Sickle Cell Trait, European Ancestry, and Longitudinal Tracking of HbA_{1c} Among African Americans: The Jackson Heart Study

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Studies of differences in glycosylated hemoglobin (HbA_{1c}) 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_{1c} relation and whether PEA tracks HbA_{1c} 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_{1c} 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. 1*A*) corresponding to regressions of *1*) SCT on HbA_{1c} (*c*), *2*) SCT on PEA (*a*), and *3*) both SCT and PEA on HbA_{1c} levels (c'). The indirect effect of PEA on HbA_{1c} 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. 1*A*).

We used mixed models to test longitudinal changes in HbA_{1c} 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_{1c} 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. 1*A*) (β_{PEA} [SE] = -0.009 [0.007], $P = 0.23$). There was a significant association between SCT and HbA_{1c} (*c*) (β_{SCT} [SE] = -0.18 [0.03], $P < 0.001$), which was not affected by PEA (c') (β_{PEA} [SE] = -0.19 [0.10], $P = 0.089$). Because $c - c' = 0$, PEA has no mediating effect on the SCT and HbA_{1c} relation.

Without accounting for SCT, HbA_{1c} 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_{1c} between high-PEA and low-PEA individuals became apparent after stratification by SCT (Fig. 1*B*). Across the three study visits, individuals with low PEA had significantly higher HbA_{1c} 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_{1c} 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. 1*C*). Among non-SCT individuals, HbA_{1c} 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_{1c} compared with high-PEA individuals (difference 0.05 [SE 0.01], $P = 0.011$).

Across visits and PEA status, HbA_{1c} 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 G6DP deficiency (difference 0.22 [SE 0.04], $P < 0.001$).

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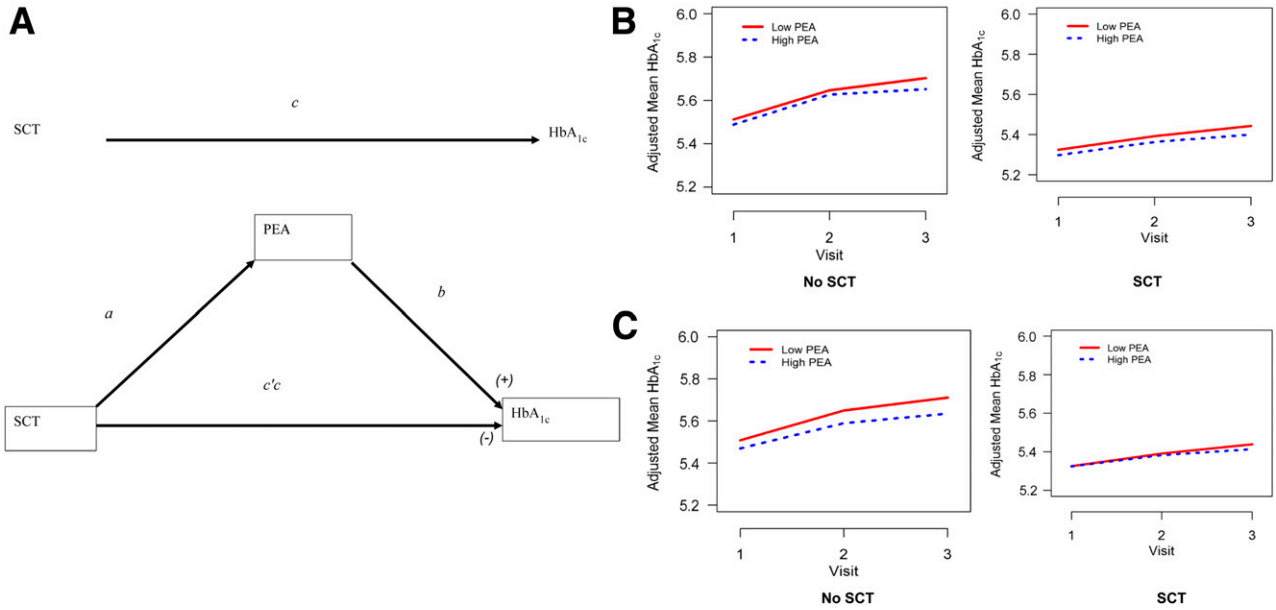

Figure 1—*A*: Schematic conceptual framework for the mediation analysis investigating the relations among SCT, PEA, and HbA_{1c}. *B*: Adjusted mean of HbA_{1c} across Jackson Heart Study visits by SCT and PEA status across the three study visits. *C*: Adjusted mean of HbA_{1c} by SCT and PEA status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

Among blacks without diabetes, we observed higher HbA_{1c} 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_{1c} 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_{1c} 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_{1c}-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.

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