LETTER TO THE EDITOR

Adverse clinical outcomes associated with sickle cell trait at high altitude

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Supplementary Information

For article: *Adverse clinical outcomes associated with sickle cell trait at high altitude*

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Contents:

	Sickle cell trait patients	Controls
Patient selection		
Inclusion	D57.3 Sickle-cell trait	
Exclusion		D57.3 Sickle-cell trait
	D57.0 HbSS disease with crisis	D57.0 HbSS disease with crisis
	D57.1 HbSS disease without crisis	D57.1 HbSS disease without crisis
	D57.2 Sickle-cell/HbC disease	D57.2 Sickle-cell/HbC disease
	D57.4 Sickle-cell thalassemia	D57.4 Sickle-cell thalassemia
	D57.8 Other sickle-cell disorder	D57.8 Other sickle-cell disorder
	D58 Other hereditary hemolytic anemias	D58 Other hereditary hemolytic anemias
	D59 Acquired hemolytic anemia	D59 Acquired hemolytic anemia
Outcomes Defined by ICD prefix (e.g. ICD-10-CM code matching first 2-5 characters specified in this table)	I26 Pulmonary embolism I82.4 Deep vein thrombosis R31 Hematuria N18 Chronic kidney disease M62.82 Rhabdomyolysis D73.5 Splenic infarction O14 Pre-eclampsia O36.4 Intra-uterine death	
Laboratory data LOINC codes	32683-5: Hemoglobin S/Hemoglobin.total in Blood by Electrophoresis 20572-4: Hemoglobin A/Hemoglobin.total in Blood by Electrophoresis 718-7: Hemoglobin [Mass/volume] in Blood	

Supplemental Table 1: A table of all diagnostic and laboratory codes used in this analysis. International Classification of Diseases, Tenth Revision Clinical Modification (ICD-10-CM) codes were used for diagnoses that defined populations and outcomes. Logical Observation Identifiers Names and Codes (LOINC) codes were used to collect relevant laboratory data.

	UCHealth high-altitude cohort Stafford et al. 2024 SCT = 1460. Median age 38 years (IQR 31 – 50. Diagnosis codes for SCT status and outcomes. Adjusted for age, sex, race.	**UK BioBank** Hulsizer et al. 2022[1] SCT = 69. Median age 51.5 (IQR 46-59.5). Black only. Genotyped or diagnosis code SCT status. Diagnosis codes for outcomes. Adjusted for age at recruitment, sex, and genetic background.	**All of Us** Wossenseged et al. 2022[2] SCT = 982. Mean age of 55 years (range 21-87). Genotyped SCT status. Electronic health record diagnosis codes & self-reported outcomes.	**ARIC Study** Folsom et al. 2015[3] SCT = 268. Mean age 53.8 years (SD = 5.9). African Americans. Genotyped SCT status. Clinical review of hospitalized DVT/PE.	**Meta-analysis USA prospective health studies** Naik et al. 2014[4] SCT =1247. Mean age 57 years. Genotyped SCT status. Laboratory defined CKD. Adjusted for age, sex, region, race, hypertension, diabetes.	**Kaiser Foundation Research Institute** Bucknor et al. 2014[5] SCT = 2642. Mean age 52.9 (SD = 14.4). Non-hispanic African American. Diagnosis code or laboratory evidence of SCT. Adjusted for age, health plan duration, gender, obesity, diabetes, hyperlipidemia.	**Hospitalized cohort Atlanta, GA** Austin et al. 2007[6] SCT = 91. Median age 48 (IQR 38-56). Genotyped SCT status. Cases w/VTE, controls w/o VTE. In-hospital confirmation of VTE.
CKD	3.2 (2.5-4.1)*	1.6 (1.1-2.3)*	4.1 (2.8-6.0)*		1.6 (1.3-1.8)*	1.1 (1.0-1.2)*‡	
DVT	2.5 (1.7-3.5)*	1.1 (0.7-1.7)	2.0 (1.2-3.3)*	1.2 (0.6-2.3) †		1.3 (0.9-2.0)‡	0.9 (0.6-1.4)†
PE	4.3 (3.1-6.0)*	1.4 (0.8-2.1)		2.2 (1.2-3.9)*†		1.4 (1.1-1.8)*‡	3.3 (2.1-5.2)*†
Hematuria	2.5 (2.0-3.2)*	1.2 (0.8-1.7)	2.9 (2.1-4.0)*				
Rhabdo-myolysis	3.1 (1.6-6.1)*	5.1 (2.1-11.4)*					
Splenic infarction	55.9 (19.9-156.8)*	2.4 (0.5-7.7)					

Supplemental Table 2: Comparison of ORs found in the current high-altitude cohort with prior studies. ORs with 95% confidence interval in parenthesis (rounded to single decimal place) are reported. For studies that reported hazard ratios or relative risks rather than OR, an unadjusted OR and 95% confidence intervals was calculated from published tables. Number of SCT patients in cohort and brief description of study population is described in the first row. Due to event rates generally <10%, OR approximates RR and these numbers are comparable. *Abbreviations*: Sickle cell trait (SCT), venous thromboembolism (VTE), chronic kidney disease (CKD), deep vein thrombosis (DVT), pulmonary embolism (PE), odds ratio (OR), relative risk (RR). * Associations significant at alpha < 0.05. † Denotes unadjusted odds ratio calculated from published tab. ‡ Denotes adjusted relative risk

	Intra-uterine death	Pre-eclampsia	Pregnancy-induced hypertension
UCHealth high-altitude cohort (2024) SCT = 1460 Diagnosis code based SCT status. OR adjusted for age, African American race.	4.6 (2.0 – 10.5)*	3.7 (2.6 – 5.2)*	
Hulsizer et al.[7] **(2023)** SCT = 581 Genotyped & diagnosis code based SCT status. RR adjusted for number of live births, age at first birth and genetic background.	0.9 (0.5 – 1.6)‡	2.4 (1.1 – 5.2)*‡	
Canelón et al.[8] **(2021)** SCT = 1904 Diagnosis code based SCT status. OR adjusted for race, ethnicity, and year (category).	8.9 (1.1 – 75.8)*		
O'hara et al.[9] **(2020)** SCT = 5,004 Military database. SCT diagnosed by diagnosis or lab code.		1.8 (1.4 – 2.2)*†	2.0 (1.8 – 2.2)*†
Wellenstein et al. [10] **(2019)** SCT = 868 Screening by risk factor with electrophoresis confirmation, ICD diagnosis code outcomes. OR adjusted for age, race, hypertension, BMI, education.			1.0 (0.8 – 1.2)
Tita et al.[11] **(2007)** SCT = 1818 with 3019 pregnancies African American population, screen with electrophoresis confirmation. Internal clinical database of outcomes. OR adjusted for maternal age, parity, smoking, twin pregnancy, maternal diabetes or chronic hypertension, and alcohol or drug use.	0.6 (0.3 – 0.9)*	1.0 (0.8 –1.2)	1.1 (0.9–1.2)
Taylor et al.[12] **(2006)** SCT = 180 Sickledex screen with electrophoresis confirmation. Clinical confirmation of outcomes.	3.0 (1.2 – 7.9)*†	0.8 (0.4 – 1.5)†	
Stamilio et al.[13] **(2003)** SCT = 87 Sickledex screen with electrophoresis confirmation. Clinical confirmation of outcomes. OR adjusted for BMI, hypertension, prior pre-eclampsia, primiparity, gestational diabetes class A2, chronic hypertension.		0.5 (0.2 – 1.6)	
Larrabee et al.[14] **(1997)** SCT = 162 Sickledex screen with electrophoresis confirmation. Clinical confirmation of outcomes.		2.9 (2.0 – 4.3)*†	

Supplemental Table 3: Comparison of ORs found in the current high-altitude cohort with prior studies of SCT-related maternal outcomes. For studies that reported hazard ratios or incidence rate ratio rather than OR, an unadjusted OR and 95% confidence intervals was calculated from published tables. Due to event rates <10%, OR approximates RR and these numbers are comparable. *Abbreviations*: odds ratio (OR), sickle cell trait (SCT), relative risk (RR)

* Associations significant at alpha < 0.05.

† Denotes unadjusted odds ratio calculated from published table.

‡ Denotes adjusted relative risk.

Supplemental References:

1. Hulsizer J, Resurreccion WK, Shi Z, et al. Sickle Cell Trait and Risk for Common Diseases: Evidence from the UK Biobank. Am J Med 2022;135(8):e279–e287.

2. Wossenseged F, Ramirez HC, Buscetta AJ, Naik RP, Bonham VL. Examining Sickle Cell Trait Associated Clinical Outcomes in the All of Us research Program. Blood 2022;140(Supplement 1):1960–1961.

3. Folsom AR, Tang W, Roetker NS, et al. Prospective study of sickle cell trait and venous thromboembolism incidence. Journal of Thrombosis and Haemostasis 2015;13(1):2–9.

4. Naik RP, Derebail VK, Grams ME, et al. Association of Sickle Cell Trait With Chronic Kidney Disease and Albuminuria in African Americans. JAMA 2014;312(20):2115–2125.

5. Bucknor MD, Goo JS, Coppolino ML. The Risk of Potential Thromboembolic, Renal and Cardiac Complications of Sickle Cell Trait. Hemoglobin 2014;38(1):28–32.

6. Austin H, Key NS, Benson JM, et al. Sickle cell trait and the risk of venous thromboembolism among blacks. Blood 2007;110(3):908–912.

7. Hulsizer J, Rifkin AS, Shi Z, et al. Association of sickle cell trait with adverse pregnancy outcomes in a population-based cohort. Acta Obstet Gynecol Scand 2023;102(8):1100–1105.

8. Canelón SP, Butts S, Boland MR. Evaluation of Stillbirth Among Pregnant People With Sickle Cell Trait. JAMA Network Open 2021;4(11):e2134274–e2134274.

9. O'Hara C, Singer DE, Niebuhr DW. The Risk of Pregnancy Related Hypertension Disorder Associated with Sickle Cell Trait in U.S. Service Women. Military Medicine 2020;185(1–2):e183–e190.

10. Wellenstein WL, Sullivan S, Darbinian J, Ritterman Weintraub ML, Greenberg M. Adverse Pregnancy Outcomes in Women with Sickle Cell Trait. AJP Rep 2019;9(4):e346–e352.

11. Tita ATN, Biggio JR, Chapman V, Neely C, Rouse DJ. Perinatal and maternal outcomes in women with sickle or hemoglobin C trait. Obstet Gynecol 2007;110(5):1113–1119.

12. Taylor MY, Wyatt-Ashmead J, Gray J, Bofill JA, Martin R, Morrison JC. Pregnancy loss after first-trimester viability in women with sickle cell trait: time for a reappraisal? Am J Obstet Gynecol 2006;194(6):1604–1608.

13. Stamilio DM, Sehdev HM, Macones GA. Pregnant Women with the Sickle Cell Trait Are Not at Increased Risk for Developing Preeclampsia. Am J Perinatol 2003;20(1):41–48.

14. Larrabee KD, Monga M. Women with sickle cell trait are at increased risk for preeclampsia. Am J Obstet Gynecol 1997;177(2):425–428.