Does Genetic Ancestry Explain Higher Values of Glycated Hemoglobin in African Americans?

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OBJECTIVE—Glycated hemoglobin (HbA_{1c}) values are higher in African Americans than whites, raising the question of whether classification of diabetes status by HbA_{1c} should differ for African Americans. We investigated the relative contribution of genetic ancestry and nongenetic factors to HbA_{1c} values and the effect of genetic ancestry on diabetes classification by HbA_{1c} in African Americans.

RESEARCH DESIGN AND METHODS—We performed a cross-sectional analysis of data from the community-based Atherosclerosis Risk in Communities (ARIC) Study. We estimated percentage of European genetic ancestry (PEA) for each of the 2,294 African Americans without known diabetes using 1,350 ancestry-informative markers. HbA_{1c} was measured from whole-blood samples and categorized using American Diabetes Association diagnostic cut points (<5.7, 5.7–6.4, and ≥6.5%).

RESULTS—PEA was inversely correlated with HbA_{1c} (adjusted $r = -0.07$; $P < 0.001$) but explained <1% of its variance. Age and socioeconomic and metabolic factors, including fasting glucose, explained 13.8% of HbA_{1c} variability. Eleven percent of participants were classified as having diabetes; adjustment for fasting glucose decreased this to 4.4%. Additional adjustment for PEA did not significantly reclassify diabetes status (net reclassification index = 0.034; $P = 0.94$) nor did further adjustment for demographic, socioeconomic, and metabolic risk factors.

CONCLUSIONS—The relative contribution of demographic and metabolic factors far outweighs the contribution of genetic ancestry to HbA_{1c} values in African Americans. Moreover, the impact of adjusting for genetic ancestry when classifying diabetes by HbA_{1c} is minimal after taking into account fasting glucose levels, thus supporting the use of currently recommended HbA_{1c} categories for diagnosis of diabetes in African Americans. ***Diabetes* 60:2434–2438, 2011**

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Glycated hemoglobin (HbA_{1c}) values are significantly higher in African Americans compared with whites even after adjustment for fasting blood glucose (1–4). Whether this racial difference in HbA_{1c} reflects true differences in hyperglycemia or differences in biologic determinants of HbA_{1c} unrelated to hyperglycemia is controversial (5–7), especially in the context of the American Diabetes Association recommendation to use HbA_{1c} ≥6.5% for diagnosis of diabetes (8).

Self-reported African American race is associated with many socioeconomic factors that influence health (9), particularly diabetes risk (10). Genetically derived ancestry can be used to partially deconstruct race as it places each individual on a continuous spectrum of race as opposed to grouping all individuals into one racial group. Therefore, our main objective was to determine the contribution of genetic ancestry to HbA_{1c} in self-reported African Americans. Genetic ancestry may be associated with HbA_{1c} through direct biological effects unrelated to hyperglycemia or indirectly through social and demographic determinants of hyperglycemia (11,12). Because epidemiologic studies report higher HbA_{1c} values in African Americans compared with whites independent of their fasting glucose (1–4), we examine the ancestral genetic contribution to HbA_{1c} after accounting for fasting glucose levels. We hypothesized that *1*) percentage of European ancestry (PEA) explains only a small proportion of the variability in HbA_{1c} in African Americans; *2*) PEA and HbA_{1c} are associated with similar social and biologic factors; and *3*) PEA does not significantly alter diabetes classification by HbA_{1c} independent of fasting glucose levels.

RESEARCH DESIGN AND METHODS

Study population. We included 2,294 African American participants without known diabetes and with a complete set of covariates of interest presenting to visits 1 and 2 of the Atherosclerosis Risk in Communities (ARIC) Study, an ongoing prospective cohort study of adults from four U.S. communities who were 45–64 years of age at the baseline visit in 1987–1989 (13).

Estimation of percentage of European ancestry from ancestry-informative markers. We included single nucleotide polymorphisms (SNPs) whose frequencies differ significantly between Caucasian and African ancestral populations, ancestry-informative markers (AIMs), to estimate the PEA among African Americans, an admixed population (14). The race-specific frequency of each SNP in the AIM panel was estimated using West African and European samples to provide a Bayesian prior for ancestral allele frequencies (14).

Genotyping methods for estimating genetic ancestry in African Americans in the ARIC Study have been described previously (14). In brief, genotyping was performed on stored DNA from visit 1 using the Illumina BeadLab platform (15) at the Center for Inherited Disease Research (Johns Hopkins University). Evaluation of 218,461 blind duplicate genotypes yielded a mismatch rate of 0.1% (14). We used standard filters for quality control of individual SNP genotyping. Samples were excluded for duplicity, low call rate, lack of sex concordance, or excess heterozygosity. We used ANCESTRYMAP software to estimate PEA for each participant (14). Additional detail regarding study population and genotyping is provided in the Supplementary Data.

Measurement of glycated hemoglobin and other variables. HbA_{1c} was measured from frozen, whole-blood samples from visit 2 using ion-exchange, high-performance liquid chromatography (Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer in 2003–2004 and Tosoh G7 Instruments in 2007–2008; Tosoh Corp., San Francisco, CA). These methods are aligned to the Diabetes Control and Complications Trial assay (11). We classified participants according to guidelines from the American Diabetes Association for HbA_{1c}: <5.7%, "lowest risk of diabetes (normoglycemia)"; 5.7–6.4%, "increased risk for diabetes (prediabetes)"; and ≥6.5%, "undiagnosed diabetes" (8).

Participants self-reported race, sex, education (<high school, high school, or >high school), combined family income (<$35,000, ≥$35,000, or unknown), employment (unemployed, employed, or retired), family history of diabetes, and physical activity (using the Baecke questionnaire [16]) at visit 1. Participants self-reported age, smoking status (current/former or never), and alcohol use (current or former/never) at visit 2.

Methods for measurement of glucose (11), lipids (17), BMI, waist-to-hip ratio (18), and blood pressure (19) at visit 2 were described previously. Hypertension was defined by current use of antihypertensive medication or mean of two blood pressure measurements ≥140/90 mmHg.

Statistical analysis. We evaluated for trends across quartiles of PEA using linear regression for means, Cuzick extension of the Wilcoxon rank-sum test for medians (20), and Goodman and Kruskal γ for proportions (21). We used Spearman rank correlation coefficients to evaluate unadjusted linear relationships and Kendall partial τ (ranked partial correlation coefficient) to estimate adjusted correlations (22). We estimated variance in HbA_{1c}, explained by each variable from the square of these correlation coefficients.

For the analyses that examined the impact of covariates, including PEA and fasting glucose, on reclassification of diabetes status, we obtained the adjusted values of HbA_{1c} from several regression models. In Model 1, HbA_{1c} was adjusted for fasting glucose, representing the variation in HbA_{1c} in the population that is independent of hyperglycemia. Model 2 further adjusted for PEA (Model 1 + PEA); Model 3 further adjusted for demographic and socioeconomic factors (Model 2 + age, sex, site, education, income, and employment); and Model 4 included other metabolic risk factors (Model 3 + BMI, waist-to-hip ratio, hypertension status, LDL and HDL cholesterol, triglycerides, family history of diabetes, alcohol use, physical activity, and smoking status). Using the predicted (adjusted) HbA_{1c} values from each model, we obtained the proportion of participants classified into the three HbA_{1c} categories. The base, unadjusted model indicates the classification of diabetes status using measured HbA_{1c}; Model 1 accounts for fasting glucose measured at the same visit; and Model 2 displays the effect of genetic ancestry (PEA) on diabetes status independent of fasting glucose. Recognizing that Model 1 is not directly relevant to clinical practice (as is often the case), as clinicians do not adjust for variables such as fasting glucose in the interpretation of other measures, we use Model 1 to estimate the proportion of variation in HbA_{1c} that is independent of fasting glucose levels and to illustrate whether genetic ancestry can still contribute to HbA_{1c} independent of fasting glucose levels.

We calculated the percentage of participants reclassified for each category as $(N_i - N_0)/N_0$, where N_0 is the number of participants in a given HbA_{1c} category for fasting glucose–adjusted HbA_{1c} (Model 1) and N_i is the number of participants in a given HbA_{1c} category for the i^{th} model (Models 2, 3, or 4). We then compared classification into and out of each of the three categories of diabetes status between the nested models, Models 2 (HbA_{1c} adjusted for fasting glucose and PEA) and 1 (HbA_{1c} adjusted for fasting glucose), with unadjusted (measured) HbA_{1c} as a reference (23): $p_l = [n_{i,k} + n_{i,k+1} - n_{j,k} - n_{j,k+1}]/N_o$ (i = number shifted into a given category, j = number shifted out of the category, k = model, N_o = number in category from reference model, and l = HbA_{1c} category). We then calculated the overall net reclassification index: $P = \sum_{l=1}^{3} p_l$. HbA_{1c} values were log transformed.

We used Stata version 11.1 (StataCorp LP, College Station, TX) for statistical analyses. Institutional review boards approved the study protocol at each study site, and written informed consent was obtained from each participant.

RESULTS

Population characteristics. PEA was right-skewed with a median (interquartile range [IQR]) of 14% (8–22) (Supplementary Fig. 1). Participants with lower PEA were more likely to have less than a high school education and were more likely to have an annual combined family income <$35,000 (Table 1). Median HbA_{1c} and mean BMI were higher in lower quartiles of PEA, and the prevalence of hypertension was highest in the lowest quartile of PEA (Table 1). HbA_{1c} was significantly and positively associated with age, family history of diabetes, prevalence of hypertension, BMI, glucose, LDL cholesterol, and triglycerides and inversely associated with education, income, HDL cholesterol, and current alcohol use (results not shown).

Contribution of PEA to HbA_{1c}. PEA was significantly correlated with HbA_{1c} but explained only 0.5% of the variance in HbA_{1c} on adjusted analyses (Table 2). On the other hand, a single fasting glucose explained the largest fraction of variance in HbA_{1c} (10%). Fasting glucose and PEA were not significantly correlated (r = 0.01; P = 0.63).

Contribution of PEA to classification of diabetes status by recommended HbA_{1c} categories. Two hundred forty-four participants (11%) had diabetes defined by

TABLE 1
Characteristics of African American participants without diabetes in the ARIC Study by quartile of percentage of European ancestry (N = 2,294)

	Q1	Q2	Q3	Q4	P trend*
Percentage of European ancestry	5.2 (3.1–6.5)	10.9 (9.4–12.3)	17.4 (15.4–19.7)	30.4 (25.9–38.1)	–
Age (years)	56 (6)	56 (5)	56 (6)	57 (6)	0.045
Women	380 (66)	365 (63)	363 (64)	362 (63)	0.385
<High school education	418 (73)	404 (70)	385 (68)	288 (50)	<0.001
Unemployed	18 (3)	19 (3)	15 (3)	19 (3)	0.981
Family income <$35,000†	451 (78)	429 (74)	419 (74)	367 (64)	<0.001
Family history of diabetes	137 (24)	153 (27)	146 (26)	131 (23)	0.654
Hypertension	330 (57)	305 (53)	311 (55)	279 (49)	0.010
BMI (kg/m^2)	30.3 (6.6)	30.2 (6.3)	30.0 (6.3)	28.5 (5.6)	<0.001
Waist-to-hip ratio	0.91 (0.08)	0.91 (0.08)	0.91 (0.07)	0.91 (0.08)	0.320
HbA_{1c} (%)	5.8 (5.4–6.1)	5.8 (5.5–6.1)	5.7 (5.4–6.0)	5.6 (5.3–6.0)	<0.001
Fasting glucose (mmol/L)	5.98 (1.07)	6.21 (1.87)	6.10 (1.49)	6.06 (1.43)	0.582
LDL cholesterol (mmol/L)	3.45 (0.98)	3.35 (0.99)	3.50 (0.98)	3.46 (0.98)	0.323
HDL cholesterol (mmol/L)	1.40 (0.43)	1.38 (0.44)	1.38 (0.42)	1.35 (0.42)	0.040
Triglycerides (mmol/L)	1.15 (0.59)	1.16 (0.59)	1.18 (0.54)	1.24 (0.62)	0.011
Current/former smoking	280 (49)	331 (57)	303 (53)	338 (59)	0.003
Current alcohol use	173 (30)	207 (36)	195 (34)	244 (43)	<0.001

Characteristics presented as mean (SD) or median (IQR) for continuous variables and n (%) for categorical variables. *P trend across quartiles estimated using linear regression (means), Cuzick extension of Wilcoxon rank-sum (medians) (20), and Goodman and Kruskal γ (proportions) (21). †Income was unknown for n = 52, 60, 67, and 64 for quartiles 1, 2, 3, and 4, respectively.

TABLE 2
Percentage of variance in HbA_{1c} explained by percentage of European ancestry, demographic, socioeconomic status, and traditional diabetes and cardiovascular disease risk factors

	Unadjusted (%)	Adjusted (%)*
Fasting glucose	24.4	10
BMI	6.6	1.0
Triglycerides	5.0	0.9
Age	1.8	0.6
Percentage of European ancestry	1.2†	0.5‡
Alcohol use§	0.9	0.4
Education‖	1.7	0.3
Hypertension¶	1.6	0.1
Family history of diabetes	0.2	0

*Adjusted percentage of variance is the square of the partial correlation coefficient obtained from a model including the other variables listed in table. †$r = -0.11$ ($P < 0.001$). ‡$r = -0.07$ ($P < 0.001$). §Alcohol use classified as current or former/never. ‖Education classified as < high school, high school, ≥college education. ¶Measured blood pressure ≥140/90 mmHg or report of antihypertensive medication use.

HbA_{1c} ≥6.5%. Accounting for fasting glucose (Model 1) shifted higher HbA_{1c} values downward and lower HbA_{1c} values upward. Consequently, diabetes prevalence decreased to 4.4%, and the prevalence of prediabetes and normal HbA_{1c} increased (Table 3 and Supplementary Fig. 2). Further adjustment for PEA (Model 2) did not reclassify diabetes status substantially (Table 3 and Fig. 1). Normal HbA_{1c} status and prediabetes status changed negligibly with net reclassification of −1% ($P = 0.21$) and 4% ($P < 0.001$), respectively, and there was no net reclassification of diabetes status. Taking these individual category-level changes into account, the overall classification of normal HbA_{1c}, prediabetes, and diabetes status did not change with adjustment of fasting glucose–adjusted HbA_{1c} for PEA (net reclassification index 0.034; $P = 0.94$). Additional adjustment for demographic and socioeconomic factors (Model 3) and traditional metabolic risk factors (Model 4) did not substantially affect reclassification (Table 3 and Fig. 1).

DISCUSSION

In our study, we show that there is not a substantial (<1%) contribution of genetic ancestry to HbA_{1c} among African Americans; thus, ancestral genetic differences are unlikely to significantly explain the observed black–white difference in HbA_{1c}. Furthermore, a recent admixture scan failed to identify an HbA_{1c} locus among African Americans (C.-Y.C., N.M.M., personal communication), suggesting the absence of a genetic variant that varies enough in frequency between whites and African Americans (i.e., a variant of African ancestral origin) to explain the observed racial disparity in HbA_{1c} values.

The hypothesis that HbA_{1c} values are higher among African Americans for reasons unrelated to hyperglycemia stems from evidence that HbA_{1c} values are higher in African Americans when adjusted for fasting glucose and/or postload glucose measurements (1–4). However, HbA_{1c} reflects average glucose over 2–3 months (24) and may reflect racial disparities in socioeconomic and biologic factors. In our study, we show that hyperglycemia, as indicated by a fasting glucose value, accounts for the largest proportion of HbA_{1c}, and that adjustment for fasting glucose results in substantial reclassification of diabetes status. Moreover, after accounting for fasting glucose, additional adjustment for PEA does not significantly reclassify diabetes status.

Strengths. We used of a large number of AIMs (1,350) to estimate PEA in an admixed population well described by AIMs, thus enhancing our ability to accurately assign percentage of genetic ancestry. Nonetheless, in this African American population, PEA was skewed toward lower values; the contribution of PEA to HbA_{1c} might be further clarified in a population with a more uniform distribution of PEA.

Limitations. To evaluate the effect of PEA on classification of diabetes status by HbA_{1c} independent of fasting glucose, we adjust HbA_{1c} for fasting glucose. While not relevant to clinical practice, our approach directly addresses questions surrounding the interpretation of higher HbA_{1c} values in African Americans as representing hyperglycemia because of observed racial differences in HbA_{1c} even after glucose adjustment (6,7).

By estimating the global percentage of European ancestry for each individual, we may overlook local ancestry that could explain the observed racial differences in HbA_{1c}. A recent admixture scan to evaluate for specific regions that associate with HbA_{1c} did not reveal a locus in African Americans (C.-Y.C., N.M.M., personal communication).

Conclusions. In this large community-based population of African Americans, PEA was associated with, but explained

TABLE 3
Reclassification of diabetes status* upon adjustment for fasting glucose, percentage of European ancestry, demographic, socioeconomic status, and traditional diabetes and cardiovascular disease risk factors (N = 2,294)

	Diabetes	Prediabetes	Normal	Adjustments
Measured HbA_{1c}	244 (10.6)	824 (35.9)	1,226 (53.4)	None
Adjusted HbA_{1c}				
Model 1	102 (4.4)	883 (38.5)	1,309 (57.1)	Fasting glucose
Model 2	104 (4.5)	940 (41.0)	1,250 (54.5)	Fasting glucose, PEA
Model 3	113 (4.9)	917 (40.0)	1,264 (55.1)	Fasting glucose, PEA, age, sex, site, SES†
Model 4	115 (5.0)	955 (41.6)	1,224 (53.4)	Fasting glucose, PEA, age, sex, site, SES†, BMI, WHR, hypertension‡, LDL and HDL cholesterol, triglycerides, family history of diabetes, physical activity§, alcohol use‖, smoking¶

SES, socioeconomic status; WHR, waist-to-hip ratio. *Diabetes, HbA_{1c} ≥6.5%; prediabetes, HbA_{1c} 5.7–6.4%; normal, HbA_{1c} <5.7%. †Employment (unemployed, employed, or retired), income (combined family income <$35,000, ≥$35,000, or unknown), and education (<high school, high school, or ≥college education). ‡Measured blood pressure ≥140/90 mmHg or report of antihypertensive medication use. §Leisure sport activity assessed with the Baecke questionnaire (16). ‖Alcohol use classified as current or former/never. ¶Smoking classified as current/former or never.

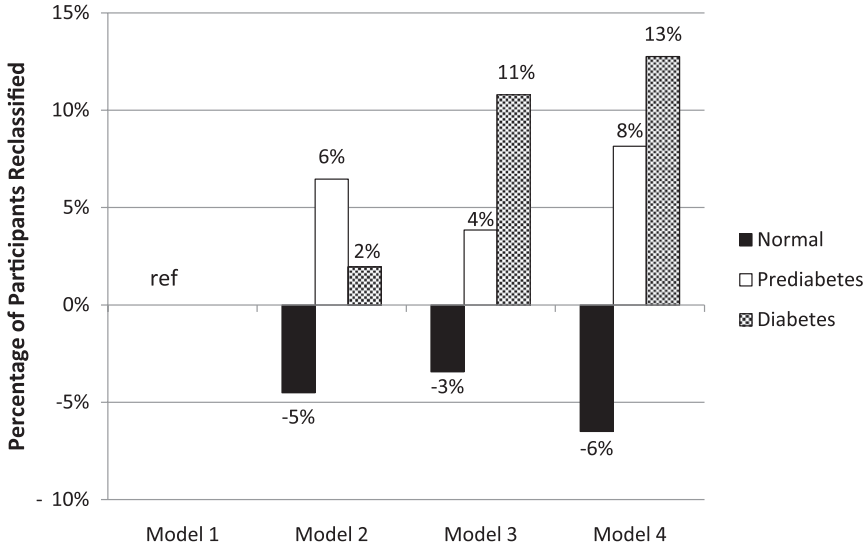

FIG. 1. Percent reclassification of diabetes status relative to fasting glucose–adjusted HbA_{1c}. Percentage of participants reclassified by HbA_{1c} as having normal HbA_{1c} (<5.7%), prediabetes (5.7–6.4%), or diabetes (≥6.5%). Model 1 is the reference model. Bars for Models 2, 3, and 4 represent percentages of participants reclassified into each diabetes category based on predicted HbA_{1c} relative to fasting glucose–adjusted HbA_{1c}. Black bars, normal; white bars, prediabetes; hatch-marked bars, diabetes. Numbers above/below bars represent numbers of participants shifted into or out of a given category. Model 1, adjustment for fasting glucose; Model 2, additional adjustment for percentage of European ancestry; Model 3, additional adjustment for age, sex, site, employment (unemployed, employed, or retired), combined family income (< or ≥$35,000), and education (<high school, high school, or ≥college education); and Model 4, additional adjustment for BMI, waist-to-hip ratio, hypertension status (measured blood pressure 140/90 or report of antihypertensive medication use), LDL and HDL cholesterol, triglycerides, family history of diabetes, physical activity (assessed with the Baecke questionnaire [16]), alcohol use (current or former/never), and smoking (current/former or never).

little of, the variance in HbA_{1c}. Importantly, after accounting for a single fasting glucose measurement, PEA did not significantly affect classification of diabetes status using HbA_{1c}.

Our results suggest that elevated HbA_{1c} values in African Americans are likely not determined by ancestral genetic differences in the biology of HbA_{1c} but instead may reflect a true disparity in glycemia likely mediated by socioeconomic and other downstream factors. These findings support the use of the currently recommended HbA_{1c} categories for diagnosis of diabetes and classification of future diabetes risk (8) in African Americans. Consistent with this, previous studies have demonstrated that HbA_{1c} is equally predictive of cardiovascular disease and all-cause mortality in African Americans and whites (11). Future research should address the environmental reasons for disparities by PEA among African Americans and focus on methods to eliminate these disparities.

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N.M.M. refined the study design, analyzed data, and wrote the manuscript. W.H.L.K. refined the study design and reviewed and edited the manuscript. J.M.C. and F.L.B. reviewed and edited the manuscript. C.-Y.C. analyzed data and reviewed the manuscript. J.S.P. reviewed and edited the manuscript. E.S. refined the study design and reviewed and edited the manuscript.

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