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Adverse clinical outcomes associated with sickle cell trait at high altitude

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Running Title: Sickle cell trait complications at altitude

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Sickle cell trait (SCT) is a prevalent condition affecting more than 300 million individuals worldwide. Although formerly regarded as a benign carrier state, with complications rarely occurring outside of high-altitude or extreme physiologic conditions, recent population-level data has revealed an increased risk for chronic kidney disease (CKD) and pulmonary embolism (PE) in general populations.[1] In this study, we sought to evaluate whether chronic, moderately high altitude exposure can increase the breadth and severity of SCT complications compared to sea-level cohorts. We used data from Colorado, which has the highest mean elevation of any State in the USA (2,070 m). We found that the risk for known SCT complications such as CKD and PE, as well as other clinical outcomes in which prior evidence was either weak or mixed, were significantly increased. In the latter category, adverse pregnancy outcomes including pre-eclampsia and intra-uterine death were particularly notable. The strength of the associations observed in this study generally exceeds prior reports and suggests that SCT patients living at high-altitude are at greater risk for morbidity than their sea-level counterparts.

Compared with sickle cell disease (SCD), the lower HbS concentration in SCT means that red blood cell (RBC) sickling rarely occurs during regular vascular transit but can be induced by added insults such as hypoxia or acidosis. These conditions can occur either systemically (e.g. with high-altitude exposure, sepsis) or locally (e.g. within the inner renal medulla or splenic pulp).[2,3] Sickling of RBCs in SCD is associated with membrane changes, including decreased deformability, loss of phospholipid asymmetry, and microvesiculation, that result in chronic activation of coagulation and inflammatory pathways.[4,5] Evidence to support SCT as an intermediate phenotype in these respects includes data showing moderately increased coagulation activation,[6,7] circulating cell-free mitochondrial DNA (a driver of chronic inflammation in SCD),[8] and markers of metabolic dysfunction and oxidative stress[9] in SCT patients at a level above healthy controls, but below those seen in SCD.

This retrospective cohort study used de-identified electronic health record data from UCHealth, a large regional health system in Colorado that includes an academic medical center, 13 community-based hospitals, and more than 200 outpatient clinics. This study is classified as not human subjects research and did not require specific consent or institutional review board approval. Data from the 12 largest primary statistical areas of Colorado, which includes ~95% of Colorado's population, estimates the weighted average elevation for a Colorado resident at ~1,600 meters, which results in an ~20% decrease in the inspired partial pressure of oxygen compared to sea level.[10–12]

Diagnostic codes were used to define case and control cohorts and outcomes of interest (*Supplementary Table S1*). Individuals 18 years or older with a diagnosis of SCT were analyzed for known and possible associated outcomes, and were compared to a 1:5 randomized matched sample of controls without SCT (matched on age within 2 years, race, ethnicity, sex, and entry into the database within 2 years). Data from 2004 – 2023 were included in this analysis. Individuals with diagnosis codes for sickle cell anemia (HbSS), sickle/HbC disease (HbSC), sickle-β thalassemia (HbS-β^{thal}), other sickle cell disorders, and hemolytic anemias were excluded from both case and control groups.

Outcomes of interest included CKD, PE, deep vein thrombosis (DVT), hematuria, rhabdomyolysis, splenic infarction, pre-eclampsia, and intra-uterine death. Odds ratios (OR) with 95% confidence intervals (CI) were estimated using multivariate logistic regression adjusted for age and Black or African American race, as well as sex when applicable. De-identified subject data were analyzed using Python version 3.11.4. Logistic regression models were built using StatsModel version 0.14.0.

We included 1460 SCT patients with complete demographic data, along with 7300 matched controls (n = 8760). There were 1060 (72.6%) women and 400 (27.4%) men in the case cohort, and matching proportions in the control group. A majority (76.0%) were black or African American. The median age of the cohort was 38 years (IQR = 31 - 50).

We found significant associations for CKD (OR = 3.2, 95% CI: 2.5 - 4.1), DVT (2.5, 95% CI: 1.7 – 3.5), PE (OR = 4.3, 95% CI: 3.1 – 6.0), hematuria (OR= 2.5, 95% CI: 2.0 - 3.2), rhabdomyolysis (OR = 3.1, 95% CI 1.6 – 6.1), splenic infarction (OR = 55.9, 95% CI 19.9 – 156.8), pre-eclampsia (OR = 3.7, 95% CI 2.6 – 5.2), and intra-uterine death (OR = 4.6, 95% CI 2.0 – 10.5) (Table 1). Male sex was strongly associated with rhabdomyolysis (OR 14.3, 95% CI 5.9 – 34.6) and splenic infarction (OR 8.8, 95% CI 4.4 – 17.6), and was moderately associated with CKD (OR = 1.5, 95% CI 1.2 – 1.9).

To confirm the validity of our SCT cohort, we analyzed laboratory data to confirm that hemoglobin concentration was normal, and that HbS and HbA percentages were within the expected ranges in SCT (<50% and >50%, respectively). We included the highest hemoglobin for each patient to avoid capturing acute blood loss events. Lab values were consistent with SCT and showed a median hemoglobin of 14.3 g/dL (IQR 13.2 – 15.3, N=1270), a median HbS of 38.4% (IQR 34.4 – 40.2%, N=193), and a median HbA of 58.4% (IQR 56.4 – 63.2%, N=291).

For 33/41 of the splenic infarction cases, SCT was diagnosed at the same encounter, suggesting that many SCT patients are unaware of their HbS carrier status. In support of previous reports,[3] we found an association between race and splenic infarction (Chi-squared $p<0.001$), with univariate logistic regression suggesting that Black or African American race is protective (OR = 0.3, 95% CI 0.1 – 0.5) and White race is a risk factor (OR = 5.5, 95% CI 2.8 – 10.9). Of note, all 4 cases of splenic infarction in the control group occurred in individuals who self-identified as Black, suggesting that undiagnosed SCT could be contributing to these outcomes.

We speculate that chronic exposure to hypoxia as experienced in Colorado augments the underlying pathophysiology of SCT by promoting polymerization of deoxyHbS. However, it is possible that this high-altitude "stress test" has implications for sea-level patients, who may be experiencing the same pathophysiologic processes at a sub-clinical or more sporadic rate. It is unclear how much of this effect was due to chronic exposure to high altitude versus acute and/or repeated exposure to very high altitudes, which is common for Colorado residents recreating in the mountains. Future studies incorporating geolocation data, potentially via wearable devices, could help address this question. The predominance of child-bearing age women in our cohort suggests that the diagnosis of SCT was established (or confirmed) through antepartum screening, but also makes the substantial rates of venous thromboembolism and CKD in our young cohort especially alarming.

A potential limitation in our study is the use of diagnosis codes rather than globin genotyping to define SCT status. However, by evaluating the hematologic profiles of enrolled subjects with SCT, we were able to rule out other forms of SCD or other anemias and confirm that the range of total Hb concentration and percentage of HbS were as expected in SCT. For instance, this enabled us to verify that compound sickle cell syndromes such as sickle-beta thalassemia, which are occasionally misclassified as SCT but can be identified by their unique hematologic profiles (Hb S>50%, Hb A<50%), did not have a substantial impact on our results. In this analysis, we did not include subjects less 18 years of age, where the majority of chronic complications associated with SCT (such as CKD) are presumably very rare. While we were unable to directly measure socioeconomic status in this data set, our experimental design has helped control for this potential confounder by exactly matching cases and controls based on age, sex, race, and ethnicity. Lastly, because many adults are unaware of their SCT status, it is possible that a significant proportion of our control cohort may also have SCT, which biases towards a null effect. This null bias should be considered when comparing the magnitude of our results to genotyping-based studies (*Supplementary Table S2, S3*).

The association between SCT and adverse outcomes of pregnancy is controversial. Complications that previously received attention in SCT include pregnancy-related hypertensive disorders, intra-uterine death, pre-term delivery, low birth weight and bacteriuria.[13] The strong associations we found for pre-eclampsia and intra-uterine death are clinically concerning and higher than most prior reports (*Supplementary Table S3*). Independently, high altitude has been associated with low birth weight and pre-eclampsia in a general maternal population.[14,15] In combination with our data, this suggests that pregnant women with SCT may be particularly vulnerable to adverse perinatal outcomes in high altitude environments.

Advancing recognition and management of SCT-associated health outcomes is an important health disparity issue, as SCT disproportionately affects underserved populations. Future prospective research should address whether improved identification and prevention of SCT-related morbidity could help reduce ongoing disparities in cardiovascular disease, kidney disease, and maternal health.

In summary, our findings suggest that chronic hypoxia in a high-altitude environment may exacerbate known SCT-associated outcomes such as CKD, and may escalate lower-strength associations such as morbidity in pregnancy toward clinical significance. Improving knowledge of the potential morbidities associated with SCT may assist clinicians in providing personalized, preventive care.

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Tables:

N (%)	**Sickle trait patients** *N=1460*	**Matched Controls** *N=7300*	**Odds ratio** (95% Confidence interval)
Chronic kidney disease	136 (9.3%)	273 (3.7%)	3.2 (2.5 – 4.1)*
Deep vein thrombosis	46 (3.2%)	97 (1.3%)	2.5 (1.7 – 3.5)*
Pulmonary Embolism	70 (4.8%)	87 (1.2%)	4.3 (3.1 – 6.0)*
Hematuria	117 (8.0%)	246 (3.4%)	2.5 (2.0 – 3.2)*
Rhabdomyolysis	14 (1.0%)	23 (0.3%)	3.1 (1.6 – 6.1)*
Splenic infarction	41 (2.8%)	4 (0.1%)	55.9 (19.9 – 156.8)*
Pre-eclampsia	58 (4.0%)	82 (1.1%)	3.7 (2.6 – 5.2)*
Intra-uterine death	11 (0.8%)	12 (0.2%)	4.6 (2.0 – 10.5)*

Table 1: Association between sickle cell trait and clinical outcomes. Odds ratios with 95% confidence intervals (CI) were estimated using multivariate logistic regression adjusted for age and Black or African American race, as well as sex when applicable.
* Associations significant at alpha < 0.05.

Supplementary Information

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

Authors: Katherine A. Stafford, Soravis Osataphan, Rushad Patell, Nigel S. Key

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.

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