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White Blood Cell Count and Incidence of Coronary Heart Disease and Ischemic Stroke and Mortality from Cardiovascular Disease in African-American and White Men and Women

Atherosclerosis Risk in Communities Study

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The authors examined the association between white blood cell (WBC) count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in 13,555 African-American and White men and women from the Atherosclerosis Risk in Communities (ARIC) Study. Blood was drawn at the ARIC baseline examination, beginning in 1987–1989. During an average of 8 years of follow-up (through December 1996), there were 488 incident coronary heart disease events, 220 incident strokes, and 258 deaths from cardiovascular disease. After adjustment for age, sex, ARIC field center, and multiple risk factors, there was a direct association between WBC count and incidence of coronary heart disease ($p < 0.001$ for trend) and stroke (p for trend < 0.001) and mortality from cardiovascular disease (p for trend < 0.001) in African Americans. The African Americans in the highest quartile of WBC count (≥7,000 cells/mm^3) had 1.9 times the risk of incident coronary heart disease (95% confidence interval (CI): 1.19, 3.09), 1.9 times the risk of incident ischemic stroke (95% CI: 1.03, 3.34), and 2.3 times the risk of cardiovascular disease mortality (95% CI: 1.38, 3.72) as their counterparts in the lowest quartile of WBC count (<4,800 cells/mm^3). These associations were similar in Whites and in never smokers. An elevated WBC count is directly associated with increased incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women. *Am J Epidemiol* 2001;154:758–64.

cardiovascular diseases; cerebrovascular accident; coronary disease; leukocyte count; leukocytes; prospective studies

An elevated total white blood cell (WBC) count is a risk factor for atherosclerotic vascular disease. WBC-derived macrophages and other phagocytes are believed to contribute to vascular injury and atherosclerotic progression (1, 2). Several prospective studies have shown a positive and independent association between WBC count and coronary heart disease incidence or mortality (3–11). However, little is known about this association in African Americans.

WBC count is associated with several cardiovascular disease risk factors (12–14). WBC count is higher in smokers than in nonsmokers (12–14). Some investigators have reported that elevated WBC count is associated with increased risk of coronary heart disease mortality in both smokers and nonsmokers (9, 10), while other studies have not found an association among never smokers (7). WBC count is inversely associated with physical activity, high density lipoprotein cholesterol, and family income (12–14). Studies consistently report a lower WBC count in African Americans than in Whites, although the reason is unclear. There has been little research on the relation between WBC count and cardiovascular disease incidence or mortality in African Americans (7). Therefore, we investigated the associations between WBC count and incidence of coronary heart disease and ischemic stroke and between WBC count and mortality from cardiovascular disease in African-American and White men and women from the Atherosclerosis Risk in Communities (ARIC) Study.

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; WBC, white blood cell.

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MATERIALS AND METHODS

Study population

The ARIC Study is a population-based cohort study designed to investigate the etiology of atherosclerosis in a biracial population. The study population comprises 15,792 men and women aged 45–64 years. Participants were

recruited in 1987–1989 from four US communities: Forsyth County, North Carolina; Jackson, Mississippi; Washington County, Maryland; and the northwestern suburbs of Minneapolis, Minnesota. The response rates in these communities were 66 percent, 46 percent, 65 percent, and 67 percent, respectively. All participants from Jackson and 12 percent of the participants from Forsyth County were African-American, whereas 99 percent of participants from the other two communities were White. The complete study design, sampling strategy, and examination techniques used have been described previously (15).

The baseline examination included a home interview and a clinical examination. The home interview assessed participants' health habits, demographic characteristics, and medical histories. The clinical examination included a physical examination, blood pressure measurement, blood tests, collection of anthropometric data, a 12-lead electrocardiogram, and a B-mode ultrasound examination. Details on the examination procedures have been published elsewhere (6, 13, 15, 16).

All participants gave their informed consent for the clinical examination and were asked to fast for the previous 12 hours. Serum, plasma, and whole blood samples were drawn from an antecubital vein (15, 16). WBC count was determined by automated particle counters within 24 hours after venipuncture in local hospital hematology laboratories. The reliability coefficient for the WBC count measurement was greater than 0.96 (13). Levels of plasma total cholesterol and high density lipoprotein cholesterol were measured by an enzymatic method. Seated blood pressure was measured after 5 minutes' rest using a random-zero sphygmomanometer. Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dl, a nonfasting glucose level ≥200 mg/dl, use of hypoglycemic agents, or a history of physician-diagnosed diabetes mellitus. Body weight and height were measured with a vertical metal rule and a calibrated scale. Waist girth was measured at the level of the umbilicus with a steel or fiberglass tape measure. Cigarette smoking, alcohol intake, family income, and educational level were assessed by means of standardized questionnaires. Subjects' smoking status was classified as never smoking, formerly smoking, or currently smoking. Alcohol intake status was classified as never drinking, formerly drinking, or currently drinking. Annual family income was classified as low (<$25,000), medium ($25,000–<$50,000), or high (≥$50,000). Educational level was classified by number of years of education: less than high school, completion of high school, or college graduation or more. Physical activity in sports was assessed by an adaptation of the Baecke et al. (17) physical activity questionnaire, scored from 1 (low) to 5 (high), and was classified as low (<2), moderate (2–<4), or high (≥4).

Ascertainment of disease incidence or mortality

All participants were followed from the baseline examination to the date of disease incidence/death or loss to follow-up, or through December 31, 1996. ARIC participants were contacted annually by telephone for identification of all hospitalizations and deaths, and lists of discharges from local hospitals were scanned for events. For patients who had been hospitalized with potential myocardial infarction, trained abstractors recorded the presenting signs and symptoms and photocopied up to three 12-lead electrocardiograms for Minnesota coding (18). For assessment of potential stroke, the abstractors recorded relevant signs and symptoms and photocopied neuroimaging and other diagnostic reports. Deaths were identified from death certificates, and potential out-of-hospital fatal coronary heart disease events were investigated by interviewing one or more next of kin and by the completion of a questionnaire by the patient's physician. All coronary heart disease events were validated by a committee of physicians using standardized criteria (19). Incident strokes were validated by a combination of computerized algorithm and physician review (20).

We defined a *coronary heart disease* event as a definite or probable hospitalized myocardial infarction or definite fatal coronary heart disease. Unstable angina or coronary revascularization was not included, because of concerns about ethnic differences in diagnosis and use of procedures. An *ischemic stroke* event was defined as a definite or probable hospitalized embolic or thrombotic stroke. Transient ischemic attacks and a small number of undocumented fatal strokes were excluded. *Cardiovascular disease death* was based only on the death certificate and included any underlying cause of death (codes 390–459) as coded by state health departments according to the *International Classification of Diseases*, Ninth Revision.

Statistical analysis

We included 13,555 men and women aged 45–64 years who participated in the ARIC baseline examination from 1987 to 1989. Excluded were those with a history of coronary heart disease, stroke, or cancer at baseline; those who had a WBC count of >15,000 cells/mm^3 or <2,000

TABLE 1. Baseline white blood cell count and age of participants in the Atherosclerosis Risk in Communities (ARIC) Study, by race and sex, 1987–1989

Variable	Black men (*n* = 1,373)		White men (*n* = 4,590)		Black women (*n* = 2,248)		White women (*n* = 5,344)		All subjects (*n* = 13,555)	
	Mean	SD*	Mean	SD	Mean	SD	Mean	SD	Mean	SD
White blood cell count (×1,000 cells/mm^3)	5.5	1.9	6.4	1.8	5.6	1.8	6.1	1.8	6.1	1.8
Age (years)	53.5	5.9	54.4	5.7	53.2	5.7	53.8	5.7	53.9	5.7

* SD, standard deviation.

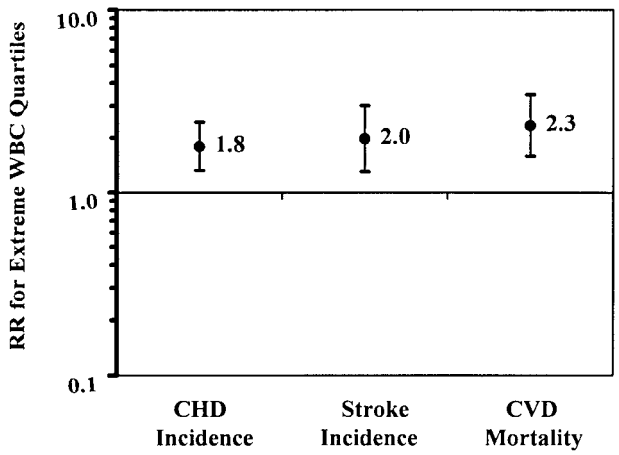

FIGURE 1. Relative risk (RR) of coronary heart disease (CHD) and ischemic stroke incidence and mortality from cardiovascular disease (CVD), by quartile of white blood cell (WBC) count (highest quartile vs. lowest), among participants in the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1996. Data were adjusted for age (single year), sex, race, ARIC field center, family income, education, cigarette smoking, alcohol intake, physical activity, waist girth, high density lipoprotein cholesterol and total cholesterol levels, diabetes mellitus, systolic blood pressure, and use of antihypertensive medication. Bars, 95% confidence interval.

cells/mm^3; and those missing baseline WBC counts or other covariate values. Proportional hazards regression was used to examine the overall associations between WBC count and incidence of coronary heart disease and stroke and between WBC count and mortality from cardiovascular disease (21). Race-specific models were used to examine this association in African Americans and Whites separately. We also examined the association between WBC count and disease incidence or mortality by smoking status. WBC counts were grouped into quartiles (<4.8, 4.8–<5.8, 5.8–<7.0, and ≥7.0 × 1,000 cells/mm^3). Relative risks and 95 percent confidence intervals for incidence or mortality were estimated after adjustment for age, sex, and ARIC field center and after further adjustment for family income, education, cigarette smoking, physical activity, alcohol intake, waist girth, high density lipoprotein cholesterol and total cholesterol levels, diabetes, systolic blood pressure, and use of antihypertensive medication. The lowest WBC quartile (<4,800 cells/mm^3) was the reference category.

Inspection of empirical cumulative hazards plots indicated that the proportional hazards assumption was justified. Trends across WBC counts were tested by treating WBC count categories as an ordinal score. Additionally, we tested WBC count differences between race and sex groups with two-factor analysis of variance. We also examined the relations between differential WBC count and incidence of

TABLE 2. Relative risk of incident coronary heart disease and ischemic stroke according to quartile of white blood cell count in African Americans and Whites: The Atherosclerosis Risk in Communities (ARIC) Study, 1987–1996

Disease and race	No. of cases	Quartile of white blood cell count (×1,000 cells/mm^3)							
		<4.8*	4.8–<5.8		5.8–<7.0		≥7.0		*p* for trend
			RR†	95% CI†	RR	95% CI	RR	95% CI	
Incident coronary heart disease									
Whites (*n* = 9,934)	347								
Adjusted relative risk‡		1.00	1.29	0.84, 1.98	1.85	1.24, 2.77	3.25	2.24, 4.73	<0.001
Multivariate adjusted relative risk§		1.00	1.05	0.68, 1.61	1.25	0.83, 1.88	1.69	1.13, 2.53	0.001
Blacks (*n* = 3,621)	141								
Adjusted relative risk‡		1.00	1.60	0.99, 2.58	1.73	1.06, 2.84	2.66	1.69, 4.19	<0.001
Multivariate adjusted relative risk§		1.00	1.36	0.84, 2.20	1.45	0.87, 2.39	1.91	1.19, 3.09	0.009
Incident ischemic stroke									
Whites (*n* = 9,934)	125								
Adjusted relative risk‡		1.00	1.33	0.71, 2.51	1.17	0.61, 2.26	2.74	1.55, 4.83	<0.001
Multivariate adjusted relative risk§		1.00	1.20	0.64, 2.27	0.91	0.47, 1.75	1.86	1.01, 3.44	0.04
Blacks (*n* = 3,621)	95								
Adjusted relative risk‡		1.00	1.34	0.72, 2.49	2.16	1.20, 3.87	3.01	1.73, 5.23	<0.001
Multivariate adjusted relative risk§		1.00	1.15	0.61, 2.15	1.65	0.91, 3.00	1.86	1.03, 3.34	0.02

* Reference category.
† RR, relative risk; CI, confidence interval.
‡ Adjusted for age (single year), sex, and ARIC field center.
§ Adjusted for age, sex, ARIC field center, family income, education, cigarette smoking, alcohol intake, physical activity, waist girth, high density lipoprotein cholesterol and total cholesterol levels, diabetes mellitus, systolic blood pressure, and use of antihypertensive medication.

coronary heart disease and stroke and mortality from cardiovascular disease. All statistical procedures were performed using Statistical Analysis System software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

During an average of 8 years of follow-up, we identified 488 incident coronary heart disease events, 220 incident ischemic stroke events, and 258 deaths coded as being due to cardiovascular disease. As table 1 shows, White men had a higher WBC count than did White women ($p < 0.001$), but African-American men had a WBC count similar to that of African-American women ($p = 0.15$). Both White men and White women had higher WBC counts than did African-American men and women, respectively ($p < 0.001$). Most other risk factors differed by sex and race in the expected directions and as previously reported by ARIC investigators (13).

Overall, there was a direct association of WBC count with incidence of coronary heart disease (p for trend < 0.001) and stroke (p for trend < 0.001) and with cardiovascular disease mortality (p for trend < 0.001), after adjustment for age, sex, race, and ARIC field center. Associations persisted after additional adjustment for other risk factors (figure 1). Individuals in the highest quartile of WBC count (≥7,000 cells/mm^3) had 1.8 times the risk of incident coronary heart disease (95 percent confidence interval (CI): 1.32, 2.43; $p < 0.001$), 2.0 times the risk of incident stroke (95 percent CI: 1.29, 2.99; $p = 0.002$), and 2.3 times the risk of cardiovascular disease mortality (95 percent CI: 1.58, 3.44; $p < 0.001$) as did individuals in the lowest WBC count category.

Although there was no significant interaction of WBC count with race ($p = 0.37$) or sex ($p = 0.77$), we were interested in examining the race-specific association between WBC count and cardiovascular disease events. Table 2 shows that there was a direct association between WBC count and coronary heart disease incidence in both African Americans (p for trend < 0.001) and Whites (p for trend < 0.001) after adjustment for age, sex, and ARIC field center. After additional adjustment for the covariates, the relative risk for persons in the highest quartile of WBC count versus the lowest was 1.9 among African Americans (95 percent CI: 1.19, 3.09) and 1.7 among Whites (95 percent CI: 1.13, 2.53. Stroke incidence showed trends similar to those of coronary heart disease incidence. An elevated WBC count was positively associated with stroke incidence after adjustment for age, sex, and ARIC field center. The relative risk for the highest quartile of WBC count versus the lowest was 3.0 (95 percent CI: 1.73, 5.23) in African Americans and 2.7 (95 percent CI: 1.55, 4.83) in Whites. This relation remained but was attenuated after further adjustment for other risk factors.

Figure 2 shows that cardiovascular disease mortality also increased with increasing WBC count in both African Americans and Whites. After adjustment for multivariate risk factors, the relative risks for cardiovascular disease mortality across WBC count categories were 1.00 (referent), 1.15 (95 percent CI: 0.67, 1.98), 1.61 (95 percent CI: 0.95, 2.73), and 2.26 (95 percent CI: 1.38, 3.72) in African Americans (p for trend < 0.001) and 1.00 (referent), 1.00 (95 percent CI: 0.47, 2.10), 1.40 (95 percent CI: 0.70, 2.80), and 2.22 (95 percent CI: 1.13, 4.37) in Whites (p for trend = 0.001).

We also observed a positive association between WBC count and cardiovascular disease endpoints across categories of smoking status (table 3). After adjustment for all risk factors, there was a direct relation between WBC count and cardiovascular disease mortality among current smokers (p for trend = 0.03) and among individuals who had never smoked (p for trend < 0.001). Similar patterns were observed for incidence of coronary heart disease and stroke (table 3). Among never smokers, the fully adjusted relative

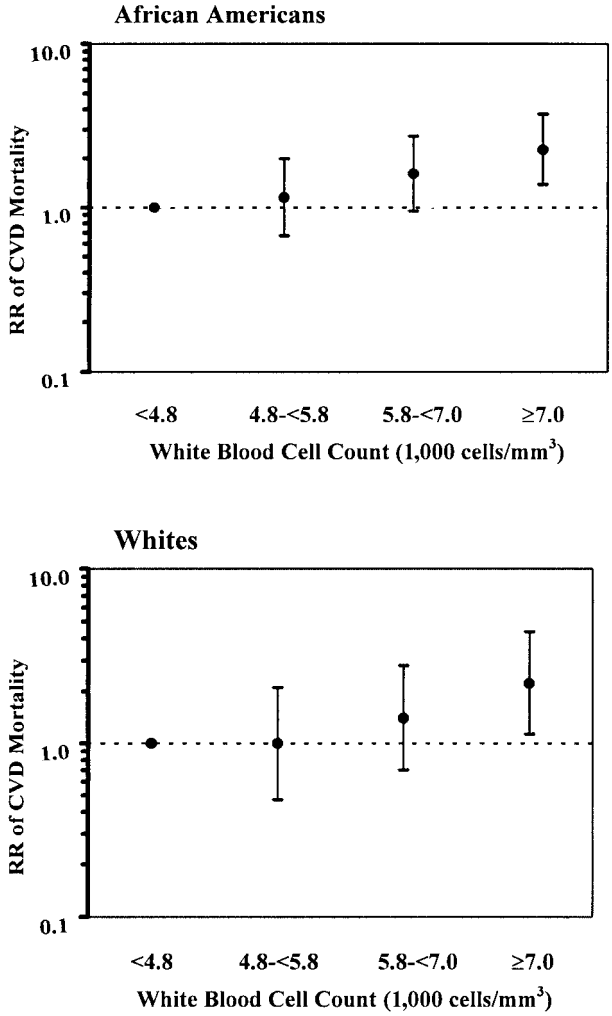

FIGURE 2. Relative risk (RR) of cardiovascular disease (CVD) mortality, by quartile of white blood cell count (referent: lowest quartile), for African-American and White participants in the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1996. Data were adjusted for age (single year), sex, ARIC field center, family income, education, cigarette smoking, alcohol intake, physical activity, waist girth, high density lipoprotein cholesterol and total cholesterol levels, diabetes mellitus, systolic blood pressure, and use of antihypertensive medication. Bars, 95% confidence interval.

TABLE 3. Multivariate relative risk* of coronary heart disease and ischemic stroke incidence and mortality from cardiovascular disease, according to quartile of white blood cell count and baseline smoking status, in men and women: The Atherosclerosis Risk in Communities (ARIC) Study, 1987–1996

Smoking status and disease	No. of cases or deaths	Quartile of white blood cell count (×1,000 cells/mm³)							
		<4.8†	4.8–<5.8		5.8–<7.0		≥7.0		*p* for trend
			RR‡	95% CI‡	RR	95% CI	RR	95% CI	
Current smoker (*n* = 3,468)									
Coronary heart disease incidence	187	1.00	0.90	0.44, 1.88	1.19	0.60, 2.33	1.44	0.76, 2.73	0.06
Ischemic stroke incidence	80	1.00	2.89	0.96, 8.75	1.64	0.51, 5.28	3.15	1.07, 9.23	0.07
Cardiovascular disease mortality	97	1.00	1.14	0.44, 2.96	1.52	0.62, 3.70	2.03	0.88, 4.68	0.03
Former smoker (*n* = 4,282)									
Coronary heart disease incidence	155	1.00	1.61	0.93, 2.78	1.57	0.90, 2.72	2.01	1.16, 3.47	0.02
Ischemic stroke incidence	56	1.00	1.14	0.50, 2.65	1.23	0.53, 2.85	2.13	0.97, 4.69	0.05
Cardiovascular disease mortality	66	1.00	1.06	0.48, 2.33	1.16	0.53, 2.55	1.62	0.76, 3.45	0.17
Never smoker (*n* = 5,805)									
Coronary heart disease incidence	146	1.00	1.00	0.62, 1.63	1.10	0.68, 1.78	1.73	1.08, 2.79	0.03
Ischemic stroke incidence	84	1.00	0.90	0.47, 1.70	1.27	0.69, 2.33	1.59	0.85, 2.30	0.10
Cardiovascular disease mortality	95	1.00	1.05	0.55, 2.00	1.57	0.86, 2.85	2.69	1.52, 4.78	<0.001

* Data were adjusted for age, sex, race, ARIC field center, family income, education, alcohol intake, physical activity, waist girth, high density lipoprotein cholesterol and total cholesterol levels, diabetes mellitus, systolic blood pressure, and use of antihypertensive medication.
† Reference category.
‡ RR, relative risk; CI, confidence interval.

risks in the highest quartile of WBC count (versus the lowest) were 1.7 (95 percent CI: 1.08, 2.79) for coronary heart disease incidence and 1.6 (95 percent CI: 0.85, 2.30) for ischemic stroke incidence.

We further examined the association between differential WBC count and disease incidence or mortality. As table 4 shows, the associations between WBC count and the study endpoints were strongest for granulocytes, somewhat weaker for monocytes, and weak and not independent of other risk factors for lymphocytes.

DISCUSSION

Although an elevated WBC count is considered a risk marker for cardiovascular disease incidence and mortality (3–11), there has been little research on this relation in African Americans. Our major finding was that elevated WBC count is directly associated with risk of coronary heart disease and stroke incidence and mortality from cardiovascular disease in African Americans. The incidence of coronary heart disease was 1.9-fold higher in African Americans with WBC counts ≥7,000 cells/mm^3 than in those with counts <4,800 cells/mm^3, after adjustment for multiple risk factors. The association was similar in Whites. This finding is consistent with results from the NHANES I Epidemiologic Follow-up Study (7), in which African Americans with WBC counts >7,000 cells/mm^3 had twice the incidence of coronary heart disease as those with WBC counts <5,500 cells/mm^3. We also observed a positive association between WBC count and ischemic stroke incidence in African Americans, and to our knowledge this is the first prospective report of such an association. This study also showed a direct relation of WBC count to cardiovascular disease mortality in African Americans, with a relative risk of 2.3 for the highest quartile of WBC count after adjustment for multiple risk factors. This finding is somewhat different from that of the NHANES I Epidemiologic Follow-up Study, which showed only a weak association between WBC count and cardiovascular disease mortality in African Americans after adjustment for multiple risk factors (7).

In our study, a dose-response relation between WBC count and cardiovascular disease mortality persisted with and without adjustment or stratification for cigarette smoking. Although cigarette smoking increases WBC count and the pool of phagocytes (1), studies have not consistently observed a positive association between WBC count and coronary heart disease mortality in both smokers and nonsmokers (3, 7, 9, 10). Our finding of strong associations among never smokers suggests that a higher WBC count is a risk factor for cardiovascular disease events independently of smoking.

It is plausible that an elevated WBC count may enhance atherogenesis. Granulocytes and monocytes are believed to be involved in the pathogenesis of atherosclerosis. Monocyte-derived macrophages produce oxidants that can induce endothelial cell injury and subsequent thrombus formation (2). Activated WBCs also reflect the inflammatory

TABLE 4. Multivariate relative risk* of coronary heart disease and ischemic stroke incidence and mortality from cardiovascular disease, according to differential white blood cell count, in men and women: The Atherosclerosis Risk in Communities (ARIC) Study, 1987–1996

Cell type and disease	Quartile of differential white blood cell count							
	1†	2		3		4		*p* for trend
		RR‡	95% CI‡	RR	95% CI	RR	95% CI	
	Quartile of granulocyte count (×1,000 cells/mm³)							
	<2.6	2.6–<3.4		3.4–<4.5		≥4.5		
Granulocytes								
Coronary heart disease incidence	1.00	1.07	0.79, 1.45	1.04	0.77, 1.39	1.45	1.10, 1.92	0.001
Ischemic stroke incidence	1.00	1.49	0.98, 2.26	1.30	0.85, 1.99	1.87	1.25, 2.79	0.006
Cardiovascular disease mortality	1.00	1.59	1.08, 2.35	1.37	0.91, 2.05	2.50	1.75, 3.58	<0.001
	Quartile of monocyte count (×1,000 cells/mm³)							
	<0.24	0.24–<0.33		0.33–<0.44		≥0.44		
Monocytes								
Coronary heart disease incidence	1.00	0.81	0.60, 1.10	1.16	0.89, 1.51	1.25	0.97, 1.60	0.02
Ischemic stroke incidence	1.00	1.08	0.70, 1.66	1.23	0.82, 1.87	1.68	1.17, 2.43	0.004
Cardiovascular disease mortality	1.00	0.85	0.56, 1.27	0.98	0.67, 1.44	1.40	1.01, 1.96	0.04
	Quartile of lymphocyte count (×1,000 cells/mm³)							
	<1.5	1.5–<1.9		1.9–<2.3		≥2.3		
Lymphocytes								
Coronary heart disease incidence	1.00	0.86	0.65, 1.13	0.96	0.73, 1.26	0.99	0.76, 1.29	0.90
Ischemic stroke incidence	1.00	1.14	0.76, 1.71	0.96	0.62, 1.48	1.33	0.90, 1.95	0.23
Cardiovascular disease mortality	1.00	1.60	1.10, 2.32	1.23	0.82, 1.83	1.39	0.96, 2.01	0.24

* Data were adjusted for age, sex, race, ARIC field center, family income, education, cigarette smoking, alcohol intake, physical activity, waist girth, high density lipoprotein cholesterol and total cholesterol levels, diabetes mellitus, systolic blood pressure, and use of antihypertensive medication.
† Reference category.
‡ RR, relative risk; CI, confidence interval.

activity of atherosclerosis that perpetuates vascular injury and tissue ischemia (1).

Some studies have reported that WBC count is associated with several cardiovascular disease risk factors. These findings include positive associations with body weight, systolic blood pressure, cigarette smoking, fasting glucose level, and fasting insulin level and negative associations with high density lipoprotein cholesterol level, family income, alcohol consumption, and physical activity or physical fitness (12–14). Our data show that although African Americans have less favorable cardiovascular disease risk factor profiles, they have lower WBC counts than Whites (table 1). African Americans have lower neutrophil counts and higher lymphocyte counts than Whites (22). Further studies are needed to determine whether lifestyle differences are related to WBC variability across race and sex groups.

A strength of this study is that African Americans were recruited from two US communities; our study represents the largest cohort study of WBC count and cardiovascular disease in African Americans yet conducted. Our study's biggest drawbacks are that most African Americans were from one community and that we did not have measurements of C-reactive protein, a specific marker of inflammation that is also associated with cardiovascular disease (23, 24). The independent role of WBC count versus C-reactive protein in the prediction of cardiovascular disease must be clarified, and to our knowledge C-reactive protein has not been studied in African Americans.

In conclusion, we found that an elevated WBC count is a risk factor for coronary heart disease and ischemic stroke incidence and cardiovascular disease mortality in African Americans. Despite a lower WBC count among African Americans, our finding suggests that inflammation plays similar roles in atherosclerotic cardiovascular disease for African Americans and Whites.

ACKNOWLEDGMENTS

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