High-Density Lipoprotein Cholesterol and Ischemic Stroke in the Elderly

The Northern Manhattan Stroke Study

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Context Elevated high-density lipoprotein cholesterol (HDL-C) levels have been shown to be protective against cardiovascular disease. However, the association of specific lipoprotein classes and ischemic stroke has not been well defined, particularly in higher-risk minority populations.

Objective To evaluate the association between HDL-C and ischemic stroke in an elderly, racially or ethnically diverse population.

Design Population-based, incident case-control study conducted July 1993 through June 1997.

Setting A multiethnic community in northern Manhattan, New York, NY.

Participants Cases (n=539) of first ischemic stroke (67% aged ≥65 years; 55% women; 53% Hispanic, 28% black, and 19% white) were enrolled and matched by age, sex, and race or ethnicity to stroke-free community residents (controls; n=905).

Main Outcome Measure Independent association of fasting HDL-C levels, determined at enrollment, with ischemic stroke, including atherosclerotic and nonatherosclerotic ischemic stroke subtypes.

Results After risk factor adjustment, a protective effect was observed for HDL-C levels of at least 35 mg/dL (0.91 mmol/L) (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.39-0.72). A dose-response relationship was observed (OR, 0.65; 95% CI, 0.47-0.90 and OR, 0.31; 95% CI, 0.21-0.46) for HDL-C levels of 35 to 49 mg/dL (0.91-1.28 mmol/L) and at least 50 mg/dL (1.29 mmol/L), respectively. The protective effect of a higher HDL-C level was significant among participants aged 75 years or older (OR, 0.51; 95% CI, 0.27-0.94), was more potent for the atherosclerotic stroke subtype (OR, 0.20; 95% CI, 0.08-0.50), and was present in all 3 racial or ethnic groups studied.

Conclusions Increased HDL-C levels are associated with reduced risk of ischemic stroke in the elderly and among different racial or ethnic groups. These data add to the evidence relating lipids to stroke and support HDL-C as an important modifiable stroke risk factor.

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STROKE IS A MAJOR CAUSE OF death and disability in the United States and is a growing public health concern. The latest projections estimate that more than 1 million strokes will occur every year by the year 2010. Moreover, stroke has a disproportionate impact on elderly, black, and Hispanic persons, who are among the fastest growing segments of the US population. Many studies have provided strong evidence for lipids as a risk factor for coronary artery disease (CAD). These studies demonstrate a direct relationship between total cholesterol, low-density lipoprotein cholesterol (LDL-C), and CAD and an inverse relationship between high-density lipoprotein cholesterol (HDL-C) and CAD.[1-4] These relationships have not been as clearly established for ischemic stroke with some studies even questioning whether cholesterol is a risk factor for stroke.

The advent of statin agents, which significantly lower lipid levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, has focused more research on lipids in all vascular outcomes, in particular stroke. Compelling data from statin trials show impressive reductions in stroke risk among persons with CAD.[5] Some researchers have suggested that the

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improvement in cardiovascular and cerebrovascular end points with statin agents cannot be completely explained by the baseline or treated LDL-C levels alone.[6-8] Furthermore, several studies have suggested that low levels of HDL-C without high levels of LDL-C characterizes 20% to 30% of patients with CAD in the United States.[9,10] The benefits of statins for stroke reduction have reinitiated discussions of the role of lipids as a stroke risk factor.

Few studies have examined the relation between fractionated cholesterol and stroke. None of these studies analyzed data based on stroke subtype and age category or in a population that included black, Hispanic, and white persons all residing in the same geographic sampling frame. The purpose of this study was to examine the association of specific lipoprotein classes and ischemic stroke among elderly Hispanic, black, and white persons, residing in the same community, as part of the Northern Manhattan Stroke Study (NOMASS).

METHODS

Selection of Cases

We conducted a population-based case-control study in the northern Manhattan community.[11] Methods for case detection in NOMASS have been previously described.[12] Briefly, 688 incident cases were prospectively enrolled between July 1, 1993, and June 30, 1997, based on the following criteria: (1) diagnosed as having a first cerebral infarction, fatal or nonfatal; (2) older than age 39 years at onset of stroke; and (3) a resident of Northern Manhattan in a household with a telephone. Patients with intracerebral or subarachnoid hemorrhage and transient ischemic attack were excluded.

Case surveillance included screening of all admissions, discharges, and head computed tomographic scans at the Columbia-Presbyterian Medical Center, the only hospital in the community. Cases were also identified through discharge lists from other hospitals and through a comprehensive community-based surveillance system for nonhospitalized persons with stroke. Because lipid profiles were not obtained from patients who were admitted at some of the other hospitals, only 539 of the cases were analyzed in this study. To ensure that the 539 cases did not differ substantially from the entire NOMASS cohort, we compared baseline variables available in both groups. We found that the study group was representative of the entire sample with no significant differences in the baseline demographics, risk factors, and total cholesterol levels.

Selection of Controls

Methods of control recruitment and enrollment have also been described in previous publications.[13,14] Stroke-free community subjects were identified by random-digit dialing using dual frame sampling to identify both published and unpublished telephone numbers. When a household was contacted, the research objectives were explained and a resident aged 39 years or older was interviewed briefly to record age, sex, race or ethnicity, and risk factors. These telephone interviews were conducted by Audits and Surveys, Inc, New York, NY, using trained bilingual interviewers. Approximately 46453 numbers were dialed to reach 9608 households, 876 people refused an interview (telephone response rate 91%).

Telephone interview data from control-eligible subjects were downloaded to the NOMASS computer system and assigned to cells defined by age, sex, and race or ethnicity. Patients were randomly selected from cells matched to the accumulating case group by age, sex, and race or ethnicity and were recontacted by the NOMASS staff. The in-person participation rate for selected and matched controls was 75%. Therefore, our overall control response rate was 68%. Appointments were made for in person evaluations at the hospital or home for those who could not come in-person (7% were done at home). Approximately 80% of the cases were matched to 2 controls, and 12% were matched to 1 control; 8% were matched to other case-control strata. The institutional review boards of Columbia-Presbyterian Medical Center and the other hospitals approved the study, and written informed consent was obtained at the time of the in-person visit.

Evaluation of Index Cases and Controls

Data were collected through interviews of cases and controls by trained bilingual research assistants using standardized data collection instruments, medical record review, physical and neurological examination by the study physicians, in-person measurements, and fasting blood specimens for lipid, glucose, and cholesterol level determinations as previously described.[15] Race or ethnicity, hypertension, diabetes mellitus, any cardiac disease, physical activity, smoking status, alcohol use, and body mass index (BMI) were defined using standardized criteria as outlined in prior publications.[13-15] When the subject was unable to answer questions, a proxy who was knowledgeable about the patient's history was interviewed. Proxy respondents were used for 26% of cases and 1% of controls. Reliability studies between proxies and subjects showed excellent concordance for specific risk factors questions including alcohol consumption ($r=0.81$; $P<.001$) and physical activity ($r=0.69$; $P<.01$). Moreover, measurement of serum glucose and lipids were used in the definitions of stroke risk factors.

Cases of ischemic stroke were classified into infarct subtype categories based on the results of their neurovascular evaluation. Stroke subtype was determined after review of all the available data by a diagnostic committee as described in prior reports.[16] In this analysis, patients were subdivided into 2 groups: infarction due to atherosclerosis that included extracranial or intracranial atherosclerosis, and nonatherosclerotic infarction that included cardioembolism, lacune, and cryptogenic infarction.

Lipid and Lipoprotein Analysis

Fasting blood samples were drawn within several days of study enroll-

ment, usually within 72 hours of admission. 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 (apo B) containing lipoproteins by phosphotungstic acid. Low-density lipoprotein cholesterol concentrations were calculated by the Friedewald formula.[17]

Statistical Analysis

Univariate and multivariable conditional logistic regression models for matched case-control data were used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for HDL-C level and ischemic stroke after adjusting for potential confounding variables (hypertension, diabetes, heart disease, current smoking status, BMI, physical activity, and education level as a marker of socioeconomic status[18]). Several analyses also adjusted for total cholesterol, LDL-C, and triglyceride levels. High-density lipoprotein cholesterol level was examined continuously, dichotomously, and as 3 categories, based on standard criteria set by the second report of the National Cholesterol Education Program (NCEP).[19] The categorical approach was preferred because it permitted the calculation of ORs that gave more clinical interpretable measures of risk. Analyses were conducted overall and stratified by age, sex, race or ethnicity, and ischemic stroke subtype. All tests were 2 sided; significance was determined to be $P<.05$. Statistical analyses were performed using SAS software (SAS Institute, Cary, NC).

RESULTS

We analyzed 539 ischemic stroke cases and 905 controls (TABLE 1). Among the cases, 67% were aged 65 years or older; 55% were women; 53%, Hispanic; 28%, black; and 19%, white. Subjects in the "Other" race or ethnic category were not included in the analyses discussed in this article because of the small numbers.

The median total cholesterol, HDL-C, and LDL-C levels were lower in cases than in the controls, while the median triglyceride levels were higher in the cases (TABLE 2). A higher percentage of participants in the control group than

Table 1. Distribution of Sociodemographics and Vascular Risk Factors Among Cases and Controls in the Northern Manhattan Stroke Study*

Characteristics	No. (%) of Patients: Cases (n = 539)	Controls (n = 905)	*P* Value
Age ≥65 y	363 (67)	623 (69)	. . .
Women	296 (55)	544 (60)	. . .
Race-ethnicity			
Hispanic	283 (53)	424 (47)	. . .
Black	150 (28)	282 (31)	. . .
White	100 (19)	192 (21)	. . .
Other	6 (1)	7 (1)	. . .
Hypertension	383 (71)	487 (54)	<.001
Diabetes	178 (33)	178 (20)	<.001
Cardiac disease	205 (38)	228 (25)	<.001
Current smoking status	113 (22)	161 (18)	.01
Heavy alcohol use (≥5 drinks/d)	20 (4)	16 (2)	.02
Physical inactivity	295 (55)	278 (31)	<.001
Hypercholesterolemia by history	168 (31)	316 (35)	.17
Obesity	199 (40)	384 (43)	.18
Education ≥high school	175 (33)	453 (50)	<.001
Medicaid or no insurance	289 (54)	344 (38)	<.001

*Ellipses indicate not applicable because cases and controls were matched by age, sex, and race or ethnicity.

Table 2. Univariate Comparisons of Mean, Median, and Frequency Distributions of Fasting Lipid Values Among Cases and Controls*

	Cases (n = 539)	Controls (n = 905)	*P* Value†
Total cholesterol, mg/dL			
Mean (SD)	193 (45)	203 (42)	<.001
Median	191	201	
≤200	317 (59)	436 (48)	<.001
201-239	141 (26)	315 (35)	
≥240	81 (15)	153 (17)	
LDL-C, mg/dL			
Mean	122 (40)	129 (89)	.04
Median	121	126	
≤130	328 (61)	496 (55)	.06
131-159	126 (23)	256 (28)	
≥160	84 (16)	152 (17)	
HDL-C, mg/dL			
Mean	40 (12)	47 (15)	<.001
Median	38	45	
≤34	186 (34)	185 (20)	<.001
35-49	251 (47)	384 (42)	
≥50	105 (19)	336 (37)	
Triglycerides, mg/dL			
Mean	153 (73)	147 (84)	.16
Median	136	127	
≤199	435 (81)	758 (84)	.13
≥200	104 (19)	146 (16)	

*Data are presented as number (percentage) unless otherwise indicated. To convert total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) from mg/dL to mmol/L, multiply by 0.0259. To convert triglyceride concentration from mg/dL to mmol/L, multiply by 0.0113.
†Significant χ^2 test for the categorized lipid levels and *t* test for the means.

Table 3. Univariate and Multivariable Analyses of the Protective Dose-Response Effect of High-Density Lipoprotein Cholesterol (HDL-C) on Ischemic Stroke*

	Unadjusted†		Adjusted for Risk Factors‡		Adjusted for LDL-C, Triglycerides, and Risk Factors§	
Variables	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Dichotomous						
HDL-C ≥35 mg/dL	0.50 (0.39-0.65)	<.001	0.53 (0.39-0.72)	<.001	0.50 (0.37-0.70)	<.001
Dose response						
HDL-C 35-49 mg/dL	0.65 (0.49-0.85)	<.01	0.65 (0.47-0.90)	.01	0.63 (0.45-0.88)	<.01
HDL-C ≥50 mg/dL	0.29 (0.21-0.41)	.001	0.31 (0.21-0.46)	<.001	0.29 (0.19-0.44)	<.001

*OR indicates odds ratio; CI, confidence interval. To convert HDL-C from mg/dL to mmol/L, multiply by 0.0259.
†Matched by age, sex, and race or ethnicity.
‡Matched by age, sex, and race or ethnicity and adjusted for hypertension, diabetes mellitus, cardiac disease, current smoking status, body mass index, physical activity, and education.
§The levels of low-density lipoprotein cholesterol (LDL-C) are at least 130 mg/dL (3.4 mmol/L) and triglyceride levels are at least 200 mg/dL (2.3 mmol/L).

Table 4. Protective Effect of High-Density Lipoprotein Cholesterol Levels Higher Than 35 mg/dL and Ischemic Stroke Stratified by Age, Sex, and Race or Ethnicity*

Variables	OR (95% CI)
Age, y	
<65	0.76 (0.44-1.32)
65-74	0.38 (0.22-0.65)
≥75	0.51 (0.27-0.94)
Sex	
Women	0.48 (0.30-0.76)
Men	0.51 (0.33-0.79)
Race or ethnicity	
White	0.22 (0.09-0.50)
Black	0.52 (0.26-1.04)
Hispanic	0.54 (0.35-0.82)

*Adjusted for hypertension, diabetes mellitus, cardiac disease, current smoking status, body mass index, physical activity, and educational level. OR indicates odds ratio; CI, confidence interval. To convert high-density lipoprotein cholesterol from mg/dL to mmol/L multiply by 0.0259.

in the case group had HDL-C levels of 50 mg/dL (1.29 mmol/L) or higher than those in the case group. When HDL-C levels were examined dichotomously, unadjusted for other risk factors, a protective effect was seen for ischemic stroke in patients with levels of at least 35 mg/dL (0.91 mmol/L) or higher (OR, 0.50; 95% CI, 0.39-0.65) (TABLE 3). The protective effect was greater for patients with HDL-C levels of 50 mg/dL (1.29 mmol/L) or higher than patients with HDL-C levels between 35 and 49 mg/dL (0.91-1.27 mmol/L). In multivariable analysis, adjusted for hypertension, diabetes, cardiac disease, current smoking status, BMI, physical activity, and educational level, the protective effects of HDL-C were similar. Although the use of aspirin and cholesterol-lowering medications was low in this community sample (20% taking aspirin; 9%, cholesterol-lowering medications), multivariate analyses adjusting for these medications did not alter our model.

In multivariable analyses, adjusting for LDL-C levels of 130 mg/dL (3.4 mmol/L) or higher and triglyceride levels of 200 mg/dL (2.3 mmol/L) or higher had no effect on the protective effect of HDL-C against ischemic stroke (Table 3). When total cholesterol levels of 240 mg/dL (6.2 mmol/L) or higher were added to the multivariate model, the ORs were unchanged (Data not shown). When HDL-C levels were examined as a continuous variable in a multivariate model including stroke risk factors and LDL-C and triglyceride levels, a protective effect was found with an OR of 0.81 (95% CI, 0.77-0.86) for a 5-mg/dL (0.13-mmol/L) increase in the HDL-C level. This translated into a 19% odds reduction for stroke.

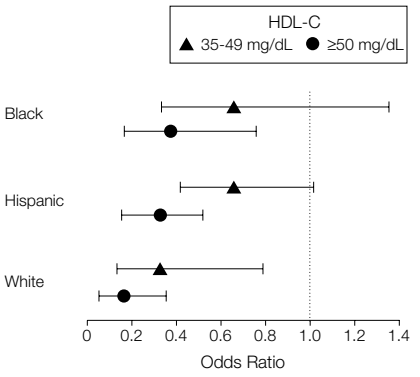
The protective effects of HDL-C levels were analyzed by age, sex, and race or ethnic subgroups and were found to be similar for all groups with a statistically significant protective effect evident in patients aged 75 years or older (adjusted OR, 0.51; 95% CI, 0.27-0.94) (TABLE 4). A similar dose-response relationship was observed in all 3 race or ethnic groups (FIGURE). When ischemic stroke was stratified by atherosclerotic ischemic stroke and nonatherosclerotic ischemic stroke (nonatherosclerotic infarction) subtype in the multivariable model, a clear protective effect was seen for both stroke subtypes (TABLE 5). The protective effect of HDL-C was significantly more pronounced for the atherosclerotic stroke subtype than the nonatherosclerotic subtype (test for heterogeneity, $z=2.18$; $P=.02$).

COMMENT

This population-based case-control study has demonstrated a protective effect of greater HDL-C level for ischemic stroke in an elderly, multiethnic population of men and women. Higher HDL-C levels were significantly more protective against atherosclerotic ischemic stroke than nonatherosclerotic stroke subtypes. The protective dose-response relationship was observed even when HDL-C levels were adjusted for total cholesterol or LDL-C and triglyceride levels suggesting that this protective effect is not mediated by relationships between HDL-C and other measured lipid levels. Our effect estimates for HDL-C levels were adjusted for multiple potential confounders and for other known stroke risk factors including hypertension, diabetes, cardiac disease, current smoking status, physical activity, BMI, and educational level as a marker of socioeconomic status. These adjustments had little effect on the magnitude of the protective effect of HDL-C levels for ischemic stroke. These results imply a need to examine fractionated cholesterol levels when assessing stroke risk, since HDL-C is a potentially modifiable stroke risk factor.

The relationship between abnormalities of serum lipids and stroke has been less clear than for CAD.[20] Some prospective cohort studies including the Framingham Heart Study have found no association between total serum cholesterol or HDL-C level and cerebral infarction.[21] Others have found a modest relationship. In the Multiple Risk Factor Intervention Trial, mortality from ischemic stroke was greater among men with high total cholesterol levels.[22] In the Honolulu Heart Program, there was a continuous and progres-

Figure. Protective-Dose Response Relationship of High-Density Lipoprotein Cholesterol (HDL-C) and Stroke Risk Stratified by Race and Ethnicity



Matched for age and sex and adjusted for hypertension, diabetes mellitus, body mass index, corornary artery disease, physical activity, and educational level. To convert HDL-C from mg/dL to mmol/L, multiply by 0.0259. Error bars indicate 95% confidence intervals.

Table 5. Protective Effect of High-Density Lipoprotein Cholesterol (HDL-C) Level Stratified by Stroke Subtype

Variables	Atherosclerotic (81 Cases, 145 Controls) OR (95% CI)	*P* Value	Nonatherosclerotic (411 Cases/735 Controls) OR (95% CI)	*P* Value
Dichotomous				
HDL-C ≥35 mg/dL†	0.20 (0.08-.50)	<.001	0.60 (0.42-0.85)	<.01
Dose response				
HDL-C 35-49 mg/dL	0.24 (0.09-0.63)	<.01	0.76 (0.52-1.10)	.14
HDL-C ≥50 mg/dL	0.13 (0.04-0.43)	<.001	0.34 (0.21-0.53)	<.001

*OR indicates odds ratio; CI, confidence interval. Adjusted for hypertension, diabetes mellitus, cardiac disease, current smoking, body mass index, physical activity, educational level. To convert HDL-C from mg/dL to mmol/L multiply by 0.0259.
†Test for heterogeneity, $z = 2.18$, $P = .02$.

sive increase in thromboembolic stroke rates with increasing levels of total cholesterol level, with a relative risk of 1.4 comparing highest and lowest quartiles.[23] Meta-analyses among prospective studies have found either no or only a minimally increased relative risk of stroke due to elevated total cholesterol level.[24,25] Consistent with these meta-analyses, we found no relationship between total cholesterol levels and stroke risk. The absence of a consistent relationship between total cholesterol levels and stroke in these other studies may be partially explained by the heterogeneity of stroke, the reliance on total cholesterol measurements instead of lipoprotein fractions, and the focus on cardiovascular events rather than on stroke events, which occur more frequently in those aged 65 years or older.

The protective effects of increased HDL-C levels on the risk of myocardial infarction have been established by numerous epidemiologic studies.[26,27] Few studies have examined the relationship between HDL-C level and stroke. A few case-control studies have found the concentration of HDL-C to be lower in persons who had a stroke, even after controlling for other stroke risk factors.[28-32] A strong inverse relationship between HDL-C level and ischemic stroke was observed among predominately white patients in an Israeli prospective cohort and in the Copenhagen City Heart Study.[33,34] Studies using carotid artery ultrasound technology have demonstrated an inverse relationship between HDL-C level and extracranial carotid artery atherosclerosis.[35-39] No published epidemiological studies have evaluated the relationship between HDL-C level and ischemic stroke risk in multiethnic groups or evaluated atherosclerotic stroke subtypes as we have in our study.

Although the mechanisms by which HDL-C protects against ischemic stroke are unclear, several possibilities have been suggested. High-density lipoprotein cholesterol may prevent the oxidation of LDL-C, which has been linked to atherogenesis, or HDL-C may increase the reverse transport of LDL-C from peripheral tissues to the liver where degradation occurs.[4] It has also been suggested that HDL-C may transport antioxidants to LDL-C, making LDL-C less susceptible to oxidation within the endothelium.[40] Most likely, the protective effects of HDL-C levels are multifactorial and other potential mechanisms remain to be elucidated. Furthermore, HDL-C levels may be modifiable. Exercise,[41] weight reduction,[42] moderate alcohol consumption,[43] smoking cessation,[44] and statin agents[45] have all been shown to increase HDL-C levels.

An interesting finding in our study was that HDL-C levels showed more protection for atherosclerotic stroke than nonatherosclerotic infarction but was significantly protective against both subtypes. The more pronounced effect in the atherosclerotic stroke cases underscores the value of evaluating the relationship of stroke risk factors in certain specific stroke subtypes. Not all strokes are directly due to atherosclerosis; therefore, a weaker effect for lipids in some prior epidemiological stroke studies could be due to the lower prevalence of atherosclerotic stroke subtypes. Compared with other studies, our cohort included more black and Hispanic persons who have been found to have a greater incidence of intracranial atherosclerotic stroke.[46] Plaque stabilization, regression, and protection of LDL-C from peroxidation, or both, which has been proposed in the genesis of atheroma formation, may explain why HDL-C levels would be protective against atherosclerotic stroke, but it does not easily explain why HDL-C would be protective against nonatherosclerotic infarction. Nonatherosclerotic infarction includes cardioembolic, cryptogenic, and lacunar infarcts, each of which have a different mechanism. These patients, however, could have atherosclerotic cardiovascular disease, microatheroma of the cerebral vessels, or atherosclerotic plaque in large vessels not easily detected by conventional vascular studies. High-density lipoprotein cholesterol could possibly protect against nonatherosclerotic infarction by causing stabilization or regression of plaque in some of these other conditions.

Clinical trials analyzing the efficacy of lipid-lowering strategies with statins have demonstrated impressive reductions in stroke risk among various high-risk populations with cardiac disease. In these studies, stroke was either a secondary end point, or a nonspecified end point determined based on post hoc analyses.[7,8] Meta-analyses of some of these trials have found significant reductions in stroke risk.[5,47] Two large trials in which stroke was prespecified as a secondary end point, Cholesterol and Recurrent Events (CARE) and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), have also shown significant reductions with pravastatin sodium among patients with coronary artery disease and normal to only modest elevations of cholesterol levels.[48,49] Differences may exist in the magnitude of the effect of HDL-C level in primary prevention trials. In the West of Scotland study,[8] for example, a more modest, nonsignificant stroke risk reduction of only 11% was found. Besides reducing total cholesterol and LDL-C levels, modest elevations of HDL-C levels were reported among those treated with statins.

Moreover, the efficacy of certain statins for stroke prevention has been demonstrated to be significantly greater among those with lower initial levels of HDL-C.[50] The Veterans Affairs–High density lipoprotein cholesterol Trial (VA-HIT)[51] showed an independent protective effect of HDL-C level for stroke and other vascular outcomes over the 5 years of the study. This study examined the effect of increasing HDL-C levels selectively with gemfibrozil, in men with CAD and low levels of LDL-C. The investigators found a 24% reduction in the combined outcomes of death due to CAD, nonfatal myocardial infarction, or stroke with an average 6% increase in HDL-C levels in the first year.[52] Our study demonstrated a 14% to 23% odds reduction in stroke with every 5-mg/dL (0.13 mmol/L) rise in HDL-C, which is equivalent to a 12% increase. These clinical trials demonstrate that stroke can be prevented with modern approaches to lipid lowering and that some of this benefit may be mediated through effects on HDL-C. Our data provide additional evidence for the importance of HDL-C in determining stroke risk.

Several limitations of our study design deserve discussion. The population-based approach and the matching by age, sex, and race or ethnicity, however, minimize the potential biases often associated with case-control studies. Our HDL-C measurements were performed after the stroke and may not accurately reflect prestroke exposure. By design, however, we made special efforts to collect fasting blood within 72 hours of admission. The stability of lipids after stroke is controversial. A few studies have reported that some lipid levels may not be stable after stroke; however, these studies have demonstrated that HDL-C levels are more stable after stroke than triglyceride or total cholesterol levels.[53,54] In a small study,[55] we also demonstrated the stability of HDL-C measurements in the immediate period after stroke.

Some stroke patients enrolled in the study did not have a complete lipid panel and were not included in the analysis of HDL-C; however, total cholesterol values were no different in those included in this subset compared with those without a complete lipid panel. Moreover, it is unlikely that any differential selection of controls with elevated HDL-C could have occurred to bias our results. Furthermore, despite the differential proportion of risk factor information collected by proxy in our cases vs controls, the strong concordance rates for proxy reliability and the reliance on laboratory results for HDL-C levels limit any bias in the collection of lipids and stroke risk.

Our results were adjusted for several known stroke-risk factors; however, some unknown or unmeasured confounders could have been operational. The strength and consistency of the effect of HDL-C across multiple strata minimizes this possibility. The effect of lipid treatments could not be fully evaluated. Information was obtained about lipid-lowering agents, but because so few of the patients in this community were taking these agents at the time of data collection, this variable was not used in the final analyses.

Our study has important public health implications for minority groups and elderly persons. Blacks and Hispanics have a greater mortality and incidence of stroke.[56,57] According to recent US projections, the Hispanic population is one of the fastest growing minority groups in this country. The Northern Manhattan Stroke Study has provided unique information on the incidence of stroke among whites, blacks, and Hispanics, and now has shown a significant modifiable risk factor that is pertinent to each of these ethnic groups and both sexes.[12] This study has also shown a protective effect of high HDL-C levels for ischemic stroke among the "older-elderly," a finding significant in that several researchers have questioned the need to diagnose or treat dyslipidemia in individuals older than 70 years.[58-60] These studies, which were looking primarily at cardiac events, have suggested that other risk factors may become more significant than lipids in persons older than 70 years. Our data suggest that HDL-C is still strongly protective against ischemic stroke among those older than 75 years.

The second report of the NCEP paid greater attention to HDL-C levels as a risk factor.[19] The NCEP recommended the addition of HDL-C to initial cholesterol testing, the designation of high HDL-C levels as a protective factor, and the increased emphasis on physical activity and weight loss as components of the dietary therapy of high blood cholesterol levels. In the third report of the NCEP, the level of HDL-C has been changed to 40 mg/dL (1.03 mmol/L) and the goal for LDL-C–lowering therapy has been modified for those with low levels of HDL-C.[61] The National Stroke Association's stroke prevention guidelines to reduce the risk of first stroke references the NCEP guidelines and recommends statin agents for individuals with high cholesterol levels and atherosclerotic cardiac disease.[19,61,62] This epidemiologic study provides further data to support these guidelines to prevent stroke. More effective detection of low HDL-C levels and treatments to modify this stroke risk fac-

tor could affect significantly the clinical and public health burdens of stroke.

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