Serum C-Reactive Protein and Self-Reported Stroke
Findings From the Third National Health and Nutrition Examination Survey
Earl S. Ford, Wayne H. Giles

Abstract—C-reactive protein may predict the risk of coronary heart disease, but its association with stroke has not been well studied. We used data from the Third National Health and Nutrition Examination Survey, conducted from 1988 to 1994, to examine the association between serum C-reactive protein concentrations and self-reported past history of stroke among 8850 US men and women aged ≥40 years. The unadjusted geometric mean of C-reactive protein concentration was higher among participants with stroke than those without stroke (0.45±0.02 versus 0.32±0.01, P<0.001). After adjusting for age, sex, race or ethnicity, education, smoking status, systolic blood pressure, serum cholesterol, high density lipoprotein cholesterol, history of diabetes mellitus, body mass index, and physical activity, the odds ratio for stroke among participants with C-reactive protein concentrations ≥0.55 mg/dL compared with participants with concentrations ≤0.21 mg/dL was 1.71 (95% CI 1.11 to 2.64 [odds ratio per mg/dL 1.19, 95% CI 1.05 to 1.34]). These cross-sectional data support findings from other studies suggesting that C-reactive protein concentration may be a risk factor or marker for stroke in the US population. (Arterioscler Thromb Vasc Biol. 2000;20:1052-1056.)

Key Words: cerebrovascular diseases • C-reactive protein • cross-sectional studies • health surveys • risk factors

C-reactive protein, an acute phase reactant, is a nonspecific marker of inflammation. In healthy persons, C-reactive protein concentrations are very low, but they can rise tremendously in response to a wide variety of stimuli. The exact role of C-reactive protein remains unclear, but it can stimulate mononuclear cells to release tissue factor, which initiates coagulation, activates the complement pathway, and neutralizes platelet-activating factor.1

In recent years, inflammation has emerged as an important factor in atherosclerosis,2 and the role of endothelial cells and monocytes in the inflammatory process has become better understood.3 Earlier studies had examined C-reactive protein concentrations during the course of acute myocardial infarction.4,5 These studies were followed by several angiographic series, cross-sectional studies, and case-control studies that suggested that C-reactive protein concentrations were positively associated with coronary heart disease.6–10 In addition, various studies examined C-reactive protein concentrations among patients with angina pectoris. In general, patients with angina, particularly unstable angina pectoris, had elevated concentrations of C-reactive protein.11–17 Furthermore, among patients with angina pectoris, increases in C-reactive protein concentrations were associated with unfavorable long-term outcomes12,13,15,17 but not unfavorable short-term outcomes.16

In more recent years, several nested case-control and cohort studies have also reported that the risk for cardiovascular disease was positively associated with baseline C-reactive protein concentrations.18–21 This association has been interpreted as confirmation of the role of inflammation in the pathogenesis of coronary heart disease, but any contribution of C-reactive protein to the pathogenesis of stroke has received little attention.6,9,20 We used data from the Third National Health and Nutrition Examination Survey (NHANES III)22 to examine the possible association between C-reactive protein and cerebrovascular disease.

Methods
Periodically, a representative sample of the US population is asked to participate in NHANES. The most recent survey was conducted from 1988 to 1994. Detailed methods of the survey have been published elsewhere.22,23 NHANES uses a stratified multistage probability sampling design to produce estimates generalizable to the US population. Children aged 2 months to 5 years, adults aged ≥60 years, African Americans, and Mexican Americans were oversampled. Of the 20 050 participants aged ≥17 years who were interviewed at home, 17 705 attended a mobile examination center where they completed additional questionnaires and had a series of examinations.

Participants were asked the following question: “Has a doctor ever told you that you had a stroke?” Participants who said yes were classified as having had a stroke. Date of stroke was not requested.

Participants attended an examination in the morning, afternoon, or evening. Persons in the morning sessions were asked to fast for 12 hours before arriving. Persons in the afternoon and evening sessions were asked to fast for 6 hours before the session. Serum C-reactive protein concentration was measured at the University of Washington.

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Department of Laboratory Medicine by using latex-enhanced nephelometry with a Behring Nephelometer Analyzer System (Behring Diagnostics Inc) and with an NA Latex CRP Kit (Behring Diagnostics Inc). Quality control was carried out with daily runs of diluted standards prepared by Behring Diagnostics and standardized against the World Health Organization reference preparation of C-reactive protein serum obtained from the National Institute of Biological Standards and Controls in the United Kingdom. Two types of long-term quality-control charts were used. Details about the laboratory procedures and quality control have been published.22

We included the following covariates: age (years), sex, race or ethnicity (white, African American, or Mexican American), education (years), smoking status (never, former, or current), serum cotinine concentration, systolic blood pressure, diastolic blood pressure, cholesterol concentration, HDL cholesterol concentration, body mass index, physical activity level, and history of diabetes mellitus. Serum cotinine concentrations were measured by using an ELISA. To define blood pressure, we averaged the second and third systolic and diastolic readings. We defined hypertension as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the current use of antihypertensive medication. Three levels of physical activity were defined: moderately or vigorously active, lightly active, and sedentary. Duration of participation in each activity was not asked. Moderately or vigorously active was defined as participating ≥5 times per week in an activity with a MET level of ≥6 for participants aged ≥60 years and a MET level of ≥7 for participants aged <60 years. One MET is defined as the energy expenditure of ~3.5 mL of oxygen per kilogram of body weight per minute, or 1 kilocalorie per kilogram of body weight per hour. Lightly active was defined as participation that was not vigorous or moderate. Sedentary was defined as not engaging in leisure-time physical activity.

We limited the analyses to persons aged ≥40 years who were white, African American, or Mexican American and who attended the medical examination. The sample size of the race category “other” was too small to allow meaningful analyses. Continuous data were compared by t tests; categorical data, by χ² test. Adjusted odds ratios for the exposure variables and stroke were obtained from multiple logistic regression models. We analyzed C-reactive protein concentration as a continuous variable and as a grouped variable. In creating these groups, we chose the upper group to correspond to the upper tertile of the C-reactive protein concentration distribution of the entire sample (≥0.55 mg/dL). Because 71% of participants had concentrations at or below the level of detection and were assigned a value of 0.21 mg/dL, we could not assign the remaining values into groups corresponding to the lowest and middle tertiles. Instead, we assigned participants with a concentration of ≤0.21 mg/dL into 1 group and assigned the remaining participants with concentrations of >0.21 mg/dL, to ≤0.55 mg/dL, into the middle group. We also entered the groups as an ordinal variable (1 to 3) to test for a linear dose-response relation. To examine whether the association between C-reactive protein and stroke differed by sex or race or ethnicity, we entered interaction terms into models that included a full set of covariates. All calculations were performed by using SUDAAN, a statistical software program that takes into account complex survey design.24 We calculated weighted estimates by using the medical examination clinic sampling weights.

Results
Among the 20,050 people who participated in NHANES III, 649 participants reported having had a stroke. After excluding participants aged <40 years, participants who did not attend the medical examination, and participants whose race or ethnicity designation was “other,” 454 persons with a stroke were available for analysis. After excluding persons for whom a C-reactive protein measurement was not available, 414 participants with a stroke remained for study among 8850 participants.

The distribution of C-reactive protein concentration was highly skewed to the left; values ranged from 0.21 to 25.2 mg/dL (mean 0.47, geometric mean 0.32, and median 0.21 mg/dL).

In univariate analyses, participants who had had a stroke were older, were less educated, had higher systolic blood pressures, had higher total cholesterol and lower HDL cholesterol concentrations, were less active, and were more likely to have diabetes than were persons who had not had a stroke (Table 1). The unadjusted geometric mean concentration of C-reactive protein was ≈41% higher for persons with stroke than without stroke.

Most of the risk factors for cardiovascular disease were significantly associated with C-reactive protein concentrations (Table 2). After adjusting the means and percentages for age with use of an external adjustment, the probability value for linear trend changed little.

In the age-adjusted logistic regression analyses, C-reactive protein concentration was strongly predictive of self-reported past history of stroke and increased in a dose-response fashion (Table 3). After adjusting for covariates, however, the magnitude of the odds ratio for participants with C-reactive protein concentrations ≥0.55 mg/dL compared with participants with concentrations ≤0.21 mg/dL was reduced from 2.21 to 1.71 (95% CI 1.11 to 2.64). When we divided the top group into additional categories, the odds ratios for participants with C-reactive protein concentrations of 0.21 to ≤0.33 mg/dL, >0.33 to ≤0.55 mg/dL, >0.55 to ≤1.21 mg/dL, >1.21 to ≤1.80 mg/dL, and >1.80 mg/dL were 1.71 (95% CI 0.93 to 3.12), 1.37 (95% CI 0.84 to 2.22), 1.52 (95% CI 0.89 to 2.60), 1.50 (95% CI 0.73 to 3.09), and 2.54 (95% CI 1.36 to 4.76), respectively. The odds ratios for C-reactive protein entered as a continuous variable in age-adjusted and multiple-adjusted models were 1.26 (95% CI 1.13 to 1.40) and 1.19 (95% CI 1.05 to 1.34), respectively (Table 3). We added the squared term of C-reactive protein concentration to the models to examine for possible nonlinearity of the relation between C-reactive protein and stroke. The regression coefficients were 0.5090 for C-reactive protein (P=0.003) and −0.0536 for its squared term (P=0.056), which suggested that the association might not be perfectly linear. We found no evidence that the association between C-reactive protein and stroke differed by sex (P=0.188) or by race or ethnicity (P=0.929, Table 3).

We also examined whether aspirin use might have affected the association between C-reactive protein and stroke. We categorized aspirin use by frequency of use during the month before the interview: 0, 1 to 3, 4 to 14, 15 to 29, or ≥30 times per month. Adding this term to the multiple logistic regression model for the entire sample changed the odds ratios for C-reactive protein little (1.17, 95% CI 1.03 to 1.33).

Discussion
In this large population-based cross-sectional study, we found a significant positive association between C-reactive protein and self-reported past history of stroke among men and women and among whites, African Americans, and Mexican Americans. Although the odds ratios for Mexican Americans were somewhat larger than those for the other 2 groups, the analysis showed no significant differences among the 3 racial or ethnic groups. Because the study was cross-sectional, the directionality of the association cannot be clearly established. Our findings agree with those from at least 3 previous studies.
in which C-reactive protein concentrations were higher for persons with cerebrovascular disease than for persons without such a disease.6,9,20 Our findings also agree with results from other studies that have described an association between C-reactive protein and coronary heart disease.6 –10,18 –21

In a study of 929 male patients who had had a myocardial infarction or coronary artery bypass surgery and who had been admitted to a coronary rehabilitation unit, the geometric mean concentration of C-reactive protein was 1.13 mg/L for 819 participants without a reduction of >50% in the diameter...
of ≥1 cerebral arteries (measured by ultrasound), 1.00 mg/L for 51 participants with a stenosis in 1 vessel, and 2.20 mg/L for 32 participants with stenoses in ≥2 vessels. In another study, mean C-reactive protein concentration among 11 participants with self-reported stroke or transient ischemic attack was 7.5 mg/L, and the concentration among participants not reporting these conditions was 2.0 mg/L (P=0.13). In a nested case-control study of the Physicians’ Health Study, 154 participants developed ischemic stroke during 14 years of follow-up. Compared with participants with C-reactive protein concentration ≥0.55 mg/L, odds ratios for ischemic stroke were 1.7, 1.9, and 1.9 for quartiles 2, 3, and 4, respectively. A significant trend was found. The odds ratios for stroke were somewhat smaller than those for myocardial infarction in that study. The odds ratios in our analysis may not have fully adjusted for total energy expenditure by the participants. By including only participants who attended the medical examination, it is likely that we included stroke patients who were somewhat healthier than stroke patients unable to attend the examination.

The association we found in NHANES III data may have several possible explanations. Elevated C-reactive protein may reflect the inflammatory component of the atherosclerotic process that underlies ischemic stroke and, therefore, precede stroke. However, stroke may have caused C-reactive protein concentrations to rise, which resulted in the observed differences. Persons with stroke are more incapacitated than healthy persons and, therefore, are prone to infections that raise C-reactive protein concentrations. Although we adjusted for physical activity in our analysis, we may not have fully adjusted for total energy expenditure by the participants. By including only participants who attended the medical examination, it is likely that we included stroke patients who were somewhat healthier than stroke patients unable to attend the examination.

**TABLE 2.** Means or Percentages of Selected Risk Factors for Cardiovascular Disease by Level of C-Reactive Protein Concentration Distribution Among Participants Aged ≥40 y (NHANES III, 1988–1994)

<table>
<thead>
<tr>
<th>C-Reactive Protein Concentration, mg/dL</th>
<th>Sample Size</th>
<th>Mean or Percentage±SE</th>
<th>Sample Size</th>
<th>Mean or Percentage±SE</th>
<th>Sample Size</th>
<th>Mean or Percentage±SE</th>
<th>P for Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.21</td>
<td>5317</td>
<td>56.6±0.5</td>
<td>1414</td>
<td>58.6±0.6</td>
<td>2124</td>
<td>60.5±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;0.21–&lt;0.55</td>
<td></td>
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<td></td>
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<tr>
<td>≥0.55 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>5317</td>
<td>56.6±0.5</td>
<td>1414</td>
<td>58.6±0.6</td>
<td>2124</td>
<td>60.5±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education, y</td>
<td>5286</td>
<td>12.4±0.1</td>
<td>1402</td>
<td>12.0±0.2</td>
<td>2108</td>
<td>11.3±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum cotinine, ng/mL</td>
<td>5249</td>
<td>66.2±2.7</td>
<td>1403</td>
<td>92.5±7.2</td>
<td>2099</td>
<td>74.7±4.7</td>
<td>0.074</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>5074</td>
<td>125.2±0.5</td>
<td>1363</td>
<td>129.3±0.6</td>
<td>2027</td>
<td>131.7±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>5074</td>
<td>74.3±0.4</td>
<td>1363</td>
<td>74.0±0.5</td>
<td>2027</td>
<td>73.8±0.5</td>
<td>0.408</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5300</td>
<td>5.6±&lt;0.1</td>
<td>1414</td>
<td>5.7±&lt;0.1</td>
<td>2120</td>
<td>5.7±&lt;0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>5257</td>
<td>1.3±&lt;0.1</td>
<td>1403</td>
<td>1.3±&lt;0.1</td>
<td>2104</td>
<td>1.3±&lt;0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>5301</td>
<td>26.2±0.1</td>
<td>1411</td>
<td>28.5±0.2</td>
<td>2118</td>
<td>30.2±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inactive, %</td>
<td>5317</td>
<td>14.1±1.0</td>
<td>1414</td>
<td>18.3±1.8</td>
<td>2124</td>
<td>24.5±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>5313</td>
<td>6.3±0.5</td>
<td>1412</td>
<td>9.9±0.8</td>
<td>2121</td>
<td>14.8±1.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**TABLE 3.** Adjusted Odds Ratios for Serum C-Reactive Protein and Stroke Among Participants Aged ≥40 y (NHANES III, 1988–1994)

<table>
<thead>
<tr>
<th>C-Reactive Protein Concentration, mg/dL</th>
<th>No. Stroke/No. at Risk</th>
<th>Per mg/dL</th>
<th>≤0.21 mg/dL</th>
<th>&gt;0.21–0.55 mg/dL</th>
<th>&gt;0.55 mg/dL</th>
<th>P for Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>414/8850</td>
<td>1.26 (1.13–1.40)</td>
<td>1.00</td>
<td>1.58 (1.00–2.49)</td>
<td>2.21 (1.52–3.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>210/4275</td>
<td>1.14 (1.02–1.29)</td>
<td>1.00</td>
<td>1.98 (1.17–3.36)</td>
<td>2.00 (1.06–3.80)</td>
<td>0.017</td>
</tr>
<tr>
<td>Women</td>
<td>204/4575</td>
<td>1.34 (1.12–1.61)</td>
<td>1.00</td>
<td>1.32 (0.70–2.46)</td>
<td>2.50 (1.58–3.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>247/4647</td>
<td>1.26 (1.10–1.44)</td>
<td>1.00</td>
<td>1.59 (0.94–2.68)</td>
<td>2.18 (1.44–3.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>African American</td>
<td>102/2143</td>
<td>1.25 (1.06–1.47)</td>
<td>1.00</td>
<td>1.44 (0.74–2.83)</td>
<td>2.02 (1.14–3.59)</td>
<td>0.018</td>
</tr>
<tr>
<td>Mexican American</td>
<td>65/2060</td>
<td>1.18 (1.03–1.35)</td>
<td>1.00</td>
<td>1.93 (0.92–4.07)</td>
<td>3.16 (1.65–6.06)</td>
<td>0.001</td>
</tr>
<tr>
<td>Multiple-adjusted*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>385/8292</td>
<td>1.19 (1.05–1.34)</td>
<td>1.00</td>
<td>1.49 (0.93–2.39)</td>
<td>1.71 (1.11–2.64)</td>
<td>0.014</td>
</tr>
<tr>
<td>Men</td>
<td>198/4019</td>
<td>1.08 (0.93–1.25)</td>
<td>1.00</td>
<td>1.77 (1.05–2.99)</td>
<td>1.62 (0.79–3.32)</td>
<td>0.137</td>
</tr>
<tr>
<td>Women</td>
<td>187/4273</td>
<td>1.27 (1.05–1.53)</td>
<td>1.00</td>
<td>1.30 (0.64–2.60)</td>
<td>1.82 (1.10–2.99)</td>
<td>0.020</td>
</tr>
<tr>
<td>White</td>
<td>235/4421</td>
<td>1.18 (1.01–1.37)</td>
<td>1.00</td>
<td>1.49 (0.88–2.53)</td>
<td>1.70 (1.04–2.79)</td>
<td>0.029</td>
</tr>
<tr>
<td>African American</td>
<td>86/1974</td>
<td>1.21 (1.02–1.45)</td>
<td>1.00</td>
<td>1.49 (0.71–3.15)</td>
<td>1.70 (0.86–3.35)</td>
<td>0.123</td>
</tr>
<tr>
<td>Mexican American</td>
<td>64/1897</td>
<td>1.18 (1.01–1.39)</td>
<td>1.00</td>
<td>1.70 (0.74–3.87)</td>
<td>2.79 (1.23–6.33)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex (except for sex-specific models), race or ethnicity (except for race- or ethnicity-specific models), education, smoking status, systolic blood pressure, serum cholesterol, HDL cholesterol, history of diabetes mellitus, body mass index, and physical activity.
In addition to the cross-sectional design of the present study already noted, several limitations deserve mention. We were unable to separate ischemic from hemorrhagic stroke. In the present study, stroke was self-reported; however, the validity of self-reported stroke has been reported as good (sensitivity 95%, specificity 96%).

In conclusion, our results support those from a few other studies that have shown an association between C-reactive protein and cerebrovascular disease. The significance of these findings is unclear, but they support the presence of an inflammatory component in the pathogenesis of stroke. Data from additional prospective studies are needed to confirm these findings and better define the magnitude of the risk for stroke associated with elevated C-reactive protein concentration. Furthermore, studies of C-reactive protein concentrations and cardiovascular disease among women and minority populations are needed. Measuring C-reactive protein in people who do not have an obvious reason for having an elevated concentration may offer a method for identifying people at risk for cardiovascular disease.

References
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doi: 10.1161/01.ATV.20.4.1052
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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