

Implications of Increased C-Reactive Protein for Cardiovascular Risk Stratification in Black and White Men and Women in the US

Mary Cushman,^{1*} Leslie A. McClure,² Virginia J. Howard,³ Nancy S. Jenny,⁴ Susan G. Lakoski,⁵ and George Howard²

BACKGROUND: We evaluated prevalence and correlates of increased high-sensitivity C-reactive protein (hsCRP) in a large population of blacks and whites, and the impact of hsCRP measurement on coronary heart disease risk reclassification.

METHODS: We studied 19 080 participants of the REGARDS (REasons for Geographic And Racial Differences in Stroke) study (age >45 years, without vascular diagnoses, and living dispersed across the US). A total of 8309 nondiabetic participants not using lipid-lowering medications were classified into 4 risk categories based on the Framingham vascular disease risk score. Participants with hsCRP <1 mg/L were reclassified to the next lower risk group, and those with hsCRP >3 mg/L to the next higher risk group. We also assessed reclassification of risk based on the Reynolds vascular risk score, incorporating hsCRP and family history.

RESULTS: Overall, 40% of participants had hsCRP >3 mg/L. Blacks, women, and obese people were at highest risk for increased hsCRP. Among nondiabetic women at 5%–20% Framingham vascular predicted risk, hsCRP data led to reclassification of 48% to a higher risk group and 19% to a lower risk group. For men, these percentages were 24% and 40%. Blacks were more often reclassified to a higher risk group than whites. Reynolds vascular risk score data led to reclassification of 85% of women and 67% of men, almost exclusively to a lower risk group than the Framingham vascular score.

CONCLUSIONS: In this national study, a majority of participants, especially blacks and women, were reclassified to a different 10-year vascular risk category on the basis of hsCRP testing after risk assessment. With the inclusion of hsCRP testing data, the Reynolds risk score

classified the population differently than the new Framingham vascular score.

© 2009 American Association for Clinical Chemistry

Increased C-reactive protein (CRP)⁷ as measured using a high-sensitivity assay (hsCRP) identifies patients at increased cardiovascular risk (1). A consensus group convened by the CDC and the American Heart Association issued a statement in 2003 to guide physicians on measurement of hsCRP in clinical practice (1). The guideline suggested that patients who are at intermediate risk (10%–20% 10-year predicted risk) for future cardiovascular events and who also have increased hsCRP (>3 mg/L) be considered for more aggressive vascular disease prevention strategies, such as lipid-lowering therapy (2). Additional data have suggested that vascular risk is even greater with hsCRP >10 mg/L (3, 4) and that those with a low predicted risk of 5%–10% also should be considered for hsCRP testing (5). In addition, a new risk prediction score incorporating hsCRP (the Reynolds risk score) has been proposed for cardiovascular risk assessment in women (6) and men (7).

Stroke mortality in the US is approximately 50% greater in the southeastern “stroke belt” states (8). Stroke mortality also differs in ethnic groups, with rates about 50% higher among blacks compared to whites (9, 10). Differences in prevalences of traditional risk factors for stroke may only partly explain these geographic and ethnic group differences in stroke risk (11, 12), so differences in newer risk factors such as hsCRP may play a role.

Because of possible ethnic variation in hsCRP distribution (13–18), and also ethnic and regional differences in vascular risk, there is a need for population-

¹ Departments of Medicine and Pathology, University of Vermont, Burlington, VT; Departments of ² Biostatistics and ³ Epidemiology and International Health, University of Alabama at Birmingham, Birmingham, AL; ⁴ Department of Pathology, University of Vermont, Burlington, VT; ⁵ Department of Internal Medicine/Cardiology, University of Texas Southwestern Medical Center, Dallas, TX.
* Address correspondence to this author at: 208 South Park Dr. Colchester, VT,

05446. Fax +802-656-8965; e-mail mary.cushman@uvm.edu.

Received December 9, 2008; accepted May 29, 2009.

Previously published online at DOI: 10.1373/clinchem.2008.122093

⁷ Nonstandard abbreviations: CRP, C-reactive protein; hs, high-sensitivity; REGARDS, REasons for Geographic And Racial Differences in Stroke; NHANES, National Health and Nutrition Examination Survey.

based information on ethnic and regional differences in hsCRP concentrations to guide clinicians in risk assessment in these selected populations. We are not aware of studies reporting geographic variation of hsCRP in the US.

We evaluated the prevalence of increased hsCRP by sex, ethnic group, and US region in a large national population-based observational study. We studied whether differences in adiposity or other risk factors explained observed differences in hsCRP associated with these factors. We further assessed how knowledge from hsCRP measurement would reclassify individuals' 10-year predicted cardiovascular disease risk, based on the Framingham vascular disease risk score and the Reynolds risk score, both of which are designed to predict total cardiovascular disease, and the Framingham coronary risk score, designed to predict coronary events.

Materials and Methods

STUDY PARTICIPANTS

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is a national population-based cohort study. Between February 2003 and September, 2007, 30 101 individuals older than 45 years were enrolled. Selected participants were targeted for equal representation of whites and blacks and men and women (19); 56% resided in the stroke belt (NC, SC, GA, AL, MS, TN, AR, and LA) and the rest were from the other 40 contiguous states. Individuals were recruited from a commercial list by use of mail and telephone contact. Demographic and medical history was obtained using a computer-assisted telephone interview. At an in-home examination written informed consent was obtained, and blood pressure, anthropomorphic measures, blood samples, electrocardiogram, and medication inventory were assessed using standardized protocols. Questionnaires were left with the participant to assess family history of vascular disease. Participants are followed by telephone every 6 months for surveillance of medical events. Study methods were reviewed and approved by the institutional review boards at each study institution.

Of 30 101 participants, we excluded 9074 (30%) reporting a vascular diagnosis. Vascular disease was considered present if participants reported being told by a health professional that they had myocardial infarction, stroke, peripheral arterial disease, transient ischemic attack, carotid endarterectomy, peripheral artery bypass surgery/angioplasty, leg amputation, or coronary artery angioplasty or stenting, or if electrocardiogram showed myocardial infarction. Excluding 1189 (5%) participants with missing data for hsCRP and 758 with missing covariates, there were 19 080 par-

ticipants included in most analyses. Main analyses of the Framingham and Reynolds risk scores included only nondiabetic individuals because diabetes is a coronary disease risk equivalent (limiting the role for novel risk factors) (20). We also excluded from these analyses 4690 participants who were using lipid-lowering medication, because this risk assessment is used to decide whether to prescribe these medications. For Reynolds risk score analyses, data on family history of heart disease was not yet coded for 6081 participants at the time of analysis, leaving 8309 participants in these analyses.

LABORATORY ANALYSIS

Phlebotomy was performed by trained personnel using standardized procedures. Samples were collected after patients had fasted for 10–12 h. Within 2 h of collection (mean 97 min, SD 127 min), samples were centrifuged and serum or plasma separated and shipped overnight on ice packs to the University of Vermont. Of study participants from whom samples were obtained, overnight shipping of their samples was achieved for 95%. On arrival, samples were centrifuged at 30 000g and 4 °C, and either analyzed (general chemistries) or stored at –80 °C.

hsCRP was analyzed in batches by particle-enhanced immunonephelometry using the BNII nephelometer (N High Sensitivity CRP; Dade Behring) with interassay CVs of 2.1%–5.7%. There was no difference in hsCRP distribution by number of sample shipping days. Cholesterol, HDL cholesterol, triglycerides, and glucose were measured by colorimetric reflectance spectrophotometry using the Ortho Vitros Clinical Chemistry System 950IRC instrument (Johnson & Johnson Clinical Diagnostics).

DEFINITIONS

Increased hsCRP was defined as >3 mg/L (1). Self-reported education level of study participants was categorized as shown in Table 1. Hypertension was defined as systolic blood pressure \geq 140 mmHg, diastolic pressure \geq 90 mmHg, or self-reported high blood pressure with use of antihypertensive medications. Prehypertension was defined as systolic pressure 120–140 mmHg or diastolic pressure 80–90 mmHg. Obesity was a body mass index >30 kg/m², and overweight was 26–30 kg/m². Region of residence was analyzed as the stroke belt or the remainder of the states. Diabetes was defined by self-reported physician diagnosis with use of antidiabetic medications, fasting glucose >6.99 mmol/L or nonfasting glucose >11.1 mmol/L; impaired fasting glucose was defined as fasting glucose 6.10–6.99 mmol/L. Family history of heart disease was defined as parental history of myocardial infarction before age 60 years.

Table 1. Baseline characteristics by sex.^a

Characteristic	Men (n = 8077)	Women (n = 11 003)
Age	64.6 (9.1)	63.8 (9.2)
Race, black	2882 (36%)	4965 (45%)
Region, belt	4248 (53%)	6376 (58%)
Education		
<High school	767 (10%)	1239 (11%)
High school graduate	1781 (22%)	2986 (27%)
Some college	2074 (26%)	3159 (29%)
Postmenopausal hormone therapy	NA	1599 (15%)
Current smoking	1144 (14%)	1515 (14%)
Prehypertension/hypertension	6333 (78%)	8283 (75%)
Impaired fasting glucose/diabetes	1911 (24%)	2475 (22%)
Body mass index, kg/m ²	28.5 (5.1)	29.9 (6.9)
Obesity	2556 (32%)	4723 (43%)
Cholesterol, mmol/L	4.87 (0.96)	5.21 (1.0)
HDL, mmol/L	1.20 (0.36)	1.49 (0.42)
Triglyceride, mmol/L	1.52 (1.06)	1.41 (0.85)
CRP, mg/L; median, (IQR)	1.6 (2.8)	2.7 (4.9)
Median Framingham 10-year predicted coronary risk, %	10.9	4.3
Median Framingham 10-year predicted vascular risk, %	21.6	8.6
Median Reynolds 10-year predicted vascular risk, %	10.0	2.8

^a Data are presented as mean (SD) or frequency (%) unless otherwise indicated. NA, not applicable; IQR, interquartile range.

The Framingham 10-year vascular and coronary disease risk scores were calculated using age, total and HDL cholesterol, current smoking, systolic pressure, and antihypertensive medication use (21, 22). The Reynolds risk score, which also includes parental history of myocardial infarction and hsCRP, was calculated (6, 7).

STATISTICAL ANALYSIS

We used χ^2 tests to compare prevalences of increased hsCRP by sex, ethnicity, region, and cardiovascular risk factors among groups. Multivariable logistic regression was used to determine whether sex, ethnicity, and regional differences in prevalence of increased hsCRP were explained by differences in risk factors related to hsCRP. Excluding study participants with diabetes and those on lipid-lowering medication, values for hsCRP were used to reclassify Framingham risk score groups (very low, low, intermediate, high): for hsCRP <1 mg/L, participants were reclassified to the next lower

risk group; for hsCRP >3 mg/L they were reclassified to the next higher risk group.

Results

Participant characteristics by sex are shown in Table 1. Women were more likely to be black and obese and had higher cholesterol and hsCRP than men, but had a median 10-year predicted vascular disease risk about 60% lower than men, based on the Framingham and Reynolds scores.

Of 19 080 participants without vascular diagnoses, the median hsCRP was 2.2 mg/L, with 25th and 75th percentile values of 0.93 mg/L and 4.9 mg/L, respectively. A total of 7568 participants (40%) had increased hsCRP defined as >3 mg/L, and 1697 (9%) had hsCRP >10 mg/L.

Median hsCRP and prevalence of increased hsCRP (>3 mg/L) by categories of cardiovascular risk factors and the 2 risk scores are shown in Table 2. Increased hsCRP was more common among women than men and blacks than whites (both $P < 0.0001$). Black women had the highest prevalence of increased hsCRP and white men the lowest with these percentages: 61% of 4969 black women, 40% of 6043 white women, 36% of 2884 black men, and 27% of 5195 white men. This pattern was similar for prevalence of hsCRP >10 mg/L. The prevalence of increased hsCRP was greater in the stroke belt than the remainder of the US. Increased hsCRP was also more common in the presence of every cardiovascular risk factor examined. Among risk factors, the highest prevalence of hsCRP >3 mg/L, 56%, was seen with obesity; 50% of current smokers and 50% of diabetic individuals had hsCRP >3 mg/L. The prevalence of hsCRP >3 mg/L increased similarly across the 4 increasing categories of Framingham scores. Most risk factor associations were similar for hsCRP >10 mg/L.

The univariate and multivariable associations of demographic factors, region, and risk factors with hsCRP >3 mg/L are shown in Table 3. The unadjusted odds of increased hsCRP among women compared to men was 2-fold increased, was minimally altered after adjustment for sex differences in other factors, and was lower after exclusion of women taking hormone replacement therapy [adjusted odds ratio 1.7 (95% CI 1.6–1.9)]. Blacks were 80% more likely than whites to have hsCRP >3 mg/L, and this value was reduced to a 30% higher likelihood after adjustment for other risk factors. Comparison of men and women revealed no significant difference in the odds of increased hsCRP by race (P for interaction 0.66). Stroke belt residents had 10% greater adjusted odds of increased hsCRP compared to study participants living elsewhere. Interpretation of results on differences in hsCRP by race, sex,

Table 2. Prevalence of increased C-reactive protein concentration by baseline characteristics.

Characteristics (n)	Median (interquartile range) hsCRP, mg/L	Number (%) with hsCRP >3 mg/L	Number (%) with hsCRP >10 mg/L
Age, years			
45–55 (2853)	2.1 (4.6)	1138 (40%) ^b	267 (9%) ^c
55–65 (7869)	2.3 (4.1)	3252 (41%)	735 (9%)
65–96 (8369)	2.1 (3.7)	3196 (38%)	695 (8%)
Sex			
Men (8079)	1.6 (2.8)	2443 (30%) ^a	461 (6%) ^a
Women (11012)	2.7 (4.9)	5143 (47%)	1236 (11%)
Race			
Black (7853)	2.8 (5.1)	3769 (48%) ^a	990 (13%) ^a
White (11238)	1.8 (3.2)	3817 (34%)	707 (6%)
Region			
Stroke belt (10629)	2.3 (4.2)	4402 (41%) ^a	1004 (9%) ^b
Other states (8462)	2.0 (3.7)	3184 (38%)	693 (8%)
Education			
<High school (2006)	3.1 (5.1)	1021 (51%) ^a	278 (14%) ^a
High school graduate (4767)	2.4 (4.5)	2051 (43%)	489 (10%)
Some college (5233)	2.3 (4.1)	2203 (42%)	482 (9%)
College graduate (7074)	1.7 (3.2)	2308 (33%)	448 (6%)
Postmenopausal hormone therapy (women)			
Yes (1599)	3.3 (5.1)	840 (53%) ^a	197 (12%)
No (9413)	2.6 (4.8)	4303 (46%)	1039 (11%)
Smoking status			
Never (9146)	2.0 (3.8)	3439 (38%) ^a	765 (8%) ^a
Former (7283)	2.1 (3.7)	2804 (39%)	610 (8%)
Current (2662)	3.1 (5.1)	1343 (50%)	322 (12%)
Blood pressure			
Normal (<120/80) (7544)	1.6 (3.1)	2413 (32%) ^a	971 (6%)
Prehypertension (120–139/80–90) (1465)	2.1 (3.6)	552 (38%)	115 (8%)
Hypertension (≥140/90) (10082)	2.7 (4.7)	4621 (46%)	1111 (11%)
Diabetes status			
None (14698)	2.0 (3.6)	5383 (37%) ^a	1124 (8%) ^a
Impaired fasting glucose (1050)	3.1 (5.1)	534 (51%)	131 (12%)
Diabetes (3343)	3.0 (5.2)	1669 (50%)	442 (13%)
Obesity			
None (6231)	1.3 (2.5)	1596 (26%) ^a	324 (5%) ^a
Overweight (5577)	1.9 (3.1)	1898 (34%)	317 (6%)
Obese (7283)	3.6 (5.6)	4092 (56%)	1056 (15%)
Cholesterol			
Normal (<5.18 mmol/L) (10836)	2.0 (3.9)	4156 (38%) ^a	976 (9%)
Borderline (5.18–6.19 mmol/L) (5942)	2.3 (4.0)	2439 (41%)	523 (9%)
High (≥6.20 mmol/L) (2313)	2.5 (4.0)	991 (43%)	198 (9%)
HDL cholesterol			
Normal (>1.04 mmol/L men, >1.30 mmol/L women) (11962)	1.8 (3.5)	4237 (35%) ^a	889 (7%) ^a
Low (≤1.04 mmol/L men, ≤1.30 mmol/L women) (7129)	2.7 (4.7)	3349 (47%)	808 (11%)
Triglycerides			
Normal (<1.70 mmol/L) (13937)	1.9 (3.8)	5226 (38%) ^a	1210 (9%)
Borderline (1.70–2.25 mmol/L) (2678)	2.7 (4.2)	1214 (45%)	258 (10%)
High (≥2.26 mmol/L) (2476)	2.7 (4.3)	1146 (46%)	229 (9%)
Framingham 10-year predicted coronary risk			
<0%–5% (6951)	1.9 (3.7)	2533 (36%) ^a	537 (8%)
5% to <10% (4416)	2.0 (3.6)	1592 (36%)	346 (8%)
10% to <20% (3137)	2.2 (3.7)	1241 (40%)	270 (9%)
>20% (1218)	2.6 (3.7)	536 (44%)	98 (8%)
Framingham 10-year predicted vascular risk			
<0%–5% (2996)	1.7 (3.3)	1009 (34%) ^a	214 (7%) ^d
5% to <10% (4540)	2.2 (4.3)	1849 (41%)	416 (9%)
10% to <20% (6305)	2.3 (4.0)	2479 (41%)	587 (9%)
>20% (5239)	2.3 (3.9)	2146 (41%)	480 (9%)
Reynolds 10-year predicted vascular risk			
<0%–5% (2453)	2.1 (3.5)	2253 (36%) ^a	470 (7%)
5% to <10% (3172)	2.0 (3.6)	1173 (37%)	263 (8%)
10% to <20% (6343)	1.8 (3.6)	947 (39%)	200 (8%)
>20% (1031)	2.7 (4.0)	489 (47%)	114 (11%)

^a $P < 0.0001$ by ANOVA.^b $P = 0.002$ by ANOVA.^c $P = 0.04$.^d $P = 0.003$.

Table 3. Odds ratios (OR) of increased hsCRP (>3 mg/L) by risk factors.

Risk Factor	Overall odds of hsCRP >3 mg/L		Sex-specific adjusted OR ^a of hsCRP >3 mg/L		
	Crude OR (95% CI)	Adjusted OR ^a (95% CI)	Men (n = 8079)	Women (n = 11003)	Women not on hormones (n = 9413)
Age					
55–64 years	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.2 (1.0–1.4)	1.1 (1.0–1.2)	1.1 (1.0–1.2)
>65 years	0.9 (0.9–1.0)	1.1 (1.0–1.2)	1.5 (1.3–1.8)	0.9 (0.8–1.0)	0.9 (0.8–1.1)
Sex, women	2.0 (1.9–2.1)	1.9 (1.8–2.0)	NA	NA	NA
Race, black	1.8 (1.7–1.9)	1.3 (1.2–1.4)	1.3 (1.2–1.5)	1.4 (1.2–1.5)	1.4 (1.3–1.6)
Region, belt	1.2 (1.1–1.2)	1.1 (1.1–1.2)	1.1 (0.95–1.2)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Education					
<High school	2.1 (1.9–2.4)	1.4 (1.3–1.6)	1.8 (1.5–2.1)	1.2 (1.1–1.4)	1.3 (1.1–1.5)
High school graduate	1.6 (1.4–1.7)	1.2 (1.1–1.3)	1.3 (1.2–1.5)	1.1 (1.0–1.3)	1.1 (1.0–1.3)
Some college	1.5 (1.4–1.6)	1.2 (1.1–1.3)	1.3 (1.2–1.5)	1.2 (1.1–1.3)	1.2 (1.1–1.4)
Hormone therapy (women)	NA	NA	NA	1.7 (1.5–1.9)	NA
Current smoking	1.7 (1.5–1.8)	1.8 (1.6–2.0)	2.3 (2.0–2.6)	1.5 (1.3–1.7)	1.6 (1.4–1.8)
Blood pressure					
Prehypertension	1.4 (1.3–1.5)	1.2 (1.1–1.3)	1.2 (1.0–1.4)	1.2 (1.1–1.4)	1.2 (1.1–1.4)
Hypertension	2.1 (1.9–2.2)	1.4 (1.3–1.5)	1.3 (1.1–1.5)	1.4 (1.3–1.6)	1.4 (1.3–1.6)
Diabetes status					
Impaired fasting glucose	1.8 (1.6–2.0)	1.3 (1.2–1.5)	1.2 (1.0–1.5)	1.4 (1.2–1.7)	1.5 (1.3–1.9)
Diabetes	1.7 (1.6–1.9)	1.1 (1.0–1.2)	1.1 (0.9–1.2)	1.1 (1.0–1.3)	1.1 (1.0–1.3)
Weight					
Overweight	1.5 (1.4–1.6)	1.4 (1.3–1.6)	1.2 (1.0–1.3)	1.7 (1.5–1.9)	1.6 (1.5–1.9)
Obese	3.7 (3.5–4.0)	3.0 (2.8–3.3)	2.4 (2.1–2.7)	3.7 (3.3–4.1)	3.8 (3.4–4.3)
Cholesterol >6.20 mmol/L	1.2 (1.1–1.3)	1.1 (1.0–1.2)	1.2 (1.0–1.4)	1.1 (1.0–1.2)	1.1 (1.0–1.3)
HDL ≤1.04 mmol/L men, ≤1.30 mmol/L women	1.6 (1.5–1.7)	1.3 (1.2–1.4)	1.3 (1.2–1.5)	1.3 (1.2–1.5)	1.5 (1.3–1.6)
Triglyceride ≥2.26 mmol/L	1.4 (1.3–1.5)	1.2 (1.0–1.3)	01.0 (0.9–1.1)	1.3 (1.1–1.5)	1.2 (1.0–1.4)

^a Adjusted models include all variables in the Table. NA, not applicable.

and region were not altered when model covariates were included as continuous variables; mean adjusted hsCRP concentration was 49% higher in women, 19% higher in blacks, and 9% higher in the stroke belt. When states were divided into 4 regions (south, midwest, northeast, and west), age-, sex-, and race-adjusted hsCRP were significantly higher in the south compared to each other region ($P < 0.0001$, data not shown), with other pairwise differences not significant. In the multivariable model the largest association of risk factors with increased hsCRP was for obesity. Some risk factor associations with increased hsCRP differed between men and women. Associations with age, low education, and smoking were larger among men, and associations of triglycerides and in particular obesity were larger among women. Among women, as-

sociations of risk factors with increased hsCRP were similar, excluding women using postmenopausal hormones. Associations of risk factors with hsCRP >10 mg/L were similar (data not shown), although odds ratios were lower for obesity (2.3, 95% CI 2.0–2.6), overweight (1.0, 95% CI 0.8–1.20), and triglyceride (1.0, 95% CI 0.8–1.1).

The percentage of nondiabetic participants in each Framingham score category that would be potentially reclassified into a different risk group if hsCRP was measured after Framingham risk assessment is shown in Fig. 1. Analyses excluded study participants using lipid-lowering medication. Blacks and women were more likely than whites and men to be potentially reclassified to a higher risk category. For example, considering the Framingham coronary

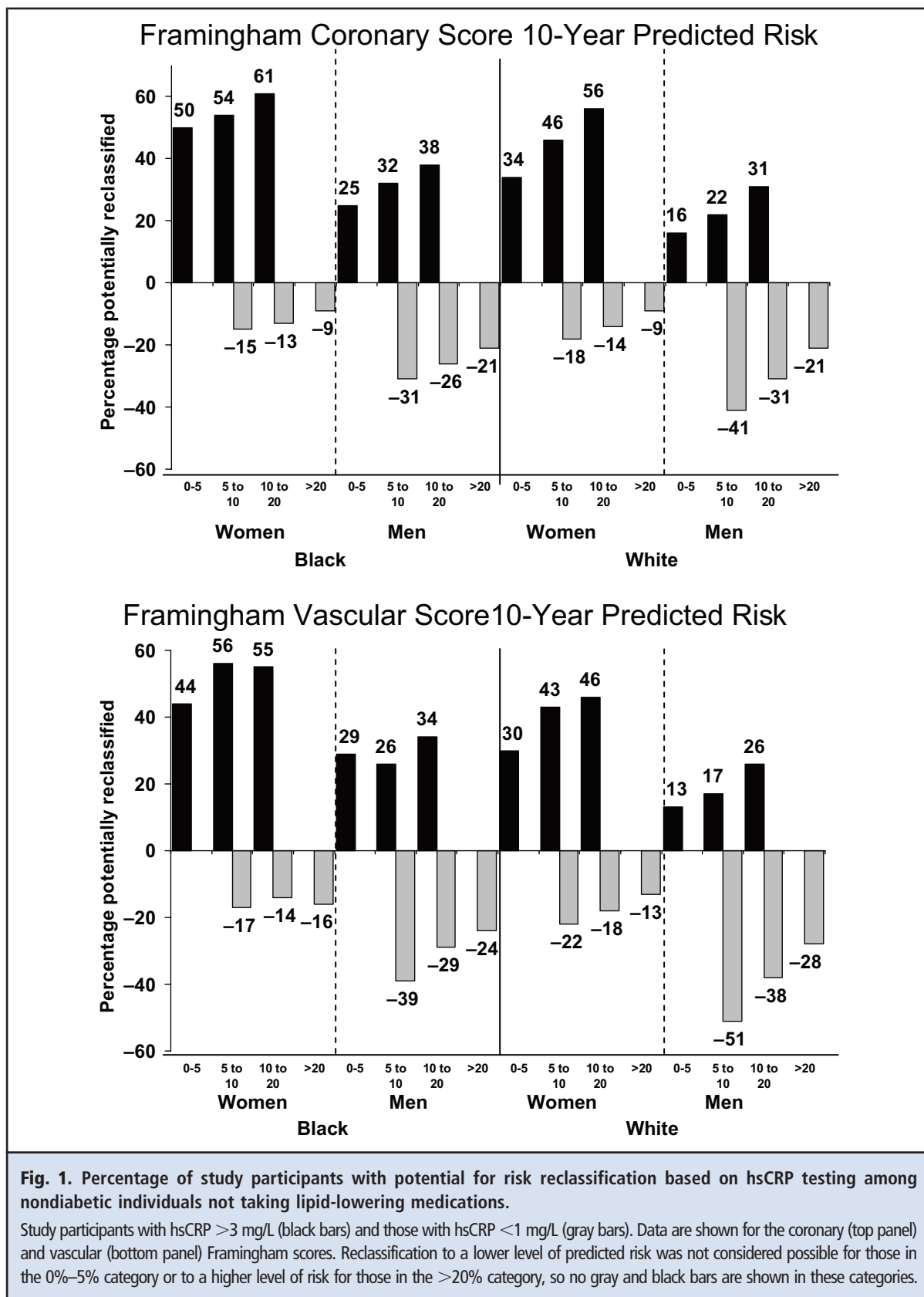


Table 4. Ten-year predicted risk by 3 different risk scores among 8309 nondiabetic study participants not taking lipid-lowering medication.

10-Year predicted risk	Framingham coronary risk score	CRP reclassification of Framingham coronary risk score	Framingham vascular risk score	CRP reclassification of Framingham vascular risk score	Reynolds risk score
Women (n = 4767)					
0 to <5%	3151 (66%)	2132 (48%)	1565 (33%)	1413 (30%)	3562 (75%)
5 to <10%	1104 (23%)	1640 (34%)	1662 (35%)	1272 (27%)	798 (17%)
10 to <20%	412 (9%)	669 (14%)	1346 (28%)	1223 (26%)	318 (7%)
>20%	100 (2%)	326 (7%)	194 (4%)	838 (18%)	89 (2%)
Men (n = 3542)					
0 to <5%	551 (16%)	902 (25%)	89 (3%)	372 (11%)	662 (17%)
5 to <10%	1179 (33%)	920 (26%)	586 (17%)	695 (20%)	1132 (32%)
10 to <20%	1234 (35%)	882 (25%)	1357 (38%)	1006 (28%)	1165 (33%)
>20%	578 (16%)	838 (24%)	1510 (43%)	1469 (42%)	583 (16%)

score, 61% of black women and 38% of black men at 10% to <20% predicted risk would be potentially reclassified to higher risk based on hsCRP >3 mg/L, compared to 56% of white women and 31% of white men. For both races, men were more likely than women to be reclassified to a lower level of risk based on hsCRP <1 mg/L, and these sex differences were larger for the vascular risk score than the coronary risk score.

Distributions of the 2 Framingham risk scores, the Reynolds risk score, and the 2 hsCRP-reclassified Framingham scores are shown in Table 4. Analyses excluded diabetic individuals and those using lipid-lowering medication. Among women the Reynolds score resulted in a much higher proportion at 0% to <5% risk and a lower proportion at 5% to <10% or 10% to <20% predicted risk than the 2 Framingham scores or hsCRP reclassified scores; 92% of women had a 10-year risk <10% with the Reynolds score. hsCRP reclassification of the Framingham vascular score resulted in far more women at higher levels of risk than the other scores, with 44% at >10% risk. Among men, the Reynolds score categorized far fewer men at high risk than the Framingham vascular score, which placed 43% of men at >20% risk. hsCRP reclassification of the Framingham vascular score resulted in a risk distribution fairly similar to that of the Framingham vascular score without hsCRP, with more men at 0% to <5% risk. The hsCRP-reclassified Framingham coronary score categorized roughly equal numbers of men into the 4 risk categories.

Individual level of risk obtained by reclassification of the Framingham vascular score by the Reynolds risk score is shown in Table 5. Reclassification of the Framingham vascular risk score by the Reynolds risk

score rarely reclassified a woman or man to a higher risk group (<2% of the time). Among women at 10%–20% Framingham vascular predicted risk, the Reynolds score reclassified 82% downward and only 2% upward. Among women with a Framingham vascular risk above 20%, 68% were reclassified downward. Overall, the Reynolds score reclassified 2739 of 4767 (57%) of women to a different risk group than the Framingham vascular score, but reclassified 2736 of 3202 (85%) of women with Framingham vascular predicted risk >5%. Among men with a Framingham vascular pre-

Table 5. Reclassification of the Framingham vascular risk score by the Reynolds vascular risk score in 4767 nondiabetic women and 3542 nondiabetic men not taking lipid-lowering medication.

Framingham vascular risk score category	Reynolds vascular risk score category			Total
	Lower	Same	Higher	
Women				
<5%	—	1562 (>99%)	3 (<1%)	1565
5%–10%	1448 (87%)	188 (11%)	26 (2%)	1662
10%–20%	1105 (82%)	216 (16%)	25 (2%)	1346
>20%	132 (68%)	62 (32%)	—	194
Men				
<5%	—	89 (100%)	0	89
5%–10%	426 (73%)	152 (26%)	8 (1%)	586
10%–20%	963 (71%)	378 (28%)	16 (1%)	1357
>20%	943 (62%)	567 (38%)	—	1510

dicted risk of 10% to <20%, 71% were reclassified downward and only 1% upward. Among high-risk men, 62% were reclassified downward. Overall, the Reynolds score reclassified 2356 of 3542 (67%) of men to a different risk group than the Framingham, all with a Framingham predicted risk >5%. For comparison, the Reynolds score reclassification of the Framingham coronary score is shown in Table 1 in the Data Supplement that accompanies the online version of this article at <http://www.clinchem.org/content/vol55/issue9>. With this reclassification more individuals were moved to higher levels of risk than for the Reynolds score reclassification of the Framingham vascular score.

Discussion

In this large study of geographically dispersed white and black men and women, increased hsCRP was more common among women than men and blacks than whites, and in the stroke belt compared to the rest of the US. These differences were not accounted for by other factors strongly related to hsCRP. Reclassification of Framingham coronary or vascular predicted risk by hsCRP testing suggested that well over half of participants would have their risk reclassified with the addition of data from hsCRP testing. Movement to higher risk categories was greatest among women and blacks. The use of the Reynolds risk score to reclassify the Framingham vascular risk score led to reclassification of fewer people, and almost exclusively reclassified men and women to a lower risk level.

Among the more than 19 000 participants in this study, 48% of blacks and 34% of whites had hsCRP >3 mg/L. Although some of this difference was accounted for by differences in vascular risk factors, blacks were 30% more likely to have increased hsCRP after confounder adjustment. The data add to growing evidence on ethnic variation in hsCRP, and support a hypothesis that higher inflammation might underlie differences in vascular risk by ethnicity. One study including 1086 nonwhite women found higher hsCRP in blacks than whites and Hispanics (who had concentrations similar to whites), whereas Asian women had much lower concentrations (15). Some, but not all of the difference in hsCRP among these groups was explained by differences in prevalence of obesity. In a study of 1250 Canadian adults, much but not all of the difference in hsCRP concentrations among ethnic groups was explained by other metabolic risk factors, with higher hsCRP in Aboriginals and South Asians, and lower hsCRP in Chinese than whites (16). Among 1940 men participating in the National Health and Nutrition Examination Survey (NHANES) 1999–2000, there was no difference in hsCRP by race among whites, blacks,

and Mexican-Americans (13). Among 1912 women in NHANES 1999–2000, Mexican-Americans had higher hsCRP than whites, but blacks had similar values (14). In the 15 341 NHANES III 1988–1994 participants, with the use of a low-sensitivity CRP assay, CRP was higher in blacks, but whether this difference was explained by differences in other CRP correlates was not studied (17). In 6814 participants of the Multi-Ethnic Study of Atherosclerosis, hsCRP was lower in Chinese and higher in Hispanics and blacks compared to whites (18). In 2 reports from the Study of Women's Health Across the Nation, among 2834 premenopausal women, differences in hsCRP by ethnicity were partly explained by dietary factors, cardiac risk factors, and physical activity level (23, 24).

In this study 47% of women had hsCRP >3 mg/L, and women had nearly twice the odds of increased hsCRP than men. Women were more likely to have increased hsCRP despite the much lower Framingham predicted risk of heart disease in women than men. In NHANES 1999–2000, 31% of women had hsCRP 3–10 mg/L, and when other risk factors were taken into account, women were 2.6-fold more likely than men to have hsCRP concentrations of 3–10 mg/L (14). In NHANES III, women were also 2.1-fold more likely to have hsCRP >3 mg/L (using a low-sensitivity assay), independent of other factors (17). The Multi-Ethnic Study of Atherosclerosis investigators also reported higher hsCRP among women after accounting for differences in other risk factor levels, with 45% of women and 25% of men having hsCRP >3 mg/L (18). Although higher hsCRP predicts vascular risk in population samples of women (25), results have been variable (4), and the high prevalence of increased hsCRP in women suggests clinical utility may be lower in women than men (4) if hsCRP values are not taken in context of other risk factors by using a risk score (6). Further follow-up in the large REGARDS cohort will help clarify these questions.

To our knowledge, this is the first report of hsCRP concentrations in stroke belt residents. This regional difference was not explained by differences in traditional stroke risk factors including hypertension, diabetes, and smoking, which are more prevalent in the stroke belt (12). In a previous REGARDS report, geographic differences in stroke risk factors were predicted to explain less than one-fourth of the increased stroke risk in that region (12). Along with the findings presented here, results suggest that the higher risk of death from stroke in this region may be associated, in part, with nontraditional risk factors such as CRP.

CRP testing is being adopted in clinical practice for risk assessment for prescription of lipid-lowering treatment to prevent first cardiovascular events (26). Information used to develop CRP cutpoints for clinical

practice was derived from selected populations (1). With the use of CRP in accordance with current guidelines (1) and application of the new Framingham vascular risk score (to predict overall vascular risk), in nondiabetic REGARDS women with a Framingham vascular predicted risk of 5%–20%, 48% of these women would be potentially reclassified as higher risk and 19% as lower risk. Among men, these percentages would be 24% and 40%, respectively. Blacks would more often be reclassified to a higher risk category than whites. More people would move to a higher risk group with the use of the Framingham coronary score with CRP than with the vascular score with CRP, perhaps because the Framingham vascular score classifies more people as high risk. Although follow-up cardiovascular events are needed to determine validity of these reclassifications in this population sample, the current data raise important questions about the generalizability of standard hsCRP cutpoints among ethnic and sex groups and across geographic regions.

The Reynolds risk score includes assessment of traditional vascular risk factors, family history, and hsCRP (6, 7), and like the new Framingham vascular score, predicts overall vascular outcomes. Applying the Reynolds score in nondiabetic REGARDS women not using lipid lowering medication, 85% of 3202 women with a 10-year predicted risk >5% by Framingham would be reclassified to a different level of predicted risk with the Reynolds score, with <2% reclassified to a higher risk group. This pattern differs from the Women's Health Study, the large clinical trial population in which the Reynolds score was developed and validated (6). In that study more women were reclassified to higher risk levels; the Reynolds score was compared to standard risk scoring for coronary disease, and the sample size was smaller, which may explain the difference. Among REGARDS men, 67% of 3542 men with a 10-year predicted risk >5% by Framingham were reclassified to a different level with the Reynolds score, with only 24 men reclassified upward. In the Physicians Health Study II, in which the Reynolds score for men was developed and compared to standard coronary risk scoring, only 20% of 6884 men with a traditional predicted risk of 5%–20% were reclassified, with 12% reclassified downward and 8% upward (7). It is important to note that the Reynolds score was validated to predict myocardial infarction, stroke, coronary revascularization, and cardiovascular mortality, whereas the Framingham vascular score included these outcomes and the partly overlapping endpoints of angina, coronary insufficiency, transient ischemic attack, peripheral artery disease, and heart failure. These differences in outcomes for the scoring systems may explain some of the differences in reclassification we observed. Data for the Framingham coronary score, which predicts angina, recognized and unrecognized myocardial infarction, coronary insufficiency, and

coronary death are shown in online Supplemental Table 1. The implications of this risk reclassification in REGARDS, a cohort with characteristics differing from those of the cohorts for the Women's Health Study and Physicians Health Study II (more ethnically diverse, lower socioeconomic status, and not clinical trial participants), require further evaluation by assessing vascular outcomes in REGARDS.

Limitations of our study merit discussion. Importantly, we did not include prediction of vascular events. The various risk algorithms evaluated may not be comparable for reasons other than hsCRP inclusion because they predict different endpoints. Importantly, for the reclassification of risk based on Framingham score, we were not able to incorporate hsCRP into a model that would allow reweighting of all the risk factors, because we did not assess outcomes. Data on family history of heart disease was not yet coded for all study participants at the time of this analysis, so the Reynolds score could not be calculated. The Framingham score for these participants had a distribution similar to that for the participants with complete data. Strengths of this analysis include generalizability and large sample size. Our study population included 7847 blacks and 11 003 women, whereas most previous data have primarily included male or white populations. In our study the cohort was geographically dispersed so geographic associations could be studied, a strategy that also improves confidence in the generalizability of our findings compared to the field-center-based studies on which most previous data are based.

In conclusion, in this large population-based sample of white and black men and women there was a higher prevalence of increased hsCRP than has been observed in most other studies. Women, blacks, and individuals living in the stroke belt had a higher prevalence of increased hsCRP. All studied vascular risk factors and lower socioeconomic status were associated with increased hsCRP, but these variables did not explain the observed differences by sex, race, and region. If hsCRP testing was included in vascular risk prediction algorithms in this population and these findings were used to alter lipid prescription (26), larger numbers of people than previously reported, especially blacks and women, would be reclassified to a different level of predicted vascular risk. Follow-up of this cohort for clinical outcomes will determine the significance of these findings.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting

or revising the article for intellectual content; and (c) final approval of the published article.

Authors' Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.

Consultant or Advisory Role: M. Cushman, Glaxo-Smith-Kline; G. Howard, ARRIVE study for Bayer.

Stock Ownership: None declared.

Honoraria: None declared.

Research Funding: Cooperative agreement U01 NS041588 from the National Institute of Neurological Disorders and Stroke, NIH, US Department of Health and Human Services. M. Cushman, Glaxo-Smith-Kline; V.J. Howard and immediate family member, NIH-NINDS.

Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

Acknowledgments: The authors acknowledge participating investigators: University of Alabama at Birmingham: Libby Wagner, Virginia Wadley, Rodney Go, Monika Safford, Ella Temple, Margaret Stewart; University of Vermont: Rebekah Boyle; Wake Forest University: Ron Prineas; Alabama Neurological Institute: Camilo Gomez; University of Arkansas: LeaVonne Pulley; University of Cincinnati: Brett Kissela; Examination Management Services: Andra Graham; National Institute of Neurological Disorders and Stroke: Claudia Moy.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health.

References

1. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499–511.
2. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation* 2003;108:2292–7.
3. Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. *Circulation* 2004;109:1955–9.
4. Cushman M, Arnold AM, Psaty BM, Manolio TA, Kuller LH, Burke GL, et al. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. *Circulation* 2005;112:25–31.
5. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. *Ann Intern Med* 2006;145:21–9.
6. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;297:611–9.
7. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation* 2008;118:2243–51.
8. Howard G. Why do we have a stroke belt in the southeastern United States? A review of unlikely and uninvestigated potential causes. *Am J Med Sci* 1999;317:160–7.
9. Howard G, Anderson R, Sorlie P, Andrews V, Backlund E, Burke GL. Ethnic differences in stroke mortality between non-Hispanic whites, Hispanic whites, and blacks. *The National Longitudinal Mortality Study. Stroke* 1994;25:2120–5.
10. Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, et al. The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. *Stroke* 1998;29:415–21.
11. Gillum RF, Ingram DD. Relation between residence in the southeast region of the United States and stroke incidence. The NHANES I Epidemiologic Followup Study. *Am J Epidemiol* 1996;144:665–73.
12. Cushman M, Cantrell RA, McClure LA, Howard G, Prineas RJ, Moy CS, et al. Estimated 10-year stroke risk by region and race in the United States: geographic and racial differences in stroke risk. *Ann Neurol* 2008;64:507–13.
13. Ford ES, Giles WH, Myers GL, Mannino DM. Population distribution of high-sensitivity C-reactive protein among US men: findings from National Health and Nutrition Examination Survey 1999–2000. *Clin Chem* 2003;49:686–90.
14. Ford ES, Giles WH, Mokdad AH, Myers GL. Distribution and correlates of C-reactive protein concentrations among adult US women. *Clin Chem* 2004;50:574–81.
15. Albert MA, Glynn RJ, Buring J, Ridker PM. C-Reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). *Am J Cardiol* 2004;93:1238–42.
16. Anand SS, Razak F, Yi Q, Davis B, Jacobs R, Vuksan V, et al. C-reactive protein as a screening test for cardiovascular risk in a multiethnic population. *Arterioscler Thromb Vasc Biol* 2004;24:1509–15.
17. Miller M, Zhan M, Havas S. High attributable risk of elevated C-reactive protein level to conventional coronary heart disease risk factors: the Third National Health And Nutrition Examination Survey. *Arch Intern Med* 2005;165:2063–8.
18. Lakoski SG, Cushman M, Criqui M, Rundek T, Blumenthal RS, D'Agostino RB Jr, Herrington DM. Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. *Am Heart J* 2006;152:593–8.
19. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, et al. The REasons for Geographic And Racial Differences in Stroke Study: objectives and design. *Neuroepidemiology* 2005;25:135–43.
20. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–97.
21. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837–47.
22. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743–53.
23. Matthews KA, Sowers MF, Derby CA, Stein E, Miracle-McMahill H, Crawford SL, Pasternak RC. Ethnic differences in cardiovascular risk factor burden among middle-aged women: Study of Women's Health Across the Nation (SWAN). *Am Heart J* 2005;149:1066–73.
24. Kelley-Hedgpeth A, Lloyd-Jones DM, Colvin A, Matthews KA, Johnston J, Sowers MR, et al. Ethnic differences in C-reactive protein concentrations. *Clin Chem* 2008;54:1027–37.
25. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836–43.
26. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–207.