

# Low-Density Lipoprotein Cholesterol and the Risk of Dementia With Stroke

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**V**ASCULAR DEMENTIA IS CONSIDERED the second major cause of dementia after Alzheimer disease in Western populations.<sup>1</sup> While the role of coincident vascular disease in patients with Alzheimer disease has received attention,<sup>2</sup> the origin of vascular dementia remains unclear. Previously we found that an apolipoprotein E  $\epsilon 4$  (*APOE*  $\epsilon 4$ ) allele increased the risk of dementia with stroke in a population-based case-control investigation.<sup>3</sup> *APOE* could influence the pathogenesis of dementia with stroke through its effects on lipid metabolism and atherosclerosis,<sup>4</sup> but the relationship between lipids and the risk of dementia in the presence or absence of the *APOE*  $\epsilon 4$  allele has not been investigated. Plasma lipids and lipoprotein fractions were studied in a multiethnic elderly population to test the hypothesis that dyslipidemia could be an independent risk factor for the development of dementia with stroke.

## METHODS

### Subjects

Participants were selected from a random sample of healthy Medicare beneficiaries 65 years or older residing within the community of Washington Heights in northern Manhattan (New

**Context** Next to Alzheimer disease, vascular dementia is the second most common form of dementia in the elderly, yet few specific risk factors have been identified.

**Objective** To investigate the relationship of plasma lipids and lipoproteins to dementia with stroke.

**Design and Setting** Prospective longitudinal community-based study over a 7-year period (1991-1998).

**Participants** A total of 1111 nondemented participants (mean [SD] age, 75.0 [5.9] years) were followed up for an average of 2.1 years (range, 1-7.8 years).

**Main Outcome Measure** Incident dementia with stroke according to standardized criteria, by baseline levels of total plasma cholesterol and triglycerides, low-density lipoprotein (LDL) cholesterol, LDL levels corrected for lipoprotein(a), high-density lipoprotein cholesterol, lipoprotein(a), and apolipoprotein E genotype.

**Results** Two hundred eighty-six (25.7%) of the 1111 subjects developed dementia during follow-up; 61 (21.3%) were classified as having dementia with stroke and 225 (78.7%) as having probable Alzheimer disease. Levels of LDL cholesterol were significantly associated with an increased risk of dementia with stroke. Compared with the lowest quartile, the highest quartile of LDL cholesterol was associated with an approximately 3-fold increase in risk of dementia with stroke, adjusting for vascular risk factors and demographic variables (relative risk [RR], 3.1; 95% confidence interval [CI], 1.5-6.1). Levels of LDL corrected for lipoprotein(a) were an even stronger predictor of dementia with stroke in the adjusted multivariate analysis. Compared with the lowest quartile, the RR of dementia with stroke for the highest quartile of lipoprotein(a)-corrected LDL cholesterol was 4.1 (95% CI, 1.8-9.6) after adjusting for vascular factors and demographic variables. Lipid or lipoprotein levels were not associated with the development of Alzheimer disease in our cohort.

**Conclusions** Elevated levels of LDL cholesterol were associated with the risk of dementia with stroke in elderly patients. Further study is needed to determine whether treatment of elevated LDL cholesterol levels will reduce the risk of dementia with stroke.

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York City), NY. The sampling procedures have been described elsewhere.<sup>5</sup> The institutional review board of Columbia-Presbyterian Medical Center reviewed and approved this project.

Each participant underwent an in-person interview of general health and function at the time of study entry followed by a standard assessment, which

included taking a medical history, performing a physical and neurological examination, and administering a neuropsychological battery previously developed for use in this community.<sup>6</sup> Ethnic origin was classified by self-report using the format of the 1990 US Census.<sup>7</sup> These same clinical assessments were used in the annual fol-

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low-up of all participants. This study was conducted from 1991 through 1998.

Among the 2128 individuals who underwent the initial assessment, 211 (9.9%) died after the initial examination, 492 (23.1%) were not available for subsequent follow-up for reasons of refusal (n = 311), relocation (n = 67), or unable to locate (n = 114), while 71 refused phlebotomy, leaving 1354 individuals eligible for this study. There were no major differences among those categories by age, sex, or education, but more Hispanics (47.4%) than blacks (32.0%) and whites (20.0%) were available for follow-up. For this analysis, we excluded data from 243 individuals (17.9%) because of evidence of dementia at the initial examination. Thus, we restricted the analysis to 1111 individuals without dementia at baseline for whom both fasting lipid levels and APOE genotype were determined.

### Diagnosis of Stroke

Stroke was defined according to the World Health Organization criteria.<sup>8</sup> The diagnosis was based on direct questioning of the participant and the next of kin or caregiver supplemented by a neurological examination, brain imaging, and/or review of existing medical records at the initial and follow-up assessments. We were notified by e-mail of admissions of study participants to our medical center during follow-up and information from telephone follow-up calls, and, in cases of death, review of medical records and death certificates were used to search for the occurrence of stroke. The medical center has been the major health care provider in northern Manhattan and Statewide Planning and Research Cooperative System data have shown that approximately 80% of all patients with stroke in that region are hospitalized there.<sup>9</sup> We included patients with prior stroke in our study because a history of stroke is frequent in stroke patients and their inclusion allowed the sample to be more representative.<sup>10</sup>

### Diagnosis of Dementia

Based on all available information gathered from the initial and follow-up clinical

assessments, existing medical records, and imaging studies, dementia was determined by consensus at a conference of physicians and neuropsychologists. The lipid measurements and APOE genotypes were not available during the diagnostic process. The diagnosis of dementia was based on standard research criteria and required evidence of cognitive deficit, including memory impairment, on the neuropsychological test battery as well as evidence of impairment in social or occupational function.<sup>11</sup> A diagnosis of dementia with stroke was considered for all patients with dementia in whom a history or clinical evidence of stroke was confirmed and was further classified as follows<sup>12</sup>: (1) stroke-related dementia (eg, new onset of dementia within 3 months of a stroke), (2) dementia due to the focal effects of stroke (eg, dementia resulting from stroke[s] in strategic areas whose singular or additive effects accounted for the observed clinical syndrome), and (3) possible Alzheimer disease with concomitant stroke (eg, progressive dementia associated with a clinical history of stroke in which the temporal relationship was impossible to establish). Our method for diagnosing dementia with stroke was consistent with guidelines later developed by Roman et al.<sup>13</sup> The clinical diagnosis of probable Alzheimer disease (ie, insidious onset of cognitive decline with progressive deterioration and the exclusion of all other causes of dementia by history, physical examination, and laboratory tests) was based on National Institute of Neurological and Cognitive Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.<sup>14</sup>

### Plasma Lipids and APOE Genotyping

Fasting plasma total cholesterol and triglyceride levels were determined at the initial assessment using standard enzymatic techniques. High-density lipoprotein (HDL) cholesterol was determined after precipitation of apolipoprotein B-containing lipoproteins with phosphotungstic acid.<sup>15</sup> Low-density lipoprotein (LDL) cholesterol levels were cal-

culated using the formula of Friedewald et al.<sup>16</sup> Lipoprotein(a) levels were analyzed as described previously.<sup>17</sup> In addition, LDL cholesterol levels were corrected for the cholesterol carried in lipoprotein(a) using the following formula:  $LDL_{corrected} = LDL - (0.3 \times \text{lipoprotein(a)})$ .<sup>18</sup>

Our lipid research laboratory participated in the Centers for Disease Control Lipid Standardization Program. APOE genotypes were determined essentially as described by Hixson and Vernier.<sup>19</sup>

### Statistical Methods

Lipid levels, APOE genotypes, and other potentially relevant factors were compared among individuals with dementia with stroke, Alzheimer disease, and those who remained free of dementia during follow-up. Continuous data were studied using analysis of variance and  $\chi^2$  tests were used for categorical data. Subanalyses were undertaken focusing on the stroke group alone. Survival analysis was used to plot age at onset of dementia distributions by lipid levels. Because the distribution of triglycerides and lipoprotein(a) was skewed, logarithmic transformation of those data was carried out before statistical tests were performed.

Proportional hazards analyses were used to estimate the relative risk (RR) of dementia associated with plasma lipid and lipoprotein levels. Lipid levels were considered as continuous variables and grouped into quartiles. APOE genotypes were classified as APOE  $\epsilon 4$  (homozygous, heterozygous, and absent APOE  $\epsilon 4$  allele) for use in multivariate modeling. As recommended for longitudinal studies,<sup>20</sup> the time-to-event variable was age at onset of dementia, which required no further age adjustment. Proportional hazards were estimated for levels of total cholesterol and triglycerides, total LDL cholesterol, and LDL corrected for lipoprotein(a), HDL cholesterol, and lipoprotein(a), while adjusting for APOE genotype, education, ethnic group, and sex. Subsequent models included adjustments for hypertension, diabetes mellitus, cardiac disease, a history of smoking, alco-

hol use, and body mass index. A final model was developed, including only significant variables or those that resulted in improvement in the log likelihood ratio. Interactions between LDL cholesterol and other covariates were assessed in the multivariate model. Subanalyses were performed restricting the data to only those subjects diagnosed as having stroke to evaluate the effects of lipids on the risk of dementia.

## RESULTS

### Baseline Characteristics and Incidence of Dementia

Baseline characteristics of the study population are given in TABLE 1. The diagnosis of stroke was based on clinical features supplemented with brain imaging and/or review of relevant medical records in 106 (86.9%) of 122 subjects, with the diagnosis based solely on clinical features in 16 subjects (13.1%).<sup>8</sup> Stroke was present at the initial assessment in 53 (43.4%) of the 122 subjects. Sixty-nine (56.6%) had a new stroke during follow-up. The mean follow-up of the cohort was 2.1 years (range, 1-7.8 years).

Although a previous study suggested temporal changes in lipid levels after acute stroke,<sup>21</sup> other work based in this population indicates that plasma lipid and lipoprotein levels remain stable during a 4-week period following cerebral ischemia.<sup>22</sup> Thus, we believe that the lipid measurements obtained at baseline in those subjects with stroke present at the initial assessment (n = 53) were a reliable estimate of their prestroke levels, while for those subjects who experienced their first stroke during follow-up (n = 69), the lipid levels obtained at baseline were also reflective of their prestroke levels.

Two hundred eighty-six (25.7%) of the 1111 subjects became demented during the follow-up period. Of those, 61 (21.3%) were classified as having dementia with stroke and 225 (78.7%) as having probable Alzheimer disease. Our data on stroke subtypes were limited since they were based only on brain imaging findings, but we found evidence of lacunar infarction in 28 (65.1%) of

43 patients, while cortical territorial infarction was found in 15 (34.9%) of 43 patients with dementia with stroke who had available brain imaging data.

### Characteristics of Subjects by Incidence of Dementia

The individuals who developed either form of dementia were older and less educated than the controls, but there were no significant differences in sex among the 4 groups (TABLE 2). There were more blacks than Hispanics and whites among the groups who developed dementia with stroke or Alzheimer disease compared with the stroke without dementia and the control groups. (When we excluded the "other" ethnic group from the analysis, the recalculated  $\chi^2$  value was essentially similar to that calculated for the significance of differences among the 4 ethnic groups.) Total cholesterol and triglyceride levels were highest in the group with dementia with stroke and lowest in the group with Alzheimer disease, while the levels in the stroke without dementia and the control groups were similar (Table 2). Levels of LDL cholesterol and LDL corrected for lipoprotein(a) were highest in the stroke group with dementia. The mean HDL cholesterol level was slightly lower in the stroke groups with and without dementia compared with the Alzheimer disease and control groups. Lipoprotein(a) levels were higher in the stroke groups with and without dementia compared with the Alzheimer disease and control groups. APOE  $\epsilon 4$  allele frequency dif-

fered among the 4 groups, with a higher frequency of APOE  $\epsilon 4$  homozygosity in those who developed Alzheimer disease, while there was no individual homozygous for the APOE  $\epsilon 4$  allele among the stroke groups with and without dementia. (When we excluded the groups having empty cells for the APOE 4/4 genotype, ie, dementia after stroke [n = 61] and stroke without dementia [n = 61], the recalculated  $\chi^2$  value was consistent with that originally calculated for the significance of differences among the 4 groups, suggesting that the difference was accounted for by an increased frequency of an APOE  $\epsilon 4$  allele in the group with Alzheimer disease compared with controls.) A history of cardiac disease, hypertension, and diabetes were each more frequent in the stroke groups with and without dementia compared with the Alzheimer disease and control groups.

In a subanalysis confined to the stroke subjects only (n = 122), total cholesterol levels were significantly higher in the demented group than in the nondemented group (P = .04) (Table 2). Levels of LDL cholesterol corrected for lipoprotein(a) were also significantly higher in the demented group compared with the nondemented group (P = .04) (Table 2), while there was a trend toward higher unadjusted LDL cholesterol in the demented group compared with the nondemented (P = .07) (Table 2). There were no significant differences in levels of total cholesterol, HDL cholesterol, LDL cholesterol, corrected LDL cholesterol, or lipopro-

**Table 1.** Baseline Characteristics of Study Subjects\*

	Overall (N = 1111)	Stroke† (n = 122)	No Stroke (n = 989)
Age, mean (SD), y	75.0 (5.9)	75.4 (6.4)	74.9 (5.9)
Education, mean (SD), y	8.7 (4.6)	8.8 (4.3)	8.7 (4.6)
Men	348 (31.3)	37 (30.3)	311 (31.4)
Ethnic group‡			
White	249 (22.4)	22 (18.0)	227 (22.9)
Black	360 (32.4)	39 (32.0)	321 (32.5)
Hispanic	495 (44.6)	59 (48.4)	436 (44.1)
Other	7 (0.6)	2 (1.6)	5 (0.5)

\*Values are expressed as number (percentage) unless otherwise indicated.

†Defined according to World Health Organization criteria.<sup>8</sup>

‡Classified by self-report using the format of the 1990 US census.<sup>7</sup>

tein(a) between the subjects with stroke present at the initial assessment (n = 53) and those who experienced their first stroke during follow-up (n = 69). However, triglyceride levels were higher in the group with stroke present at the initial assessment compared with the group with incident stroke (2.31 [204.4] vs 1.80 [159.2] mmol/L [mg/dL];  $P = .01$ ). We did not find any relationship between stroke severity as measured by the score on a rated measure of activities of daily living and lipid levels. Furthermore, there were no significant differences in lipid levels by infarct type (cortical vs subcortical) based on brain

imaging findings in the subset of subjects with dementia with stroke who had available brain imaging findings (n = 43), but the numbers were small.

The FIGURE shows the distribution by age of the cumulative incidence of dementia with stroke according to various levels of LDL cholesterol. The curves are significantly different by the log-rank test ( $P = .03$ ).

In a proportional hazards analysis, we found that subjects with the highest quartile of LDL cholesterol had a significantly increased risk of dementia with stroke (RR, 3.1; 95% confidence interval [CI], 1.5-6.1) compared with those

with the lowest quartile, adjusting for ethnic group and vascular risk factors (TABLE 3). APOE genotype did not alter this relationship. The increase in risk associated with increasing levels of LDL cholesterol had a dose-response relationship and the linear trend for increasing levels of LDL cholesterol was significant ( $P = .001$ ). Corrected LDL levels were an even stronger predictor of dementia with stroke in the adjusted multivariate analysis, with a 4-fold increase in risk associated with the highest quartile compared with the lowest quartile (TABLE 4). A significant dose-response relationship for LDL levels cor-

**Table 2.** Characteristics of Study Population According to Incidence of Dementia\*

Characteristic	Dementia With Stroke (n = 61)	Stroke Without Dementia (n = 61)	Alzheimer Disease (n = 225)	Control Subjects (n = 764)	P Value†
Age, mean (SD), y	75.9 (6.9)	75.0 (6.1)	77.7 (6.3)	74.1 (5.5)	<.001
Education, mean (SD), y	8.2 (4.1)	9.5 (4.3)	6.9 (4.2)	9.3 (4.6)	<.001
Men	16 (26.2)	21 (34.4)	63 (28.0)	248 (32.5)	.56
Ethnic group					
White	9 (14.8)	13 (21.3)	28 (12.4)	199 (26.0)	<.01
Black	22 (36.1)	17 (27.9)	87 (38.7)	234 (30.6)	
Hispanic	29 (47.5)	30 (49.2)	109 (48.4)	327 (42.8)	
Other	1 (1.6)	1 (1.6)	1 (0.4)	4 (0.5)	
Lipid levels, mean (SD)					
Total cholesterol, mmol/L [mg/dL]	5.61 (1.18) [217.1 (45.8)]	5.06 (1.05) [195.6 (40.8)]	4.96 (0.97) [191.9 (37.4)]	5.28 (1.00) [204.1 (38.7)]	<.001
Triglycerides, mmol/L [mg/dL]‡	2.14 (1.31) [189.2 (116.1)]	2.01 (0.94) [177.7 (83.7)]	1.72 (0.71) [152.0 (62.9)]	2.02 (1.14) [179.2 (100.9)]	<.01
High-density lipoprotein cholesterol, mmol/L [mg/dL]	1.21 (0.43) [46.8 (16.8)]	1.19 (0.49) [45.9 (18.8)]	1.27 (0.37) [49.1 (14.5)]	1.24 (0.40) [47.8 (15.5)]	.44
Low-density lipoprotein cholesterol, mmol/L [mg/dL]	3.37 (1.00) [130.3 (38.9)]	3.06 (0.90) [118.2 (34.8)]	2.90 (0.87) [112.3 (33.7)]	3.12 (0.89) [120.6 (34.3)]	<.001
Corrected low-density lipoprotein cholesterol, mmol/L [mg/dL]§	3.08 (0.96) [119.1 (37.1)]	2.72 (0.89) [105.4 (34.3)]	2.60 (0.85) [100.5 (32.9)]	2.85 (0.86) [110.1 (33.3)]	<.001
Lipoprotein(a), g/L [mg/dL]‡	0.46 (0.44) [45.9 (44.2)]	0.47 (0.42) [46.6 (41.6)]	0.38 (0.32) [38.0 (32.2)]	0.36 (0.36) [36.1 (36.4)]	.06
Body mass index, mean (SD), kg/m <sup>2</sup>	27.3 (6.5)	27.6 (5.5)	26.9 (5.2)	27.8 (5.6)	.20
APOE genotype					
4/4	0 (0.0)	0 (0.0)	12 (5.4)	12 (1.6)	<.01
4/-	14 (24.6)	18 (30.0)	66 (29.5)	183 (24.9)	
-/-	43 (75.4)	42 (70.0)	146 (65.2)	541 (73.5)	
Vascular risk factors					
Cardiac disease	31 (52.5)	25 (41.0)	68 (30.5)	172 (22.5)	<.001
Hypertension	40 (67.8)	44 (72.1)	116 (51.8)	367 (48.1)	<.001
Diabetes	19 (32.2)	17 (27.9)	34 (15.2)	106 (13.9)	<.001
Smoking (ever)	25 (45.5)	29 (48.3)	77 (40.1)	357 (51.1)	.06

\*Values are expressed as number (percentage) unless otherwise indicated. Some percentages are based on an incomplete sample due to small amounts of missing data.

†Significance levels are based on analysis of variance for continuous data and  $\chi^2$  tests for categorical data and denote the overall significance of differences among the 4 groups.

‡Distributions of triglycerides and lipoprotein(a) were skewed, thus, values were log transformed prior to performing statistical testing.

§Low-density lipoprotein (LDL) levels were corrected for cholesterol carried by lipoprotein(a) by using this formula:  $LDL_{corrected} = LDL - (0.3 \times \text{lipoprotein(a)})$ .<sup>18</sup>



rected for lipoprotein(a) was also detected ( $P$  for trend = .005). The increase in RR was also found when levels of LDL cholesterol ( $P = .002$ ) and LDL corrected for lipoprotein(a) ( $P < .001$ ) were included as continuous variables in the proportional hazards models. No significant interactions were detected between LDL levels and the covariates in the multivariate analyses. Prior and incident stroke were examined separately by excluding the 53 subjects with stroke present at the initial assessment. Levels of LDL and LDL corrected for lipoprotein(a) remained significant predictors of dementia with stroke in that analysis, with RR of 4.2 (95% CI, 1.5-12.3) and 4.4 (95% CI, 1.4-14.1), respectively.

To distinguish risk factors for stroke from those for dementia with stroke, we performed a subanalysis using only nondemented stroke patients as the reference group. Although the power was limited by small numbers in each group (55 demented stroke patients and 61 nondemented stroke patients), we confirmed that LDL levels corrected for lipoprotein(a) remained a significant predictor of dementia with stroke in that analysis, with an RR of 2.6 (95% CI, 1.1-6.4) for the highest compared with the lowest quartile.

Finally, we investigated whether there was an association between lipid levels and the risk of Alzheimer dis-

ease. In a proportional hazards analysis, we found that ethnic group, years of education, and APOE genotype, but not lipid or lipoprotein levels, were associated with the development of probable Alzheimer disease in our cohort (TABLE 5).

### COMMENT

In this prospective investigation, elevated LDL cholesterol level was an independent risk factor for the development of dementia with stroke in community-dwelling elderly patients, adjusting for vascular risk factors and demographic variables. Although we had previously found an association between the APOE  $\epsilon 4$  allele and dementia with stroke in a cross-sectional study,<sup>3</sup> APOE genotype did not significantly influence the risk of dementia with stroke in the present prospective

study, but sample sizes for each APOE genotype were small. We included individuals with Alzheimer disease with concomitant stroke in our definition of dementia with stroke,<sup>12</sup> thus, some of our cases had a mixed dementia. It is important to note, however, that we found no relationship between lipid levels and the risk of probable Alzheimer disease in the same cohort, suggesting that dyslipidemia may be most relevant to the occurrence of dementia with a vascular component. The present study is one of the first to prospectively investigate the relationship among plasma lipids, APOE genotype, and the risk of dementia with stroke. Our results suggest that the level of LDL cholesterol is an independent determinant of dementia with stroke, and, of greatest importance, is a potentially modifiable risk factor.

**Table 3.** Relative Risks of Dementia With Stroke by Different Levels of Low-Density Lipoprotein Cholesterol\*

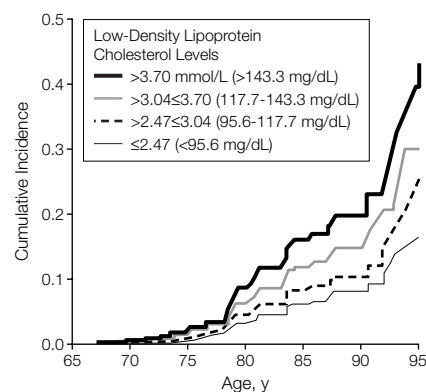
Low-density lipoprotein cholesterol, mmol/L (mg/dL)	At-Risk Population	No. (%) of Incident Dementia With Stroke	Model A, RR (95% CI)†	Model B, RR (95% CI)‡
$\leq 2.47$ (95.6)	275	7 (2.5)	1.0	1.0
$> 2.47 \leq 3.04$ (95.6-117.7)	276	12 (4.3)	1.0 (0.3-2.1)	1.1 (0.4-2.4)
$> 3.04 \leq 3.70$ (117.7-143.3)	276	14 (5.1)	1.4 (0.7-3.2)	1.6 (0.8-3.5)
$> 3.70$ (143.3)	275	25 (9.1)	2.6 (1.3-5.3)	3.1 (1.5-6.1)

\*RR indicates relative risk; CI, confidence interval.  $P$  for trend for model A is .003 and .001 for model B.

†Adjusted for sex (RR, 0.9 for women vs men), education (RR, 1.0 for highest vs lowest grade of school completed), and ethnic group (RR, 2.6 for black vs white; RR, 3.0 for Hispanic vs white).

‡Adjusted for cardiac disease (RR = 2.2), hypertension (RR = 1.6), diabetes mellitus (RR = 2.9), and ethnic group (RR, 2.6 for black vs white; RR, 2.6 for Hispanic vs white). The time-to-event variable was age at onset of dementia, which required no further age adjustment.

**Figure.** Survival Analysis by Cumulative Incidence of Dementia With Stroke



Curves are significantly different by the log-rank test ( $P = .03$ ).

**Table 4.** Relative Risks of Dementia With Stroke by Different Levels of Low-Density Lipoprotein Cholesterol Corrected for Lipoprotein(a)\*

Corrected low-density lipoprotein cholesterol, mmol/L (mg/dL)	At-Risk Population	No. (%) of Incident Dementia With Stroke	Model A, RR (95% CI)†	Model B, RR (95% CI)‡
$\leq 2.21$ (85.5)	260	8 (3.1)	1.0	1.0
$> 2.21 \leq 2.78$ (85.5-107.5)	260	11 (4.2)	1.2 (0.5-3.0)	1.8 (0.7-4.7)
$> 2.78 \leq 3.35$ (107.5-129.5)	259	14 (5.4)	1.8 (0.8-4.3)	2.4 (1.0-5.8)
$> 3.35$ (129.5)	259	22 (8.5)	2.9 (1.3-6.7)	4.1 (1.8-9.6)

\*RR indicates relative risk; CI, confidence interval.  $P$  for trend for model A is .002 and .005 for model B. Numbers differ slightly from those in Table 3 because some subjects had missing values of lipoprotein(a). Low-density lipoprotein (LDL) levels were corrected for the cholesterol carried by lipoprotein(a) by using the following formula:  $LDL_{corrected} = LDL - (0.3 \times lipoprotein[a])$ .

†Adjusted for sex (RR, 0.8 for women vs men), education (RR, 1.0 highest vs lowest grade of school completed), and ethnic group (RR, 2.5 for black vs white; RR, 2.5 for Hispanic vs white).

‡Adjusted for cardiac disease (RR = 2.2), hypertension (RR = 1.5), diabetes mellitus (RR = 3.0), and ethnic group (RR, 2.7 for black vs white; RR, 2.5 for Hispanic vs white). The time-to-event variable was age at onset of dementia, which required no further age adjustment.

**Table 5.** Proportional Hazards Model of the Effect of Low-Density Lipoprotein Cholesterol Levels on the Relative Risk of Incident Alzheimer Disease Adjusting for Demographic Factors and Other Relevant Variables\*

Variable	Relative Risk (95% Confidence Interval)
Low-density lipoprotein cholesterol, mmol (mg/dL)	
≤2.47 (95.6)	1.0
>2.47≤3.04 (95.6-117.7)	0.83 (0.56-1.23)
>3.04≤3.70 (117.7-143.3)	0.75 (0.51-1.10)
>3.70 (143.3)	0.77 (0.51-1.15)
Ethnic group (vs white)	
Black	2.17 (1.27-3.36)
Hispanic	1.77 (1.07-2.94)
Years of education	0.92 (0.89-0.96)
APOE genotype (vs no E4)	
4/-	1.11 (0.80-1.53)
4/4	3.82 (2.01-7.28)
Cardiac disease	0.94 (0.63-1.40)
Diabetes mellitus	1.21 (0.81-1.83)
Hypertension	1.09 (0.81-1.46)

\*The time-to-event variable was age at onset of dementia, which required no further age adjustment.

Few prospective cohort studies have investigated the relationship between lipid levels and the incidence of dementia with stroke. Katzman et al<sup>23</sup> found that baseline HDL cholesterol levels were lower and triglyceride levels were higher in a cohort of 80-year-old men who developed dementia with a vascular component, but relatively few men were studied. The risk of cognitive decline in community-dwelling elderly men was highest among APOE ε4 allele carriers who had high cholesterol levels, high fibrinogen levels, or diabetes,<sup>24</sup> but the measurement of cognitive function relied solely on the Mini-Mental State Examination. In the Rotterdam study,<sup>25</sup> a high total fat and saturated fat dietary intake increased the risk of dementia with a vascular component in older individuals, but no measurements of plasma lipids or lipoproteins were performed. Interestingly, high linoleic acid dietary intake, which is thought to increase the atherogenicity of LDL cholesterol through oxidative modification, was associated with the development of cognitive impairment in the Zutphen Elderly Study.<sup>26</sup> Other prospective studies have found no effect of plasma lipids on the risk of

dementia.<sup>27,28</sup> The differences between their results and this study may reflect differences in age, ethnicity, and/or application of diagnostic criteria among the populations studied.

The pathways from elevated LDL cholesterol levels to the development of dementia with stroke are unclear, but promotion of atherosclerosis by LDL cholesterol may provide a link. High concentrations of LDL cholesterol are known to be independently associated with coronary heart disease<sup>29</sup> and carotid artery atherosclerosis,<sup>30</sup> which in turn may lead to cognitive decline through cerebral embolism or hypoperfusion.<sup>31,32</sup> Prior studies are contradictory regarding the role of lipoproteins in atherothrombotic compared with lacunar infarction,<sup>33,34</sup> and there has been no prospective investigation of the relationship among lipoprotein abnormalities, stroke subtype, and the risk of cognitive decline. We found no significant differences in lipid or lipoprotein levels by infarct subtype (ie, cortical vs subcortical infarction) in the group with dementia with stroke, but the numbers were small. It is noteworthy, however, that lacunar infarction was the most frequent infarct subtype on brain imaging among the group with dementia with stroke. Earlier clinicopathological studies emphasized large macroscopic infarcts,<sup>35</sup> but later work has suggested that microvascular disease in the form of cribriform change and lacunar infarction is a common pathological feature of vascular dementia,<sup>28</sup> consistent with our brain imaging findings. Lacunar infarction and cerebral white matter disease may lead to cognitive decline through disruption of corticostriatal connections.<sup>36</sup> Thus, the role of lipid levels in small-vessel disease and lacunar infarction requires further investigation.

In addition, lipid peroxidation may be a major factor in the aging process<sup>37</sup> and hypercholesterolemic diets may lead to microglial activation<sup>38</sup> and β-amyloid plaque deposition.<sup>39</sup> Conversely, dietary restriction can reduce brain vulnerability to acute insults, such as stroke, and may also slow age-related changes in the brain.<sup>40</sup> Thus, cholesterol oxida-

tion in the brain may be particularly relevant to the pathogenesis of those cases of vascular dementia with mixed pathology (ie, Alzheimer disease with concomitant stroke).

The limitations of this study include the possibility of misclassification bias when using single baseline measurements of plasma lipids and lipoproteins and the lack of autopsy verification of the clinical diagnosis of dementia subtype. We were also unable to investigate the effect of infarct volume as a predictor of dementia with stroke due to a lack of quantitative neuroimaging.

This study showed an independent association between the level of LDL cholesterol and the risk of dementia with stroke. The association was even stronger when LDL levels were corrected for the cholesterol carried by lipoprotein(a). These findings may have important implications for the management of elderly patients with a history of stroke and should be a focus of future research. Dietary modification, physical activity, and therapy with lipid-lowering drugs are among the interventions that should be evaluated to determine whether they provide protection against dementia for elderly patients with stroke and elevated LDL cholesterol levels.

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