Altitudes and Hemoglobin A_{1c} Values: An Analysis Based on Two Nationwide Cross-sectional Studies

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People living at high altitudes require an increase in the number of erythrocytes, known as polycythemia, to compensate for decreased oxygen availability (1). Using HbA_{1c} to detect prediabetes or diabetes at high altitudes might lead to misdiagnosis due to a pseudo-increase in HbA_{1c} levels in people with polycythemia. In the current study, we aimed to present the effect of high altitudes on diagnosing prediabetes and diabetes using HbA_{1c}.

The 2010 China Noncommunicable Disease Surveillance study is a nationwide survey that used a complex, multistage, cluster sampling method to recruit participants from 162 study sites across mainland China (2). In total, 95,052 adults aged ≥18 years who were not taking antidiabetes medications were included in the analysis. The prevalences of prediabetes and diabetes at different altitudes were compared using χ^2 test that considered weights and study design. The diagnostic accuracy of HbA_{1c} for prediabetes and diabetes, defined by fasting plasma glucose (FPG) and 2-h postload glucose (2-h PG), was calculated separately in participants living below and above 2,500 m of sea level. The optimal cutoff was determined by selecting the point maximizing the Youden index. The areas under the curves (AUCs) were compared to assess the discriminatory ability of HbA_{1c} by altitude status. To assess the detection bias of HbA_{1c} caused by high altitudes, a subgroup of participants living at low to high altitudes was selected and matched for age, sex, BMI, FPG, and 2-h PG levels. A total of 2,165 participants living at an altitude above 3,750 m were 1:1:1:1 matched with the participants living below 1,250 m, between 1,250 and 2,499 m, and between 2,500 and 3,749 m. Nearest-neighbor matching was used with the caliper set at 0.05. All analyses were performed using R version 4.2.3. A two-sided *P* value of <0.05 was considered statistically significant.

There were 88,577 participants living below 2,500 m and 6,475 above 2,500 m. In almost all the categories of FPG (per 5-mg/dL increase) and 2-h PG (per 10-mg/dL increase) levels, mean HbA_{1c} values were significantly higher in those living above 2,500 m than in those living below 2,500 m. The prevalence of prediabetes and diabetes was significantly higher in the participants living below 2,500 m than in those living above 2,500 m when defined using FPG (32.4% vs. 16.9% for prediabetes; 4.9% vs. 2.2% for diabetes) (Fig. 1*A*) or 2-h PG (10.7% vs. 5.8% for prediabetes; 3.7% vs. 1.4% for diabetes) (Fig. 1*B*). In contrast, the prevalence of prediabetes and diabetes was not statistically different among participants living below 2,500 m and above 2,500 m when defined using HbA_{1c} (38.8% vs. 38.4% for prediabetes; 5.0% vs. 3.6% for diabetes) (Fig. 1*C*).

The discriminative ability of HbA_{1c} to identify prediabetes and diabetes defined by FPG and 2-h PG was significantly higher among participants living below 2,500 m versus those living above 2,500 m (AUC difference 3.6%, $P < 0.001$ for prediabetes; AUC difference 3.9%, $P = 0.048$ for diabetes) (Fig. 1*D–G*). The optimal HbA_{1c} cutoffs to detect prediabetes and diabetes were consistently higher among participants living above 2,500 m than those living below 2,500 m. By using the new data set of matched participants, the associations between altitudes and HbA_{1c} were flattened below 2,500 m and monotonically increased above 2,500 m (Fig. 1*H*). We repeated the analyses in another nationwide study population of 48,704 migrant workers aged 18–59 years (3) and obtained similar results (data not shown).

This is the largest study that assessed the impact of altitude on HbA_{1c} measurements. In line with a previous study (4), we considered that HbA_{1c} measurements were inaccurate for people living at high altitudes. A proper adjustment

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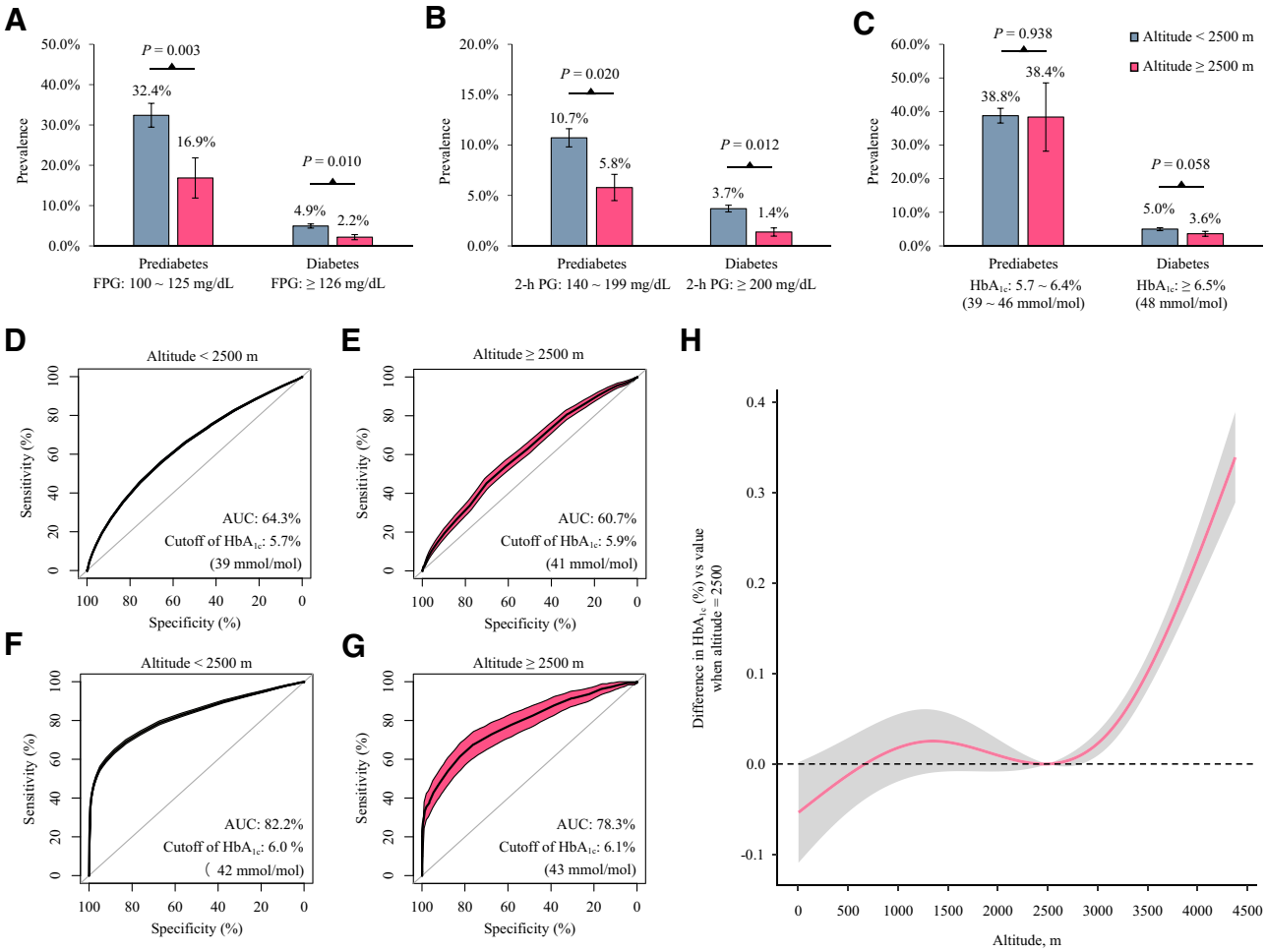

Figure 1—Effects of altitude on HbA_{1c} using data from the 2010 China Noncommunicable Disease Surveillance study. *A–C*: Prevalence of prediabetes and diabetes defined by FPG (*A*), 2-h PG (*B*), and HbA_{1c} (*C*). *D–G*: Comparison of the diagnostic ability of HbA_{1c} to identify prediabetes (*D* and *E*), defined as FPG 100–125 mg/dL or 2-h PG 140–199 mg/dL, and diabetes (*F* and *G*) defined as FPG 126 mg/dL or higher or 2-h PG 200 mg/dL or higher by altitude status (*D* and *F*, altitude <2,500 m; *E* and *G*, altitude ≥2,500 m). *H*: The new data set of matched participants was used. Possible nonlinear relationships between altitude levels and HbA_{1c} were constructed through linear regression by fitting altitude as a smooth term using a restricted cubic spline with four knots (knots located at the 0.05, 0.35, 0.65, and 0.95 percentiles of altitude levels). The reference altitude level was 2,500 m. The model was adjusted for age, sex, education, smoking status, drinking status, physical activity, household income, urban/rural habitation, regional gross domestic product per capita, BMI, FPG, and 2-h PG.

might have to be considered when using HbA_{1c} to diagnose diabetes at an altitude above 2,500 m. Our findings were not only obtained from the long-term dwellers but also applied to people who migrated to their current residence at least 6 months previously (2,3). However, we did not measure hemoglobin concentrations or red blood cell counts, which limits further interpretation. Long-term living in hypoxic environments at high altitudes not only causes an increase in erythrocyte formation but also might affect erythrocyte volume and inhibit eryptosis of mature erythrocytes (5). A longer life span of erythrocytes may prolong the time of hemoglobin exposure to blood glucose and lead to the rise of HbA_{1c} concentrations.

Overall, HbA_{1c} may be systematically overestimated for people living above 2,500 m. Therefore, a proper adjustment might have to be considered when using HbA_{1c} to diagnose diabetes at an altitude above 2,500 m. Further studies are needed to correct the detection bias of HbA_{1c} caused by high altitudes.

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and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Crapo RO, Jensen RL, Hegewald M, Tashkin DP. Arterial blood gas reference values for sea level and an altitude of 1,400 meters. Am J Respir Crit Care Med 1999;160:1525–1531

2. Xu Y, Wang L, He J, et al.; 2010 China Noncommunicable Disease Surveillance Group. Prevalence and control of diabetes in Chinese adults. JAMA 2013;310:948–959

3. Bi Y, Wang L, Xu Y, et al.; 2012 China Noncommunicable Disease and Risk Factor Surveillance in Migrant Workers Study Group. Diabetes-related metabolic risk factors in internal migrant workers in China: a national surveillance study. Lancet Diabetes Endocrinol 2016;4:125–135

4. Ren Q, Lv X, Yang L, et al. Erythrocytosis and performance of HbA1c in detecting diabetes on an oxygen-deficient plateau: a population-based study. J Clin Endocrinol Metab 2020;105:dgaa001

5. Tang F, Feng L, Li R, et al. Inhibition of suicidal erythrocyte death by chronic hypoxia. High Alt Med Biol 2019;20:112–119