# Racial Differences in and Prognostic Value of Biomarkers of Hyperglycemia

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## OBJECTIVE

**We compared levels and associations of traditional (fasting glucose, $HbA_{1c}$) and nontraditional (fructosamine, glycated albumin, and 1,5-anhydroglucitol [1,5-AG]) biomarkers of hyperglycemia with incident cardiovascular disease (CVD), incident end-stage renal disease (ESRD), and prevalent retinopathy in black and white adults.**

## RESEARCH DESIGN AND METHODS

**We included 10,373 participants without (8,096 white, 2,277 black) and 727 with diagnosed diabetes (425 white, 302 black) from the Atherosclerosis Risk in Communities (ARIC) Study. We used Cox proportional hazards models to compare hazards ratios of CVD and ESRD among blacks and whites from baseline (1990–1992) through 2012. We compared the odds ratios (from logistic regression) of retinopathy among blacks and whites. We tested for the interaction of each biomarker with race.**

## RESULTS

**Median values of biomarkers were higher among blacks versus whites (all $P < 0.001$). Relative risks for each biomarker with incident CVD and ESRD, and odds ratios for each biomarker with prevalent retinopathy, were similar by race (all $P$ values for interaction by race >0.10).**

## CONCLUSIONS

**The prognostic value of $HbA_{1c}$, fructosamine, glycated albumin, and 1,5-AG with incident CVD, incident ESRD, and prevalent retinopathy were similar by race. Our results support similar interpretation of $HbA_{1c}$ and nontraditional biomarkers of hyperglycemia among black and whites with respect to long-term complications.**


Nontraditional biomarkers of hyperglycemia (fructosamine, glycated albumin, and 1,5-anhydroglucitol [1,5-AG]) have emerged as possible adjuncts to the traditional biomarkers, fasting glucose and $HbA_{1c}$ (1,2). Fasting glucose is an acute measure of current hyperglycemia. $HbA_{1c}$ is the proportion of hemoglobin in red blood cells bound to glucose (specifically, glucose that is bound to the N-terminal valine of the β-chain of hemoglobin), and measures average glycemia over 2–3 months, based on red blood cell turnover (3,4). Fructosamine and glycated albumin are markers of glucose bound to serum proteins and estimate average glycemia over 2–4 weeks (5). 1,5-AG is a monosaccharide, mainly derived from the diet, that is normally almost completely reabsorbed by the kidney. In states of hyperglycemia (>180 mg/dL), glucose in the renal tubular lumen inhibits tubular reabsorption of 1,5-AG, and more 1,5-AG is excreted, resulting in lower serum 1,5-AG levels. Levels of 1,5-AG are inversely associated with average glycemia over the past 2–14 days (6–10).

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Higher levels of biomarkers of hyperglycemia have been associated with increased risk of microvascular and macrovascular complications in both people with and people without diabetes (11–17). However, prospective associations of nontraditional serum biomarkers of hyperglycemia with microvascular and macrovascular complications according to race have not been characterized and could shed further light on the debate over racial differences in $HbA_{1c}$. Whereas $HbA_{1c}$ is a measure of intracellular hyperglycemia and can be affected by nonglycemic factors, such as hemoglobin characteristics or alterations in red cell turnover, fructosamine, glycated albumin, and 1,5-AG are serum measures of extracellular hyperglycemia and therefore are not affected by these nonglycemic factors. Comparing associations of each of these biomarkers in blacks and whites could provide insight into whether racial differences in levels of biomarkers may be attributed to glycemic or nonglycemic factors.

Our objective was to assess the associations of fasting glucose, $HbA_{1c}$, and nontraditional serum biomarkers of hyperglycemia (fructosamine, glycated albumin, and 1,5-AG) with prevalent retinopathy and incident cardiovascular disease (CVD) and end-stage renal disease (ESRD), and to evaluate differential associations between blacks and whites.

## RESEARCH DESIGN AND METHODS

### Setting and Participants

We conducted a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) Study, a community-based cohort of 15,792 middle-aged adults recruited in 1987–1989 from four field centers in the United States: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland (18). Follow-up visits 2 through 5 took place during 1990–1992, 1993–1995, 1996–1998, and 2011–2013, respectively. We restricted our study population to ARIC participants who attended visit 2 ($n$ = 14,348) because this was the earliest visit at which all biomarkers of hyperglycemia were measured. We excluded participants who did not have values for all biomarkers of hyperglycemia ($n$ = 1,159) or were missing key covariates ($n$ = 379). We further excluded a small number of nonblack and nonwhite participants ($n$ = 38), as well as people who were not fasting for ≥8 h ($n$ = 396). Last, we excluded 1,276 people with prevalent CVD or preexisting ESRD based on linkage with the U.S. Renal Data System (USRDS) at visit 2. There were 11,100 participants included in our final study population of incident CVD and ESRD. Retinal photographs were obtained only at visit 3 in 1993–1995 (3 years after visit 2); analyses of prevalent retinopathy were restricted further to those participants who attended visit 3 and had valid retinal photographs ($n$ = 8,615).

### Biomarkers of Hyperglycemia

All biomarkers of hyperglycemia were measured using blood specimens from visit 2. Fasting glucose was measured using a hexokinase method. $HbA_{1c}$ was measured using high-performance liquid chromatography with Tosoh A1c 2.2 Plus Glycohemoglobin and Tosoh G7 Analyzers (Tosoh Bioscience, South San Francisco, CA), and was standardized to the Diabetes Control and Complications Trial assay (19). All $HbA_{1c}$ values were calibrated to account for the changes in methods (19). Fructosamine, glycated albumin, and 1,5-AG in stored serum samples were measured in 2012–2013 using a Roche Modular P800 analyzer (Roche Diagnostics, Indianapolis, IN). Fructosamine was measured using a colorimetric method (Roche Diagnostics). Glycated albumin (Lucica GA-L; Asahi Kasei Pharma Corp., Tokyo, Japan) and 1,5-AG (GlycoMark, New York, NY) were measured using enzymatic methods. Glycated albumin was expressed as a percentage of total albumin, calculated using the following equation derived by the manufacturer: ([glycated albumin concentration in g/dL ÷ serum albumin concentration in g/dL] ÷ 1.14 × 100) + 2.9. The interassay coefficients of variation were 3% for fructosamine, 1.8% for glycated albumin, and 5% for 1,5-AG. Previous studies from our group and others have demonstrated the stability and reliability of these biomarkers measured in samples stored for long periods (13,20–23).

### Covariates

We defined diagnosed diabetes as a self-reported physician diagnosis of diabetes or self-reported use of glucose-lowering medication at visit 1 or visit 2. The following covariates were self-reported by participants as responses to questionnaires at visit 2, unless otherwise specified: age, sex, race (visit 1), education level (visit 1), alcohol consumption, smoking status, and physical activity (Baecke sport activity index at visit 1) (24). Antihypertensive medication use was obtained via self-report or medication inventory. Cholesterol-lowering medication use was obtained via medication inventory.

Diastolic and systolic blood pressures were measured using a random zero sphygmomanometer and recorded as the mean of the second and third readings. BMI was calculated as measured weight (in kilograms) divided by measured height (in meters) squared. Total cholesterol, HDL cholesterol (HDL-c), LDL cholesterol (LDL-c), and triglycerides were measured in stored plasma using the Roche Cobas Bio (Roche Diagnostics). Total cholesterol and triglycerides were measured using an enzymatic method, and HDL-c was measured using a precipitation method. LDL-c was calculated from measured total cholesterol, HDL-c, and triglycerides using the Friedewald equation. Creatinine was measured using the Jaffe method with a Coulter DACOS analyzer. We used the Chronic Kidney Disease Epidemiology Collaboration equation to calculate the estimated glomerular filtration rate (eGFR) using serum creatinine, age, sex, and race (25).

### Outcomes and Follow-up

We used a composite CVD end point defined as a first coronary heart disease (CHD), stroke, or heart failure event, based on standard ARIC definitions: first occurrence of definite or probable hospitalized myocardial infarction or death caused by CHD (26); definite or probable hospitalized stroke or death caused by stroke (27); or hospitalization or death caused by heart failure, based on International Classification of Diseases, 9th Revision, code 428 or 10th Revision code I50 (28). All cardiovascular events through 31 December 2012 were ascertained via continuous surveillance of hospitalizations and death certificates, annual telephone follow-up with the participant or a proxy, and linkage to the National Death Index. CHD and stroke events were adjudicated over the entire follow-up; heart failure events were adjudicated beginning in

2005. We conducted secondary analyses with CHD, stroke, and heart failure as separate end points.

For analyses of incident ESRD, we identified treated cases through linkage with the USRDS national registry through 30 September 2011, since that was the most recent available linkage to the USRDS. The Centers for Medicare and Medicaid Services report any people receiving renal replacement therapy to the USRDS within 45 days of initiation of treatment, which includes people undergoing dialysis or a kidney transplant.

Prevalent retinopathy was measured at visit 3 (1993–1995) using fundus photography (29,30). It was defined as a score of ≥20 on the Early Treatment Diabetic Retinopathy Study scale (31).

### Statistical Analysis

We calculated descriptive statistics for demographic and clinical characteristics, stratified by diagnosed diabetes status and race. We compared median levels of $HbA_{1c}$, fructosamine, glycated albumin, and 1,5-AG within clinical categories of fasting glucose among blacks and whites separately, and we tested for differences using the Wilcoxon rank sum test.

We created a five-level variable for each biomarker based on diagnosed diabetes status and biomarker level. In people without diagnosed diabetes, we used clinical cut points recommended by the American Diabetes Association to categorize fasting glucose (<100, 100–125, ≥126 mg/dL) and $HbA_{1c}$ (<5.7, 5.7–6.4, ≥6.5%) (1). We categorized people with diagnosed diabetes based on the clinically recommended cut point of <7 vs. ≥7% for $HbA_{1c}$. Since clinical cut points have not been established for fructosamine or glycated albumin, we used cut points pegged to the clinically relevant $HbA_{1c}$ values of 5.7% (the 75th percentile) and 6.5% (the 96.5th percentile) in people without diagnosed diabetes and $HbA_{1c}$ of 7% (the 40th percentile) in people with diagnosed diabetes (1). Because of the inverse association of 1,5-AG with hyperglycemia, we used cut points at the 25th and 3.5th percentiles in people without diabetes and the 60th percentile in people with diagnosed diabetes.

We used Cox proportional hazards regression models to assess associations with incident CVD and ESRD. Follow-up for CVD and ESRD began at the visit 2 exam date (1990–1992) and continued until the time of the event, last date of follow-up, or 31 December 2012 (30 September 2011 for ESRD analyses), whichever occurred first. We used logistic regression to evaluate the associations of biomarkers of hyperglycemia with prevalent retinopathy in blacks and whites. Models included age, sex, BMI, $BMI^2$, LDL-c, HDL-c, triglycerides, cholesterol-lowering medication use,

**Table 1—Characteristics of the study population by diabetes status and race, ARIC visit 2 (1990–1992)**

| | No diagnosed diabetes | | | Diagnosed diabetes | | |
|---|---|---|---|---|---|---|
| | White (*n* = 8,096) | Black (*n* = 2,277) | *P* value* | White (*n* = 425) | Black (*n* = 302) | *P* value* |
| Age, years | 57.3 (5.6) | 56.2 (5.7) | <0.001 | 58.7 (5.7) | 57.6 (5.7) | 0.013 |
| Male sex | 43.9% | 35.8% | <0.001 | 48.0% | 29.5% | <0.001 |
| Less than HS education | 13.9% | 35.0% | <0.001 | 24.2% | 44.0% | <0.001 |
| Obese (BMI ≥ 30 kg/m$^2$) | 21.7% | 41.5% | <0.001 | 47.5% | 55.0% | 0.048 |
| Current smoking | 20.5% | 24.5% | <0.001 | 17.9% | 21.2% | 0.265 |
| Current drinking | 66.2% | 36.8% | <0.001 | 48.5% | 21.5% | <0.001 |
| Family history of diabetes | 21.9% | 25.0% | 0.002 | 41.9% | 41.1% | 0.824 |
| Hypertension† | 29.4% | 51.4% | <0.001 | 51.3% | 64.9% | <0.001 |
| Antihypertensive medication use | 21.7% | 40.3% | <0.001 | 42.6% | 57.0% | <0.001 |
| Systolic BP, mmHg | 118.8 (17.4) | 125.5 (19.9) | <0.001 | 125.2 (17.2) | 127.9 (20.1) | 0.052 |
| Systolic BP ≥140 mmHg | 11.7% | 21.0% | <0.001 | 19.8% | 22.2% | 0.428 |
| Diastolic BP, mmHg | 71.2 (9.7) | 75.7 (10.8) | <0.001 | 70.8 (9.7) | 73.0 (9.7) | 0.003 |
| Diastolic BP ≥90 mmHg | 3.8% | 10.1% | <0.001 | 3.3% | 4.3% | 0.478 |
| HDL-c, mg/dL | 50.1 (16.6) | 54.5 (17.0) | <0.001 | 42.1 (12.8) | 49.1 (13.6) | <0.001 |
| Total cholesterol, mg/dL | 209.0 (37.4) | 208.9 (40.0) | 0.921 | 208.7 (39.2) | 217.5 (45.6) | 0.005 |
| LDL-c, mg/dL | 132.8 (35.6) | 133.7 (38.3) | 0.281 | 132.6 (35.2) | 141.4 (42.7) | 0.003 |
| Triglycerides, mg/dL | 130.7 (64.5) | 103.5 (50.0) | <0.001 | 169.5 (75.3) | 134.8 (68.3) | <0.001 |
| Cholesterol-lowering medication use | 5.5% | 2.8% | <0.001 | 12.9% | 5.0% | <0.001 |
| Glucose-lowering medications‡ | — | — | — | 61.5% | 76.5% | <0.001 |
| eGFR <60 mL/min/1.73 m$^2$ | 1.2% | 1.1% | 0.670 | 2.4% | 4.6% | 0.090 |
| Prevalent retinopathy§ | 1.6% | 3.3% | <0.001 | 19.6% | 30.7% | 0.005 |
| Baecke sport index‖ | 2.5 (0.8) | 2.2 (0.7) | <0.001 | 2.4 (0.8) | 2.1 (0.6) | <0.001 |

Data are mean (SD) or percentages. BP, blood pressure; HS, high school; IQR, interquartile range. *Two-sided *P* values calculated using the Student *t* test for continuous variables and the $\chi^2$ test for categorical variables. †Hypertension defined as diastolic BP ≥90 mmHg or systolic BP ≥140 mmHg or antihypertensive medication use. ‡Among persons with diabetes, 13 black and 22 white participants are missing a response to self-reported use of glucose-lowering medication. §Retinopathy was assessed at visit 3 (1993–1995) and therefore was available for only a subset of the main study population (176 blacks and 317 whites among participants with diagnosed diabetes; 1,516 blacks and 6,561 whites among participants without diagnosed diabetes). ‖The Baecke sport index is a score of sport index during leisure time, with values ranging from 1 to 5, based on intensity (light, moderate, heavy); time (hours per week); and proportion (months per year) of activity. Higher values indicate higher levels of physical activity.

systolic blood pressure, antihypertensive medication use, eGFR, family history of diabetes, education level, alcohol consumption, cigarette smoking status, and physical activity level. We also adjusted for fasting glucose and $HbA_{1c}$ in sensitivity analyses. To test for a linear trend among whites and blacks separately, we included the categorical biomarker variable as a continuous variable and conducted a Wald test for the coefficient. We used likelihood ratio tests to evaluate interactions with race. *P* values $<0.05$ were considered statistically significant. We verified that the proportional hazards assumption was met using likelihood ratio tests (with $P > 0.05$ indicating no violation of the assumption).

In supplemental analyses, we first accounted for participants who did not have diabetes at baseline but developed it at some point during follow-up. For analyses of incident CVD and incident ESRD, we censored at the time of diabetes development people who developed diabetes after visit 2 if they either did not experience the event of interest or developed diabetes before experiencing the event of interest. For analyses of prevalent retinopathy, we excluded all people who developed diabetes during follow-up (*n* = 2,672). Second, we used Poisson regression to calculate age- and sex-adjusted race-specific incidence rates of CVD and ESRD separately in people with and without diagnosed diabetes. We included an offset term of the natural log of person-years to account for differences in follow-up time. We obtained predictive margins from logistic regression models to calculate the race-specific prevalence of retinopathy (also adjusted for age and sex). We used the Wald test to test differences in incidence rates and prevalence, comparing whites and blacks. All statistical analyses were conducted using Stata version 14.0 (StataCorp, College Station, TX).

## RESULTS

Our study population included 10,373 participants without diagnosed diabetes (8,096 white and 2,277 black) and 727 participants with diagnosed diabetes (425 white and 302 black). Baseline characteristics varied between those with and without diagnosed diabetes and according to race (Table 1). Even at similar levels of fasting glucose, blacks had higher levels of $HbA_{1c}$, fructosamine, and glycated albumin ($P < 0.001$ for all) and marginally statistically significant lower levels of 1,5-AG ($P < 0.07$ for all) compared with whites (Table 2). The magnitudes of these black/white differences were particularly large among people with diagnosed diabetes (Table 2). Among people with and without diabetes, we observed statistically significantly higher age- and sex-adjusted incidence rates of CVD and ESRD among blacks compared with whites, and the prevalence of retinopathy was higher among blacks compared with whites ($P < 0.05$ for all) (Supplementary Fig. 1).

Among 11,100 participants who were free of CVD and ESRD at baseline, there were 2,642 incident cases of CVD and 170 cases of ESRD during approximately 20 years of follow-up. Magnitudes of association were greatest for $HbA_{1c}$ compared with other biomarkers (Fig. 1 and Supplementary Table 1). The associations followed a linear trend among both whites and blacks ($P_{trend} < 0.001$ for all). These associations of biomarkers with incident CVD were similar among blacks and whites (*P* values for interaction were $>0.10$ for all biomarkers) (Fig. 1 and Supplementary Table 1). Patterns and magnitudes of associations of biomarkers

**Table 2—Baseline levels of biomarkers of hyperglycemia by diabetes status and race**

| | Median (25th, 75th percentile) | Median (25th, 75th percentile) | *P* value* |
|---|---|---|---|
| Among people without diagnosed diabetes | White (*n* = 8,096) | Black (*n* = 2,277) | |
| FG, mg/dL | 101 (95, 108) | 104 (97, 113) | <0.001 |
| FG <100 mg/dL | 94 (90, 97) | 94 (90, 97) | 0.189 |
| FG 100–125 mg/dL | 106 (102, 111) | 108 (103, 114) | <0.001 |
| FG ≥126 mg/dL | 136 (129, 151) | 138 (131, 154) | 0.150 |
| $HbA_{1c}$, % | 5.4 (5.1, 5.6) | 5.7 (5.4, 6.0) | <0.001 |
| FG <100 mg/dL | 5.3 (5.1, 5.4) | 5.5 (5.2, 5.7) | <0.001 |
| FG 100–125 mg/dL | 5.4 (5.2, 5.7) | 5.7 (5.4, 6.0) | <0.001 |
| FG ≥126 mg/dL | 6.2 (5.8, 6.8) | 6.6 (6.2, 7.2) | <0.001 |
| Fructosamine, μmol/L | 225 (214, 237) | 234 (220, 250) | <0.001 |
| FG <100 mg/dL | 224 (212, 234) | 230 (217, 242) | <0.001 |
| FG 100–125 mg/dL | 226 (214, 237) | 234 (220, 249) | <0.001 |
| FG ≥126 mg/dL | 247 (229, 268) | 260 (236, 285) | <0.001 |
| Glycated albumin, % | 12.5 (11.7, 13.3) | 13.3 (12.4, 14.3) | <0.001 |
| FG <100 mg/dL | 12.4 (11.7, 13.2) | 13.1 (12.3, 13.9) | <0.001 |
| FG 100–125 mg/dL | 12.4 (11.7, 13.2) | 13.3 (12.4, 14.3) | <0.001 |
| FG ≥126 mg/dL | 14.1 (12.8, 15.8) | 15.2 (13.6, 17.3) | <0.001 |
| 1,5-AG, μg/mL | 18.9 (15.3, 22.5) | 17.3 (13.9, 21.0) | <0.001 |
| FG <100 mg/dL | 18.6 (15.2, 22.1) | 17.3 (14.2, 21.1) | <0.001 |
| FG 100–125 mg/dL | 19.4 (15.8, 22.9) | 17.8 (14.3, 21.2) | <0.001 |
| FG ≥126 mg/dL | 15.5 (10.0, 20.4) | 14.6 (8.2, 18.7) | 0.055 |
| Among people with diagnosed diabetes | White (*n* = 425) | Black (*n* = 302) | |
| FG, mg/dL | 158 (122, 216) | 194 (136, 271) | <0.001 |
| FG <149 mg/dL | 117 (103, 133) | 120 (103, 135) | 0.517 |
| FG ≥149 mg/dL | 209 (176, 256) | 245 (191, 296) | <0.001 |
| $HbA_{1c}$, % | 7.1 (5.9, 8.6) | 8.4 (6.7, 10.6) | <0.001 |
| FG <149 mg/dL | 5.8 (5.4, 6.5) | 6.4 (5.9, 7.1) | <0.001 |
| FG ≥149 mg/dL | 8.4 (7.4, 9.8) | 9.7 (8.0, 11.4) | <0.001 |
| Fructosamine, μmol/L | 280 (241, 358) | 331 (267, 423) | <0.001 |
| FG <149 mg/dL | 240 (221, 260) | 254 (237, 281) | <0.001 |
| FG ≥149 mg/dL | 341 (290, 404) | 378 (316, 465) | <0.001 |
| Glycated albumin, % | 16.6 (13.3, 22.4) | 21.7 (16.0, 29.0) | <0.001 |
| FG <149 mg/dL | 13.1 (12.1, 14.9) | 15.0 (13.4, 16.4) | <0.001 |
| FG ≥149 mg/dL | 21.1 (17.4, 27.1) | 25.0 (21.1, 32.7) | <0.001 |
| 1,5-AG, μg/mL | 7.7 (2.4, 15.4) | 4.0 (1.5, 12.1) | <0.001 |
| FG <149 mg/dL | 15.1 (10.2, 20.1) | 13.3 (9.5, 17.3) | 0.040 |
| FG ≥149 mg/dL | 2.8 (1.4, 7.1) | 2.1 (1.2, 5.3) | 0.065 |

Among people without diagnosed diabetes, there were 3,573 whites and 772 blacks with FG <100 mg/dL; 4,133 whites and 1,266 blacks with FG 100–125 mg/dL; and 390 whites and 239 blacks with FG ≥126 mg/dL. Among people with diagnosed diabetes, there were 193 whites and 95 blacks with FG <149 mg/dL and 232 whites and 207 blacks with FG ≥149 mg/dL. FG, fasting glucose. **P* values were calculated using the Wilcoxon rank sum (Mann-Whitney *U*) test.

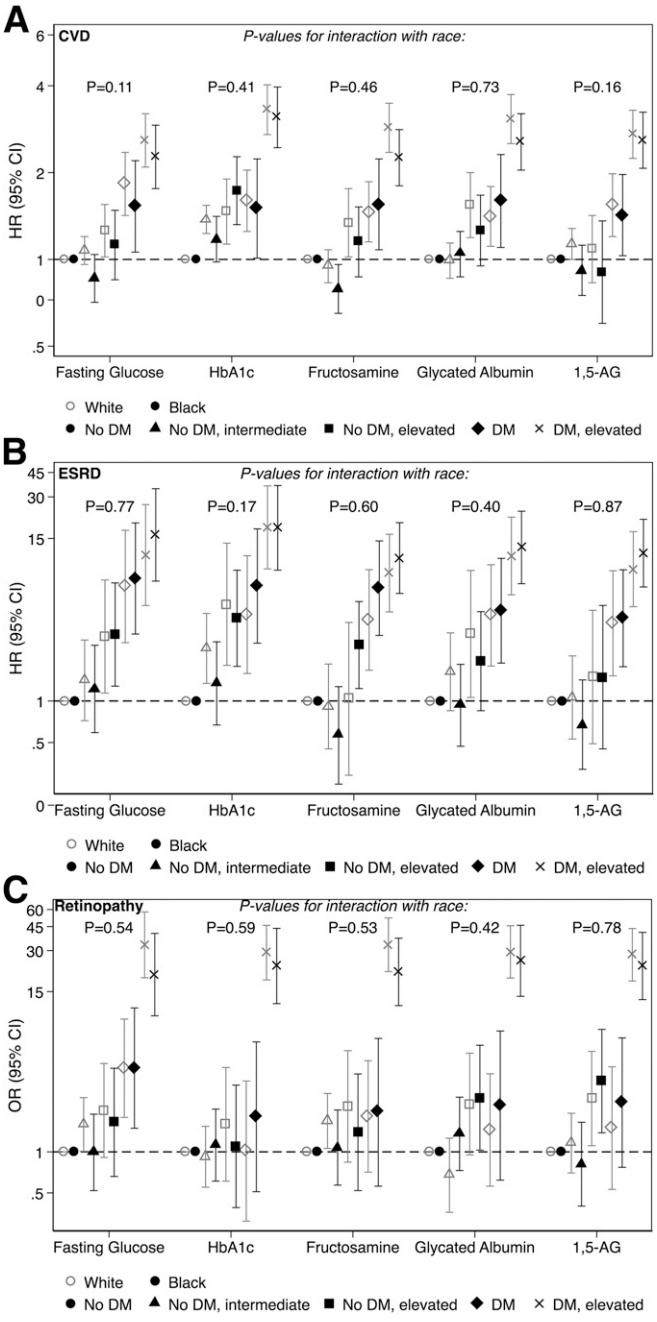


**Figure 1—**Adjusted associations of hyperglycemia with incident CVD, incident ESRD, and prevalent retinopathy by race. Hazard ratios (HRs) for CVD and ESRD were obtained using separate Cox proportional hazards regression models for white and black participants. Odds ratios for prevalent retinopathy were obtained using separate logistic regression models for white and black participants. In models that included both white and black participants, *P* values for interactions were calculated by conducting a likelihood ratio test to compare models with and without terms for the interaction between race and hyperglycemia. Models included adjustment for age; sex (male, female); BMI; $BMI^2$; LDL-c; HDL-c; triglycerides; cholesterol-lowering medication use (yes, no); systolic blood pressure; antihypertensive medication use (yes, no); eGFR; family history of diabetes (yes, no); education level (less than high school, high school or some college, college or more); alcohol consumption (current, former, never); cigarette smoking status (current, former, never); and physical activity level. Categories of diabetes—no diabetes; no diabetes, intermediate levels; no diabetes, elevated levels; diabetes; and diabetes, elevated levels—were defined using the following levels of each biomarker, respectively: fasting glucose: <100, 100–125, ≥126, <149, ≥149 mg/dL; $HbA_{1c}$: <5.7, 5.7–6.4, ≥6.5, <7.0, ≥7.0%; fructosamine: <239.8, 239.8–268.6, ≥268.7, <275.7, ≥275.7 mg/dL; glycated albumin: <13.52, 13.52–15.55, ≥15.56, <16.46, ≥16.46%; 1,5-AG: ≥15.0, 7.9–14.9, <7.9, >9.2, ≤9.2 μg/mL. Gray symbols indicate results for white participants. Black symbols indicate results for black participants. DM, diabetes.

of hyperglycemia with individual CVD outcomes (CHD, stroke, and heart failure) were similar to those of the composite CVD outcome, with no evidence of a race interaction (*P* values for interaction were >0.10 for all biomarkers and all individual outcomes) (Supplementary Tables 2–4).

Patterns of associations of biomarkers of hyperglycemia with ESRD were similar to those for CVD, but the risk of ESRD and strength of association with the biomarkers were substantially higher (Fig. 1 and Supplementary Table 5). The associations followed a linear trend among both whites and blacks ($P_{trend}$ < 0.001 for all). Associations of biomarkers of hyperglycemia with incident ESRD were similar among blacks and whites (*P* values for interaction were >0.15 for all biomarkers) (Fig. 1 and Supplementary Table 5).

Associations of biomarkers of hyperglycemia with prevalent retinopathy were of the particularly largest magnitude among people with the highest levels of hyperglycemia and diagnosed diabetes (Fig. 1 and Supplementary Table 6). Similar to CVD and ESRD, associations of biomarkers of hyperglycemia with retinopathy were similar among blacks and whites (*P* values for interaction were >0.40 for all biomarkers) (Fig. 1 and Supplementary Table 6).

Additional adjustment for continuous fasting glucose or $HbA_{1c}$ substantially attenuated the associations with outcomes, but inferences about racial comparisons of associations were similar (Supplementary Tables 1–6). Results of analyses that censored or excluded participants who developed diabetes after visit 2 were similar to those of the main analyses, with conclusions unchanged (Supplementary Table 7).

## CONCLUSIONS

We found the relative associations of both traditional and nontraditional biomarkers of hyperglycemia with CVD, ESRD, and retinopathy to be similar by race, although blacks had higher levels of hyperglycemia, higher absolute risks of CVD and ESRD, and a higher burden of retinopathy than whites. Our results suggest that the prognostic utility of $HbA_{1c}$ and nontraditional serum biomarkers of hyperglycemia, particularly

at diabetic levels, is similar among both black and white adults.

Our findings support previous studies that have shown similar associations of $HbA_{1c}$ with microvascular and macrovascular disease in blacks and whites (14,15,32,33) and that have recommended using the same $HbA_{1c}$ diagnostic cut points across races/ethnicities (34,35). To our knowledge, this is the first prospective study to conduct head-to-head comparisons of traditional and nontraditional biomarkers of hyperglycemia with major diabetic complications. The similar associations of $HbA_{1c}$ and nontraditional biomarkers with prevalent retinopathy are particularly relevant, because diagnostic cut points for diabetes are largely based on established associations with prevalent retinopathy (36).

Our study supports the idea that racial differences in biomarkers of hyperglycemia may be the result of real differences in glycemia (rather than differences in the behavior of the biomarkers studied), perhaps due to disparities in environmental factors, stress, behavior, diet, physical activity, and lifestyle factors that contribute to differences in circulating nonfasting hyperglycemia in blacks compared with whites (37). In particular, differences in postprandial glucose levels and insulin deficiency may play a role in racial differences in the levels of these biomarkers. Even after controlling for fasting glucose concentrations, we observed here that blacks had higher levels of hyperglycemia compared with whites, as indicated by higher levels of $HbA_{1c}$, fructosamine, and glycated albumin, and lower concentrations of 1,5-AG. As mentioned earlier, fructosamine, glycated albumin, and 1,5-AG are independent of the red blood cells or hemoglobin. Therefore, the observation that these nontraditional serum biomarkers of hyperglycemia exhibit a pattern of racial differences similar to that of $HbA_{1c}$ provides evidence that nonglycemic factors, such as hemoglobin glycation or red cell turnover, may not explain observed racial disparities in the overall population (38). We cannot rule out the possibility that nonglycemic determinants may be important in a subset of the population.

An important consideration in the interpretation of racial differences in biomarker levels is that blacks are at higher risk of diabetes and diabetes-related complications than whites (39,40). We confirm here that blacks had higher incidence rates of CVD and ESRD and a higher prevalence of retinopathy compared with whites in the ARIC Study. It should be noted that some of the racial differences in absolute risk of diabetes complications may be due to differences in both sociodemographics and environmental and lifestyle exposures between blacks and whites, some of which may not be readily measured in epidemiologic studies.

There were several limitations of this study. We had only single measurements of biomarkers of hyperglycemia at baseline, and 2-h glucose measurements were not conducted. There is a lack of evidence regarding the long-term stability of 1,5-AG, although measurements from stored samples were strongly associated with diabetes and $HbA_{1c}$ in the diabetic range (consistent with other studies using fresh samples [41]), and 1,5-AG measured from these stored samples in the ARIC Study was strongly associated with diabetes and its complications, demonstrating construct validity (12,23,42). Age at diabetes diagnosis was not collected at the first or second ARIC examinations, and we therefore were unable to account for potential racial differences in duration of diabetes. However, among participants who had ever reported a diagnosis of diabetes at visit 2 (the baseline examination for this study), 31% (33% of blacks and 30% of whites) did not report diabetes at visit 1, 3 years earlier, and could be considered to have new-onset diabetes. We also cannot rule out the possibility that differences in levels of biomarkers of hyperglycemia by race may be the result of cultural differences by geography, rather than race alone. In the ARIC Study, black participants were recruited almost exclusively from two of the four field centers (Jackson, Mississippi, and Forsyth County, North Carolina). Although this was one of the largest studies to address this research question, it is possible that we may have been underpowered to detect moderate but statistically significant differences in the associations of biomarkers with outcomes in whites versus blacks. However, it is important to point out that comparing the magnitudes of associations in blacks and whites (regardless of statistical significance) is also important when assessing whether there are racial differences in the prognostic value of these biomarkers.

Our study had several important strengths. This is the largest prospective study to rigorously compare associations of $HbA_{1c}$ and nontraditional serum biomarkers of hyperglycemia with long-term complications of diabetes. We also leveraged the large numbers of both black and white participants in the cohort to assess the prognostic implications of racial differences in biomarkers of hyperglycemia. The ARIC Study included rigorous assessment of retinopathy and surveillance of both CVD and ESRD over two decades.

Characterizing associations of these biomarkers of hyperglycemia with hard clinical end points is of the utmost importance because the goal of early diagnosis and improved disease management is prevention of microvascular and macrovascular complications in people with and at risk for diabetes. We found that biomarkers of hyperglycemia similarly reflect a risk of clinical outcomes in both blacks and whites. Our results suggest similar prognostic utility of $HbA_{1c}$, fructosamine, glycated albumin, and 1,5-AG in black and white adults.

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**Duality of Interest.** R.M.B. is a past volunteer of the American Diabetes Association. No other potential conflicts of interest relevant to this article were reported.

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**Author Contributions.** C.M.P. designed the study, interpreted and analyzed the data, and wrote the manuscript. A.R.S., N.M.M., R.M.B., M.E.G., and J.C. interpreted the data and reviewed and edited the manuscript. E.S. designed the study, interpreted the data, and reviewed and edited the manuscript. E.S. is the guarantor of this work and, as such, had full access to all the

data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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