



# Differences in Hemoglobin A<sub>1c</sub> Between Hispanics/Latinos and Non-Hispanic Whites: An Analysis of the Hispanic Community Health Study/Study of Latinos and the 2007–2012 National Health and Nutrition Examination Survey

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## OBJECTIVE

To determine whether, after adjustment for glycemia and other selected covariates, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) differed among adults from six Hispanic/Latino heritage groups (Central American, Cuban, Dominican, Mexican, Puerto Rican, and South American) and between Hispanic/Latino and non-Hispanic white adults without self-reported diabetes.

## RESEARCH DESIGN AND METHODS

We performed a cross-sectional analysis of data from 13,083 individuals without self-reported diabetes from six Hispanic/Latino heritage groups, enrolled from 2008 to 2011 in the Hispanic Community Health Study/Study of Latinos, and 2,242 non-Hispanic white adults enrolled during the 2007–2012 cycles of the National Health and Nutrition Examination Survey. We compared HbA<sub>1c</sub> levels among Hispanics/Latinos and between Hispanics/Latinos and non-Hispanic whites before and after adjustment for age, sex, fasting (FPG) and 2-h post-oral glucose tolerance test (2hPG) glucose, anthropometric measurements, and selected biochemical and hematologic variables and after stratification by diabetes status: unrecognized diabetes (FPG ≥7.1 mmol/L or 2hPG ≥11.2 mmol/L), prediabetes (FPG 5.6–7.0 mmol/L or 2hPG 7.8–11.1 mmol/L), and normal glucose tolerance (FPG <5.6 mmol/L and 2hPG <7.8 mmol/L).

## RESULTS

Adjusted mean HbA<sub>1c</sub> differed significantly across all seven groups ( $P < 0.001$ ). Non-Hispanic whites had significantly lower HbA<sub>1c</sub> ( $P < 0.05$ ) than each individual Hispanic/Latino heritage group. Upon stratification by diabetes status, statistically significant differences ( $P < 0.001$ ) in adjusted mean HbA<sub>1c</sub> persisted across all seven groups.

## CONCLUSIONS

HbA<sub>1c</sub> differs among Hispanics/Latinos of diverse heritage groups and between non-Hispanic whites and Hispanics/Latinos after adjustment for glycemia and other covariates. The clinical significance of these differences is unknown.

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Hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) is a widely used and accepted test for the diagnosis of prediabetes and diabetes and the assessment of glycemic control in patients with diabetes (1). Due to the erythrocytes' long lifetime and the slow, continuous, and essentially irreversible characteristics of the glycation process, HbA<sub>1c</sub> reflects the average blood glucose concentration for the preceding 2–3 months (1–4).

Prior studies have suggested and demonstrated that HbA<sub>1c</sub> may vary across racial/ethnic groups after adjustment for plasma glucose levels (5–12). In individuals without diabetes, two analyses based on the National Health Nutrition and Examination Survey (NHANES) have reported higher HbA<sub>1c</sub> levels among African Americans and Mexican Americans compared with non-Hispanic whites, and these differences persisted after adjustment for age, sex, and anthropometric, biological, or other covariates (7,8). Another analysis based on NHANES demonstrated differences in the increment in HbA<sub>1c</sub> with each decade of age among Mexican Americans, non-Hispanic blacks, and non-Hispanic whites (9). In the Diabetes Prevention Program (10), non-Hispanic white individuals with impaired glucose tolerance had baseline HbA<sub>1c</sub> levels 0.15–0.40% lower than individuals from other racial/ethnic groups (including Hispanics) before and after adjustment for glucose levels and other covariates. Another study of individuals with diabetes reported HbA<sub>1c</sub> 0.3–0.8% higher among those with ancestry other than non-Hispanic white, despite the fact that individuals from diverse racial/ethnic groups had similar mean plasma glucose levels (11).

The studies cited above reported differences in HbA<sub>1c</sub> between Hispanics/Latinos and non-Hispanic whites (with or without diabetes) that accounted for a variety of demographic, anthropometric, and biological covariates (7–11). Some of these studies specifically reported differences in HbA<sub>1c</sub> between non-Hispanic whites and Mexican Americans (7–9). Other studies did not clearly specify the composition of the Hispanic group included or account for differences by Hispanic/Latino heritage (10,11). Considering the diverse genetic admixture and socioeconomic, cultural, geographic, history, and migration patterns that characterize each U.S. Hispanic/Latino

group, it cannot be assumed that the previously reported differences in HbA<sub>1c</sub> compared with non-Hispanic whites apply to all heritage groups. One study suggested that HbA<sub>1c</sub> may differ between Dominicans and other Hispanics/Latinos with diabetes (heritage groups not specified) (12). However, it is unknown whether this difference is also observed among other Hispanic/Latino heritage groups—independent of glycemic status—and what factors may explain those differences.

Our analysis was based on data from the baseline exam (2008–2011) of the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) and the NHANES 2007–2012 exam cycles. The purpose of this analysis was to compare mean HbA<sub>1c</sub> levels (before and after adjustment for selected covariates) among six different Hispanic/Latino heritage groups represented in the HCHS/SOL, between Hispanics/Latinos (as a unitary group) from the HCHS/SOL and non-Hispanic whites from NHANES, and between individual Hispanic/Latino heritage groups and non-Hispanic whites from NHANES. In addition, these comparisons would be further stratified by diabetes status category (normal glucose tolerance [NGT], prediabetes, and unrecognized diabetes) based on the American Diabetes Association fasting plasma glucose (FPG) and 2-h post-oral glucose tolerance test plasma glucose (2hPG). Understanding the potential differences in HbA<sub>1c</sub> levels among different Hispanics/Latinos heritage groups would have important clinical implications in the use of this biomarker as a prediabetes or diabetes diagnostic criterion and in the monitoring of glycemic control in Hispanics/Latinos with diabetes.

## RESEARCH DESIGN AND METHODS

### Sampling and Examination in the HCHS/SOL

The HCHS/SOL study methods and sampling designs have previously been published (13,14). Briefly, the HCHS/SOL is a longitudinal, population-based study with objectives including description of the prevalence of selected chronic diseases, identifying their risk and/or protective factors, and quantifying incidence of fatal and nonfatal cardiovascular and pulmonary events and all-cause mortality. From March 2008 to June 2011, 16,415 persons, aged 18–74 years at the time of screening, who self-identified as Hispanics/

Latinos were examined. Participants were recruited after a multistage probability sampling of the communities in San Diego, CA; Chicago, IL; Miami, FL; and the Bronx, NY. The study was approved by each of the field centers' and coordinating center's institutional review boards. All enrolled individuals provided signed informed consent. Approximately 93% of participants completed all interviews and tests.

In the HCHS/SOL, interviews (including demographic and self-identified Hispanic/Latino heritage group), phlebotomy, processing of biospecimens, and systolic blood pressure (SBP), diastolic blood pressure (DBP), and anthropometric measurements (including BMI) were performed by trained and certified staff following a standard protocol (13). Further detailed information is available at [www.csc.ccc.edu/hchs](http://www.csc.ccc.edu/hchs). Participants were asked to consume only water and necessary medications after 10:00 P.M. the night before the baseline visit and to refrain from smoking or physical activity before undergoing the fasting examination procedures. The examination of pregnant women was postponed until 3 months postpartum. Individuals with other chronic diseases or health conditions were not excluded from participating. All participants had FPG and HbA<sub>1c</sub> measured. After the initial venipuncture, those without self-reported diabetes or FPG  $\leq$ 150 mg/dL (8.4 mmol/L) underwent a standard 75-g 2-h oral glucose tolerance test (OGTT), from which a 2hPG was obtained. There were no other exclusions for the OGTT.

### Sampling and Examination in NHANES

Using a 2-year-cycle multistage probability sampling design, NHANES is conducted to describe health conditions and disease burden among a representative sample of the U.S. civilian noninstitutionalized population. During the 2007–2008, 2009–2010, and 2011–2012 cycles, 29,353 individuals were interviewed and examined (15). Participants' demographic and anthropometric characteristics, SBP, DBP, and a blood sample were obtained following a standard protocol (16,17). All participants had HbA<sub>1c</sub> measured. FPG was obtained after an 8- to 24-h fast from individuals who were randomly assigned to the morning examination; a 75-g OGTT was performed only on these individuals to obtain 2hPG. Pregnant

women and individuals with cancer, hemophilia, and other selected conditions were included in the examination but did not undergo the OGTT. Further NHANES information is available at <http://www.cdc.gov/nchs/nhanes.htm>.

### Laboratory Methodology

Biospecimens for the select biochemical variables in both the HCHS/SOL and NHANES 2007–2012 cycles were processed and analyzed by the Advanced Research and Diagnostics Laboratory at the University of Minnesota following similar laboratory methodology and quality-control protocols. Plasma glucose was measured in EDTA-anticoagulated plasma using a hexokinase enzymatic method; alanine aminotransferase (ALT), aspartate aminotransferase (AST), and  $\gamma$ -glutamyl aminotransferase (GGT) were measured using an  $\alpha$ -ketoglutaric enzymatic method on a Roche Modular P chemistry analyzer (Roche Diagnostics, Indianapolis, IN). A hemogram (including direct measures of hemoglobin [Hgb] and mean corpuscular volume [MCV]) was measured in EDTA whole blood using a Sysmex XE-2100 instrument (Sysmex America, Inc., Mundelein, IL). HbA<sub>1c</sub> was measured in EDTA-anticoagulated whole blood using a Tosoh G7 automated, non-porous ion-exchange high-performance liquid chromatography analyzer. Serum insulin was measured using an ELISA assay (Mercodia AB, Uppsala, Sweden) (from 1 October 2006 to 28 October 2009) and a sandwich immunoassay method with the Roche Elecsys 2010 analyzer (Roche Diagnostics) (from 29 October 2009 to 30 June 2011). The glomerular filtration rate was estimated (eGFR) using the MDRD equation.

### Definition of Hispanic/Latino Heritage and Non-Hispanic White Categories

In the HCHS/SOL, participants were asked what Hispanic/Latino group best described their heritage (Central American, Cuban, Dominican, Mexican, Puerto Rican, South American, more than one heritage, or other) and, in addition to being of Hispanic/Latino heritage, which other categories they would use to describe themselves (American Indian or Alaskan Native, Asian, Native Hawaiian or Pacific Islander, black or African American, white, more than one race, unknown, or not reported [13, [www.csc.unc.edu/hchs](http://www.csc.unc.edu/hchs)]). Approximately 54% of HCHS/SOL participants responded “unknown/refused”

or “multiracial” to the questions about race. Therefore, analyses based on race were not performed within the context of Hispanic/Latino heritage. In the NHANES, participants were asked if they considered themselves to be Hispanic or Latino, and what race or races they considered themselves to be: American Indian or Alaskan Native, Asian, black or African American, native Hawaiian or Pacific Islander, white, other, unknown, or refused (16).

### Definition of NGT, Prediabetes, and Unrecognized Diabetes

To account for the possible confounding effects of glycemic treatment on HbA<sub>1c</sub>, we excluded participants with self-reported diabetes and/or those who were using antihyperglycemia medications from the analysis. Using FPG and 2hPG American Diabetes Association criteria (1,18), we classified the remaining participants as having unrecognized diabetes (FPG  $\geq$  7.1 mmol/L or 2hPG  $\geq$  11.2 mmol/L), prediabetes (impaired fasting glucose, FPG 5.6–7.0 mmol/L, or impaired glucose tolerance, 2hPG 7.8–11.1 mmol/L), or NGT (FPG  $<$  5.6 mmol/L and 2hPG  $<$  7.8 mmol/L). We applied the same inclusion and exclusion criteria, definitions of analysis variables, and methods of statistical analyses to the data obtained from both HCHS/SOL and NHANES.

In HCHS/SOL, the total number of enrolled individuals was 16,415 (19). The weighted mean age was 43.2 years (95% CI 43.1–43.3), and  $\sim$ 21% were born in the U.S. mainland, Puerto Rico, or other U.S. territories. Of the total, 14,071 individuals reported no history of diabetes or use of antihyperglycemia medications. Individuals with an eGFR  $<$  60 mL/min/1.73 m<sup>2</sup> ( $N = 471$ ), with age outside of the sampling required range ( $N = 5$ ), or who self-identified with more than one Hispanic/Latino heritage group ( $N = 437$ ) were excluded. Also, 75 individuals were excluded due to missing data on HbA<sub>1c</sub> ( $N = 51$ ) or Hispanic/Latino heritage group data ( $N = 24$ ). Therefore, a total of 13,083 HCHS/SOL participants who met all the criteria were included in the analyses.

In NHANES, a total of 29,353 individuals were examined during the 2007–2008, 2009–2010, and 2011–2012 exams (15). Of that total, 13,133 individuals were examined in the morning in the fasting state. Of these, 11,970 reported

no history of diabetes or use of antihyperglycemia medications. Individuals with age outside of the HCHS/SOL age range ( $N = 5,142$ ), with an eGFR  $<$  60 mL/min/1.73 m<sup>2</sup> ( $N = 589$ ), who self-identified as other than non-Hispanic white ( $N = 3,648$ ), who did not undergo an OGTT ( $N = 347$ ), and with missing HbA<sub>1c</sub> ( $N = 2$ ) were excluded. A total of 2,242 non-Hispanic whites (49.7% males) met all the criteria and were included in the analyses.

### Statistical Analysis

Weighted means (or percentages) and 95% CIs of characteristics were estimated by Hispanic/Latino heritage group, for everyone in HCHS/SOL, and for non-Hispanic whites in NHANES after merging of the two studies’ data sets. The adjusted conditional marginal means of HbA<sub>1c</sub> for each Hispanic/Latino heritage group and non-Hispanic whites were obtained from linear regression models that included various covariates: age, sex, BMI, FPG, 2hPG, fasting serum insulin (FSI), Hgb, MCV, SBP, DBP, ALT, AST, and GGT. The selection of these covariates was based on previously documented effect or relationship with HbA<sub>1c</sub> (10,11,20). We repeated this analysis stratifying by diabetes status categories (NGT, prediabetes, and unrecognized diabetes). We conducted an omnibus test for differences in Hispanic/Latino heritage groups using a Wald  $F$  test. For differences that were significant based on the Wald  $F$  test, we conducted pairwise testing on every combination of Hispanic/Latino heritage group. The  $\beta$ -coefficients (95% CI) to predict HbA<sub>1c</sub> and  $P$  values were obtained from the merged HCHS/SOL and NHANES samples. We also calculated the mean HbA<sub>1c</sub> for each HCHS/SOL Hispanic/Latino heritage group in unadjusted linear regression models and with various levels of adjustment to investigate the extent to which confounders might explain unadjusted differences in HbA<sub>1c</sub>.

The analyses described above were also performed in each data set separately. The results were very similar and have been included in Supplementary Tables 2–4 and Supplementary Fig. 1.

All statistical analyses were performed using SAS, version 9.2, and SAS-callable SUDAAN, version 11.0.1, to account for the complex sampling

designs, including unequal probabilities of selection, oversampling, and nonresponse.

**RESULTS**

Of the 13,083 HCHS/SOL individuals who met the inclusion criteria, 47.9% were men, and the self-identified Hispanic/Latino heritage group breakdown was 40.0% Mexican, 20.8% Cuban, 15.6% Puerto Rican, 10.3% Dominican, 7.9% Central American, and 5.4% South American. Table 1 describes the demographic, anthropometric, and biochemical characteristics of HCHS/SOL participants according to Hispanic/Latino heritage group and non-Hispanic white participants from NHANES. All the characteristics were statistically different ( $P < 0.05$ ) across groups.

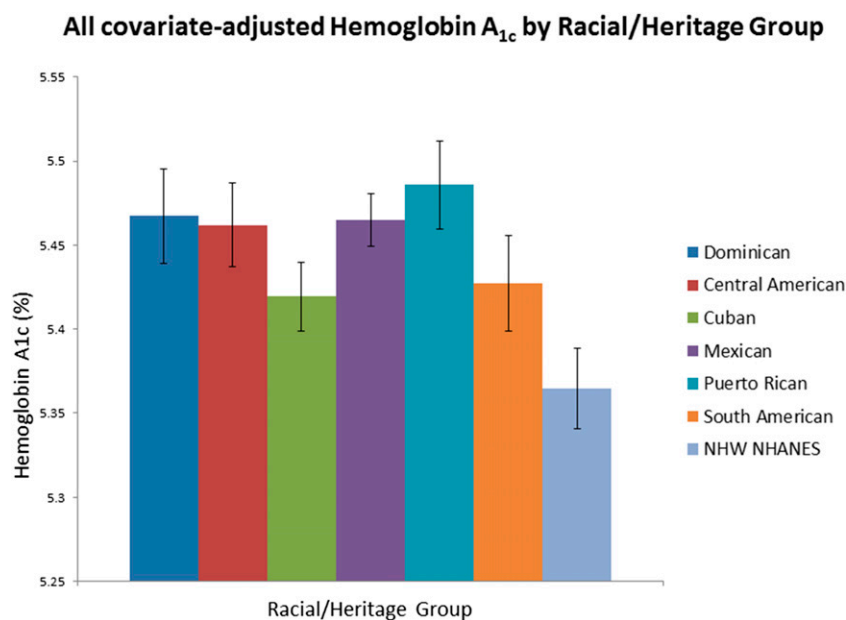
Figure 1 illustrates all covariate-adjusted mean (95% CI) HbA<sub>1c</sub> levels by racial/ethnic group. The all covariate-adjusted mean HbA<sub>1c</sub> was significantly different among Hispanic/Latino heritage groups (Wald  $F$  test,  $P < 0.001$ ). Based on pairwise comparisons, individuals of Cuban heritage had significantly ( $P < 0.05$ ) lower adjusted mean HbA<sub>1c</sub> levels (5.42% [95% CI 5.40–5.44]) compared with other individual Hispanic/Latino heritage groups, except those of South American heritage (5.43% [95% CI 5.40–5.46]). Based on pairwise comparisons, non-Hispanic whites had significantly lower (5.36% [95% CI 5.34–5.39]) adjusted mean HbA<sub>1c</sub> levels compared with each Hispanic/Latino heritage group (each  $P < 0.05$ ). We added diabetes status categories (based on FPG and 2hPG) to the adjustment model, and the differences across the seven groups persisted and remained statistically significant (data not shown).

In Table 2, we examined the differences in all covariate-adjusted mean HbA<sub>1c</sub> levels by diabetes status category. Within the NGT category, the all covariate-adjusted mean HbA<sub>1c</sub> level differed significantly according to Hispanic/Latino heritage groups (Wald  $F$  test,  $P < 0.001$ ). Pairwise comparisons showed that this difference was attributable to significant differences ( $P < 0.05$ ) in HbA<sub>1c</sub> of Cuban versus Mexican and Puerto Rican heritage groups (adjusted mean HbA<sub>1c</sub> difference 0.04–0.05% [National Glycohemoglobin Standardization Program (NGSP) units]), and Puerto Rican vs. South American heritage groups (adjusted mean HbA<sub>1c</sub> difference

**Table 1—Participants' characteristics by Hispanic/Latino heritage group from the HCHS/SOL and non-Hispanic whites from NHANES**

Characteristics of participants	HCHS/SOL: March 2008–June 2011							NHANES 2007–2012: non-Hispanic white (N = 2,242)
	Dominican (N = 1,220)	Central American (N = 1,485)	Cuban (N = 1,991)	Mexican (N = 5,426)	Puerto Rican (N = 2,016)	South American (N = 945)	All Hispanics/Latinos (N = 13,083)	
Men, %	38.7 (34.7–42.8)	47.6 (44.2–51.0)	52.5 (50.2–54.7)	46.4 (44.4–48.5)	51.9 (48.7–55.1)	45.2 (41.3–49.2)	47.9 (46.7–49.1)	49.7 (47.8–51.5)
Age, years	37.2 (35.9–38.4)	38.2 (37.3–39.2)	44.3 (43.4–45.3)	37.0 (36.3–37.7)	40.1 (39.1–41.1)	41.5 (40.0–43.0)	39.1 (38.6–39.5)	44.0 (43.1–44.9)
BMI, kg/m <sup>2</sup>	29.2 (28.6–29.9)	28.8 (28.4–29.2)	28.7 (28.4–29.0)	28.9 (28.6–29.2)	30.1 (29.6–30.6)	27.8 (27.4–28.3)	29.0 (28.9–29.2)	28.1 (27.8–28.5)
HbA <sub>1c</sub> , %	5.45 (5.41–5.49)	5.50 (5.45–5.54)	5.49 (5.46–5.53)	5.51 (5.47–5.54)	5.51 (5.48–5.54)	5.46 (5.42–5.49)	5.49 (5.47–5.50)	5.37 (5.34–5.40)
HbA <sub>1c</sub> , mmol/mol	36.1 (35.6–36.6)	36.6 (36.1–37.1)	36.6 (36.2–37.0)	36.7 (36.4–37.1)	36.7 (36.4–37.1)	36.2 (35.8–36.6)	36.5 (36.3–36.7)	35.2 (34.9–35.5)
FPG, mmol/L	5.16 (5.10–5.21)	5.33 (5.26–5.39)	5.37 (5.32–5.42)	5.35 (5.29–5.41)	5.27 (5.22–5.32)	5.28 (5.22–5.33)	5.31 (5.28–5.34)	5.34 (5.31–5.38)
2hPG, mmol/L	6.27 (6.11–6.42)	6.52 (6.37–6.67)	6.78 (6.64–6.92)	6.50 (6.40–6.60)	6.32 (6.19–6.45)	6.56 (6.36–6.77)	6.49 (6.43–6.55)	6.07 (5.98–6.17)
FSL, pmol/L	65.2 (61.7–68.8)	78.6 (75.4–81.8)	78.3 (75.0–81.7)	75.4 (72.3–78.6)	76.9 (73.0–80.8)	66.4 (62.6–70.3)	75.0 (73.3–76.6)	67.0 (63.2–70.9)
Hgb, g/dL	13.5 (13.4–13.7)	14.0 (13.9–14.2)	14.2 (14.1–14.3)	14.0 (13.9–14.0)	13.9 (13.8–14.0)	13.8 (13.7–13.9)	14.0 (13.9–14.0)	14.6 (14.49–14.7)
MCV, fL	88.0 (87.6–88.5)	88.8 (88.3–89.2)	90.4 (90.0–90.7)	89.0 (88.7–89.3)	89.0 (88.6–89.4)	89.7 (89.2–90.2)	89.2 (89.0–89.3)	89.9 (89.5–90.2)
SBP, mmHg	119.6 (118.3–121.0)	119.7 (118.6–120.8)	122.8 (121.8–123.7)	115.6 (114.9–116.2)	120.3 (119.4–121.3)	117.5 (116.1–118.9)	118.5 (118.1–119.0)	117.5 (116.7–118.4)
DBP, mmHg	73.6 (72.8–74.4)	72.7 (71.9–73.5)	74.9 (74.3–75.6)	69.5 (69.0–70.0)	73.2 (72.6–73.9)	70.1 (69.1–71.1)	71.9 (71.5–72.2)	70.0 (69.1–70.9)
ALT, units/L	22.7 (21.4–24.0)	28.7 (27.3–30.0)	26.8 (25.7–27.8)	30.2 (28.9–31.4)	27.7 (25.9–29.5)	26.8 (25.0–28.7)	28.0 (27.4–28.6)	25.2 (24.5–25.8)
AST, units/L	22.1 (21.2–22.9)	24.4 (23.7–25.1)	23.4 (23.0–23.9)	25.3 (24.5–26.1)	25.9 (24.6–27.1)	24.0 (22.9–25.1)	24.6 (24.1–25.0)	24.9 (24.4–25.3)
GGT, units/L	25.5 (23.8–27.1)	35.2 (32.2–38.1)	33.2 (30.4–35.9)	32.5 (31.0–34.1)	36.3 (33.3–39.3)	28.7 (25.8–31.5)	32.3 (31.3–33.3)	25.4 (24.3–26.6)

Data are means (95% CI). Data were weighted and adjusted to the 2010 U.S. Census. All variables were significantly different ( $P < 0.05$ ) across all seven racial/ethnic groups.



**Figure 1**—Error bars represent 95% CIs. The covariates included sex, age, BMI, FPG, 2hPG, FSI, Hgb, MVC, SBP, DBP, ALT, AST, and GGT. The HCHS/SOL data were collected from March 2008 to June 2011, and NHANES data were collected from 2007 to 2012. NHW, non-Hispanic white.

0.04% [NGSP units]). The all covariate-adjusted mean HbA<sub>1c</sub> of non-Hispanic whites differed significantly from that of individual Hispanic/Latino heritage group (difference 0.05–0.10% [NGSP units], each  $P < 0.05$ ).

Within the prediabetes category, the all covariate-adjusted mean HbA<sub>1c</sub> differed significantly according to Hispanic/Latino heritage group (Wald *F* test,  $P < 0.001$ ). The pairwise comparisons showed that this difference was attributable to significant differences ( $P < 0.05$ ) in the HbA<sub>1c</sub> levels between the Cuban and the Central American, Dominican, and Mexican heritage groups (difference 0.06–0.10% [NGSP units]). The all covariate-adjusted mean HbA<sub>1c</sub> also differed significantly between non-Hispanic whites and each Hispanic/Latino heritage group (difference 0.09–0.19% [NGSP units], each  $P < 0.05$ ).

Within the unrecognized diabetes category, the all covariate-adjusted mean HbA<sub>1c</sub> level differed significantly among Hispanics/Latinos (Wald *F* test,  $P < 0.001$ ). This difference was attributable to significant differences between the Cuban and the Central American and Puerto Rican heritage groups (difference 0.22–0.25% [NGSP units],  $P < 0.05$ ). The difference in all covariate-adjusted HbA<sub>1c</sub> was significant between

non-Hispanic whites and Central American, Dominican, Mexican, and Puerto Rican heritage groups (difference 0.25–0.39% [NGSP units], each  $P < 0.05$ ).

In a separate analysis, we compared the all covariate-adjusted mean HbA<sub>1c</sub> level of the HCHS/SOL (unitary group), the HCH/SOL Mexican heritage group, and the NHANES non-Hispanic whites and performed a parallel analysis comparing the NHANES Mexican Americans, NHANES Hispanics (unitary group), and NHANES non-Hispanic whites. The differences between HCHS/SOL and NHANES non-Hispanic whites were similar, statistically significant, and in the same direction as the differences between NHANES Mexican American/Hispanic and non-Hispanic whites (data not shown).

We estimated the  $\beta$  of the regression model including all covariates associated with HbA<sub>1c</sub> for the combined HCHS/SOL and NHANES data without stratification by glycemic category (Supplementary Table 1). A  $\beta$  indicates the difference in HbA<sub>1c</sub> level for each category of categorical variables (e.g., heritage, sex) or for each one-unit-higher level of continuous variables (e.g., BMI, FPG). The variable is considered statistically significant when the CI does not contain zero. Age, sex, age \* sex interaction term, BMI, FPG, and 2hPG

were associated with HbA<sub>1c</sub> across all seven groups. When the regression model was evaluated in HCHS/SOL and NHANES separately (Supplementary Table 2), the same associations were observed, except the age \* sex interaction, and FSI was associated with HbA<sub>1c</sub> among Hispanics/Latinos but not among non-Hispanic whites.

Table 3 illustrates the model of adjustments of mean HbA<sub>1c</sub> according to covariates included in the combined model and by racial/heritage group. The largest changes in mean HbA<sub>1c</sub> occurred after adjustment for age, FPG, and 2hPG.

## CONCLUSIONS

The observations described in this analysis both confirm previous findings and offer new light on population-based differences in HbA<sub>1c</sub>. Compared with Hispanics/Latinos (as a group), non-Hispanic whites demonstrated significantly lower adjusted mean HbA<sub>1c</sub> levels within each glycemic category. The difference in adjusted mean HbA<sub>1c</sub> level between non-Hispanic whites and Hispanics/Latinos ranged from 0.08 to 0.24% (NGSP units) across diabetes status categories. Mean adjusted HbA<sub>1c</sub> levels also varied among Hispanic/Latino heritage groups, with differences ranging from 0.04 to 0.25% (NGSP units) across diabetes status categories. The largest difference in mean adjusted HbA<sub>1c</sub> (between non-Hispanic whites and Hispanics/Latinos and among Hispanic/Latino heritage groups or across the seven groups) was observed in the unrecognized diabetes category. Neither the difference in HbA<sub>1c</sub> between non-Hispanic whites and Hispanics/Latinos nor the differences among the Hispanic/Latino heritage groups could be explained by controlling for age, sex, BMI, plasma glucose, or hematologic or biochemical covariates. To the best of our knowledge, these are new findings that have not been described and compared before in a large sample of U.S. Hispanic/Latino adults of diverse heritage groups.

Our results confirm that there are statistically significant differences in mean HbA<sub>1c</sub> levels between Hispanics/Latinos (as a unitary group) and non-Hispanic whites with NGT, prediabetes, and unrecognized diabetes after adjustment for age, sex, BMI, FPG, 2hPG, FSI, Hgb, MCV,



**Table 2—All covariate-adjusted mean HbA<sub>1c</sub> levels\* by racial/heritage group and diabetes status category**

Diabetes status category†	HCHS/SOL: March 2008–June 2011										NHANES 2007–2012:	
	Dominican (N = 1,220)	Central American (N = 1,485)	Cuban (N = 1,991)	Mexican (N = 5,426)	Puerto Rican (N = 2,016)	South American (N = 945)	All Hispanics/Latinos (N = 13,083)	non-Hispanic white (N = 2,242)				
NGT‡	823; 5.33 (5.30–5.36)‡	919; 5.33 (5.30–5.36)‡	1,187; 5.31 (5.28–5.34)§  #	3,274; 5.35 (5.33–5.37)‡	1,256; 5.35 (5.33–5.38)¶  #	607; 5.32 (5.29–5.35)‡	8,066; 5.34 (5.32–5.35)	1,329; 5.26 (5.24–5.28)				
Prediabetes‡	327; 5.66 (5.61–5.72)‡	460; 5.62 (5.58–5.66)‡	663; 5.56 (5.53–5.59)*†  #	1,742; 5.62 (5.59–5.64)‡	613; 5.61 (5.56–5.67)‡	290; 5.58 (5.53–5.63)‡	4,095; 5.60 (5.59–5.62)	797; 5.47 (5.43–5.51)				
Unrecognized diabetes‡	70; 6.33 (6.20–6.46)‡	106; 6.44 (6.37–6.56)‡	141; 6.19 (6.06–6.32)  ††	410; 6.30 (6.21–6.40)‡	147; 6.41 (6.27–6.55)‡	48; 6.19 (5.95–6.43)	922; 6.29 (6.23–6.36)	116; 6.05 (5.93–6.18)				

Data are N, means in NGSP units (95% CI). †Adjusted for sex, age, BMI, FPG, 2hPG, FSI, Hgb, MCV, SBP, DBP, ALT, AST, and GGT. ‡Glycemic categories include NGT (FPG < 5.6 mmol/L and 2hPG < 7.8 mmol/L), prediabetes (FPG 5.6–7.0 mmol/L or 2hPG 7.8–11.1 mmol/L), and unrecognized diabetes (FPG ≥ 7.1 mmol/L or 2hPG ≥ 11.2 mmol/L). ††The Wald F test differences across all groups were statistically significant (P < 0.001). §Pairwise comparison was statistically significant (P < 0.05) compared with the Mexican heritage group. ¶Pairwise comparison was statistically significant (P < 0.05) compared with the South American heritage group. #Pairwise comparison was statistically significant (P < 0.05) compared with non-Hispanic whites. \*Pairwise comparison was statistically significant (P < 0.05) compared with the Dominican heritage group. ††Pairwise comparison was statistically significant (P < 0.05) compared with the Central American heritage group.

SBP, and hepatic enzymes, as previously demonstrated in NHANES (9), the Diabetes Prevention Program (10), and by Herman et al. (11). In addition, we observed that HbA<sub>1c</sub> had a direct relationship with age, as demonstrated in the Framingham Offspring Study and the NHANES (21).

Important strengths of our study include the diversity of Hispanic/Latino heritage groups and the large sample size—in both the HCHS/SOL and the NHANES—which provides more reliable estimates for HbA<sub>1c</sub>, the ability to exclude individuals who had conditions that might impact the relationship between HbA<sub>1c</sub> and the selected covariates, and adequate power to assess statistical differences among Hispanic/Latino heritage groups and non-Hispanic whites according to diabetes status categories.

The evaluation of differences in HbA<sub>1c</sub> levels should also be cautiously interpreted from a racial/ethnic perspective. The terms “non-Hispanic white” and “Hispanic/Latino” give the impression that these two demographic groups are distinct races or ethnicities and that each Hispanic/Latino heritage group constitutes a separate racial or ethnic entity. These interpretations assume that race is a purely biological classification of human ancestry/origins, and not a sociocultural construct (22); fail to acknowledge that Hispanics/Latinos could be of any race; and could mislead the interpretation of the observations by attributing differences exclusively to ancestry. On the other hand, the genetics of Hgb glycation have not been fully described but are currently being studied (23–25). Genetic analyses of HbA<sub>1c</sub> and other select variables assessed during the baseline examination are currently in progress and will be published separately.

The differences in covariate-adjusted mean HbA<sub>1c</sub> levels among Hispanics/Latinos or between Hispanics/Latinos and non-Hispanic whites could be interpreted in the light of mediators that were not evaluated. For instance, conditions that increase or decrease red cell turnover, including Hgb variants and hemoglobinopathies (26), history of blood transfusion (27) or blood loss, or other blood or coagulation disorders were not evaluated as part of the baseline examination in the HCHS/SOL. Differences in red blood cell morphology (28), red cell life span (29–31) or Hgb glucose

affinity and glycation (28,31,32), iron deficiency and iron deficiency anemia (33), and obstructive sleep apnea (34,35), among other factors, may have also mediated the observed differences. Some of these factors may not be intrinsically related to a specific Hispanic/Latino genetic or cultural heritage but may depend on cumulative nutritional, socioeconomic, and medical history (36) and on local community resources or exposures. In addition, although both the reliability and repeatability of the HbA<sub>1c</sub> assay in the study were high, the analyses presented in this report only represent a one-time assessment correlation and not repeated measurements over time.

Existing HbA<sub>1c</sub> assays can only detect levels within one decimal place of percent unit based on the NGSP (37). Hence, the clinical implications of the differences in HbA<sub>1c</sub> to two decimal places observed in our analysis are unknown. The precision of the observed statistically significant differences in adjusted mean HbA<sub>1c</sub> levels in the NGT and prediabetes categories would not be detected in a clinical assay, and a diagnostic or therapeutic decision might not be pursued. In contrast, adjusted mean HbA<sub>1c</sub> level in the unrecognized diabetes category would be detected and considered sufficient to prompt diagnostic or therapeutic decisions.

Similarly, the clinical significance of the observed differences in HbA<sub>1c</sub> in our analysis for long-term diabetes-related complications is unknown. In the UK Prospective Diabetes Study (UKPDS), every 1% NGSP unit reduction in HbA<sub>1c</sub> was associated with a 37% reduction in microvascular complications and 43% reduction in amputations and mortality associated with peripheral vascular disease (38). In the Diabetes Control and Complications Trial (DCCT), a sustained difference in HbA<sub>1c</sub> of 1.9% NGSP units between patients with type 1 diabetes on intensive insulin therapy and patients on conventional insulin therapy was associated with a 76% risk reduction in the onset of retinopathy and 34% risk reduction in the onset of microalbuminuria (39). Further reduction in HbA<sub>1c</sub> to the normal range (e.g., 6.0%) was expected to be associated with additional risk reduction in the onset and progression of retinopathy (40). However, the clinical significance of the smaller differences in

**Table 3—Unadjusted and adjusted mean HbA<sub>1c</sub> levels by racial/ethnic heritage group**

Adjustment variables	HCHS/SOL: March 2008–June 2011							NHANES 2007–2012: non-Hispanic white (N = 2,242)
	Dominican (N = 1,220)	Central American (N = 1,485)	Cuban (N = 1,991)	Mexican (N = 5,426)	Puerto Rican (N = 2,016)	South American (N = 945)	All Hispanics/Latinos (N = 13,083)	
Unadjusted HbA <sub>1c</sub> (%)	5.45 (5.41–5.49)	5.50 (5.45–5.54)	5.49 (5.46–5.53)	5.51 (5.47–5.54)	5.51 (5.48–5.54)	5.46 (5.42–5.49)	5.49 (5.48–5.51)	5.37 (5.34–5.40)
Sex	5.45 (5.41–5.49)	5.50 (5.45–5.54)	5.49 (5.46–5.53)	5.51 (5.47–5.54)	5.51 (5.47–5.54)	5.46 (5.42–5.49)	5.49 (5.48–5.51)	5.37 (5.34–5.40)
Age	5.51 (5.47–5.55)	5.54 (5.50–5.58)	5.46 (5.43–5.49)	5.57 (5.53–5.60)	5.53 (5.50–5.56)	5.46 (5.43–5.49)	5.52 (5.51–5.54)	5.34 (5.32–5.37)
Age * sex interaction**	5.51 (5.47–5.55)	5.54 (5.50–5.58)	5.46 (5.43–5.49)	5.57 (5.53–5.60)	5.53 (5.50–5.56)	5.46 (5.43–5.49)	5.52 (5.51–5.54)	5.34 (5.32–5.37)
BMI (kg/m <sup>2</sup> )	5.44 (5.40–5.48)	5.49 (5.45–5.54)	5.49 (5.45–5.52)	5.50 (5.47–5.53)	5.48 (5.45–5.51)	5.47 (5.43–5.51)	5.49 (5.47–5.50)	5.38 (5.35–5.41)
FPG and 2hPG (mg/dL)	5.47 (5.44–5.49)	5.45 (5.42–5.48)	5.43 (5.41–5.45)	5.44 (5.43–5.46)	5.49 (5.47–5.52)	5.43 (5.40–5.46)	5.45 (5.44–5.46)	5.37 (5.35–5.40)
FSI (μU/mL)	5.46 (5.42–5.50)	5.48 (5.44–5.53)	5.48 (5.44–5.51)	5.50 (5.47–5.53)	5.50 (5.47–5.53)	5.46 (5.42–5.50)	5.49 (5.47–5.50)	5.38 (5.35–5.41)
Hgb (g/dL)	5.44 (5.40–5.49)	5.50 (5.45–5.54)	5.49 (5.46–5.53)	5.50 (5.47–5.54)	5.50 (5.47–5.54)	5.46 (5.42–5.49)	5.49 (5.47–5.51)	5.37 (5.34–5.40)
MCV (fL)	5.44 (5.39–5.48)	5.49 (5.45–5.54)	5.50 (5.46–5.53)	5.50 (5.47–5.54)	5.50 (5.47–5.54)	5.46 (5.42–5.49)	5.49 (5.47–5.51)	5.37 (5.35–5.40)
SBP and DBP (mmHg)	5.44 (5.40–5.48)	5.49 (5.44–5.53)	5.46 (5.42–5.49)	5.52 (5.49–5.56)	5.49 (5.46–5.52)	5.46 (5.43–5.50)	5.49 (5.47–5.51)	5.38 (5.35–5.41)
ALT, AST, GGT (units/L)	5.46 (5.42–5.50)	5.48 (5.44–5.53)	5.48 (5.44–5.51)	5.49 (5.46–5.53)	5.50 (5.47–5.53)	5.45 (5.42–5.49)	5.48 (5.47–5.50)	5.38 (5.35–5.41)
All covariates	5.47 (5.44–5.50)	5.46 (5.44–5.49)	5.42 (5.40–5.44)	5.46 (5.45–5.48)	5.49 (5.46–5.51)	5.43 (5.40–5.46)	5.46 (5.45–5.47)	5.36 (5.34–5.39)

Data presented as means in NGSP units (95% CI). \*\*This model included age, sex, and an interaction term for age \* sex.

HbA<sub>1c</sub> (e.g., 0.25% and 0.39%) observed between Hispanics/Latinos and non-Hispanic whites with unrecognized diabetes in this study is unknown. These differences are not the result of an intervention to reduce glycemic levels and may not reflect differences in glycemia, since mean HbA<sub>1c</sub> levels were adjusted for FPG and 2hPG. Since HCHS/SOL participants have been followed annually and a second examination is being conducted, assessment of risk for diabetes and macro- and microvascular complications associated with baseline and follow-up HbA<sub>1c</sub> will be possible in the future.

The findings presented in this analysis suggest that statistically significant differences in HbA<sub>1c</sub> exist between Hispanics/Latinos and non-Hispanic whites and among different Hispanic/Latino heritage groups. The mechanisms and clinical implications behind these differences need to be further investigated. Understanding the relationship between HbA<sub>1c</sub> and nonglycemic factors and incorporating them into the interpretation of HbA<sub>1c</sub> tests may prove valuable to the diagnosis of diabetes and monitoring glycemic control of Hispanics/Latinos.

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