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Relative elevation in baseline leukocyte count predicts first cerebral infarction

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Abstract—*Background:* Atherosclerosis is an inflammatory disease, and leukocyte levels are associated with future risk of ischemic cardiac disease. *Objective:* To investigate the hypothesis that relative elevations in leukocyte count in a stroke-free population predict future ischemic stroke (IS). *Methods:* A population-based prospective cohort study was performed in a multiethnic urban population. Stroke-free community participants were identified by random-digit dialing. Leukocyte levels were measured at enrollment, and participants were followed annually for IS, myocardial infarction (MI), and cause-specific mortality. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% CIs for IS, MI, and vascular death after adjustment for medical, behavioral, and socioeconomic factors. *Results:* Among 3,103 stroke-free community participants (mean age 69.2 ± 10.3 years) with baseline leukocyte levels measured, median follow-up was 5.2 years. After adjusting for stroke risk factors, each SD in leukocyte count (1.8×10^9 cells/L) was associated with an increased risk of IS (HR 1.22, 95% CI 1.05 to 1.42), and IS, MI, or vascular death (HR 1.13, 95% CI 1.02 to 1.26). Compared with those in the lowest quartile of leukocyte count, those in the highest had an increased risk of IS (adjusted HR 1.75, 95% CI 1.08 to 2.82). The effect on atherosclerotic and cardioembolic stroke was greater than in other stroke subtypes. *Conclusion:* Relative elevations in leukocyte count are independently associated with an increased risk of future ischemic stroke and other cardiovascular events.

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Known risk factors fail to account for all cases of ischemic stroke and (IS) cardiovascular disease. Recent evidence suggests that atherosclerosis is a chronic 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 Several studies provide evidence that relative elevations in leukocyte count, even within the normal range, identify individuals at higher risk of future coronary artery disease.^{3,4} Few prospective studies have studied the association between leukocyte levels and stroke, however, and no studies have assessed the association between leukocytes and stroke in Hispanic individuals.^{4–8} Those studies that have been conducted, moreover, have incompletely adjusted for smoking and other important stroke risk factors and have not investigated individual IS subtypes. We sought to determine whether leukocyte count is associated with risk of IS and other vascular events in a stroke-free, elderly,

predominantly Hispanic urban population after adjusting for other atherosclerotic risk factors.

Methods. The Northern Manhattan Study, a population-based study designed to determine stroke incidence and risk factors in a multiethnic, urban population, has been previously described.⁹ The race-ethnic mixture consists of 63% Hispanic, 20% non-Hispanic black, and 15% non-Hispanic white residents.

The methods of stroke-free participant recruitment and enrollment have been described previously.⁹ In brief, participants were identified by random-digit dialing using dual-frame sampling to identify both published and unpublished telephone numbers, and they were enrolled in a prospective cohort study between 1993 and 2001 if they 1) had never been diagnosed with stroke, 2) were over age 39, and 3) resided in Northern Manhattan for ≥ 3 months in a household with a telephone. In-person evaluations were performed at the hospital or at home for those who could not come in person (6% were done at home). The study was approved by the Institutional Review Board at Columbia University Medical Center. All participants gave informed consent to participate in the study.

Data regarding baseline status and risk factors were collected through interviews of participants by trained bilingual research assistants, physical and neurologic examination by study physicians, in-person measurements, and analysis of fasting blood specimens.⁹ Data were obtained directly from participants using standardized data collection instruments, as previously described.⁹

Race-ethnicity was determined by self-identification. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control and Pre-

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vention regarding the following conditions: hypertension, diabetes, hypercholesterolemia, peripheral vascular disease, TIA, cigarette smoking, and cardiac conditions.¹⁰ Standard techniques were used to measure blood pressure, height, weight, and fasting glucose and lipid panels as previously described.⁹ Hypertension was defined as systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure of ≥ 90 mm Hg based on the average of the two blood pressure measurements, a physician diagnosis of hypertension, or a patient's self-report of a history of hypertension or antihypertensive use. Diabetes mellitus was defined as fasting blood glucose level of ≥ 126 mg/dL or the patient's self-report of such a history or of insulin or hypoglycemic use.

Leukocyte counts were measured using automated cell counters via standard techniques (Coulter STK-R and Coulter STK-S [Coulter Electronics, Hialeah, FL]; Sysmex SE-9500 [TOA Medical Electronics, Kobe, Japan]). Whole blood was collected in 5 mL of ethylenediaminetetra-acetate-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, white blood cells were counted using a standard direct current detection method. Normal values for white blood cells in the hematology laboratory are 3.54 to $9.06 \times 10^9/L$. Quality control is maintained by the laboratory using standard procedures. The coefficient of variation for repeated measurements on samples from individual hospitalized patients is maintained at $\leq 2.5\%$.

Follow-up evaluations were conducted annually by telephone among all cohort participants to assess vital status, functional status, intercurrent hospitalizations, or illness and to screen for symptoms consistent with either stroke, TIA, or myocardial infarction (MI), as previously described.⁹ Two neurologists classified the strokes independently after review of all data. Final stroke subtype, including IS subtype, was decided by consensus of the two neurologists, and any disagreements were adjudicated by a third neurologist evaluator. Strokes were classified as extracranial atherosclerotic, intracranial atherosclerotic, lacunar (small vessel), cardioembolic, or cryptogenic, using the results of the diagnostic evaluation according to a modified Stroke Data Bank scheme.¹¹ MI was validated by review by a study cardiologist.

Stroke was defined by the first symptomatic occurrence of any type of stroke including intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction, according to World Health Organization criteria, as previously described.⁹ MI was defined by criteria adapted from the Cardiac Arrhythmia Suppression Trial¹² and the Lipid Research Clinics Coronary Primary Prevention Trial.¹³ Cause of death was verified by a study physician, and deaths were classified as vascular or nonvascular.

Statistical analyses. The distribution of leukocyte count and other risk factors was estimated, both overall and by subject characteristics, including demographics and risk factors. Eight participants with markedly elevated baseline leukocyte counts ($>15.0 \times 10^9$ cells/L) were excluded from analyses. Cox proportional hazards regression modeling was used to calculate the hazard ratios (HRs) and 95% CIs for cerebrovascular and cardiovascular endpoints. The primary analysis was performed by calculating the HR per SD of leukocyte level both unadjusted and after adjusting for potential confounding risk factors, including demographic risk factors (age, sex, race-ethnicity, and educational level) and medical and behavioral risk factors (hypertension, coronary artery disease, atrial fibrillation, diabetes, high-density lipoprotein, low-density lipoprotein, current smoking, past smoking, body mass index, waist-hip ratio, and metabolic syndrome). Adjusted analyses were performed overall and in secondary analyses stratified by age (<70 and ≥ 70 years), sex, race-ethnic group, smoking status, history of other vascular diseases (coronary artery disease or peripheral arterial disease), and IS subtype. Further secondary analyses were conducted using quartile of leukocyte count as the independent variable.

Results. The enrolled Northern Manhattan Study cohort ($n = 3,298$) was similar to the random telephone sample with regard to sociodemographics and risk factors. A total of 3,103 (94.1%) participants had a baseline leukocyte count and at least 1 year of follow-up. Distribution of demographic and other baseline characteristics in this sam-

Table 1 Characteristics of participants

Characteristic	Value
n	3,103
Mean \pm SD age, y	69.0 \pm 10.3
Men, n (%)	1,159 (37.4)
Race-ethnicity, n (%)	
Hispanic	1,631 (52.6)
Non-Hispanic black	762 (24.6)
Non-Hispanic white	639 (20.6)
High school diploma, n (%)	1,432 (46.2)
Insurance status	
Uninsured	327 (10.5)
Medicaid	1,030 (33.2)
Medicare	1,284 (41.4)
Private insurance	462 (14.9)
Risk factors, n (%)	
Hypertension	2,100 (67.7)
Diabetes mellitus	674 (21.7)
Hyperlipidemia	1,393 (44.9)
Metabolic syndrome	1,319 (44.1)
History of smoking	1,645 (53.1)
Current smoking	538 (17.6)
History of coronary artery disease	648 (20.9)
History of myocardial infarction	222 (7.2)
History of atrial fibrillation	130 (4.2)
History of peripheral arterial artery disease	467 (15.1)
Physiologic measures, mean \pm SD	
Systolic blood pressure, mm Hg	143.7 \pm 21.1
Total cholesterol, mg/dL	202.8 \pm 40.2
Low-density lipoprotein, mg/dL	129.3 \pm 35.9
High-density lipoprotein, mg/dL	46.9 \pm 14.4
Body mass index	27.5 \pm 5.4
Waist-hip ratio	0.9 \pm 0.09
Leukocyte count, $\times 10^9/L$	6.2 \pm 1.8

ple are shown in table 1. This group was representative of the overall Northern Manhattan Study cohort.

The median follow-up of those who did not have an event was 5.2 years (range 1.0 to 10.6 years). There were 163 strokes of all types, including 142 ISs, 124 MIs, and 218 vascular deaths. Of the ISs, 19 (13.3%) were attributed to large-vessel atherosclerosis, 40 (28.2%) lacunar, 43 (30.3%) cardioembolic, 33 (23.2%) cryptogenic, and 7 other causes.

The mean leukocyte count was $6.2 \pm 1.8 \times 10^9$ cells/L (median 5.9, interquartile range 4.9 to 7.2×10^9 cells/L, range 1.5 to 14.6×10^9 cells/L). The stability of leukocyte levels measured over time was good. Among a subgroup of 114 event-free participants who had four or more leukocyte measurements repeated annually, the within-individual variability in leukocyte levels was 1.1×10^9 cells/L. Those who had serial leukocyte levels measured were less likely to be Hispanic (28.1 vs 36.0% for non-Hispanics; $p <$

Table 2 Risk of ischemic stroke and other events associated with leukocyte count

Event	Hazard ratio (95% CI)*		
	Unadjusted	Adjusted for demographic factors†	Adjusted for demographics and risk factors‡
Ischemic stroke	1.27 (1.10–1.47)	1.31 (1.13–1.51)	1.22 (1.05–1.42)
Total stroke	1.26 (1.09–1.44)	1.29 (1.12–1.48)	1.19 (1.03–1.39)
Ischemic stroke, myocardial infarction, or vascular death	1.20 (1.09–1.31)	1.25 (1.14–1.38)	1.13 (1.02–1.26)

* Risk expressed per SD in leukocyte level (1.8×10^9 cells/L).

† Demographic factors are age (continuous by year), sex, race-ethnicity, and education (high school graduate vs not).

‡ Risk factors are history of hypertension, diabetes mellitus, current cigarette smoking, atrial fibrillation, and levels of high-density lipoprotein and low-density lipoprotein, and body mass index.

0.0001) and to have atrial fibrillation (0 vs 4.4%; $p = 0.02$), but they did not differ with respect to any other stroke risk factors.

Leukocyte counts were lower among non-Hispanic blacks ($5.8 \pm 1.8 \times 10^9$ cells/L) than among non-Hispanic whites and Hispanics (6.4 ± 1.7 and $6.3 \pm 1.8 \times 10^9$ cells/L; $p < 0.0001$). Leukocyte count was not associated with educational status but was associated with other socioeconomic factors including type of occupation (mean leukocyte level $6.3 \pm 1.9 \times 10^9$ cells/L among unskilled workers and $6.1 \pm 1.7 \times 10^9$ cells/L among skilled workers; $p = 0.009$) and health insurance ($6.3 \pm 1.8 \times 10^9$ cells/L among the uninsured, $6.3 \pm 1.9 \times 10^9$ cells/L among those with Medicaid, $6.2 \pm 1.8 \times 10^9$ cells/L among those with Medicare, and $5.9 \pm 1.7 \times 10^9$ cells/L among those with private insurance; $p < 0.0001$). Leukocyte counts were higher among those with a history of smoking (6.4 ± 1.9 vs $6.0 \pm 1.7 \times 10^9$ cells/L; $p < 0.0001$) and for those currently smoking (6.8 ± 2.0 vs $6.0 \pm 1.7 \times 10^9$ cells/L; $p < 0.0001$). Leukocyte counts were also higher among those with a history of diabetes mellitus, metabolic syndrome, and coronary artery disease ($p < 0.0001$ for each risk factor). Leukocyte counts were not significantly higher for those with history of peripheral arterial disease.

Leukocyte count as a predictor of IS. Leukocyte count was associated with an increased risk of IS (unadjusted HR per SD in leukocyte count 1.27, 1.10 to 1.47; table 2). This increased risk changed minimally after adjusting for age, sex, race-ethnicity, education, hypertension, diabetes mellitus, current cigarette smoking, atrial fibrillation, body mass index, and levels of high-density lipoprotein and low-density lipoprotein (adjusted HR 1.22, 1.05 to 1.42). Leukocyte count also predicted with the same approximate magnitude the risk of the combined endpoint of ischemic and hemorrhagic stroke (adjusted HR 1.19, 1.03 to 1.39). Other significant predictors of cerebral infarction were age (adjusted HR per year of age 1.06, 1.03 to 1.08), hypertension (adjusted HR 1.59, 1.04 to 2.44), and diabetes mellitus (adjusted HR 2.42, 1.71 to 3.42). Leukocyte counts were drawn a median of 3.1 years (interquartile range 1.7 to 4.7 years) prior to events.

Because leukocyte count was also correlated with the metabolic syndrome and a history of coronary artery disease, analyses further adjusted for these risk factors were also performed, with minimal change in the results (adjusted odds ratio 1.21, 1.04 to 1.41). The results did not

change when a history of ever smoking was used in place of current smoking or when waist-hip ratio was substituted for body mass index. Leukocyte count also remained a significant predictor of stroke risk in analyses further adjusting for type of work and insurance status.

The effect of leukocyte count on a combined ischemic endpoint of IS, MI, and vascular death was similar to that for IS alone (unadjusted HR per SD in leukocyte count 1.20, 1.09 to 1.31; see table 2). The effect was attenuated slightly, but remained significant, after adjusting for demographic and medical risk factors (adjusted HR 1.13, 1.02 to 1.26). Other predictors of IS, MI, or vascular death were age, hypertension, diabetes mellitus, atrial fibrillation, and current smoking.

In analyses by quartile of leukocyte count, there was a significant increase in risk of IS with each quartile (adjusted HR per increase in quartile 1.19, 1.02 to 1.39). Kaplan-Meier estimates of the risk of stroke and other vascular events associated with each quartile of leukocyte count are shown in the figure. Those in the highest quartile had a significantly increased risk of IS (unadjusted HR 1.97, 1.25 to 3.10) compared with those in the lowest quartile, which was attenuated slightly after adjusting for other risk factors (adjusted HR 1.75, 1.08 to 2.82; see figure E-1 on the *Neurology* Web site at www.neurology.org). The risk of IS, MI, and vascular death (adjusted HR 1.38, 1.02 to 1.87) was also increased for those in the fourth quartile. Because the range of the leukocyte count levels differed by race-ethnicity, analyses were also performed using race-ethnic-specific quartiles, but the results were not materially changed.

Analyses by subgroup and stroke subtype. Analyses stratified by age, sex, and race-ethnicity showed an increased risk associated with elevations in leukocyte count for each group. The increase in risk was similar among groups, with HR ranging from 1.19 to 1.28. In addition, the effect of leukocyte count on stroke risk was very similar for those with and without a past history of coronary artery or peripheral artery disease (adjusted HR 1.21, 95% CI 0.96 to 1.53 for those with a history and adjusted HR 1.25, 95% CI 1.04 to 1.51 for those without a history of either of these vascular diseases). In analyses by quartile (see table E-1 on the *Neurology* Web site), the greatest increase in risk for those in the highest quartile (compared with the lowest) was seen in men, those younger than 70 years, and

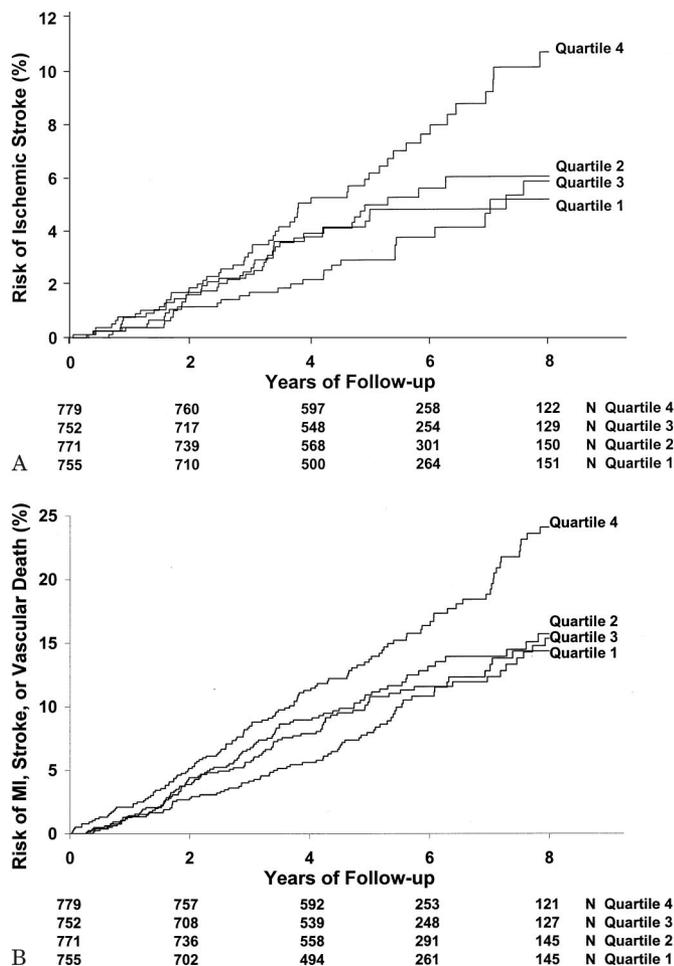


Figure. Kaplan-Meier estimates of risk of ischemic stroke (A) and ischemic stroke, myocardial infarction, and vascular death (B) associated with leukocyte count quartiles.

smokers, but there was no evidence of any significant interactions.

Additional analyses were performed to assess the association of leukocyte count with specific IS subtypes. The association was strong for those with atherosclerotic stroke (adjusted HR 1.48, 0.98 to 2.24 per SD of leukocyte count), although these comprised the smallest percentage of stroke patients. The risks were independently significant for those with cardioembolic strokes as an outcome (adjusted HR 1.33, 1.01 to 1.76) and slightly elevated for those with cryptogenic strokes (adjusted HR 1.19, 0.86 to 1.66). Leukocyte count did not predict lacunar stroke (adjusted HR 1.03, 0.74 to 1.43). Associations between the risk of each stroke subtype and the fourth quartile of leukocyte count (compared with the lowest quartile) also demonstrated a stronger effect in atherosclerotic and cardioembolic stroke than in the other subtypes (see table E-1).

Discussion. Our study provides evidence that leukocyte count predicts future IS. This increase in risk was present after adjusting for other major stroke risk factors. Overall, there was a 20% increase in risk per SD in leukocyte count, or an increment of 1.8×10^9 cells/L. Leukocytes were also associated with increased risk of other ischemic events. The

increased risk, although not independently significant in each subgroup, was present in young and old, men and women, and all three race-ethnic groups in our population. It was also present among smokers and nonsmokers and those with and without prior history of coronary or peripheral artery disease. Leukocyte count was associated with atherosclerotic and cardioembolic stroke and with cryptogenic stroke to a lesser degree. It was not clearly associated with lacunar stroke.

Prospective studies have found an association between leukocytes and risk of atherosclerotic heart disease,^{3,4} but few have found an association with stroke.⁵⁻⁷ In a Japanese cohort, elevated leukocytes were associated with increased risk of cerebral infarction, but the investigators were unable to completely adjust for smoking and other risk factors.⁶ In other data,⁵ leukocytes no longer predicted stroke risk after adjusting for smoking and also did not predict risk in white women or blacks. In an Italian rural population,⁷ leukocytes predicted stroke in women and not men, but that study was not limited to incident stroke. Stroke mortality was increased in those with elevated baseline leukocyte levels in another study,⁸ even after adjusting for smoking, but incidence was not assessed, and elevated leukocyte count could be a marker for worse prognosis after stroke.¹⁴ In the Atherosclerosis Risk in Communities Study,⁴ there was an independent association between leukocyte count and risk of incident stroke among whites and African Americans. We examined the association of leukocyte count with stroke risk in Hispanics and specific IS subtypes.

We found the magnitude of the association of leukocytes with stroke risk was greater among those with atherosclerotic and cardioembolic stroke, although relatively small numbers make it difficult to draw definitive conclusions about subgroups. These findings are consistent with the hypothesis that leukocyte count, as a surrogate for inflammation, is primarily associated with atherosclerosis. This also explains the strong associations between leukocyte count and coronary artery disease.^{3,4} There was no clear association of leukocytes with lacunar stroke, although lacunes were common in our population. Whereas atheromatous disease may play a role in causing lacunes,¹⁵ other data indicate that atherosclerosis probably accounts for only 9% of lacunar stroke.¹¹ Our data provide indirect evidence that the mechanisms involved in lacunar stroke may differ from those in large-vessel atherosclerosis.

Among studies that found leukocyte count to predict clinical cardiovascular events, participants were generally under age 60.^{3,4} In studies of both middle-aged and older participants,¹⁶ the effect was stronger in those under 65 years of age. Inflammation may be a more important risk marker in younger populations in which the burden of more traditional risk factors such as hypertension is less common. We similarly found that the association was slightly more prominent among those under age 70, although

there was also a trend among those over age 70. Because our population has a high burden of hypertension, diabetes, and other risk factors, our study provides evidence that the risk associated with leukocytes may be as important as that associated with more common risk factors.

Leukocytes may be associated with stroke risk through several mechanisms. According to the prevailing hypothesis, atherosclerosis is an inflammatory disease.¹ Macrophages and T lymphocytes are prominent in human atheromas, even at the earliest stages of the disease process.¹⁷ Previous data from our laboratory support a role for leukocytes in chronic atherosclerosis.¹⁸ Leukocytes may also participate in causing plaque rupture, thereby inducing acute thrombotic events. Alternatively, leukocytes may not be causative but may serve as a marker of risk due to the presence of traditional risk factors. Although our study provides evidence that leukocytes increase risk independently of other risk factors, residual confounding remains possible owing to our inability to ascertain other risk factors perfectly.

The strengths of our study include a prospective cohort design and collection of detailed information on several potential confounders. In addition, we were able to estimate the risk in Hispanics and non-Hispanic blacks as well as non-Hispanic whites. Non-Hispanic blacks have lower leukocyte counts, on average, than whites or Hispanics, but the association between leukocytes and vascular risk appears to be present in all three major race-ethnic groups.

Our study also has limitations. We did not have information about presence of infection. The participants in this study were all stroke-free subjects from the community selected at random, however, and it is therefore unlikely that many harbored significant chronic infections at baseline. Our fourth quartile began at a leukocyte count of 7.2×10^9 cells/L, within the normal range. We did not have repeated measures of leukocyte levels in all participants. Our data in those that did have repeated measurements, however, demonstrated stability over time. Hispanics and those with atrial fibrillation were underrepresented in that sample, but this is unlikely to have significantly affected our results. In addition, we did not have data on leukocyte differentials. Other studies have found that neutrophils are more likely to be present in IS patients^{3,19} and that circulating levels of specific leukocytes, such as the CD4⁺CD28^{null} subset of T lymphocytes, may be associated with unstable angina and recurrence after first stroke.^{20,21} Finally, we did not have levels of other potentially important inflammatory markers such as C-reactive protein²² in our entire cohort. Future studies should

attempt to assess leukocyte differential counts and other molecular markers of inflammatory activity.

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