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## Association Between Hemoglobin A1c and Glycemia in African Americans with and without Sickle Cell trait and Whites, Results from CARDIA and the Jackson Heart Study

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### Abstract

**1.1. Background:** It was reported that Hemoglobin A1c (HbA1c) values of African-Americans (AAs) were on average higher than whites whereas AAs with Sickle-Cell-Trait (SCT) had lower HbA1c values compared to AAs without SCT despite controlling for average glycaemia. We evaluated the HbA1c-glucose relationship between AAs with and without SCT, and whites using data from two cohort studies.

**1.2. Methods:** We pooled data from Coronary-Artery-Risk-Development-Study-in-Young-Adults (CARDIA, n= 5,115, 2005–2011) and the Jackson-Heart-Study (JHS, n=5,301, 2000–2013). Whole exome sequencing in JHS and TaqMan-SNP-Genotyping Assays in CARDIA determined the SCT status in AAs. HbA1c was measured by two NGSP-certified assays without reportedly clinically significant interference from hemoglobin S. Participants without data on SCT or with hemoglobin SS, CC or AC were excluded, resulting in 6,623 participants (n=3,575 from CARDIA and n=3,048 from JHS). Generalized-estimating-equations estimated the cross-sectional

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<sup>9</sup>.Conflicts of Interest

None of the authors have any conflicts of interest to disclose.

association between fasting glucose and HbA1c(outcome) amongst whites, AAs with SCT, and AAs without SCT controlling for clinical-demographic factors.

**1.3. Results:** Our analyses included 2,003 whites, 4,253 AAs without SCT and 367 AAs with SCT. AAs with and without SCT had similar clinical-demographic characteristics, whereas whites have lower fasting- and 2-hour-glucose values than AAs. Despite higher fasting-glucose values in AAs with SCT versus whites, their HbA1c values were similar ( $p=0.39$ ). In the subset with 2-hour-glucose values, HbA1c values in AAs with SCT were lower than whites ( $p=0.007$ ) despite higher 2-hour-glucose values.

**1.4. Conclusions:** AAs with SCT have at least similar, if not lower, levels of mean HbA1c values than whites despite higher levels of glycaemia. Future research is warranted to assess whether these findings translate to clinical outcomes.

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## 2. Introduction

It has been previously shown that for any given level of glycaemia, African Americans (AAs) have higher average Hemoglobin A1c (HbA1c) values compared to whites [1]. However, it was recently reported that among AAs the presence of Sickle Cell Trait (SCT) may affect the HbA1c-glucose relationship. Specifically, for any given fasting or 2-hour-postprandial glucose level, HbA1c was approximately 0.3 percentage points lower among AAs with SCT compared to AAs without SCT [2]. An accompanying editorial interpreted these findings as suggesting that AAs with SCT have an HbA1c-glucose relationship that is similar to whites. We sought to directly evaluate this untested hypothesis using data from two longitudinal community-based cohort studies.

## 3. Methods

We pooled data from participants of the Coronary Artery Risk Development Study in Young Adults (CARDIA,  $n=5,115$ , 2005–2011) and the Jackson Heart Study (JHS,  $n=5,301$ , 2000–2013) with data on HbA1c and either 8-hr fasting (both cohorts) or 2-hr post-prandial (oral glucose tolerance test, CARDIA only) glucose levels [3,4]. All participants included in the analyses provided written informed consent and institutional review board from each of the participating institutions in both CARDIA (University of Alabama at Birmingham, Northwestern University, University of Minnesota, and Johns Hopkins University School of Medicine) and JHS (University of Mississippi Medical Center) approved the study. Whole exome sequencing in JHS and TaqMan SNP Genotyping Assays (Life Technologies, Grand Island, NY) in CARDIA were used to determine SCT status in AAs. HbA1c was measured by two NGSP-certified assays (Tosoh 2.2 and Tosoh G7) reportedly without clinically significant interference from hemoglobin S [5]. Participants without data on SCT, with hemoglobin SS, with hemoglobin CC or hemoglobin AC were excluded, resulting in 6,623 participants in the analysis ( $n=3,575$  from CARDIA and  $n=3,048$  from JHS). We assumed SCT to be absent in whites given its very low prevalence in this population (0.3%) [6].

We compared participant characteristics amongst whites, AAs with SCT and AAs without SCT using  $\chi^2$  tests and ANOVA for discrete and continuous variables, respectively. We used Generalized-Estimating-Equations (GEE) using random effects at the participant level

and an exchangeable correlation matrix to estimate the cross-sectional association between glucose measures (fasting and 2-hour glucose) and HbA1c (outcome) amongst whites, AAs with SCT, and AAs without SCT while accounting for repeated measures within individuals over time.

## 4. Results

Our analyses included 2,003 whites, 4,253 AAs without SCT and 367 AAs with SCT with a total of 10,997 observations with fasting glucose and 4,043 with 2-hr glucose from two follow-up visits in CARDIA (years 20 and 25 from 2005–2011), and three visits in JHS (baseline and years 5 and 10 follow-ups from 2000–2013). Compared to AAs (with and without SCT), whites were more likely to be male and younger, to have lower BMI, ferritin, and fasting and 2-hour glucose values; and less likely to have diabetes or be on diabetes medications (Table 1).

### 4.1. AAs with SCT versus Whites

Despite significantly higher mean fasting glucose values in AAs with SCT ( $102.7 \pm 34.2$  mg/dL) versus whites ( $97.7 \pm 21.3$  mg/dL),  $p=0.0002$ , regression analyses revealed similar mean HbA1c values in AAs with SCT (5.83%, 95% CI: 5.75, 5.91) compared to whites (5.86%, 95% CI: 5.80%, 5.92%),  $p=0.39$ , after adjustment for age, gender, BMI, ferritin, estimated glomerular filtration rate, diabetes, current use of diabetes medications, physical activity, diet and smoking status (Figure 1). In the subset of CARDIA participants with glucose tolerance test results ( $n=2900$ ), adjusted analyses (Figure 2) showed that mean HbA1c values in AAs with SCT (5.40%, 95% CI: 5.26%, 5.55%) were significantly lower than whites (5.54%, 95% CI: 5.41%, 5.66%),  $p=0.007$ , despite significantly higher mean 2-hour post-prandial glycemic values in AAs with SCT ( $116.1 \pm 39.0$  mg/dL) versus whites ( $104.17 \pm 36.3$  mg/dL),  $p=0.005$ .

### 4.2. AAs without SCT versus Whites

Adjusted analyses showed that after controlling for fasting glucose and same covariates listed above, mean HbA1c values in AAs without SCT (6.16%, 95% CI: 6.10 – 6.21) were still significantly higher than whites,  $p<0.0001$ . Results remained similar for the subset of participants with 2-hour glucose values, where AAs without SCT had significantly higher mean HbA1c values (5.76%, 95% CI: 5.64% - 5.89%) than whites,  $p<0.0001$ , even after adjustment for 2-hour glucose values and the same covariates listed above.

## 5. Discussion

In this analysis of 2 large, well-established cohorts, despite significantly higher mean fasting glucose values in AAs with SCT versus whites, mean HbA1c values in AAs with SCT were similar compared to whites. In the subset of participants with 2-hour postprandial glucose values, mean HbA1c values in AAs with SCT were significantly lower than whites despite significantly higher mean 2-hour post-prandial glycemic values in AAs with SCT. To our knowledge, this study is one of the first to report this relationship with important clinical implications given previous data showing AAs to have higher HbA1c values than whites [1].

These findings suggest that generalizations about AAs having higher levels of HbA1c than whites for similar levels of glycaemia are unnecessary simplifications.

Consistent with previous literature [1], this report also showed that, mean HbA1c values in AAs without SCT were significantly higher than whites, despite adjustment for fasting (overall study sample) or 2-hour (CARDIA only) glucose values. The potential mechanisms for the observed differences in HbA1c between the white and the AA population with or without SCT are likely multifactorial given the lack of a gold standard for HbA1c values and the inherent variation within assays being employed. Discrepancy in HbA1c values observed can be biological as supported by studies that utilized continuous plasma glucose monitoring (gold standard for which HbA1c is intended to measure), that suggest differences in red blood cell lifespan and hemoglobin glycation kinetics as potential sources of variation [7]. On the other hand, reports from Rohlfing, Hanson, Little and colleagues have consistently shown a statistically significant negative bias in the assays utilized for HbA1c in individuals with SCT [8–11], but the assay bias alone cannot explain the A1c differences between whites and AAs without SCT. As such, we hypothesize that the observed differences are likely a combination of biological and assay mechanisms. The mechanisms above will also likely result in some discrepancy in the relationship between HbA1c and either fasting blood glucose and 2-hour glucose values observed in our study. Irrespective of the mechanism, the tests being employed in this report are common in clinical practice and the results shown in this analysis are relevant to the day-to-day clinical practice.

## 6. Conclusions

AAs with SCT have at least similar, if not lower, levels of mean HbA1c values than whites despite higher levels of fasting and 2-hour postprandial glycaemia. Further research is warranted to assess whether these findings in HbA1c levels in relation to race and SCT status translate into distinct clinical outcomes in the setting of racial variations in metabolic risk profiles.

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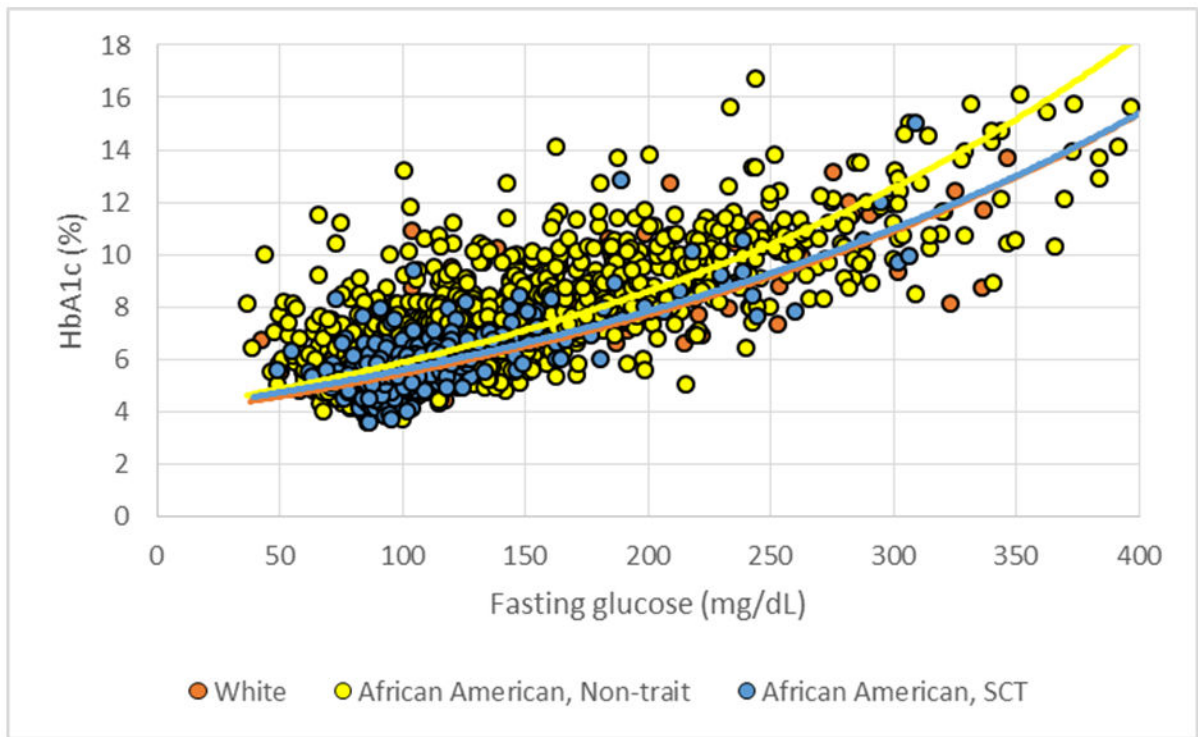
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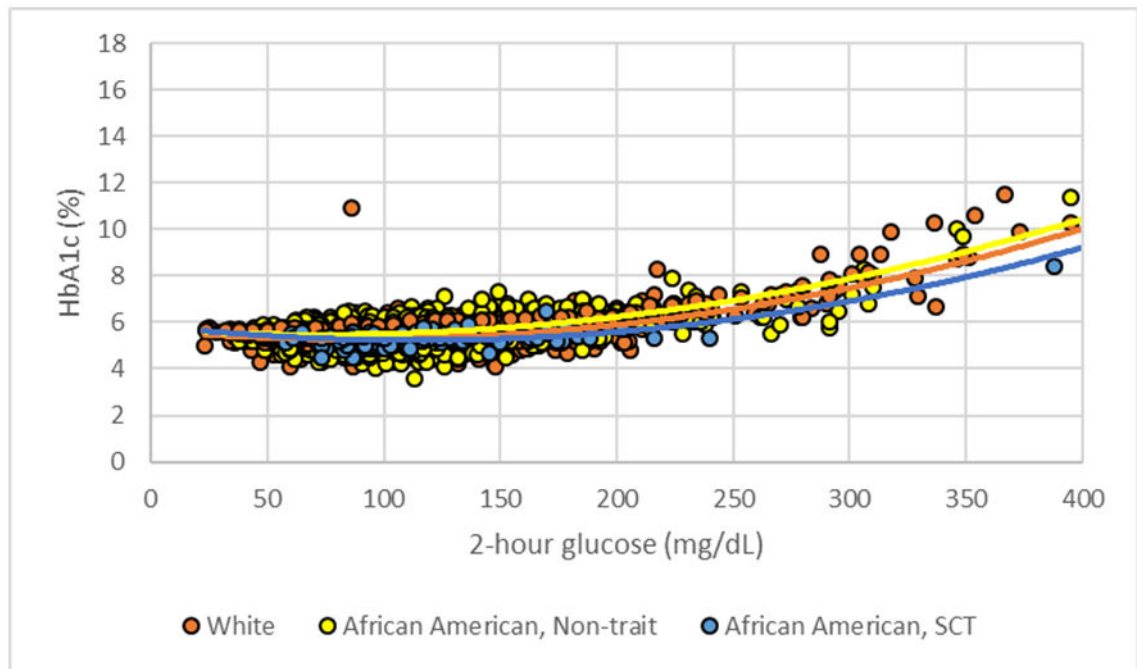
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**Figure 1:**

Scatterplot of hemoglobin A1C (%) versus fasting plasma glucose (mg/dL). Whites: Observed data points are represented by orange dots and the regression line is solid orange. AA Non-trait (African Americans without sickle cell trait): Observed data points are represented by yellow dots and the regression line is solid yellow. AA SCT (African Americans with sickle cell trait): Observed data points are represented by blue dots and the regression line is solid blue. Covariates in adjusted models are centered at the mean. Adjusted for age, BMI, ferritin, eGFR, male, diabetes medications, diabetes diagnosis, physical activity, diet and smoking.



**Figure 2:**

Scatterplot of hemoglobin A1C (%) versus 2-hour postprandial plasma glucose (mg/dL). Whites: Observed data points are represented by orange dots and the regression line is solid orange. AA Non-trait (African Americans without sickle cell trait): Observed data points are represented by yellow dots and the regression line is solid yellow. AA SCT (African Americans with sickle cell trait): Observed data points are represented by blue dots and the regression line is solid blue. Covariates in adjusted models are centered at the mean. Adjusted for age, BMI, ferritin, eGFR, male, diabetes medications, diabetes diagnosis, physical activity, diet and smoking.



**Table 1:**

Baseline Characteristics of the Study Population.

Mean (SD) unless otherwise specified	Whites (n=2003)	AA - non-SCT (n=4253)	p-value (Whites vs AA non-SCT)	AA - SCT (n=367)	p-value (Whites vs AA - SCT)
Male, n (%)	942 (47.1)	1634 (38.4)	<0.0001	15 (41.1)	0.04
Age in years	46.44 (3.8)	52.2 (11.8)	<0.0001	53.9 (12.2)	<0.0001
BMI (kg/m <sup>2</sup> )	28.0 (6.1)	31.8 (7.5)	<0.0001	31.7 (7.5)	<0.0001
Ferritin (ng/mL)	115.4 (141.0)	156.3 (171.8)	<0.0001	151.4 (143.7)	<0.0001
eGFR (ml/min/1.73m <sup>2</sup> )	93.6 (13.6)	97.5 (21.2)	<0.0001	92.5 (23.3)	0.2
Fasting Plasma Glucose (mg/dL)	97.7 (21.3)	101.5 (33.2)	<0.0001	102.7 (34.2)	0.0002
Hemoglobin A1c (%)	5.4 (0.7)	5.9 (1.2)	<0.0001	5.7 (1.2)	<0.0001
2-hour plasma glucose (mg/dL, n = 2900)	104.2 (36.3)	113.8 (44.9)	<0.0001	116.1 (39.0)	0.005
Diabetes medications, <sup>a</sup> n (%)	57 (2.9)	523 (12.5)	<0.0001	54 (14.9)	<0.0001
Diabetes diagnosis, <sup>b</sup> n (%)	172 (8.6)	622 (14.7)	<0.0001	63 (17.2)	<0.0001
Physical activity, <sup>c</sup> n (%)			<0.0001		<0.0001
Poor	20 (1.0)	1445 (34.1)		139 (38.1)	
Intermediate	419 (21.0)	1368 (32.3)		113 (31.0)	
Ideal	1559 (78.0)	1427 (33.7)		113 (31.0)	
Diet, <sup>d</sup> n (%)			<0.0001		<0.0001
Poor	616 (37.4)	2292 (58.5)		206 (59.4)	
Intermediate	961 (58.4)	1577 (40.3)		133 (38.3)	
Ideal	69 (4.2)	46 (1.2)		8 (2.3)	
Smoking, n (%)			0.001		0.33
Poor	301 (15.2)	734 (17.5)		57 (15.8)	
Intermediate	61 (3.1)	77 (1.8)		6 (1.7)	
Ideal	1621 (81.7)	3385 (80.7)		298 (82.6)	

**Abbreviations:** AA = African Americans, SCT = Sickle Cell Trait, BMI = Body Mass Index (calculated as weight in kilograms divided by height in meters squared); eGFR = Estimated Glomerular Filtration Rate (calculated using the CKD-EPI equation), A1C.

<sup>a</sup>Diabetes medications is defined as use of a medication for the treatment of diabetes taken in the 2 weeks prior to the study exam.

<sup>b</sup>Diabetes diagnosis is defined as self-reported use of diabetes medications or self-reported physician diagnosis since the goal was to control for any potential confounding that may arise as a result of treatment for diagnosed diabetes (pharmaceutical or lifestyle).

<sup>c</sup>Physical Activity is defined as Poor, Intermediate or Ideal based on minutes/week of moderate or vigorous physical activity: Poor (0 minutes/week); Intermediate (>0 - <150 minutes/week); Ideal (≥ 150 minutes/week)

<sup>d</sup>Nutrition is defined as Poor, Intermediate or Ideal based on the number of diet components achieved. Components (based on a 2000-calorie diet): 4.5 cups of fruits and vegetables/day; 7 ounces of fish/week; <1500 mg of sodium/day; <450 calories/week of sugar-sweetened beverages; 3 servings/day of whole grains. Poor Health (0-1 components); Intermediate Health (2-3 components); Ideal Health (4-5 components).

<sup>e</sup>Smoking is defined as Poor, Intermediate or Ideal based on current and former smoking status. Poor (Current smoker); Intermediate (Quit < 12 months ago); Ideal (Never smoked or quit ≥ 12 months ago).