 0.0259], HDL-C level <40 mg/dL [to convert to millimoles per liter, multiply by 0.0259], HDL-C level <40 mg/dL for men and <50 mg/dL for women, TG level >200 mg/dL [to convert to millimoles per liter, multiply by 0.0113], TG: HDL-C ratio >2, non–HDL-C level >160 mg/dL, and upper quartile of total cholesterol:HDL-C ratio). Age, race/ethnicity, sex, and treatment with any cholesterol-lowering medications (at enrollment or in follow-up) were included in all models as interaction terms. The parameter estimates were calculated unadjusted and after adjusting for demographics (age, sex, race/ethnicity, and education) and vascular risk factors (hypertension, diabetes mellitus, smoking, moderate alcohol consumption, and physical activity).

We used repeated serum samples obtained approximately annually for 5 years in the 10% random sample of the population to calculate the change per year of each of the lipid parameters using mixed-effects models. To evaluate whether the follow-up lipid panel measurements affected risk of stroke, we used repeated measures of lipids for the 10% sample to predict the values of lipids from the fitted mixed model for the rest of the sample and fitted Cox models using these predicted values as time-varying covariates. In computing standard errors, the predicted values were estimated as follows: we drew 1000 bootstrap samples from the 10% sample, repeated the procedure of generating predicted values, fitted a Cox model using those values as time-varying covariates, and obtained the log of the hazard ratio. Standard errors were computed using these 1000 values of the log of the hazard ratio. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Baseline characteristics of the cohort available for this analysis (n=2940) are shown in Table 1. The mean age of the cohort was 68.8 years; 63.5% were women. The majority of participants (53.1%) were Hispanic, with a similar proportion of non-Hispanic black and white individuals making up the rest of the cohort; 54.1% of participants did not complete high school. Mean follow-up for the cohort was 7.5 years.

Mean (SD) baseline HDL-C level for the cohort was 47.0 (14.7) mg/dL. Mean HDL-C level for women was higher than in men (50.3 mg/dL vs 44.1 mg/dL). The mean HDL-C level was highest in black individuals (52.0 mg/dL) and lowest in Hispanic individuals (43.9 mg/dL). Other lipid parameters are summarized in Table 2.

We detected 160 ischemic strokes, of which 28 were of the atherosclerotic subtype, 46 were small vessel, 47
were cardioemolic, and 35 were cryptogenic.46 Using dichotomous definitions (Table 3), baseline elevated HDL-C (adjusted hazard ratio [HR], 1.21; 95% confidence interval [CI], 0.87-1.69) and TG (adjusted HR, 1.19; 95% CI, 0.77-1.84) levels and TG:HDL-C (adjusted HR, 0.88; 95% CI, 0.62-1.26) and total cholesterol:HDL-C (adjusted HR, 0.79; 95% CI, 0.54-1.16) ratios were not associated with risk of ischemic stroke in multivariable models. An LDL-C level greater than 130 mg/dL was paradoxically associated with a lower risk of stroke in the entire cohort in univariate and multivariable models (adjusted HR, 0.71; 95% CI, 0.51-0.98). We found a statistically significant interaction term between treatment with lipid-lowering medications and LDL-C level (P = .005), non–HDL-C level (P = .01), and total cholesterol level (P = .04) and stratified results are presented in Table 3 based on the interaction term. Among those who had not received lipid-lowering medications, an LDL-C level greater than 130 mg/dL was not associated with a risk of ischemic stroke compared with those with an LDL-C level less than 130 mg/dL (adjusted HR, 1.09; 95% CI, 0.73-1.62) (Table 3). Unlike the paradoxical associations with risk of ischemic stroke among those taking lipid-lowering medications, there was a trend toward increased risk among those who had not received lipid-lowering medications. Similar results were noted using the lipid panel components as continuous variables, including a paradoxical association with LDL-C level per 10-unit increase (adjusted HR, 0.96; 95% CI, 0.92-1.00) (Table 4).

To isolate the effect of dyslipidemia from that of medications, we carried out analysis excluding those who were taking cholesterol-lowering medications. Levels of LDL-C (adjusted HR, 1.14; 95% CI, 0.77-1.70), non–HDL-C (adjusted HR, 1.24; 95% CI, 0.83-1.85), and total cholesterol (adjusted HR, 1.44; 95% CI, 0.81-2.56) showed trends toward increased risk even though statistical significance was not supported. There were insufficient numbers of atherosclerotic or lacunar stroke subtypes to analyze separately. There was no interaction between any of the lipid panel components and sex, age, or race/ethnicity.

To examine whether the lipid panel components changed over time, we constructed mixed-effects models using the 10% random sample brought back for repeated measures after adjusting for risk factors and medication use. The parameter estimates and regression equations for HDL-C and LDL-C levels are displayed in Table 5. The change in HDL-C level over time was statistically significant but not clinically important over 5 years (0.51 mg/dL per year, P < .001). For LDL-C level, the model predicted a decline of 3.1 mg/dL annually (P < .001). When considering effect modification by age and treatment with cholesterol-lowering medications, the annual decline in LDL-C level was larger among those taking medications (8.4 mg/dL annually).

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### Table 1. Baseline Characteristics of the 2940 Subjects in the Northern Manhattan Cohort With Baseline Lipid Levels Available and No History of Myocardial Infarction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>68.8 (10.3)</td>
</tr>
<tr>
<td>Men</td>
<td>1074 (36.5)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1561 (53.1)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>714 (24.3)</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>598 (20.3)</td>
</tr>
<tr>
<td>Education, completed high school</td>
<td>1350 (45.9)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2128 (72.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>613 (20.9)</td>
</tr>
<tr>
<td>Coronary artery disease*</td>
<td>508 (17.3)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>508 (17.3)</td>
</tr>
<tr>
<td>Waist circumference, in, mean (SD)</td>
<td>36.7 (63)</td>
</tr>
<tr>
<td>Physically inactive</td>
<td>1176 (40.2)</td>
</tr>
<tr>
<td>Moderate alcohol intake</td>
<td>985 (33.6)</td>
</tr>
</tbody>
</table>

*Any cardiac disease in patients without baseline myocardial infarction.

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### Table 2. Mean Serum Lipid Panel Components

<table>
<thead>
<tr>
<th>Component</th>
<th>Mean (SD) Level, mg/dL</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td>47.0 (14.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>M</td>
<td>41.4 (12.7)</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>50.3 (14.8)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>43.9 (13.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Black</td>
<td>52.0 (16.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White</td>
<td>48.8 (14.8)</td>
<td>Reference</td>
</tr>
<tr>
<td>LDL-C</td>
<td>129.5 (36.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>M</td>
<td>123.5 (34.7)</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>132.9 (36.2)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>129.6 (35.8)</td>
<td>.08</td>
</tr>
<tr>
<td>Black</td>
<td>126.8 (36.6)</td>
<td>.004</td>
</tr>
<tr>
<td>White</td>
<td>132.6 (34.9)</td>
<td>Reference</td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>156.2 (40.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>M</td>
<td>150.4 (38.7)</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>159.5 (40.5)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>158.2 (40.3)</td>
<td>.55</td>
</tr>
<tr>
<td>Black</td>
<td>149.7 (40.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White</td>
<td>159.3 (38.9)</td>
<td>Reference</td>
</tr>
<tr>
<td>TG</td>
<td>135.6 (78.9)</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>138.3 (92.2)</td>
<td>.50</td>
</tr>
<tr>
<td>F</td>
<td>134.0 (70.0)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>145.8 (82.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Black</td>
<td>115.6 (70.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White</td>
<td>135.6 (77.3)</td>
<td>Reference</td>
</tr>
<tr>
<td>TG:HDL-C ratio</td>
<td>3.4 (2.2)</td>
<td>.001</td>
</tr>
<tr>
<td>M</td>
<td>3.9 (4.1)</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>3.1 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.8 (3.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Black</td>
<td>2.7 (2.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White</td>
<td>3.4 (3.6)</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides. SI conversion factors: To convert HDL-C and LDL-C to millimoles per liter, multiply by 0.0259; TG to millimoles per liter, multiply by 0.0113.
Table 3. HRs and 95% CIs for lipid parameters and risk of ischemic stroke using dichotomous definitions

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C level (men, &lt;40 mg/dL; women, &lt;50 mg/dL)</td>
<td>1.14 (0.84-1.55)</td>
<td>1.21 (0.87-1.69)</td>
</tr>
<tr>
<td>LDL-C level &gt; 130 mg/dL</td>
<td>0.68 (0.49-0.93)</td>
<td>0.71 (0.51-0.98)</td>
</tr>
<tr>
<td>Taking cholesterol-lowering medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not taking cholesterol-lowering medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG level &gt; 200 mg/dL</td>
<td>1.4 (0.94-2.08)</td>
<td>1.19 (0.77-1.84)</td>
</tr>
<tr>
<td>TG: HDL-C ratio &gt; 2</td>
<td>1.03 (0.75-1.43)</td>
<td>0.88 (0.62-1.26)</td>
</tr>
<tr>
<td>Non-HDL-C level &gt; 160 mg/dL</td>
<td>0.75 (0.55-1.03)</td>
<td>0.74 (0.53-1.02)</td>
</tr>
<tr>
<td>Taking cholesterol-lowering medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not taking cholesterol-lowering medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol level &gt; 240 mg/dL</td>
<td>0.82 (0.54-1.25)</td>
<td>0.76 (0.48-1.18)</td>
</tr>
<tr>
<td>Taking cholesterol-lowering medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not taking cholesterol-lowering medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol: HDL-C ratio in the upper quartile</td>
<td>0.97 (0.69-1.39)</td>
<td>0.79 (0.54-1.16)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

SI conversion factors: See Table 2.

a Adjusted for age, sex, race/ethnicity, education, hypertension, diabetes mellitus, other lipid profile parameters, smoking, coronary artery disease, moderate alcohol consumption, and physical activity.

b Stratified models based on an interaction term with lipid-lowering medications, P < .05.

Table 4. HRs and 95% CIs for lipid parameters as continuous variables and risk of ischemic stroke

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C level (per 10-U increase)</td>
<td>0.98 (0.88-1.09)</td>
<td>1.02 (0.90-1.14)</td>
</tr>
<tr>
<td>LDL-C level (per 10-U increase)</td>
<td>0.96 (0.92-1.01)</td>
<td>0.96 (0.92-1.00)</td>
</tr>
<tr>
<td>Taking cholesterol-lowering medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not taking cholesterol-lowering medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG level (per 10-U increase)</td>
<td>1.00 (0.98-1.02)</td>
<td>0.99 (0.97-1.01)</td>
</tr>
<tr>
<td>TG: HDL-C ratio</td>
<td>1.00 (0.96-1.05)</td>
<td>0.98 (0.92-1.04)</td>
</tr>
<tr>
<td>Non-HDL-C level (per 10-U increase)</td>
<td>0.97 (0.94-1.01)</td>
<td>0.96 (0.92-1.00)</td>
</tr>
<tr>
<td>Total cholesterol level (per 10-U increase)</td>
<td>0.97 (0.93-1.01)</td>
<td>0.96 (0.92-1.00)</td>
</tr>
<tr>
<td>Total cholesterol: HDL-C ratio</td>
<td>0.99 (0.90-1.09)</td>
<td>0.94 (0.85-1.05)</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 3.

a Adjusted for age, sex, race/ethnicity, education, hypertension, diabetes mellitus, other lipid profile parameters, smoking, coronary artery disease, moderate alcohol consumption, and physical activity.

b Stratified models based on an interaction term with lipid-lowering medications, P < .05.

Table 5. Mixed-effects models for LDL-C

<table>
<thead>
<tr>
<th>Lipid Panel Component</th>
<th>Parameter Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>-2.54</td>
</tr>
<tr>
<td>Time × age &gt; 69 y interaction</td>
<td>-0.13</td>
</tr>
<tr>
<td>Time × &lt; high school education interaction</td>
<td>2.21</td>
</tr>
<tr>
<td>Time × cholesterol-lowering medication interaction</td>
<td>-5.9</td>
</tr>
</tbody>
</table>

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

a High-density lipoprotein cholesterol regression equation: HDL-C = 42.59 + 0.31 × time + 3.6 × black − 2.68 × Hispanic + 0.33 × age > 69 y + 0.36 × (high school education) − 7.98 × sex − 0.65 × (waist circumference) + 1.63 × (moderate alcohol use) − 0.96 × (former tobacco user) − 1.04 × (current tobacco user) − 0.33 × (blood glucose level) − 0.51 × (moderate to heavy physical activity) − 0.06 × (coronary artery disease) − 0.04 × (systolic blood pressure) + 0.19 × (diastolic blood pressure). Low-density lipoprotein cholesterol regression equation: LDL-C = 110.55 − 2.54 × time − 5.43 × black − 2.49 × Hispanic − 0.02 × age > 69 y + 1.85 × (high school education) − 9.15 × sex − 0.53 × (waist circumference) + 5.61 × (moderate alcohol use) + 3.35 × (former tobacco use) − 6.8 × (current tobacco use) + 0.04 × (blood glucose level) − 2.49 × (moderate to heavy physical activity) − 5.9 × (coronary artery disease) + 0.16 × (systolic blood pressure) + 0.15 × (diastolic blood pressure) − 0.13 × (age > 69 y × time) + 2.21 × (high school education × time) − 5.9 × (cholesterol-lowering medications × time).

To further explore whether the decline of LDL-C level over time explained our paradoxical findings, we calculated 5 years’ predicted LDL-C values for our cohort using the coefficients from the mixed-effect model. A Cox model using these as time-varying covariates indicated that an LDL-C level greater than 130 mg/dL was associated with an increased ischemic stroke risk (adjusted HR, 3.81; 95% CI, 1.53-9.51). Cox models using the actual repeated measures in the 10% sample indicated that an LDL-C level greater than 130 mg/dL was associated with a trend toward a greater risk of ischemic stroke (HR, 1.04; 95% CI, 0.42-2.37).
In this prospective cohort study, none of the lipid parameters measured at enrollment were associated with increased risk of ischemic stroke except for a paradoxical effect of elevated LDL-C, total cholesterol, and non–HDL-C levels. Patients are more likely in recent years to be prescribed statins, and this may in part explain our findings. Statins have been associated with a significantly reduced risk of ischemic stroke in several clinical trials, and the target LDL-C level has been steadily decreasing, given this evidence. One meta-analysis found that in clinical trials reductions in LDL-C level were associated with a significant relative risk reduction in stroke for the atherosclerotic subtype. We found that treatment with cholesterol-lowering medications modified the effect of an elevated LDL-C level such that those not taking medications did not have an association with ischemic stroke risk. When excluding those taking medications, we no longer observed our paradoxical results, and there was a trend toward an increased risk of ischemic stroke with an LDL-C level greater than 130 mg/dL.

Level of LDL-C decreased over time in our cohort. To explore whether a decrease in LDL-C level over time explained our results of a paradoxical association between elevated LDL-C level and risk of ischemic stroke, we performed analyses using time-dependent covariates accounting for changes in LDL-C level over time. Our results suggest that repeated measurements of LDL-C and measurements closer to the event may be a better predictor of ischemic stroke than levels measured at a single baseline point. These analyses, while exploratory, may be interpreted as providing evidence that LDL-C levels closer to stroke, as well their change over time, are more important than baseline levels measured several years prior to the stroke. These models provide an explanation for our apparent paradoxical results of a decreased risk of stroke associated with elevated LDL-C levels, as well as the varying results in the literature.

Our results differ from those of some other case-control and cohort studies. The protective effect of HDL-C on ischemic stroke risk was reported in several case-control and population-based studies. Fewer studies have included elderly or more ethnically diverse populations such as ours. Prospective cohorts of Japanese men and women, as well as predominantly white participants in the Systolic Hypertension in the Elderly Program, indicated a protective effect from an elevated HDL-C level. In a prior case-control study involving northern Manhattan residents, we reported a strong protective effect for HDL-C level on ischemic stroke in all ethnic groups, in those older than 75 years, and strongest in the atherosclerotic subtype.

The effect of lipids on ischemic stroke has not been observed in all populations, however. In the Atherosclerosis Risk in Communities study and the Cardiovascular Health Study, there was no association between HDL-C or LDL-C levels and ischemic stroke. The Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study were different from previously noted positive studies in that they involved large communities in the United States with a higher representation of black individuals and subjects who were 65 years or older. In that respect, the demographics of these studies are similar to ours, and this may explain the similarities in our results. The reasons for the differences with other studies are not clear but could be related to a selection bias against younger adults who have had vascular disease related to dyslipidemia in our study or a selection of a healthier older population.

The present prospective cohort study design may provide a more reliable estimate of the association between baseline levels of lipids and stroke than our prior case-control study. One difference between this study and our case-control study relates to the timing of lipid measurement. One criticism of case-control studies involving cholesterol, and particularly HDL-C, is that levels at the time of ischemic stroke may be lower. This is likely an incomplete explanation for our findings, as prior data from NOMAS provided some evidence of the stability of lipid levels after stroke, and the HDL-C level did not change in a clinically important fashion in our mixed-effects models.

The lack of association between ischemic stroke and plasma lipid components could also be explained by the pathophysiology of cerebrovascular disease. In particular, stroke is a heterogeneous disease and combining ischemic stroke into one disease for the purposes of these analyses may underestimate effects of particular risk factors. Lacunar strokes, arising from lipohyalinosis of small perforating arteries, may be primarily related to hypertension and diabetes, while cardioembolic stroke is related to the formation of thrombin-rich clots that form in the heart. Carotid and intracranial artery atherosclerosis are other risk factors for ischemic stroke, and their development is influenced by the serum lipid profile. In our study, the numbers of each stroke subtype were not sufficient to determine an effect in subtypes. In addition, the categorization of strokes into subtypes is imperfect and misclassification could also lead to underestimation of an effect.

Our study has several strengths, including minimal loss to follow-up, repeated measures in a subsample of the cohort allowing for analysis of time-varying covariates, and a representative sample of 3 different race/ethnic groups. This study also has weaknesses, however. The number of ischemic strokes may have been too small to detect subtle protective effects from an elevated HDL-C level or other abnormalities in the plasma lipid profile, especially if the effect was mostly in the atherosclerotic subtype. In NOMAS, we only collected a fasting lipid panel, and we therefore may not have been able to detect the effects that others have noted for nonfasting TG level. We had insufficient numbers to detect interaction by sex, age, or race/ethnicity, and so we cannot conclude if the effect is differential in segments of our cohort. Nonetheless, our findings are in keeping with other large population-based cohorts that included subjects older than 65 years and nonwhite individuals.

Our study has public health implications, especially as elderly individuals continue to live longer and there is more of a need to understand which vascular risk factors require treatment in individuals already taking mul-
mplete medications. It may be that stroke risk reduction strategies aimed at reducing all components of the plasma lipid profile will have limited benefits. While it is well established that statins reduce the risk of first and recurrent ischemic stroke in patients,\textsuperscript{18,41} our data indicate that the effect may be mediated by the effect on LDL-C and non-HDL-C levels.

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Author Contributions: Dr Willey 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. Study concept and design: Willey, Xu, Boden-Albala, Paik, Sacco, and Elkind. Acquisition of data: Boden-Albala and Paik. Analysis and interpretation of data: Willey, Xu, Boden-Albala, Paik, Moon, Sacco, and Elkind. Drafting of the manuscript: Willey and Xu. Critical revision of the manuscript for important intellectual content: Willey, Boden-Albala, Paik, Moon, Sacco, and Elkind. Statistical analysis: Willey, Xu, Boden-Albala, Paik, and Moon. Obtained funding: Sacco. Administrative, technical, and material support: Sacco. Study supervision: Boden-Albala, Paik, Sacco, and Elkind.

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Error in Author Affiliation. In the Original Contribution titled “Diffusion Abnormalities in the Primary Sensorimotor Pathways in Writer’s Cramp” by Delmaire et al, published in the April issue of the Archives (2009; 66[4]:502-508), an error occurred in the Author Affiliations paragraph on page 507. In that paragraph, the affiliation for Christophe Lenglet, PhD, was incorrect. The entire paragraph should have appeared as follows:

“Author Affiliations: Department of Neuroradiology, Centre Hospitalier Regional Universitaire Roger Salengro, Lille, France (Dr Delmaire); Center for Neuroimaging Research (Drs Delmaire, Valabregue, and Lhericy), Institut National de la Sante et de la Recherche Medicales (INSERM) U610 (Drs Delmaire and Lhericy), Departments of Neurology (Drs Vidalh et and Sangla) and Neuroradiology (Dr Lhericy), and INSERM U679 (Dr Vidalh et), Groupe Hospitalier Pitié-Salpêtrière, Université Pierre et Marie Curie-Paris, and Department of Neurology, Hôpital Foch (Dr Bourdain), Paris, France; Institut National de Recherche en Informatique et en Automatique, Odyssee Project Team, Sophia Antipolis, France (Mr Wassermann and Drs Descoteaux, Lenglet, and Deriche); and Department of Physiology, Centre Hospitalier Universitaire Nantes, Nantes, France (Dr Terrier). Dr Lenglet is now with the Center for Magnetic Resonance Research, Departments of Radiology and Electrical and Computer Engineering, University of Minnesota, Minneapolis.”