Elevated White Blood Cell Count and Carotid Plaque Thickness

The Northern Manhattan Stroke Study

Mitchell S. Elkind, MS, MD; Jianfeng Cheng, MS, MD; Bernadette Boden-Albala, MPH; Myunghee C. Paik, PhD; Ralph L. Sacco, MS, MD

Background and Purpose—Elevated leukocyte count has been associated with cardiovascular and cerebrovascular disease in several epidemiological studies. We sought to determine whether white blood cell count (WBC) is associated with carotid plaque thickness in a stroke-free, multiethnic cohort.

Methods—For this cross-sectional analysis, WBC was measured in stroke-free community subjects undergoing carotid duplex Doppler ultrasound. Maximal internal carotid plaque thickness (MICPT) was measured for each subject. Demographic and potential medical confounding factors were analyzed with linear and logistic regression to calculate the effect of quartile of WBC on MICPT. Odds ratios (ORs) and 95% confidence intervals (CIs) for the effect of quartile of WBC on MICPT ≥75th percentile were calculated. All analyses were stratified by race-ethnicity.

Results—The mean age of the 1422 subjects was 68.6±10.2 years; 40.0% were men; 24.4% were white, 46.9% Hispanic, and 26.7% black. Among Hispanics, compared with the lowest quartile of WBC, those in the highest quartile had significantly increased MICPT (mean difference=0.30 mm, \( P=0.0086 \)) after adjustment for age, sex, and other atherosclerotic risk factors. There was no significant increase for blacks or whites. The OR for MICPT ≥75th percentile (1.9 mm) was significantly increased for Hispanics (OR, 2.8; 95% CI, 1.4 to 5.6), marginally elevated for black non-Hispanics (OR, 1.6; 95% CI, 0.8 to 3.2), and not increased for white non-Hispanics (OR, 0.5; 95% CI, 0.2 to 1.1).

Conclusions—Relative elevation in WBC is associated with carotid atherosclerosis, but this relationship differs by race-ethnicity. The association is strongest in Hispanics, intermediate in black non-Hispanics, and not present in white non-Hispanics in this population. Chronic subclinical infection or inflammation may account for this association.

Key Words: atherosclerosis ■ cerebrovascular disorders ■ epidemiology ■ risk factors

Kn own risk factors fail to account for all cases of ischemic stroke and cardiovascular disease. Recent evidence suggests that atherosclerosis is an inflammatory disease.\(^1\) Chronic infection with Chlamydia pneumoniae, Helicobacter pylori, cytomegalovirus, and other organisms has been postulated as a potential risk factor for atherosclerosis, heart disease, and stroke.\(^2-5\) Recent data have also suggested that carotid duplex Doppler ultrasound is a useful way to study atherosclerotic risk factors, because asymptomatic carotid wall thickening and plaque formation may be a precursor to clinical vascular events. Several studies, including earlier work from our own laboratory,\(^7,8\) have shown that maximal internal carotid plaque thickness (MICPT) is associated with vascular risk factors, such as diabetes mellitus, hypertension, hypercholesterolemia, and smoking. We sought to determine whether white blood cell count (WBC) is associated with MICPT in a cross-sectional analysis of a stroke-free, elderly, multiethnic urban population.

Subjects and Methods

The Northern Manhattan Stroke Study (NOMASS) includes an ongoing population-based cohort study designed to determine stroke incidence, risk factors, and prognosis in a multiethnic, urban population. Northern Manhattan consists of the area north of 145th Street and south of 218th Street that is bordered on the west by the Hudson River and on the east by the Harlem River. In 1990, ~260 000 people lived in the community, with 40% older than 39 years of age and a race-ethnic mixture consisting of 20% black, 63% Hispanic, and 15% white residents.\(^9\)

Selection of NOMASS Cohort

The methods of subject recruitment and enrollment have been described in previous publications.\(^7,10\) Briefly, random digit dialing of ~29 000 households was performed by Audits and Surveys, Inc.
Community participants were enrolled if they (1) had never been diagnosed with stroke, (2) were >40 years of age, and (3) resided in Northern Manhattan for ≥3 months in a household with a telephone. In-person evaluations were performed at the hospital; those subjects who were not able to come to the hospital did not undergo Doppler imaging and were not included in this analysis. The telephone response rate was 94%, and 70% of those respondents participated in an in-person evaluation. The study was approved by the Institutional Review Board at Columbia-Presbyterian Medical Center. All participants gave consent directly or through a surrogate when appropriate.

Index Evaluation of Subjects
Data were collected through interviews, in-person measurements, and collection of fasting blood specimens for lipid and glucose measurements by trained research assistants, and physical and neurological examinations were done by the study physicians, as described elsewhere. When possible, data were obtained directly from subjects with the standardized data collection instruments. When the subject was unable to provide answers, a proxy knowledgeable about the subject’s history was interviewed. Direct subject data were obtained from 99% of stroke-free subjects.

Assessments were conducted in English or Spanish, depending on the primary language of the subject and their preferred cell identification was self-identification through a series of interview questions modeled after the US Census and conforming to the standard definitions outlined by Directive 15. All participants responding affirmatively to being of Spanish origin or identifying themselves as Hispanic were classified as such. All participants classifying themselves as white without any Hispanic origin or as black without any Hispanic origin were classified as white, non-Hispanic or black, non-Hispanic, respectively.

Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control and Prevention regarding the following conditions: hypertension, diabetes, hypercholesterolemia, peripheral vascular disease, transient ischemic attack, cigarette smoking, and cardiac conditions, such as myocardial infarction, coronary artery disease, angina, congestive heart failure, atrial fibrillation, other arrhythmias, and valvular heart disease. Standard techniques were used to measure blood pressure, height, weight, and fasting glucose as described in prior publications. Fasting lipid panels (including total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein, and triglycerides) were measured with a Hitachi 705 automated spectrometer (Boehringer). Hyperglycemia was defined as in prior publications, and diabetes mellitus was defined as a fasting blood glucose level ≥127 mg/DL, the subject’s self-report of such a history, or insulin or oral hypoglycemic use. The definitions are noted in the table footnotes.

Assessment of WBC
WBCs were measured with automated cell counters via standard techniques (Coulter STK-R and Coulter STK-5, Coulter Electronics, and Sysmex SE-9500, TOA Medical Electronics). Whole blood was collected in 5-cm³ EDTA-anticoagulated tubes by a trained phlebotomist. The automated cell counter aspirated a sample from the collection tube, and after lysis of red blood cells and platelets, WBCs were counted by use of a standard direct current detection method. Normal values for WBC in the hematology laboratory are 3.5 to 10.5 × 10⁹/L. Quality control is maintained by the laboratory with standard procedures. The coefficient of variation for repeated measurements on samples from individual hospitalized patients is maintained at ≤2.5%.

Assessment of MICPT
The method for assessment of MICPT has been described in a previous publication. Briefly, MICPT was assessed by trained ultrasonographers experienced in the use of duplex ultrasonography for research purposes and blinded to the participant’s risk factors. Ultrasonography was performed on a Siemens Quantum 2000 duplex ultrasound system with 7.5-MHz scanning frequency in B mode and 5.0-MHz frequency in pulsed Doppler mode. With the subject lying in a supine position, the extracranial carotid arteries were imaged in the longitudinal (anterior, lateral, and posterior views) and transverse planes. Both internal carotid arteries were examined for the presence of atherosclerotic plaque, defined as an area of focal hypechoic wall thickening. If no atherosclerosis was identified, MICPT was recorded as zero. If plaque was imaged, the view showing the thickest plaque was frozen, and the intimal-medial wall thickness (including the plaque) was measured with an electronic cursor and recorded as the MICPT for that artery. For this analysis, the greater of the right and left MICPT was used.

Statistical Analyses
Means were calculated for continuous variables, and proportions were calculated for categorical variables. Bonferroni-corrected t-tests were conducted for comparisons of means; χ² tests, for comparisons of proportions. Regression analysis using linear and quadratic terms was first performed with WBC as a continuous independent variable and MICPT as the dependent variable, stratified by each of the 3 race-ethnic subgroups. Residual plots were examined, and several subsequent analyses were performed, excluding influential points to establish the robustness of the associations. Subjects were then divided into 4 quartiles defined by WBC. Multivariate linear regression using a nonautomated procedure, and incorporating demographic and clinical variables, was then used to build models for the association of WBC and MICPT, stratified by race-ethnicity. The dependent variable for these analyses, MICPT, was expressed as a continuous variable, despite a skewed distribution, because of the large sample size and stable variance. Conventional atherosclerotic risk factors were chosen for the final model on the basis of an association with MICPT in univariate analysis or findings of a significant association in previous analyses from our laboratory. Analyses were then conducted to determine the effect of quartile of WBC on MICPT as a dichotomous variable using multivariate logistic regression, with an MICPT ≥75th percentile (1.9 mm) as the cutoff. Additional logistic regression analyses were then performed with subjects stratified by sex to analyze differences in the associations of MICPT and plaque thickness among the different populations. Statistical significance was determined at the α = 0.05 level with 2-sided tests. Statistical analyses were conducted with SAS computer software (SAS Institute).

Results
The mean age of the 1422 participants was 68.6 ± 10.2 years (median, 69 years; range, 40 to 99 years). Forty percent (n = 569) were men; 24.4% (n = 347) of the participants were white non-Hispanic, 26.7% (n = 379) black non-Hispanic, 46.9% (n = 667) Hispanic, and 2.0% (n = 29) “other.” White non-Hispanics (mean age, 72.7 ± 9.6 years) were older than the black non-Hispanics (mean age, 70.3 ± 10.3 years) and Hispanics (mean age, 65.6 ± 9.4 years). The distribution of sociodemographic factors, comorbid vascular diseases, and conventional atherosclerotic risk factors is shown in Table 1. The mean WBC for the entire cohort was 5.69 ± 2.01 × 10⁹/L (median, 6.0 × 10⁹/L; interquartile range, 4.9 to 7.3 × 10⁹/L; range, 1.5 to 25.7 × 10⁹/L; Table 2). In univariate linear regression models stratified by race-ethnicity, WBC considered as a continuous variable was significantly associated with MICPT among Hispanics (β = 0.098, P < 0.001) but not among blacks or whites (β = 0.03, P = 0.33 and β = 0.03, P = 0.35, respectively). Attempts to fit quadratic models showed no improvement in the models. Analysis after deletion of possible influential points did not change the main results. Further analyses were conducted with WBC quartiles as the independent variable, with those in the lowest quartile as the reference group (WBC < 4.9 × 10⁹/L). There were differences between the different
TABLE 1. Characteristics of Participants

<table>
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<tr>
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<th>n</th>
<th>Prevalence, % or mean ± SD</th>
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<tbody>
<tr>
<td>Completed high school</td>
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<tr>
<td>Hypertension</td>
<td>820</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>21.8</td>
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<tr>
<td>Cardiac disease</td>
<td>282</td>
<td>19.9</td>
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<tr>
<td>Current smoking</td>
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<td>15.0</td>
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<tr>
<td>Ever smoked</td>
<td>775</td>
<td>54.6</td>
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<tr>
<td>Total cholesterol, mg/dL</td>
<td>1378</td>
<td>205 ± 40.9</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>1374</td>
<td>47.3 ± 22.6</td>
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<tr>
<td>LDL, mg/dL</td>
<td>1372</td>
<td>130.6 ± 37.3</td>
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HDL indicates high-density lipoprotein. Hypertension was defined as a systolic blood pressure recording of ≥160 mm Hg or a diastolic blood pressure recording of ≥95 mm Hg or the patient’s self-report of a history of hypertension or antihypertensive use. Diabetes mellitus was defined by a fasting blood glucose level >126 mg/dL, the patient’s self-report of such a history, or insulin or hypoglycemic use.

race-ethnic groups in WBC (Table 2). Black non-Hispanics had the lowest mean WBC (P < 0.0001).

The mean MICPT for the entire cohort was 1.14 ± 1.23 mm (median, 1.0 mm; interquartile range, 0 to 1.9 mm). There were also significant differences in MICPT among the 3 major racial-ethnic groups (Table 2). MICPT among Hispanics was significantly less than that among non-Hispanics, but there was no significant difference between white and black non-Hispanics. Among Hispanics, the mean MICPT values in each of the 4 quartiles of WBC were 0.72, 0.75, 0.74, and 1.19 mm. The difference between mean MICPT in the highest and the other 3 quartiles was significant (P < 0.05). There was no difference between mean MICPT by quartile of WBC among the other race-ethnic subgroups.

In linear regression models including quartile of WBC only and stratified by race-ethnicity, among Hispanics those in the highest quartile of WBC had a significantly increased MICPT compared with those in the lowest quartile (mean difference = 0.47, P < 0.0001; Table 3). For the second and third quartiles, there was no significant association (Table 3). After adjustment for demographic variables (age and sex), there remained an association for Hispanics (β = 0.41, P = 0.004) but not for black or white non-Hispanics (Table 3). After multiple linear regression analysis adjusting for potential confounders, a statistically significant association for the highest quartile of WBC and MICPT remained among Hispanics, although inclusion of the covariates attenuated the relationship (β = 0.30, P = 0.0086). Thus, among Hispanics, on average those in the highest quartile for WBC had an MICPT that was 0.3 mm thicker than those in the lowest quartile. The final model also included the following covariates, which were significantly associated with MICPT among Hispanics: age from 65 to 80 years (β = 0.41, P < 0.0001), age >80 years (β = 1.03, P < 0.0001), male sex (β = 0.19, P < 0.02), LDL (β = 0.0038, P < 0.0003), coronary artery disease (β = 0.37, P = 0.0005), and current cigarette smoking (β = 0.46, P = 0.0002). Current smoking was highly significantly associated with WBC level among Hispanics, with mean WBC among current smokers and current nonsmokers of 7.56 and 6.23 × 10⁹/L (P < 0.0001), respectively. Inclusion of smoking in the model, however, did not eliminate the effect of WBC on MICPT but did reduce the magnitude of the effect (β = 0.40, P = 0.0004 in model without smoking; β = 0.30, P = 0.0086 in the model with smoking). Hypertension and diabetes mellitus were also included in the final model because of their recognized importance as risk factors for atherosclerosis and because they were associated with MICPT in the black or white populations but not conventionally significant among Hispanics.

Among white non-Hispanics, further models revealed no significant association of WBC quartile with plaque thickness (Table 3). Age from 65 to 80 years (β = 0.39, P = 0.02), age >80 years (β = 1.00, P < 0.0001), hypertension (β = 0.46, P = 0.0004), current cigarette smoking (β = 0.53, P = 0.007), and coronary artery disease (β = 0.37, P = 0.01) were significantly associated with plaque thickness, but sex, LDL, and diabetes mellitus were not. Similarly, among black non-Hispanics, there was no association of WBC with plaque thickness (Table 3). Age from 65 to 80 years (β = 0.77, P < 0.0001), diabetes mellitus (β = 0.51, P = 0.001), and current smoking (β = 0.75, P < 0.0001) were associated with plaque thickness among black non-Hispanics. Because blacks are known to have a lower WBC than white populations¹⁵ (a condition known as benign leukopenia), additional analyses were performed with the use of within-group quartiles for blacks, but this produced no material change in the results.

TABLE 2. Distribution of WBC and MICPT by Race-Ethnicity

<table>
<thead>
<tr>
<th></th>
<th>Hispanic (n=667)</th>
<th>White Non-Hispanic (n=347)</th>
<th>Black Non-Hispanic (n=379)</th>
<th>Overall* (n=1422)</th>
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<tbody>
<tr>
<td>WBC, ×10⁹/L</td>
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<tr>
<td>Mean ± SD</td>
<td>6.40 ± 1.97</td>
<td>6.53 ± 2.01</td>
<td>5.88 ± 2.07</td>
<td>6.25 ± 1.92</td>
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<tr>
<td>Median</td>
<td>6.3</td>
<td>6.1</td>
<td>5.5</td>
<td>6.0</td>
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<tr>
<td>Interquartile range</td>
<td>5.1–7.6</td>
<td>5.1–7.3</td>
<td>4.5–6.9</td>
<td>4.9–7.3</td>
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<tr>
<td>MICPT, mm</td>
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<tr>
<td>Mean ± SD</td>
<td>0.87 ± 1.09</td>
<td>1.40 ± 1.27</td>
<td>1.38 ± 1.32</td>
<td>1.14 ± 1.23</td>
</tr>
<tr>
<td>Median MICPT</td>
<td>0.0</td>
<td>1.3</td>
<td>1.2</td>
<td>1.0</td>
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<tr>
<td>Interquartile range</td>
<td>0.0–1.5</td>
<td>0.0–2.0</td>
<td>0.0–2.2</td>
<td>0.0–1.9</td>
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</table>

*Twenty-nine subjects were characterized as other race-ethnicity.
Further analyses used a dichotomous outcome variable, MICPT $\geq$75th percentile (1.9 mm), to assess the effect of WBC quartile on marked thickening of the vessel wall (Table 4). Among Hispanics, compared with those in the lowest quartile of WBC, those in the highest quartile had a significantly elevated risk of MICPT $\geq$1.9 mm after adjustment for demographic and other risk factors. There was no significant increase for those in the intermediate quartiles. Among black non-Hispanics, a significant increase in risk was found in a model adjusted for demographic factors for both the third and fourth quartiles, but this was attenuated after adjustment for the other atherosclerotic risk factors. Among white non-Hispanics, there was no evidence of an association.

We further stratified our Hispanic population by sex to determine whether the association of WBC with MICPT held for both men and women (Table 5). An increase in the odds for MICPT $\geq$1.9 mm was found for both men and women, although the magnitude of this risk was greater for men than women (odds ratio [OR], 3.29; 95% confidence interval [CI], 1.24 to 9.58; and OR, 2.61; 95% CI, 1.02 to 7.41, respectively). A formal test for an interaction between sex and WBC did not reveal any significant effect.

**Discussion**

This cross-sectional study supports a previously described association between WBC and subclinical carotid plaque formation and suggests that the association may vary among particular race-ethnic groups. We found an association of WBC and MICPT in an elderly, urban, mostly Hispanic population in whom the burden of stroke and other vascular diseases is high. There also may be variation by sex, because the relationship appears stronger among men than women.

### Table 3. Predicted Mean Differences and 95% CIs in MICPT by Quartile of WBC Stratified by Race and Adjusted for Demographic and Other Risk Factors

<table>
<thead>
<tr>
<th>Quartile of WBC</th>
<th>Hispanic</th>
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<th>Non-Hispanic White</th>
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<th>Non-Hispanic Black</th>
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<td>$\beta$</td>
<td>95% CI</td>
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<td>Adjusted for demographic factors* $(n=667)$</td>
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<tr>
<td>Quartile 2</td>
<td>0.05</td>
<td>-0.18–0.29</td>
<td>0.03</td>
<td>-0.19–0.26</td>
<td>0.42</td>
<td>0.20–0.65</td>
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<tr>
<td>Quartile 3</td>
<td>0.38</td>
<td>-0.19–0.26</td>
<td>0.03</td>
<td>-0.34–0.41</td>
<td>0.36</td>
<td>0.01–0.70</td>
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<tr>
<td>Quartile 4</td>
<td>0.42</td>
<td>0.20–0.65</td>
<td>0.08</td>
<td>-0.46–0.29</td>
<td>0.24</td>
<td>-0.10–0.58</td>
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<td>$(n=363)$</td>
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<tr>
<td>Quartile 2</td>
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<td>Quartile 3</td>
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<td>-0.06</td>
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<td>0.24</td>
<td>-0.09–0.58</td>
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<tr>
<td>Quartile 4</td>
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<td>0.08–0.53</td>
<td>-0.24</td>
<td>-0.62–0.15</td>
<td>-0.04</td>
<td>-0.39–0.32</td>
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*Demographic factors are age and sex.
†First quartile is the referent group.
‡Conventional risk factors are LDL, hypertension, diabetes mellitus, coronary artery disease, and current cigarette smoking.

### Table 4. ORs for Association of Quartile of WBC With MICPT $\geq$1.9 mm

<table>
<thead>
<tr>
<th>Quartile of WBC</th>
<th>Hispanic</th>
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<th>Non-Hispanic White</th>
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<td>OR</td>
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<tr>
<td>Quartile 2</td>
<td>1.61</td>
<td>0.80–3.30</td>
<td>0.58</td>
<td>0.29–1.17</td>
<td>1.30</td>
<td>0.69–2.43</td>
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<td>Quartile 3</td>
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<td>0.84</td>
<td>0.43–1.64</td>
<td>1.95</td>
<td>1.05–3.64</td>
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<td>Quartile 4</td>
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<td>2.07</td>
<td>1.10–3.91</td>
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<td>Quartile 1†</td>
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<td>Quartile 2</td>
<td>1.80</td>
<td>0.87–3.81</td>
<td>0.55</td>
<td>0.26–1.17</td>
<td>1.22</td>
<td>0.62–2.40</td>
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<td>Quartile 3</td>
<td>1.04</td>
<td>0.49–2.23</td>
<td>0.75</td>
<td>0.37–1.53</td>
<td>1.76</td>
<td>0.91–3.43</td>
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<td>Quartile 4</td>
<td>2.77</td>
<td>1.44–5.59</td>
<td>0.51</td>
<td>0.24–1.10</td>
<td>1.55</td>
<td>0.77–3.15</td>
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*Demographic factors are age and sex.
†First quartile is the referent group.
‡Conventional risk factors are LDL, hypertension, diabetes mellitus, coronary artery disease, and current cigarette smoking.
Previous studies of atherosclerotic risk factors using high-resolution carotid duplex Doppler ultrasound have examined WBC among other hemostatic and infectious risk factors. One study found WBC to be independently predictive of progression of atherosclerosis over 2 years in a small sample of Finnish men. Another study that investigated several hematologic factors did not find an association, but that study examined patients with established arterial diseases. Studies of clinical atherosclerotic outcome events have found an association between leukocyte count and risk of atherosclerotic heart disease and stroke. Our study provides additional evidence that in certain populations elevations in WBC may be independently associated with a marker of subclinical atherosclerosis.

In the population examined in this study, the association of leukocytes with atherosclerosis differed by race-ethnicity. Among Hispanics, there appeared to be a threshold for the relationship of WBC with MICPT, with the increase in MICPT occurring only in the highest quartile of WBC. It is important to recognize, however, that even the highest quartile, WBC $\geq 7.3 \times 10^7$/L, still fell mostly within the normal range of WBC. Among black non-Hispanics, there was a trend toward an increased MICPT in those with WBC in the third and fourth quartiles, but this association was not statistically significant after adjustment for other risk factors. The number of black non-Hispanics was small relative to the Hispanic groups, making the results less robust for that group.

We and others have found other differences in the prevalence of carotid wall thickening between Hispanics and non-Hispanics. Hispanics have less MICPT, even after adjustment for age and other conventional risk factors, than do non-Hispanic whites and blacks in our population. The different distribution of MICPT among Hispanics compared with non-Hispanic groups in our population does not explain the difference in the association of WBC with MICPT, however. Our analyses were stratified by race-ethnicity, so the findings within each group represent true findings. Whether an association among WBC and MICPT would be found among white or black populations with different distributions of MICPT is unclear from these data. Moreover, using group-specific thresholds for the quartile values of WBC and the MICPT cutoff for the dichotomous analysis did not change the results.

Other studies have found an association between WBC and cardiovascular disease among whites, but ours did not. Our white population may differ from the white populations examined in other studies, however. Among the studies that found WBC to be a predictor of clinical cardiovascular events, such as the Framingham, Multiple Risk Factor Intervention, Caerphilly, and Speedwell studies, the participants were generally <60 years of age. The mean age of our white population, however, was 72.7 years compared with mean ages among our Hispanics of 65.6 years and among our black population of 70.3 years. In the intima-media thickness progression study of men from Finland, participants ranged from 42 to 60 years of age. In that population, moreover, hypertension was not found to be associated with IMT progression, whereas in our study, hypertension was associated with MICPT among whites. In studies that looked at both middle-aged and older participants, the effect of WBC was stronger in those <65 years of age. In addition, the number of participants in the white non-Hispanic group was relatively small (n=379) compared with the black non-Hispanic and Hispanic subgroups, making the results less robust for that group.

The effect of risk factors other than WBC on atherosclerosis may also differ between Hispanics and non-Hispanics.
LDL\textsuperscript{7} and the ratio of apolipoprotein (apo)B to apoA-I\textsuperscript{8} are also associated with increasing MICPT in Hispanics but not in the other race-ethnic groups in our population. Other studies have found that the effect of cardiovascular risk factors may differ between blacks and whites.\textsuperscript{27,28} The majority (88%) of our Hispanic population is composed of Caribbean Hispanics from the Dominican Republic, Puerto Rico, or Cuba. Risk factors in this group could also differ from those in other Hispanic groups in the United States, such as Mexicans and those from other countries. However, although Caribbean Hispanics may differ from Mexican Hispanics, it is also possible that Hispanics from these different Caribbean countries also differ from one another in important ways. It should be emphasized that American Hispanics are a heterogeneous group, that the classification of individuals as “Hispanic” can be problematic,\textsuperscript{29} and that analyses based on any assumptions of homogeneity should be viewed cautiously. Nonetheless, we used the method of self-identification to determine race-ethnicity, which is subscribed to by the US Census and recommended for all research studies.\textsuperscript{11} Moreover, if the term “Hispanic” is insufficiently accurate, nondifferential misclassification by race-ethnicity should only serve to underestimate the effects of any findings.

The findings that Hispanics in our population have less carotid plaque and that their atherosclerosis may be associated with different risk factors (LDL, WBC) than their non-Hispanic neighbors may have important implications. The recognition that atherosclerotic risk factors may have specificity for certain race-ethnic populations may be of help in targeting particular risk factor reduction strategies to those populations. The underlying cause of this race-ethnic variability remains uncertain. Genetic, dietary, and other environmental factors may all play a role. One of the benefits of the NOMASS study design is that it allows the study of 3 different race-ethnic groups living in the same relatively limited geographic area within northern Manhattan and thereby minimizes some of the environmental heterogeneity that comes from studying populations from different regions of the country. There may still be important cultural differences among the different race-ethnic groups, however, that lead to different effective environments. We did not include dietary data, for example, in this analysis.

The magnitude of the effect of elevated WBC on MICPT among Hispanics in our population is probably clinically meaningful. Those in the highest quartile of WBC had an adjusted increase in plaque thickness of 0.3 mm compared with those in the lowest quartile. In the Cardiovascular Health Study (CHS) in which measurements were made with a slightly different technique, for every 0.55-mm increase in intima-media thickness of the internal carotid artery, there was a 30% increase in risk of stroke or myocardial infarction.\textsuperscript{30} For those with an intima-media thickness of \( \geq 1.81 \) mm in CHS, the relative risk of stroke or myocardial infarction was 2.47 (95% CI, 1.59 to 3.85). The cutoff of 1.81 mm in CHS represented the 80th percentile and is very similar to the 75th percentile threshold of MICPT \( \geq 1.9 \) mm in our dichotomous model.

Elevated leukocytes may lead to clinical atherosclerotic events either by an effect on chronic atherosclerosis or by inducing acute thrombotic events. Prospective observational studies have found elevations in WBC to be predictive of ischemic stroke and coronary artery disease, perhaps by an effect on plaque rupture.\textsuperscript{19,24} Data from experimental work on animals and in vitro data show that leukocytes also play an important role in atherogenesis.\textsuperscript{1} Macrophages and T lymphocytes are prominent in human atheromas, even in the earliest stages of the disease process,\textsuperscript{31} suggesting that immune processes also may play an initiating or early role in the development of the lesion in human beings. Our data support at least a partial role for leukocytes in the chronic process of atherosclerosis.

It is not known whether this association between relatively elevated leukocyte count and atherosclerosis reflects ongoing chronic subclinical infection. Several observational epidemiological studies,\textsuperscript{5,6,32} including one in our own population,\textsuperscript{33} have suggested an association between chronic infection with \textit{C pneumoniae} and stroke risk. The Atherosclerosis Risk in Communities (ARIC) Study Investigators\textsuperscript{3} reported a similar magnitude of association of \textit{C pneumoniae} IgG antibodies with asymptomatic carotid atherosclerosis among patients 45 to 64 years of age (adjusted OR, 2.0; 95% CI, 1.2 to 3.4). Other ways in which leukocytes could affect atherosclerosis include inflammatory mechanisms independent of infection.

Smoking is likely to be a partial confounder in the relationship between WBC and atherosclerosis. We and others have found that current cigarette smoking is associated with WBC\textsuperscript{34} and subclinical atherosclerosis.\textsuperscript{16,35} Smoking can increase the mortality from chronic bronchitis\textsuperscript{36} and possibly other infections.\textsuperscript{37} Smoking itself may thus be the cause of the increased MICPT, with elevated WBC also resulting from the smoking. We found, however, that there is an increase in MICPT even after adjustment for current smoking among Hispanics. Residual confounding or differential reporting of smoking history dependent on WBC status could mask the effect of smoking on MICPT even among the Hispanic population. Other risk factors are also associated with elevated WBC,\textsuperscript{35} and could confound the relationship between MICPT and WBC.

Further prospective studies of the relationship between WBC, as well as other inflammatory and infectious markers, and ischemic stroke are needed. Although many studies have investigated the relationship between infection and atherosclerotic heart disease, these may not reflect the relationship between infection and stroke. In northern Manhattan, large-artery atherosclerosis accounts for a minority (only 10% to 20%) of ischemic stroke;\textsuperscript{38} embolic and small-vessel causes of stroke are probably more common. Further studies need to take into account the several etiological subtypes of stroke.

Our study has several limitations. Because of our cross-sectional design, we are unable to claim that elevated WBC leads to an increase in plaque thickness. The converse, that participants with greater carotid plaque thickness develop elevated WBC, could just as well be true. The participants in this study were all stroke-free subjects from the community selected at random; thus, it is unlikely that there would be a selection bias for a high incidence of infections. Our study
also assesses a measure of subclinical atherosclerosis, MICPT, rather than clinical end points such as myocardial infarction or stroke. Several recent studies, however, have shown that these measures are predictive of clinical ischemic events.\textsuperscript{30,39,40}

Our measurement of MICPT also differs from that used in other studies of carotid wall thickness. For these analyses, we used the maximum thickness of the internal carotid artery plaque. This measurement differs from the measurement of intima-media thickness made in several other studies.\textsuperscript{4,16,30,40–42} We have previously reported on the use of this method and found associations with atherosclerotic risk factors, including age, smoking, hyperglycemia, hypertension, LDL, apoA-I and apoB, consistent with findings in studies using methods which measure intima-media thickness.\textsuperscript{7,8} Additionally, some\textsuperscript{50,41,42} have suggested that the common carotid artery wall thickness is the most reliable measurement for studies of preclinical studies of atherosclerosis. Others have shown, however, that internal carotid artery measurements\textsuperscript{39} or combined measurements of internal and common carotid arteries\textsuperscript{43} are as reliable and useful in predicting clinical events as are those of the common carotid artery alone. We are currently measuring intima-media thickness at several sites in the common and internal carotid arteries and in the future may have further data on the association of WBC and other risk factors and intima-media thickness, as well as on the relative merits of intima-media thickness and MICPT.

Our study did not provide serological data on infection or data on other markers of inflammation, such as C-reactive protein or leukocyte adhesion molecules. Further studies are ongoing to determine the association of specific cytokine markers with carotid atherosclerosis in this population. We also did not have data on clinical infection and therefore were unable to make statements about the underlying causes of the elevated WBC. Although this information would be useful, it is difficult to know how to apply it to the development of atherosclerosis. In asymptomatic populations, the role of elevated WBC may be more chronic. Also, it would be useful to know whether the measurements we made of WBC are elevated WBC may be more chronic. Also, it would be useful to know whether the measurements we made of WBC are

It would also be helpful to have data on the leukocyte differentials of the WBC of the subjects. It is unclear whether the elevated risk of MICPT is associated primarily with neutrophils or lymphocytes. Recent evidence suggests that circulating levels of specific white cell types, such as the CD4\textsuperscript{+}CD28\textsuperscript{dim} subset of T lymphocytes, may be associated with unstable angina.\textsuperscript{48} It remains unknown whether circulating levels of specific WBC types might be associated with subclinical atherosclerosis.

In summary, our study supports an association between WBC and carotid atherosclerosis in at least some populations. Evidence from pilot clinical trials in patients with coronary artery disease,\textsuperscript{45–47} as well as animal studies,\textsuperscript{48} already suggests that the role of atherosclerotic disease associated with certain infections, such as \textit{C pneumoniae}, may be modifiable. Corroboration from larger, prospective studies of the role of inflammatory and infectious markers in atherosclerosis and stroke might lead to clinical trials with novel anti-inflammatory or anti-infectious therapies to retard atherosclerosis or prevent incident and recurrent stroke.

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Elevated White Blood Cell Count and Carotid Plaque Thickness: The Northern Manhattan Stroke Study
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