



# Sickle Cell Trait, European Ancestry, and Longitudinal Tracking of HbA<sub>1c</sub> Among African Americans: The Jackson Heart Study

Justin B. Echouffo-Tcheugui,<sup>1</sup>  
Stanford E. Mwasongwe,<sup>2</sup> Mario Sims,<sup>3</sup>  
Samuel Dagogo-Jack,<sup>4</sup>  
Sherita H. Golden,<sup>1</sup> Adolfo Correa,<sup>3</sup> and  
Solomon K. Musani<sup>3</sup>

Diabetes Care 2019;42:e166–e167 | <https://doi.org/10.2337/dc19-0982>

Studies of differences in glycosylated hemoglobin (HbA<sub>1c</sub>) have defined race/ethnicity as a social construct (1,2), not using objective biological parameters, and thus comparisons may have been confounded (3). Among blacks without diabetes, we investigated whether the proportion of European genetic ancestry (PEA) mediates the sickle cell trait (SCT) and HbA<sub>1c</sub> relation and whether PEA tracks HbA<sub>1c</sub> levels over time accounting for SCT.

We used data from three Jackson Heart Study (JHS) visits (2000–2004, 2005–2008, and 2009–2013), occurring at 4-year intervals. We excluded participants with diabetes (use of glucose-lowering medication or fasting blood glucose [FBG]  $\geq 126$  mg/dL) or prediabetes (FBG  $\geq 100$  mg/dL) at visit 1. We estimated PEA using 1,444 ancestry-informative markers. The *rs334* variant defined SCT, and *rs1050828* indicated glucose-6-phosphate dehydrogenase (G6PD) deficiency. HbA<sub>1c</sub> was assessed by high-performance liquid chromatography (Tosoh analyzer; assays coefficient of variation 1.4–1.9%).

Using visit 1 data, we estimated three relations (Fig. 1A) corresponding to regressions of 1) SCT on HbA<sub>1c</sub> (*c*), 2) SCT on PEA (*a*), and 3) both SCT and PEA on HbA<sub>1c</sub> levels (*c'*). The indirect effect of PEA on HbA<sub>1c</sub> was estimated using the

difference between *c* and *c'*. Complete mediation is observed when *c' = 0* and partial mediation when *c - c'  $\neq 0$*  (Fig. 1A).

We used mixed models to test longitudinal changes in HbA<sub>1c</sub> and their differences between groups (defined by PEA and SCT). We also conducted analyses restricted to 1) participants free of diabetes across the three visits or 2) individuals without G6PD deficiency. In all models, we adjusted for baseline age, sex, educational attainment, current smoking, FBG, HOMA of insulin resistance, and ferritin levels.

At enrollment (visit 1, *n = 3,569*), mean  $\pm$  SD age was  $53 \pm 13$  years (63% women), mean HbA<sub>1c</sub> was  $5.45\% \pm 0.45\%$ , and mean FPG was  $87.8 \pm 6.2$  mg/dL.

Using visit 1 data, we observed no association between PEA and SCT (*a* in Fig. 1A) ( $\beta_{PEA}$  [SE] =  $-0.009$  [0.007], *P = 0.23*). There was a significant association between SCT and HbA<sub>1c</sub> (*c*) ( $\beta_{SCT}$  [SE] =  $-0.18$  [0.03], *P < 0.001*), which was not affected by PEA (*c'*) ( $\beta_{PEA}$  [SE] =  $-0.19$  [0.10], *P = 0.089*). Because *c - c' = 0*, PEA has no mediating effect on the SCT and HbA<sub>1c</sub> relation.

Without accounting for SCT, HbA<sub>1c</sub> did not differ between the low PEA and high PEA groups (difference 0.055 [SE 0.036], *P = 0.120*) across visits. Differences in HbA<sub>1c</sub> between high-PEA and low-PEA

individuals became apparent after stratification by SCT (Fig. 1B). Across the three study visits, individuals with low PEA had significantly higher HbA<sub>1c</sub> compared with individuals with high PEA in the non-SCT group (difference 0.06 [SE 0.01], *P = 0.005*). In the SCT group, there was no significant HbA<sub>1c</sub> difference between the high-PEA and low-PEA groups (difference 0.02 [SE 0.04], *P = 0.750*). Similar results were observed among participants free of diabetes across the three visits in the non-SCT and SCT groups (Fig. 1C). Among non-SCT individuals, HbA<sub>1c</sub> was higher in the low-PEA group versus the high-PEA group (difference 0.06 [SE 0.01], *P = 0.008*). After excluding individuals with G6PD deficiency, the results remained unchanged in the non-SCT and SCT groups. In the non-SCT group, low-PEA individuals had higher HbA<sub>1c</sub> compared with high-PEA individuals (difference 0.05 [SE 0.01], *P = 0.011*).

Across visits and PEA status, HbA<sub>1c</sub> was significantly lower in the SCT group versus the non-SCT group (difference 0.23 [SE 0.04], *P < 0.001*). Similar results were observed among individuals without diabetes at all three visits (difference 0.22 [SE 0.04], *P < 0.001*) or without G6PD deficiency (difference 0.22 [SE 0.04], *P < 0.001*).

<sup>1</sup>Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Johns Hopkins University, Baltimore, MD

<sup>2</sup>Jackson Heart Study, Jackson State University, Jackson, MS

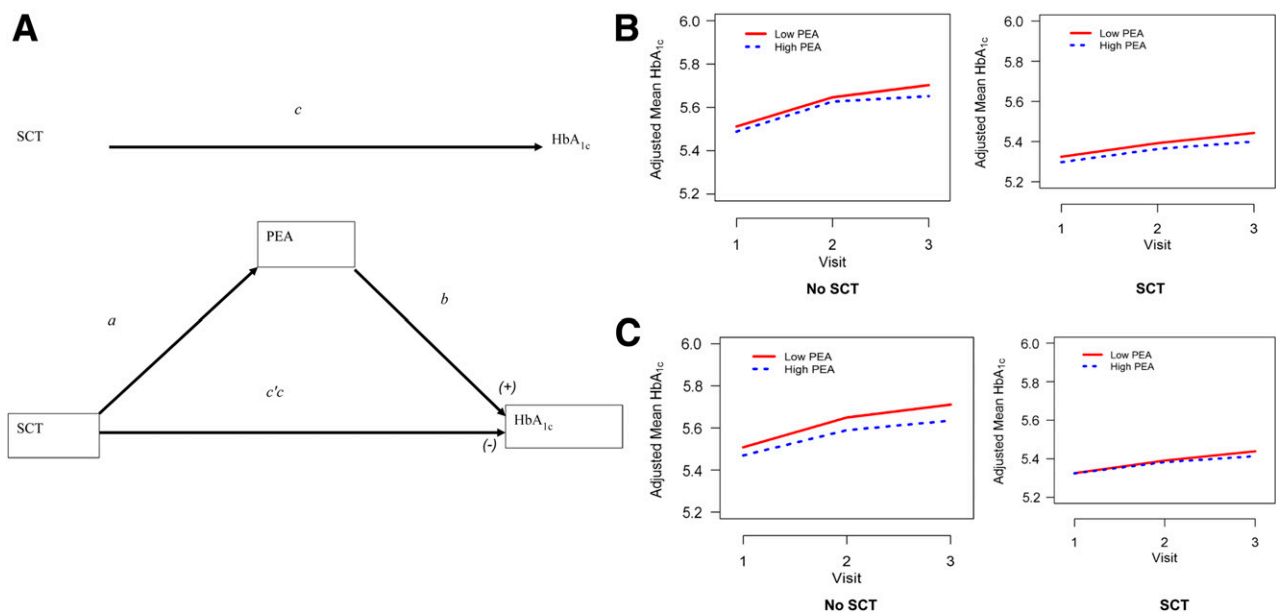
<sup>3</sup>Department of Medicine, University of Mississippi Medical Center, Jackson, MS

<sup>4</sup>Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Tennessee, Memphis, TN

Corresponding author: Justin B. Echouffo-Tcheugui, [jchouf1@jhmi.edu](mailto:jchouf1@jhmi.edu)

Received 16 May 2019 and accepted 17 July 2019

© 2019 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.



**Figure 1**—A: Schematic conceptual framework for the mediation analysis investigating the relations among SCT, PEA, and HbA<sub>1c</sub>. B: Adjusted mean of HbA<sub>1c</sub> across Jackson Heart Study visits by SCT and PEA status across the three study visits. C: Adjusted mean of HbA<sub>1c</sub> by SCT and PEA status among Jackson Heart Study participants remaining free of diabetes across the three study visits.

Among blacks without diabetes, we observed higher HbA<sub>1c</sub> levels among individuals with low PEA versus those with high PEA in the non-SCT group, but not in the SCT group. This suggests independent PEA and SCT effects, with a predominance of the SCT effect. Our findings are consistent with prior evidence of differences in HbA<sub>1c</sub> between blacks and whites (1), including the effect of SCT status (4). However, our investigation differs from prior studies, which examined SCT only (5) or genetic ancestry only (3), seldom accounted for G6PD (3,5), included individuals with prediabetes or diabetes, and did not track HbA<sub>1c</sub> over time (3–5).

The inclusion of individuals from a single racial/ethnic group but with a heterogeneous ancestry allowed a better disaggregation of ancestry-specific HbA<sub>1c</sub>-related genetic determinants from the social factors that correlate with race/ethnic groupings. The observed differences among individuals without diabetes or prediabetes suggest that PEA captures nonglycemic

factors. The PEA effect was explained by neither SCT nor G6PD.

**Acknowledgments.** The authors thank the staff and participants of the Jackson Heart Study.

**Funding.** The Jackson Heart Study is supported through collaborations with Jackson State University (HHSN2682018000131), Tougaloo College (HHSN2682018000141), the Mississippi State Department of Health (HHSN2682018000151), and the University of Mississippi Medical Center (HHSN2682018000101, HHSN2682018000111, and HHSN2682018000121) contracts from the National Heart, Lung, and Blood Institute and the National Institute on Minority Health and Health Disparities.

The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute, the National Institutes of Health, or the U.S. Department of Health & Human Services.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** J.B.E.-T. and S.K.M. conceived and designed the study and drafted the manuscript. J.B.E.-T., S.E.M., M.S., S.D.-J., S.H.G., A.C., and S.K.M. analyzed and interpreted the data. S.E.M., M.S., S.D.-J., S.H.G., and A.C. critically revised the manuscript for important intellectual content. J.B.E.-T. had final approval of the manuscript. S.K.M. provided statistical

expertise. J.B.E.-T. 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.

## References

- Cavagnoli G, Pimentel AL, Freitas PAC, Gross JL, Camargo JL. Effect of ethnicity on HbA<sub>1c</sub> levels in individuals without diabetes: systematic review and meta-analysis. *PLoS One* 2017;12: e0171315
- Wheeler E, Leong A, Liu C-T, et al.; EPIC-CVD Consortium; EPIC-InterAct Consortium; Lifelines Cohort Study. Impact of common genetic determinants of hemoglobin A<sub>1c</sub> on type 2 diabetes risk and diagnosis in ancestrally diverse populations: a transethnic genome-wide meta-analysis. *PLoS Med* 2017;14: e1002383
- Lacy ME, Wellenius GA, Sumner AE, et al. Association of sickle cell trait with hemoglobin A<sub>1c</sub> in African Americans. *JAMA* 2017;317:507–515
- Hivert M-F, Christophi CA, Jablonski KA, et al. Genetic ancestry markers and difference in A1c between African-American and white in the Diabetes Prevention Program. *J Clin Endocrinol Metab* 2019;104:328–336
- Maruthur NM, Kao WHL, Clark JM, et al. Does genetic ancestry explain higher values of glycated hemoglobin in African Americans? *Diabetes* 2011;60:2434–2438