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

Joan T. Moroney, MD, MRCPI
Ming-Xin Tang, PhD
Lars Berglund, MD
Scott Small, MD
Carole Merchant, MD
Karen Bell, MD
Yaakov Stern, PhD
Richard Mayeux, MD, MSc

VASCULAR DEMENTIA IS CONSIDERED the second major cause of dementia after Alzheimer disease in Western populations. While the role of coincident vascular disease in patients with Alzheimer disease has received attention, the origin of vascular dementia remains unclear. Previously we found that an apolipoprotein E ε4 (APOE ε4) allele increased the risk of dementia with stroke in a population-based case-control investigation. APOE could influence the pathogenesis of dementia with stroke through its effects on lipid metabolism and atherosclerosis, but the relationship between lipids and the risk of dementia in the presence or absence of the APOE ε4 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 York City). NY. The sampling procedures have been described elsewhere. 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. Ethnic origin was classified by self-report using the format of the 1990 US Census. These same clinical assessments were used in the annual fol-

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


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.

©1999 American Medical Association. All rights reserved.
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. 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 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. 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.

**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. 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: (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. 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. plasma lipid and lipoprotein levels. Lipid levels were considered as continuous variables and grouped into quartiles. APOE genotypes were classified as APOE ε4 (homozygous, heterozygous, and absent APOE ε4 allele) for use in multivariate modeling. As recommended for longitudinal studies, the time-to-event variable was age at onset of dementia, which required no further age adjustment. Proportional hazards were estimated for several potential factors, including plasma 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, cardiovascular disease, a history of smoking, alcohol consumption, and dietary factors. The model was adjusted for potential confounders, including age, sex, education, and ethnicity. The adjusted risk estimates were then compared with those obtained by using unadjusted models.

**Statistical Methods**

Lipid levels, APOE genotypes, and other potentially relevant factors were compared among individuals with dementia and stroke, Alzheimer disease, and those who remained free of dementia during follow-up. Continuous data were analyzed using analysis of variance and χ² 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 ε4 (homozygous, heterozygous, and absent APOE ε4 allele) for use in multivariate modeling. As recommended for longitudinal studies, the time-to-event variable was age at onset of dementia, which required no further age adjustment. Proportional hazards were estimated for several potential factors, including plasma 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, cardiovascular disease, a history of smoking, alcohol consumption, and dietary factors. The model was adjusted for potential confounders, including age, sex, education, and ethnicity. The adjusted risk estimates were then compared with those obtained by using unadjusted models.

**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. Low-density lipoprotein (LDL) cholesterol levels were calculated using the formula of Friedewald et al. Lipoprotein(a) levels were analyzed as described previously. In addition, LDL cholesterol levels were corrected for the cholesterol carried in lipoprotein(a) using the following formula: LDL_corrected = LDL − (0.3 × lipoprotein(a)).

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.

©1999 American Medical Association. All rights reserved.
LIPOPROTEIN CHOLESTEROL AND DEMENTIA RISK

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 findings, but we found evidence consistent with that originally 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 e4 allele frequency differed among the 4 groups, with a higher frequency of APOE e4 homozygosity in those who developed Alzheimer disease, while there was no individual homozygous for the APOE e4 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 e4 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 group (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 Subjectsa |
|---------------------------------|-----------------|-----------------|
| Overall (N = 1111)               | Stroke† (n = 122) | No Stroke (n = 989) |
| Age, mean (SD), y                | 75.0 (5.9)       | 75.4 (6.4)       | 74.9 (6.9)       |
| 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)          |

aValues are expressed as number (percentage) unless otherwise indicated.†Defined according to World Health Organization criteria.‡Classified according to World Health Organization criteria.

©1999 American Medical Association. All rights reserved.
LIPOPROTEIN CHOLESTEROL AND DEMENTIA RISK

tin(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*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dementia With Stroke (n = 61)</th>
<th>Stroke Without Dementia (n = 61)</th>
<th>Alzheimer Disease (n = 225)</th>
<th>Control Subjects (n = 764)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>75.9 (6.9)</td>
<td>75.0 (6.1)</td>
<td>77.7 (6.3)</td>
<td>74.1 (5.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>8.2 (4.1)</td>
<td>9.5 (4.3)</td>
<td>6.9 (4.2)</td>
<td>9.3 (4.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Men</td>
<td>16 (26.2)</td>
<td>21 (34.4)</td>
<td>63 (28.0)</td>
<td>248 (32.5)</td>
<td>.56</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>9 (14.8)</td>
<td>13 (21.3)</td>
<td>28 (12.4)</td>
<td>199 (26.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Black</td>
<td>22 (36.1)</td>
<td>17 (27.9)</td>
<td>87 (38.7)</td>
<td>234 (30.6)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>29 (47.5)</td>
<td>30 (49.2)</td>
<td>109 (48.4)</td>
<td>327 (42.8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>1 (0.4)</td>
<td>4 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Lipid levels, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.61 (1.18) [217.1 (45.8)]</td>
<td>5.06 (1.05) [196.6 (40.8)]</td>
<td>4.96 (0.97) [191.9 (37.4)]</td>
<td>5.28 (1.00) [204.1 (38.7)]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.14 (1.31) [189.2 (116.1)]</td>
<td>2.01 (0.94) [177.7 (83.7)]</td>
<td>1.72 (0.71) [152.0 (62.9)]</td>
<td>2.02 (1.14) [179.2 (100.9)]</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cholesterol, mmol/L</td>
<td>1.21 (0.43) [46.8 (16.8)]</td>
<td>1.19 (0.49) [45.9 (18.8)]</td>
<td>1.27 (0.37) [49.1 (14.5)]</td>
<td>1.24 (0.40) [47.8 (15.5)]</td>
<td>.44</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cholesterol, mmol/L</td>
<td>3.37 (1.00) [130.3 (38.9)]</td>
<td>3.06 (0.90) [118.2 (34.8)]</td>
<td>2.90 (0.87) [112.3 (33.7)]</td>
<td>3.12 (0.89) [120.6 (34.3)]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Corrected low-density lipoprotein cholesterol, mmol/L</td>
<td>3.08 (0.96) [119.1 (37.1)]</td>
<td>2.72 (0.89) [105.4 (34.3)]</td>
<td>2.60 (0.85) [100.5 (32.9)]</td>
<td>2.86 (1.00) [110.1 (33.3)]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lipoprotein(a), g/L</td>
<td>0.46 (0.44) [45.9 (44.2)]</td>
<td>0.47 (0.42) [46.6 (41.6)]</td>
<td>0.38 (0.32) [38.0 (32.2)]</td>
<td>0.36 (0.36) [36.1 (36.4)]</td>
<td>.06</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>27.3 (6.5)</td>
<td>27.6 (5.5)</td>
<td>26.9 (5.2)</td>
<td>27.8 (5.6)</td>
<td>.20</td>
</tr>
<tr>
<td>APOE genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/4</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>12 (5.4)</td>
<td>12 (1.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>4/−</td>
<td>14 (24.6)</td>
<td>18 (30.0)</td>
<td>66 (29.5)</td>
<td>183 (24.9)</td>
<td></td>
</tr>
<tr>
<td>4/−</td>
<td>43 (75.4)</td>
<td>42 (70.0)</td>
<td>146 (65.2)</td>
<td>541 (73.5)</td>
<td></td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>31 (52.5)</td>
<td>25 (41.0)</td>
<td>68 (30.5)</td>
<td>172 (22.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40 (67.8)</td>
<td>44 (72.1)</td>
<td>116 (51.8)</td>
<td>367 (48.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (32.2)</td>
<td>17 (27.9)</td>
<td>34 (15.2)</td>
<td>106 (13.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking (ever)</td>
<td>25 (45.5)</td>
<td>29 (48.3)</td>
<td>77 (40.1)</td>
<td>357 (47.1)</td>
<td>.06</td>
</tr>
</tbody>
</table>

*Significance levels are based on analysis of variance for continuous data and x² 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 × lipoprotein(a)).

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

©1999 American Medical Association. All rights reserved.
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 DL3 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 disease. 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 ε4 allele and dementia with stroke in a cross-sectional study, 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, 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**

<table>
<thead>
<tr>
<th>Low-density lipoprotein cholesterol, mmol/L (mg/dL)</th>
<th>At-Risk Population</th>
<th>No. (%) of Incident Dementia With Stroke</th>
<th>Model A, RR (95% CI)†</th>
<th>Model B, RR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.47 (95.6)</td>
<td>275</td>
<td>7 (2.5)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;2.47–3.04 (95.6-117.7)</td>
<td>276</td>
<td>12 (4.3)</td>
<td>1.0 (0.3-2.1)</td>
<td>1.1 (0.4-2.4)</td>
</tr>
<tr>
<td>&gt;3.04–3.70 (117.7-143.3)</td>
<td>276</td>
<td>14 (5.1)</td>
<td>1.4 (0.7-3.2)</td>
<td>1.6 (0.8-3.5)</td>
</tr>
<tr>
<td>&gt;3.70 (143.3)</td>
<td>275</td>
<td>25 (9.1)</td>
<td>2.1 (1.3-3.3)</td>
<td>3.1 (1.5-6.1)</td>
</tr>
</tbody>
</table>

†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.

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

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

†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 = 1.8), 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.
LIPOPROTEIN CHOLESTEROL AND DEMENTIA RISK

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*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-density lipoprotein cholesterol, mmol (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>&lt;2.47 (95.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;2.47–3.04</td>
<td>0.83 (0.56-1.23)</td>
</tr>
<tr>
<td>(95.6-117.7)</td>
<td></td>
</tr>
<tr>
<td>&gt;3.04–3.70</td>
<td>0.75 (0.51-1.10)</td>
</tr>
<tr>
<td>(117.7-143.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;3.70 (143.3)</td>
<td>0.77 (0.51-1.15)</td>
</tr>
<tr>
<td>Ethnic group (vs white)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>2.17 (1.27-3.36)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.77 (1.07-2.94)</td>
</tr>
<tr>
<td>Years of education</td>
<td>0.92 (0.89-0.96)</td>
</tr>
<tr>
<td>APOE genotype (vs no E4)</td>
<td></td>
</tr>
<tr>
<td>4/4</td>
<td>1.11 (0.80-1.53)</td>
</tr>
<tr>
<td>4/3</td>
<td>3.62 (2.01-7.28)</td>
</tr>
<tr>
<td>3/4</td>
<td>0.94 (0.63-1.40)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>1.21 (0.81-1.83)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.21 (0.81-1.83)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.09 (0.81-1.46)</td>
</tr>
</tbody>
</table>

*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 al23 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 e4 allele carriers who had high cholesterol levels, high fibrinogen levels, or diabetes,34 but the measurement of cognitive function relied solely on the Mini-Mental State Examination. In the Rotterdam study,25 a high total fat and saturated fatty acid dietary intake increased the risk 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 disease29 and carotid artery atherosclerosis,30 which in turn may lead to cognitive decline through cerebral embolism or hypoperfusion.31,32 Prior studies are contradictory regarding the role of lipoproteins in atherothrombosis compared with lacunar infarction,33,34 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,35 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,36 consistent with our brain imaging findings. Lacunar infarction and cerebral white matter disease may lead to cognitive decline through disruption of corticosubcortical connections.36 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 process37 and hypercholesterolemic diets may lead to microglial activation38 and β-amyloid plaque deposition.39 Conversely, dietary restriction can reduce brain vulnerability to acute insults, such as stroke, and may also slow age-related changes in the brain.40 Thus, cholesterol oxidation 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.

Funding/Support: This study was supported in part by grants AG 07232, AG 10963, and K08 NS 02051 from the National Institutes of Health (Bethesda, Md) and grant 2 M01 RR 00645 from the General Clinical Research Center. Support was also provided by the Blanche L. Hoeker Rockefeller Fund (New York, NY) and the Charles S. Robertson gift from the Banbury Fund (Cold Spring Harbor, NY). Dr Moroney is the recipient of a Mentored Clinical Scientist Development Award from the National Institutes of Health. Dr Burglund is an Established Scientist of the American Heart Association (New York City, NY, affiliate).

Previous Presentation: Portions of this work were presented at the 123rd Annual Meeting of the American Neurological Association; Montreal, Quebec; October 22, 1998.

Acknowledgment: We thank Ralph L. Sacco, MD, MS, for his critical review of the manuscript and we gratefully acknowledge the valuable assistance of project coordinators Rosann Costa, MA, and Maria J. Gonzalez, BS.

REFERENCES
lipoprotein E-4 and the risk of dementia with stroke. JAMA. 1997;277:818-821.
can Americans, whites, and Hispanics. JAMA. 1998,
279:751-755.
ment of a neuropsychological paradigm and quanti-
ﬁed correction for education. Arch Neurol. 1992;49:
453-460.
12. Census of Population and Housing: Summary Tape File 1, Technical Documentation [computer dis-
13. Hatano S. Experience from a multicenter stroke reg-
1976;54:541-553.
15. Sacco RL, Shi T, Zamanillo MC, Kargman DE. Pre-
dictors of mortality and recurrence after hospitalized cere-
bral infarction in an urban community: the Northern Man-
16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edi-
tion, Revised. Washington, DC: American Psychiat-
ric Association; 1987.
17. Tatemichi TK, Desmond DW, Mayeux R, et al. De-
mentia after stroke: baseline frequency, risks, and clinical
features in a hospitalized cohort. Neurology. 1992;
42:1185-1193.
18. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vas-
cular dementia: diagnostic criteria for research stud-
ies: report of the NINDS-AIREN International Work-
mer’s disease: report of the NINCDS-ADRDA Work
Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer’s Dis-
20. Lopes-Virella MF, Stone P, Ellis S, Cowell JA. Cho-
sterol determination in high-density lipoprotein sepa-
rated by three different methods. Clin Chem. 1977;
23:882-884.
21. Friedewald WT, Levy RI, Fredrickson DS. Estima-
tion of the concentration of low-density lipoprotein cho-
22. Tuck CH, Holleran S, Berglund L. Hormonal regu-
lation of lipoprotein(a): levels of estrogen re-
placement therapy on lipoprotein(a) and acute phase re-
actants in postmenopausal women. Arterioscler Thromb.
1997;17:1822-1829.
23. Nauck M, Winkler K, Marx W, Wieland H. Quan-
titative determination of high-, low-, and very-low-
density lipoproteins and lipoprotein(a) by agarose gel
24. Hixson J, Vernier D. Restriction isotyping of hu-
mans apolipoprotein E by gene amplification and cleav-
25. Korn EL, Graubard BI, Williams D. Time-to-
event analysis of longitudinal follow-up of a survey:
choice of the time scale. Am J Epidemiol. 1997;145:
72-80.
26. Mendez I, Hachinski V, Wolfe B. Serum lipids af-
27. Kargman DE, Tuck C, Berglund L, et al. Lipid and
lipoprotein levels remain stable in acute ischemic stroke:
the Northern Manhattan Stroke Study. Atheroscle-
ment of dementing illnesses in an 80-year-old co-
29. Kalmijn S, Feskens EJM, Laufer LJ, Kromhout D. Cerebrovascular disease, the apolipoprotein E-
4 allele, and cognitive decline in a community-based study
30. Kalmijn S, Laufer LJ, Ott A, Witteman J, Hof-
man A, Breteler MMB. Dietary fat intake and the risk
of incident dementia in the Rotterdam study. Ann Neu-
31. Kalmijn S, Feskens EJM, Laufer LJ, Kromhout D. Polyunsaturated fatty acids, antioxidants, and cognitive
function in very old men. Am J Epidemiol. 1997;145:
33-41.
lipids and lipoproteins and the incidence of cardiovas-
cular disease in the very elderly: the Bronx Aging Study.
and risk factors of vascular dementia and Alzheimer’s
disease in a deﬁned elderly Japanese population: the
the expert panel on population strategies for blood
cholesterol reduction: a statement from the National
Cholesterol Education Program, National Heart, Lung,
and Blood Institute, National Institutes of Health. Cir-
culation. 1991;83:2154-2232.
35. Sharrett AR, Patsch W, Sorlie PD, Heiss G, Bond
MC, Davis CE, for the ARIC Investigators. Associa-
tions of lipoproteins cholesterol, apolipoproteins A-1
and B, and triglycerides with carotid atherosclerosis
and coronary heart disease: the Atherosclerosis Risk
in Communities Study. Arterioscler Thromb Vasc Biol.
36. Breiteler MMB, Claus JJ, Grobbebe DE, Hofman A.
Cardiovascular disease and distribution of cognitive
function in elderly people: the Rotterdam Study. BMJ.
37. Tatemichi TK, Desmond DW, Prohovnik I, Edel-
berg D. Dementia associated with bilateral carotid oc-
cclusions: neuropsychological and haemodynamic course
after extracranial to intracranial bypass surgery. J Neu-
38. Pedro-Botet I, Senti M, Nogues X, et al. Lipopro-
tein and apolipoprotein proﬁle in men with ischemic
stroke: role of lipoprotein(a), triglyceride-rich lipopro-
teins, and apolipoprotein E polymorphism. Stroke.
1992;23:1556-1562.
39. Fujiwara Y, Nishihara H, Nakanishi T, Hasegawa T,
Tagami S, Wakahami Y. Elevation of plasma lipid peroxides in non-insulin dependent diabetics with mul-
tiple lacunar inﬁrcts. J Atheroscler Thromb. 1997;4:
90-95.
40. Tomlinson BE, Blessed G, Roth M. Observations on
the brains of demented old people. J Neurol Sci.
41. Tatemichi TK, Desmond DW, Prohovnik I, et al.
Confusion and memory loss from capsular genu in-
farction: a thalamocortical disconnection syndrome.
43. Strett W, Sparks DL. Activation of microglia in the
brains of humans with heart disease and hypercholes-
44. Sparks DL, Scheff SW, Hunsaker JC, Liu H, Land-
ers T, Gross DR. Induction of Alzheimer-like beta-
amyloid immunoreactivity in the brains of rabbits with
45. Bruce-Keller AJ, Umeberger G, McFall R, Mattson
MP. Food restriction reduces brain damage and im-
poves behavioral outcome following excitotoxic and

©1999 American Medical Association. All rights reserved.