pediatric stroke

# Exploring Health Disparities in the Treatment of Pediatric Patients with Sickle Cell Disease and Cerebral Vasculopathy

Taeya Mayes, BS[1]; Salvador F. Gutierrez-Aguirre, MD[2,3]; Otavio F de Toledo, MD[2,3]; Asmaa Hatem, MD[1]; Fernanda Erazu, MD[2,3]; John M Pederson, MD[4,5]; Ricardo A. Hanel, MD[2]; Aleksandra S Dain[6], MD; Philipp R Aldana, MD[7]

Affiliations:

[1]Department of Neurosurgery, University of Florida College of Medicine - Jacksonville and Wolfson Children's Hospital, Jacksonville, Florida, USA.

[2]Lyerly Neurosurgery, Baptist Neurological Institute, Jacksonville, FL, USA

[3]Research Department, Jacksonville University, Jacksonville, FL, USA

[4]Superior Medical Experts, St. Paul, Minnesota, USA.

[5]Nested Knowledge, St. Paul, Minnesota, USA.

[6]Division of Hematology/Oncology, Nemours Children's Hospital, Wilmington DE, USA

[7]Division of Neurosurgery, Nemours Children's Health Jacksonville

Corresponding author:

Philipp R Aldana, MD

Nemours Children's Health Jacksonville, FL, USA

Work Telephone Number: 904-697-4610

Email: Philipp.Aldana@nemours.org

**ABSTRACT**

**Background:** Despite ongoing efforts to reduce health disparities among individuals with sickle cell disease (SCD), significant inequities persist. This study investigates how sociodemographic variables—used as markers for social determinants of health (SDOH)—influence treatment access and outcomes in children with SCD and cerebral vasculopathy.

**Methods:** We conducted a retrospective, multicenter study of pediatric patients with SCD and confirmed cerebral vasculopathy, focusing on the impact of sociodemographic variables on the occurrence of cerebral vascular events (CVEs). Variables analyzed included sex, insurance status, estimated household income and distance to the treatment center (based on ZIP code), and the presence of a household smoker.

**Results:** A total of 140 patients were included in the analysis. Estimated household income and distance to the treatment center were not significantly associated with CVE occurrence. Most patients were insured, with only two uninsured. Descriptively, the uninsured patients had a higher risk of CVEs compared with those on Medicaid/Medicare in univariate analyses (HR = 4.15, 95% CI: 2.03–8.47, $p < .001$); however, this finding is limited by the very small sample size and the inability to adequately adjust for measured clinical factors such as age and treatment modality. Patients who underwent surgical revascularization tended to come from slightly higher-income areas, with higher estimated median household incomes compared to those managed medically ($49,741 [IQR: $40,724–$64,905] vs. $46,705 [IQR: $31,238–$63,008], $p = .083$). No sociodemographic variable significantly influenced age at treatment initiation or treatment discontinuation, although patients with private insurance tended to have a lower rate of medical treatment cessation compared with those on Medicaid/Medicare (HR = 0.37, 95% CI: 0.11–1.24, $p = .107$), and uninsured patients

descriptively had the highest rate of treatment cessation.

**Conclusion:** SDOH may contribute to disparities in the level of care received, indirectly impacting treatment and outcomes. However, the study's retrospective design and limited sample size underscore the need for further research to better understand this complex relationship.

## 1 INTRODUCTION

Sickle cell disease (SCD), a multisystem disorder affecting 100,000 individuals in the United States, disproportionately impacts racial and ethnic minorities. SCD is associated with vaso-occlusive events, reduced life expectancy, and diminished lifetime earnings. [1–3] Both reduced life expectancy and increased risk for stroke, a leading cause of death and disability, impact this population.[2,4] Prior to the implementation of Transcranial Doppler (TCD) screening and chronic transfusions in patients with SCD, 11% of individuals with the disease experienced symptomatic stroke before the age of 20.[5] With the introduction of TCD screening guidelines and transfusions, this risk has decreased [6] Even so, the global sickle cell population has continued to increase by 41.4% between 2000 to 2021, reaching 7.74 million individuals. [4] Within this expanding population, children bear the highest mortality burden and significant disability, positioning SCD as a severe economic burden and a public health issue.[4]

In the U.S., these challenges are intensified by complex sociodemographic and structural factors, where SCD predominantly affects African American communities, a racial group with one of the lowest household incomes, historically limited access to healthcare, and inadequate health infrastructure.[1,7,8] Social Determinants of Health (SDOH), including education, income, residence in high-poverty ZIP codes, and health insurance status, potentially contribute to disparities in stroke prevention and treatment outcomes for pediatric patients with SCD. [1,9,10]

Current treatment options for patients with SCD and cerebral vasculopathy, such as Moyamoya syndrome, primarily focus on preventing stroke and managing symptoms. Standard therapies for primary stroke prevention include monthly blood transfusions and oral

hydroxyurea. [11–13] For patients with diagnosed cerebral vasculopathy who have experienced cerebral ischemia, additional evaluation and treatments are provided, which may include cerebral revascularization surgery (CRS) and stem cell transplant.[14,15] However, research shows that access to care for patients with SCD is limited by various sociodemographic variables, further exacerbating disparities in care and outcomes. [1,16]

While extensive literature exists on the health disparities observed in SCD alone, there is limited discussion on the impact of the SDOH in patients with SCD and cerebral vasculopathy. This study aims to address this gap, focusing on how specific measures of SDOH affects the treatment and outcomes of children with SCD and cerebral vasculopathy.

## 2 METHODS

### 2.1 Patient Selection

Data from a previous retrospective, multicenter study was utilized to identify differences in treatment outcomes in pediatric patients with SCD and cerebral vasculopathy. [14]

Patients with SCD and moyamoya syndrome who were determined to be at risk for strok (including screening transcranial doppler (TCD) > 200cm/s or history of previous CVE) via their center's SCD screening program and initiated stroke prevention therapy between the ages aged 0–18 were included. Patients were identified through electronic medical record (EMR) data, as previously described. [14] Exclusion criteria included: 1) other central nervous system pathology not related to SCD or stroke or 2) less than one year of hematology clinic follow-up. Follow-up continued until the earliest of December 31, 2018, or the last known hematology or neurosurgery encounter. For time-to-event analyses, patients were followed until their first CVE. Patients were treated per their center's protocol to decrease their risk for stroke either with regular red blood cell transfusions or hydroxyurea (HU) therapy, with evaluation for CRS or hematopoietic stem cell transplant per center's practice.

### 2.2 Patient Demographics and Social Determinants of Health

Social Determinants of Health variables collected included sex, presence of household smokers, ZIP codes, and health insurance status. Median and mean income figures were estimated based on ZIP codes and data from the 2017 US Census Bureau's American Community Survey 5-Year-Projection.[17] Income distribution metrics were also derived from these ZIP codes, offering a broader perspective on the socioeconomic landscape.

Furthermore, ZIP codes were used to approximate the geographical distance between the center of each ZIP code and the designated treatment center. This was quantified in miles through the application of Google Maps. This distance estimation facilitated the assessment of potential geographical barriers that patients might face in accessing the treatment center. Health insurance status was categorized as private, Medicaid/Medicare, other, uninsured, or unknown. Patients categorized as “other” included those with Tricare, both Medicaid/Medicare and Private insurance, and both Medicaid/Medicare and Tricare. These classifications were grouped in analyses due to the sparse number of events among individual insurance categories.

**2.3 Study Outcome**

The primary outcome was CVE, defined as stroke (symptomatic or silent) or TIA after treatment (medical vs. surgical) initation. Outcomes were identified via manual chart review.

**2.4 Statistical Analysis**

A full description of the statistical methods is provided in the *Supplementary Methods*.

The primary objective was to evaluate whether sociodemographic variables were associated with the risk of CVEs in pediatric patient with SCD in the follow up period. CVEs included transient ischemic attacks, ischemic strokes, hemorrhagic strokes, and events of unknown type. Descriptive statistics were stratified by CVE occurrence, with continuous data reported as medians (IQR) and categorical data as counts (percentages).

Univariate associations between each sociodemographic variable (income, insurance status, sex, household smoking, and distance to the treatment center) and CVE risk were assessed using separate Cox proportional hazards models. Patients were followed from study entry until the occurrence of their first CVE. Individuals who did not experience a CVE during follow-up were censored at the time of their last known observation or at last follow-up. Multivariable Cox models were subsequently fitted for insurance status, sex, and household smoking, adjusting for key clinical covariates known to influence CVE risk (age at treatment start, time of moyamoya diagnosis, prior CVE, and treatment type). For these analyses, treatment was modeled as a time-varying covariate to account for changes during follow-up. For multivariable inference, sparse insurance categories (uninsured and not specified) were combined with the "Other" category to improve model stability and are included as a control variable rather than for direct inference. Other sociodemographic variables (income, distance, race, and ethnicity) were not pursued in multivariable analyses due to negligible observed effects, ecological measurement limitations, or insufficient sample sizes for meaningful inference. Effect sizes are reported as hazard ratios (HR) with 95% confidence intervals (CI), and p-values $<0.05$ were considered statistically significant. Given the exploratory nature of this study, analyses were designed to identify potential associations and patterns rather than to support definitive causal inference; findings should therefore be interpreted with caution and viewed as hypothesis-generating.

Continuous variables with missing values (income [n = 3], distance [n = 2], and time of moyamoya diagnosis [n = 2]) were imputed using the mean of observed values. Categorical

variables with unspecified values were treated as a separate “missing” category and included as an explicit level in the analyses.

All analyses were performed in RStudio (version 2026.01.0 Build 392) using R version 4.5.2. Cox regression analyses were conducted using the ‘survival’ package for R (version 3.4-0).

## 3 RESULTS

### 3.1 Patient characteristics

A total of 140 patients were included in the analysis, comprising 75 (54%) female patients and 65 (46%) males. The median age at treatment initiation was 5.9 years (IQR: 3.8 – 8.6), ranging from 0.1 to 16.9 years. The median follow-up interval from the time of initial treatment start was 9.0 years (IQR: 5.2–12.7), spanning 0.5 to 24.1 years. In total, there were 1,279 patient-years of follow-up from the time of first treatment start to the last known follow-up. Among the 63 patients with available smoking exposure data, 15 (24%) had a smoker in their household. Initially, all patients received medical management with chronic transfusion therapy (CTT) or HU, while 78 (56%) subsequently underwent surgical revascularization after a median interval of 4.0 years (IQR: 1.5 – 7.3), ranging from 0.02 to 16.6 years. The estimated median income was $48,559 (IQR: $37,326 – $63,672), with a range of $15,089 to $137,547. The median estimated distance to the treatment center was 17.0 miles (IQR: 8.8 – 39.3), spanning from 1.5 to 952 miles.

### 3.2 Effect of SDOH on Treatment Outcome

Patients meeting inclusion criteria received their initial CVE-reducing medical management between January 1, 1990, and December 31, 2017. At study baseline, before stroke prevention treatment was initiated 98 patients (70%) had a history of CVE. During follow-up, 72 (51%) remained free of new CVEs, while 68 (49%) experienced at least one CVE after treatment initiation. The median time to first CVE after treatment initiation among patients with baseline CVE was 2.5 years (IQR: 1.3 – 4.5) and ranged from 0.02 to 14.9 years. Sociodemographic variables categorized by CVE status during follow-up are presented in **Table 1**.

Household income, distance to the hospital, sex and household smoking exposure were also subject to univariate analysis and did not exhibit significant hazard ratios. Estimated household income and distance to the hospital were not associated with new CVE occurrence, with hazard ratios of 1.00 per $1,000 increase in income (95% CI: 0.99–1.01) and 1.00 per 5-mile increase in distance (95% CI: 0.99–1.01), respectively.

Insurance status demonstrated possible heterogeneity in risk. Compared with patients insured through Medicaid/Medicare, privately insured patients had a lower but non-significant hazard (HR 0.83, 95% CI: 0.46–1.48). Uninsured patients exhibited a higher hazard (HR 4.15, 95% CI: 2.03–8.47); however, this estimate was based on only two patients, contributing 18.5 patient-years of follow-up, and should therefore be interpreted with substantial caution. Patients with undocumented insurance status also experienced a high proportion of CVEs (5 of 6 patients, 83%), contributing 14 events over 85 patient-years. Because this category may include uninsured individuals but individual status could not be reliably ascertained, it was

treated as a missing indicator in the primary analysis; the corresponding hazard ratio relative to Medicaid/Medicare was imprecise (HR 1.66, 95% CI: 0.65–4.25). Male sex was associated with a numerically higher hazard compared with female patients (HR 1.27, 95% CI: 0.79–2.05), though estimates were imprecise. Household smoking exposure was similarly associated with a higher but non-significant hazard (HR 1.18, 95% CI: 0.53–2.61), with substantial missingness limiting interpretation.

Based on these univariate results, further multivariable modeling focused on insurance status, sex, and household smoking. Other sociodemographic variables either had negligible effects and are subject to ecological bias (income, distance) or were too sparse for meaningful inference (race, ethnicity). For insurance, further inference was not pursued for uninsured or not-specified patients due to very small numbers; these observations were combined with the "Other" category, which served as a control variable to support model stability rather than for inference.

Multivariable modeling largely mirrored the univariate results. When adjusted for key clinical factors, male sex had a larger but non-significant effect size compared to the univariate model (HR 1.40, 95% CI: 0.86–2.28). The contrast of privately insured versus Medicaid/Medicare remained largely unchanged (HR 0.85, 95% CI: 0.47–1.54), and the effect estimate for presence of a household smoker was also consistent (HR 1.18, 95% CI: 0.56–2.48). **Figure 1** presents the probability of remaining free of CVEs over time for the overall sample and stratified by the sociodemographic variables retained in the final model.

### 3.3 Comparison of SDOH by treatment modality received

Distributions of sex, race, ethnicity, and presence of household smokers were similar between groups. The CRS group tended to have a slightly higher estimated median income compared to patients who received medical management alone, but the difference was not significant ($49,741 [IQR: $40,724 – $64,905] vs. $46,705 [IQR: $31,238 – $63,008], *p*=.083; **Figure S1**). Sensitivity analyses using 1,000 Monte Carlo simulations, incorporating ACS-reported margins of error based on 90% confidence intervals, estimated a median difference of $3,427 (90% interval: $1,371–$5,477). The CRS group also tended to have a longer distance to the treatment center compared to the medical group, but the difference was not significant (20.6 miles [IQR: 7.3 – 59.4] vs. 15.5 miles [IQR: 9.7 – 24.8]

### 3.4 Effect of SDOH on age at treatment start

None of the sociodemographic variables exhibited a statistically significant influence on the age at which medical treatment was initiated (**Table S1** and **Figure S2**). Furthermore, no statistically significant impacts on the age at which CRS was undertaken were identified (**Table S2** and **Figure S3**).

### 3.5 Effect of SDOH on total treatment time

Most patients were on medical management with CTT and/or HU for their entire follow-up period (79% [111/140]). Of the 29 patients that had intermittent use of medical management, the median proportion of time spent on treatment relative to their follow-up length was 85.0% (IQR: 59%-98.8%) and ranged from ~0% to 99.6%. After conducting Cox regression analyses, none of the sociodemographic variables had a statistically significant impact on

treatment cessation. Although not significant, patients with private insurance tended to have a lower rate of treatment cessation compared to patients on Medicaid/Medicare (HR=0.37 [95% CI: 0.11-1.24]). Uninsured patients had the highest rate of treatment cessation, but data is again limited to only 2 patients. No notable differences were observed among the other subgroups by insurance status. Regression results are displayed in **Table S3**, and rates of treatment cessation partitioned by sociodemographic variables are displayed visually in **Figure S4**.

### 3.6 Illustrative Cases: Uninsured Patients

Two patients in the cohort were uninsured. One was a male patient aged 7.9 years at treatment initiation who received CTT, and the other was a female patient aged 4.6 years at the start of HU. Both patients experienced CVEs during follow-up (approximately 9 years for each), including hemorrhagic stroke and transient ischemic attack. Although uninsured, both patients had estimated household incomes above the cohort median ($52,234 and $93,434, respectively).

For the male patient, approximately 38.5% of follow-up time was spent off disease-modifying therapy (CTT or HU), and the hemorrhagic stroke occurred during a period when CTT was not being administered, 3.4 years after CTT initiation. The female patient experienced a transient ischemic attack 1.3 years after HU initiation and prior to the start of CTT. Both patients demonstrated disease progression and subsequently underwent cerebrovascular revascularization surgery following their initial CVEs. No additional CVEs

were observed after revascularization, with 5.75 and 6.7 years of remaining follow-up, respectively.

## 4 DISCUSSION

In our cohort of 140 pediatric patients with SCD and cerebral vasculopathy, sociodemographic factors such as estimated household income, distance to the treatment center, sex, and household smoking exposure were not significantly associated with the risk of CVEs, age at treatment initiation, or treatment adherence. Insurance status showed some variability in CVE risk; however, the small number of uninsured patients precluded reliable inference, and this category was not included in multivariable modeling. Multivariable models focusing on sex, household smoking, and insurance largely mirrored the univariate results, with none of these factors reaching statistical significance. Male sex and the presence of a household smoker were associated with numerically higher hazards for CVEs, but effect estimates were imprecise. Overall, these findings suggest that, within this cohort, commonly measured sociodemographic variables had no discernible impact on treatment outcomes. However, the limited sample size, incomplete data for some variables, and small numbers in certain subgroups mean that modest but potentially clinically meaningful effects cannot be ruled out, and formal equivalence cannot be established. These results should therefore be interpreted as exploratory and hypothesis-generating, providing a foundation for larger studies to more fully evaluate the influence of sociodemographic factors on clinical outcomes in this population.

It is important to recognize the bidirectional relationship between disease management and the social environment. The challenges discussed are intensified by complex sociodemographic and structural factors. Sickle cell disease predominantly affects African American communities, which have been disproportionately impacted by structural racism, contributing to longstanding health inequities. These inequities include historically limited access to healthcare and inadequate health infrastructure. Care fragmentation may be exacerbated by structural barriers such as appointment and medication costs, lost wages associated with medical visits, and disruptions in insurance coverage during the transition from pediatric to adult care, all of which can limit access to and continuity of care for pediatric patients with SCD, a population at risk for significant chronic morbidity. [18–20]

Prior literature indicates that lack of insurance and limited access to comprehensive sickle cell care centers may contribute to healthcare inequities among patients with SCD and cerebral vasculopathy.[1] A 2021 study on pediatric patients with Moyamoya disease found that patients with private insurance were more likely to receive care.[21] In our cohort, the adjusted hazard ratio for CVEs among privately insured patients compared with those on Medicaid/Medicare was 0.85 (95% CI: 0.47–1.54). While the point estimate suggests a possible lower risk of CVEs among privately insured patients, the confidence interval is wide and includes the null, reflecting substantial uncertainty. These data do not provide definitive evidence that insurance type influences CVE outcomes, but they also do not rule out a meaningful effect. Although inference is very limited for uninsured patients (n = 2, contributing 18.5 patient-years of follow-up), these observations are consistent with the broader concept that lack of insurance may restrict access to preventative and comprehensive

care. Larger studies are needed to more reliably evaluate the impact of insurance status on outcomes in this population.

We also found that treatment cessation may have varied by insurance status. Although not significant, patients with private insurance tended to have a lower rate of treatment cessation compared to patients on Medicaid/Medicare (HR=0.37 [95% CI: 0.11-1.24]). Additionally, uninsured patients had the highest treatment cessation rate, but data was again very limited (n=2). These findings mirror previous studies on patient adherence to treatment. Specifically, studies have shown that low income and lack of insurance are related to a patient's adherence or time on treatment, supporting that the ability to afford prescription and treatment is crucial in medical compliance.[22–24] Uninsured patients likely experience higher costs and limited access to providers compared to patients with private insurance.[23,25] For pediatric patients, it is also important to consider additional barriers to compliance to treatment plans or attendance to medical care visits. For example, the financial constraints on parents due to missing work and transportation barriers for the young patient. [26,27] In chronic conditions such as SCD, regular follow up and treatment are important to reduce adverse outcomes, yet it may not be possible due to these barriers.[28]

Our study found a higher incidence of CVEs in male patients, but this result was not statistically significant (HR = 1.40, 95% CI: 0.86 – 2.28). Current literature suggests similar results, specifically, male patients with HbSS had worse outcomes and disease course compared to females.[29,30] In one study, male patients had increased hospital stays, more blood transfusions, and increased risk of cerebrovascular disease including vascular malformations and stroke. [29] Gender differences in CVE risk may be influenced by nitric oxide production,

which increases after puberty as a compensatory response to vascular injury.[31] Hormonal production likely contributes to differences in nitric oxide production and vascular response, potentially explaining the gender-related outcome differences.[32]

Income and distance from the treatment center did not significantly influence the incidence of CVEs in our study. This contrasts with previous studies that reported worse outcomes for low-income patients and those living farther from treatment centers.[33] According to Reshetnyak et al., income, ZIP code poverty, and other factors were associated with a higher risk of stroke.[34] Additionally, increased distance from the treatment center intertwined with the financial burden associated with chronic treatment can be compounded by transportation barriers. [35,36] These factors often influence access to care, leading to unfavorable outcomes. The minimal observed impact of income and distance in our cohort may reflect the limited sample size, potential referral bias, and the use of area-level proxies rather than individual-level income data.

There was not a statistically significant difference in CVE with the presence of a household smoker. This was a surprising finding as literature posits that tobacco smoke negatively affects children with SCD. For example, one study found that children with SCD who were exposed to secondhand smoke were more likely to be hospitalized for an acute sickle cell crisis compared to those who were not exposed.[37] Literature also supports that secondhand smoke is associated with pulmonary function abnormalities and acute chest syndrome in patients with SCD.[38] This result may be secondary to underreporting of tobacco use, differences in the severity of exposure, small sample size, or various other factors.

**Limitations**

This study is limited by its retrospective design and relatively small sample size. It only included sickle cell disease patients who developed moyamoya syndrome, which could introduce selection bias. The presence of missing data, specifically the incomplete insurance data, could significantly affect the results. Key social determinants of health exposures (parental education, neighborhood poverty index, transportation insecurity, missed-visit frequency, health system characteristics) were not available, and no inferences can be made regarding their impact. Moreover, the exact address of the patient was not known so income and distance from the treatment center were estimated from ZIP codes. The study's enrollment spanned nearly 28 years, during which the impact of socioeconomic variables, such as income and insurance status, may have varied depending on the prevailing economic conditions. The included proxies of SDOH were obtained at intake, so change throughout the follow-up period were not able to studied. Notably, the population being studied is homogenous, consisting mainly of African American and Hispanic individuals, who typically have lower income levels. Future studies that include a larger number of uninsured individuals as well as individuals from higher income levels would increase the strength of outcome comparison between groups. Additionally, the outcomes of the treatment may have been influenced by specific characteristics of the treatment centers. It is challenging to fully comprehend the impact of the center on the outcome due to the limited number of observations and the diversity in treatment approaches.

In contrast with existing literature where several factors affect outcomes and increase disparities, this study found no definitive associations between the included sociodemographic variables and risk of CVE or other aspects of treatment. Although

uninsured patients appeared more likely to experience CVEs, this observation was based on data from only two patients. As a result, the effect of uninsured status is likely overestimated and should be examined in a larger sample. Most of the variation in patient outcomes was likely driven by known factors, such as timing of treatment and treatment modalities received, which were shown to have a large effect on patient outcomes in our previous report of the SiSCRS study.

**Conclusion**

This study provides descriptive insight into the sociodemographic characteristics of pediatric patients with SCD and cerebral vasculopathy, as well as patterns in clinical outcomes and treatment receipt. Findings highlight variability in SDOH and their potential influence on access to care, treatment, and adherence. Analyses using ZIP code-level proxies did not reveal clear trends, but this should not be interpreted as evidence of no effect, underscoring the need for prospective studies with individual-level data. While most variables showed no definitive associations, effect sizes for patient sex, household smoking, and insurance were potentially clinically meaningful and warrant further study in larger cohorts. These initial descriptive results point to the need for further study to ensure consistent quality and accessible care

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**References**


1. Lee L, Smith-Whitley K, Banks S, Puckrein G. Reducing Health Care Disparities in Sickle Cell Disease: A Review. *Public Health Rep*. 2019;134(6):599-607. doi:10.1177/0033354919881438

2. Lubeck D, Agodoa I, Bhakta N, et al. Estimated Life Expectancy and Income of Patients With Sickle Cell Disease Compared With Those Without Sickle Cell Disease. *JAMA Netw Open*. 2019;2(11):e1915374. doi:10.1001/jamanetworkopen.2019.15374

3. Pinto VM, Balocco M, Quintino S, Forni GL. Sickle cell disease: a review for the internist. *Intern Emerg Med*. 2019;14(7):1051-1064. doi:10.1007/s11739-019-02160-x

4. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000–2021: a systematic analysis from the Global Burden of Disease Study 2021. *Lancet Haematol*. 2023;10(8):e585-e599. doi:10.1016/S2352-3026(23)00118-7

5. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular Accidents in Sickle Cell Disease: Rates and Risk Factors. *Blood*. 1998;91(1):288-294. doi:10.1182/blood.V91.1.288

6. Guy D, Bagnall R, Morgan RL, et al. Impact of transcranial Doppler screening on stroke prevention in children and adolescents with sickle cell disease: A systematic review and meta-analysis. *Blood Rev*. 2025;69:101253. doi:10.1016/j.blre.2024.101253

7. Kassim AA, DeBaun MR. Sickle Cell Disease, Vasculopathy, and Therapeutics. *Annu Rev Med*. 2013;64(1):451-466. doi:10.1146/annurev-med-120611-143127

8. CDC. Data and Statistics on Sickle Cell Disease. Sickle Cell Disease (SCD). May 22, 2024. Accessed October 22, 2024. https://www.cdc.gov/sickle-cell/data/index.html

9. Lee H, Kim D, Lee S, Fawcett J. The concepts of health inequality, disparities and equity in the era of population health. *Appl Nurs Res*. 2020;56:151367. doi:10.1016/j.apnr.2020.151367

10. Social Determinants of Health - Healthy People 2030 | health.gov. Accessed March 6, 2023. https://health.gov/healthypeople/priority-areas/social-determinants-health

11. Lee MT, Piomelli S, Granger S, et al. Stroke Prevention Trial in Sickle Cell Anemia (STOP): extended follow-up and final results. *Blood*. 2006;108(3):847-852. doi:10.1182/blood-2005-10-009506

12. Bushnell C, Kernan WN, Sharrief AZ, et al. 2024 Guideline for the Primary Prevention of Stroke: A Guideline From the American Heart Association/American Stroke Association. *Stroke*. 2024;55(12):e344-e424. doi:10.1161/STR.0000000000000475

13. Ware RE, Davis BR, Schultz WH, et al. TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, randomised controlled trial. *Lancet Lond Engl*. 2016;387(10019):661-670. doi:10.1016/S0140-6736(15)01041-7

14. Aldana PR, Hanel RA, Piatt J, et al. Cerebral revascularization surgery reduces cerebrovascular events in children with sickle cell disease and moyamoya syndrome: Results of the stroke in sickle cell revascularization surgery retrospective study. *Pediatr Blood Cancer*. 2023;70(7):e30336. doi:10.1002/pbc.30336

15. Khemani K, Katoch D, Krishnamurti L. Curative Therapies for Sickle Cell Disease. *Ochsner J*. 2019;19(2):131-137. doi:10.31486/toj.18.0044

16. Pokhrel A, Olayemi A, Ogbonda S, Nair K, Wang JC. Racial and ethnic differences in sickle cell disease within the United States: From demographics to outcomes. *Eur J Haematol*. 2023;110(5):554-563. doi:10.1111/ejh.13936

17. Bureau UC. Data Profiles. Census.gov. Accessed May 3, 2025. https://www.census.gov/programs-surveys/acs/

18. Catanzarite A, Bouck JR, Matthes M, et al. Impact of Neighborhood Disadvantage on Preventive and Acute Care Utilization in Sickle Cell Disease. *Pediatr Blood Cancer*. 2025;72(1):e31422. doi:10.1002/pbc.31422

19. Tan JY, San BJ, Yeo YH, et al. Social Vulnerability and Sickle Cell Disease Mortality in the US. *JAMA Netw Open*. 2024;7(9):e2440599. doi:10.1001/jamanetworkopen.2024.40599

20. Long KA, Blakey AO, Amaro CM, et al. Bidirectional processes linking social determinants of health and pediatric sickle cell anemia management: A qualitative study. *Pediatr Blood Cancer*. 2023;70(10):e30539. doi:10.1002/pbc.30539

21. Chiu R, Chaker A, McGuire LS, et al. Socioeconomic Inequities in the Surgical Management of Moyamoya Disease. *World Neurosurg*. 2021;155:e188-e195. doi:10.1016/j.wneu.2021.08.033

22. Fernandez-Lazaro CI, Adams DP, Fernandez-Lazaro D, Garcia-González JM, Caballero-Garcia A, Miron-Canelo JA. Medication adherence and barriers among low-income, uninsured patients with multiple chronic conditions. *Res Soc Adm Pharm*. 2019;15(6):744-753. doi:10.1016/j.sapharm.2018.09.006

23. Huguet N, Hodes T, Liu S, et al. Impact of Health Insurance Patterns on Chronic Health Conditions Among Older Patients. *J Am Board Fam Med JABFM*. 2023;36(5):839-850. doi:10.3122/jabfm.2023.230106R1

24. Rohatgi KW, Humble S, McQueen A, et al. Medication adherence and characteristics of patients who spend less on basic needs to afford medications. *J Am Board Fam Med JABFM*. 2021;34(3):561. doi:10.3122/jabfm.2021.03.200361

25. McWilliams JM. Health Consequences of Uninsurance among Adults in the United States: Recent Evidence and Implications. *Milbank Q*. 2009;87(2):443-494. doi:10.1111/j.1468-0009.2009.00564.x

26. Shi Q, Castillo F, Viswanathan K, Kupferman F, MacDermid JC. Facilitators and Barriers to Access to Pediatric Medical Services in a Community Hospital. *J Prim Care Community Health*. 2020;11:2150132720904518. doi:10.1177/2150132720904518

27. Wolf ER, O'Neil J, Pecsok J, et al. Caregiver and Clinician Perspectives on Missed Well-Child Visits. *Ann Fam Med*. 2020;18(1):30. doi:10.1370/afm.2466

28. Webb J. Social aspects of chronic transfusions: addressing social determinants of health, health literacy, and quality of life. *Hematol Am Soc Hematol Educ Program*. 2020;2020(1):175-183. doi:10.1182/hematology.2020000104

29. DI Mauro M, Nardo‐marino A, Stuart-Smith S, et al. MALE PATIENTS WITH SCD HAVE A HIGHER RISK OF CEREBROVASCULAR DISEASE, INCREASED INFLAMMATORY MARKERS, AND POORER RESPONSE TO HYDROXYUREA. *HemaSphere*. 2023;7(Suppl):e81245b4. doi:10.1097/01.HS9.0000967988.81245.b4

30. Masese RV, Bulgin D, Knisely MR, et al. Sex-based differences in the manifestations and complications of sickle cell disease: Report from the Sickle Cell Disease Implementation Consortium. *PLoS ONE*. 2021;16(10):e0258638. doi:10.1371/journal.pone.0258638

31. Nevzati E, Shafighi M, Bakhtian KD, Treiber H, Fandino J, Fathi AR. Estrogen induces nitric oxide production via nitric oxide synthase activation in endothelial cells. *Acta Neurochir Suppl*. 2015;120:141-145. doi:10.1007/978-3-319-04981-6_24

32. Krause DN, Duckles SP, Pelligrino DA. Influence of sex steroid hormones on cerebrovascular function. *J Appl Physiol*. 2006;101(4):1252-1261. doi:10.1152/japplphysiol.01095.2005

33. Kelly C, Hulme C, Farragher T, Clarke G. Are differences in travel time or distance to healthcare for adults in global north countries associated with an impact on health outcomes? A systematic review. *BMJ Open*. 2016;6(11):e013059. doi:10.1136/bmjopen-2016-013059

34. Reshetnyak E, Ntamatungiro M, Pinheiro LC, et al. Impact of Multiple Social Determinants of Health on Incident Stroke. *Stroke*. 2020;51(8):2445-2453. doi:10.1161/STROKEAHA.120.028530

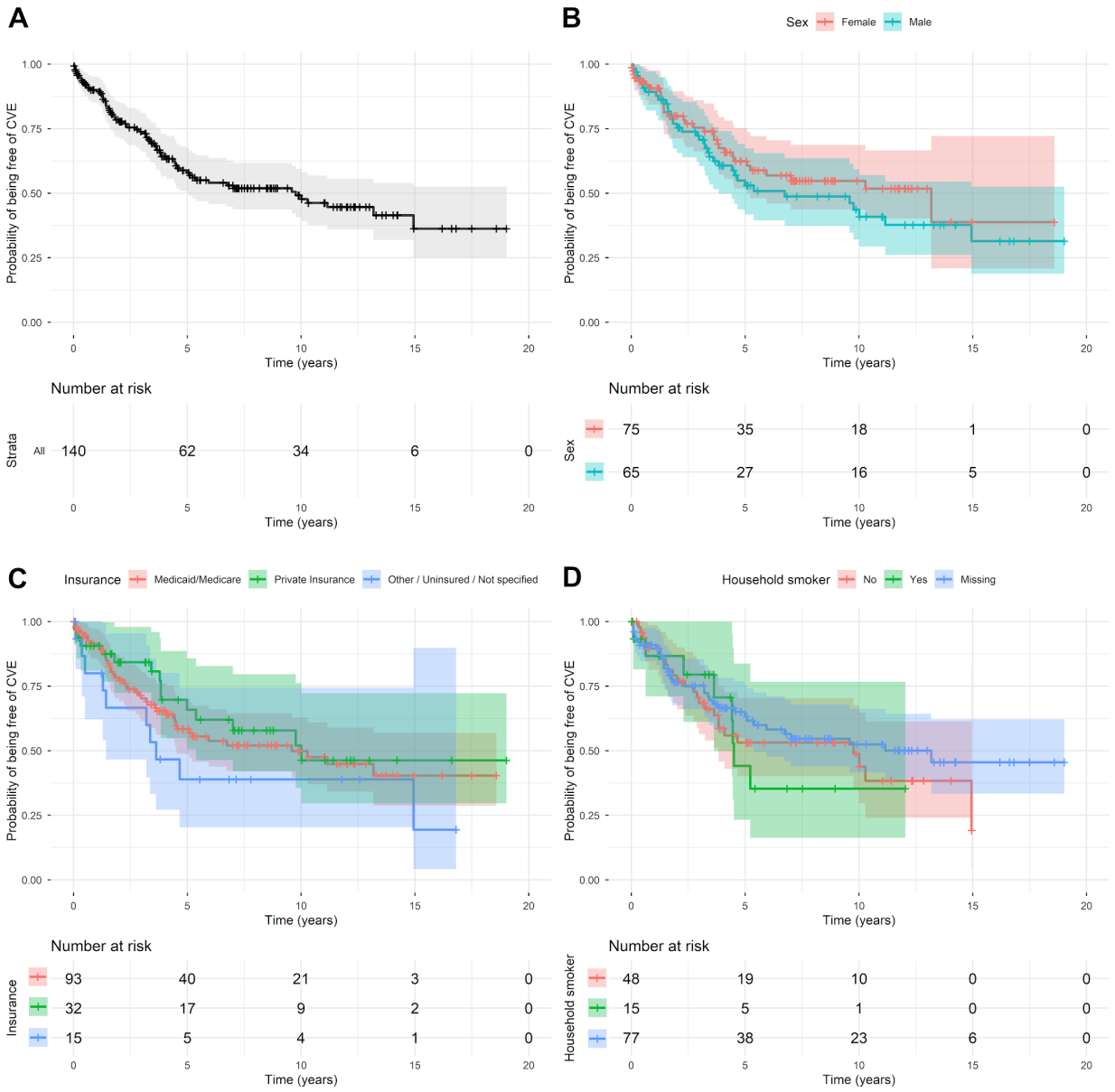
35. Keeves J, Ekegren CL, Beck B, Gabbe BJ. The relationship between geographic location and outcomes following injury: A scoping review. *Injury*. 2019;50(11):1826-1838. doi:10.1016/j.injury.2019.07.013

36. Creary M, Williamson D, Kulkarni R. Sickle Cell Disease: Current Activities, Public Health Implications, and Future Directions. *J Womens Health*. 2007;16(5):575-582. doi:10.1089/jwh.2007.CDC4

37. West DC, Romano PS, Azari R, Rudominer A, Holman M, Sandhu S. Impact of Environmental Tobacco Smoke on Children With Sickle Cell Disease. *Arch Pediatr Adolesc Med*. 2003;157(12):1197. doi:10.1001/archpedi.157.12.1197

38. Sadreameli SC, Kopp BT, Creary SE, Eakin MN, McGrath-Morrow S, Strouse JJ. Secondhand Smoke Is an Important Modifiable Risk Factor in Sickle Cell Disease: A Review of the Current Literature and Areas for Future Research. *Int J Environ Res Public Health*. 2016;13(11):1131. doi:10.3390/ijerph13111131

**Figure 1.** Probability of being free of CVE over time across socioeconomic variables. Probability of being free of CVE based on **A)** Overall patient sample, **B)** stratified by sex, **C)** stratified by insurance status, and **D)** stratified by presence or absence of a household smoker. Shaded areas around lines represent 95% confidence bands.



## TABLES

**Table 1**. Univariate analyses and descriptive patient characteristics stratified by CVE occurrence.

| Variable | 0 CVE (N=72) | ≥1 CVE (N=68) | Hazard Ratio | 95% CI | P-value |
|---|---|---|---|---|---|
| Income ($USD) | $49,394 (35,575 – 65,891) [N=70] | $47,161 (37,777 – 58,784) [N=67] | 1.00 *(per $1,000)* | (0.99 – 1.01) | .907 |
| *Sensitivity Analysis** | - | - | 1.00 *(per $1,000)* | (90% CI: 1.00 – 1.00) | - |
| Health insurance† | - | - | - | - | - |
| Medicaid/Medicare | 49 / 71 (69%) | 43 / 63 (68%) | *Reference* | | |
| Private | 18 / 71 (25%) | 15 / 63 (24%) | 0.83 | (0.46 – 1.48) | .519 |

| | | | | | |
|---|---|---|---|---|---|
| Other | | | 0.94 | (0.26 – 3.49) | .932 |
| Tricare | 1 / 71 (1%) | 0 / 63 (0%) | - | - | - |
| Medicaid/ Medicare+ Private | 3 / 71 (4%) | 2 / 63 (3%) | - | - | - |
| Medicaid/ Medicare+ Tricare | 0 / 71 (0%) | 1 / 63 (2%) | - | - | - |
| Uninsured | 0 / 71 (0%) | 2 / 63 (3%) | 4.15 | (2.03 – 8.47) | <.001 |
| Not specified / Missing | 1 (1%) | 5 (7%) | 1.66 | (0.65 – 4.25) | .288 |
| Distance to hospital (miles) | 20.0 (11.0 – 39.4) [N=71] | 14.7 (6.8 – 35.4) [N=67] | 1.00 *(per 5 miles)* | (0.99 – 1.01) | .964 |
| Sex | - | - | - | - | - |
| Female | 43 (60%) | 32 (47%) | *Reference* | | |

| | | | | | |
|---|---|---|---|---|---|
| Male | 29 (40%) | 36 (53%) | 1.27 | (0.79 – 2.05) | .329 |
| Race† | - | - | - | - | - |
| African American | 63 / 66 (95%) | 59 / 63 (94%) | - | - | - |
| African/Native American | 1 / 66 (2%) | 0 / 63 (0%) | - | - | - |
| White | 0 / 66 (0%) | 1 / 63 (2%) | - | - | - |
| Other | 2 / 66 (3%) | 3 / 63 (5%) | - | - | - |
| Not specified / Missing | 6 (8%) | 5 (7%) | - | - | - |
| Ethnicity† | - | - | - | - | - |
| Hispanic/Latino | 2 / 60 (3%) | 2 / 63 (3%) | - | - | - |
| Non-Hispanic /Latino | 58 / 60 (97%) | 60 / 63 (95%) | - | - | - |
| Other | 0 / 60 (0%) | 1 / 63 (2%) | - | - | - |
| Not specified / Missing | 12 (17%) | 5 (7%) | - | - | - |
| Smoker in Household | - | - | - | - | - |

| | | | | | |
|---|---|---|---|---|---|
| No | 23 / 30 (77%) | 25 / 33 (76%) | *Reference* | | |
| Yes | 7 / 30 (23%) | 8 / 33 (24%) | 1.18 | (0.53 – 2.61) | .356 |
| Not specified / Missing | 42 (58%) | 35 (51%) | 0.78 | (0.47 – 1.31) | .692 |

Descriptive statistics are reported as event count (percentage of total) or as median (IQR). Adjusted denominators are reported for variables with missing observations, and the number of missing observations is separately recorded. Inferential statistics are reported as hazard ratios derived from separate Cox regression models fit for each predictor variable.

* Median incomes were extracted from the 2017 U.S. Census Bureau American Community Survey (ACS) 5-Year Estimates. To account for uncertainty in ZIP-code–level income, a Monte Carlo sensitivity analysis was performed: for each of 1,000 iterations, ZIP-code medians were randomly sampled from normal distributions defined by the reported ACS median and its 90% margin of error, and a Cox proportional hazards model was fit using the simulated values.

† Hazard ratios are relative to the reference category (Medicaid/Medicare). Some categories include very few patients or events; in particular, “Uninsured” includes only 2 patients, and “Not specified / Missing” reflects patients whose insurance status could not be reliably ascertained. Sparse categories were retained for descriptive purposes but should not be interpreted as robust

estimates and were not included in subsequent multivariable models.

† Data too sparse for meaningful comparisons between categories

**Table 2**. Multivariable analyses of socioeconomic variables on CVE occurrence.

| Model | Variable | HR | 95% CI | P-value |
|---|---|---|---|---|
| 1: Sex | Male (ref = Female) | 1.40 | 0.86 – 2.28 | 0.182 |
| 2: Household Smoker | Yes (ref = No) | 1.18 | 0.56 – 2.48 | 0.654 |
| | Unknown | 0.89 | 0.53 – 1.51 | 0.678 |
| 3: Insurance | Private (ref = Medicaid/Medicare) | 0.85 | 0.47 – 1.54 | 0.591 |
| | Other / Unknown / Uninsured | 1.33 | 0.61 – 2.88 | 0.269 |

All models were adjusted for age at treatment start, time of moyamoya diagnosis, interventions received (modeled as a time-varying covariate), and history of prior CVE.

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**Table 3**. Univariate analyses and descriptive patient characteristics stratified by treatment modality.

| Variable | Medical (N=62) | Surgery (N=78) | P-value |
|---|---|---|---|
| Income ($USD) | $46,705 (31,238 – 63,008) [N=61] | $49,741 (40,724 – 64,905) [N=76] | .083 |
| *Sensitivity Analysis** | - | - | *Difference: $3,427 (90% CI: $1,371–5,477)* |
| Health insurance | - | - | *NA* |
| Medicaid/Medicare | 44 / 61 (72%) | 48 / 73 (66%) | |
| Private | 13 / 61 (21%) | 20 / 73 (27%) | |
| Tricare | 1 / 61 (2%) | 0 / 73 (0%) | |
| Medicaid/Medicare+Private | 2 / 61 (3%) | 3 / 73 (4%) | |
| Medicaid/Medicare+Tricare | 1 / 61 (2%) | 0 / 73 (0%) | |

| | | | |
|---|---|---|---|
| Uninsured | 0 / 61 (0%) | 2 / 73 (3%) | |
| Not specified (Unknown) | 1 (2%) | 5 (6%) | |
| Distance to hospital (miles) | 15.5 (9.7 – 24.8) | 20.6 (7.3 – 59.4) [N=76] | .169 |
| Sex | - | - | .497 |
| Female | 31 (50%) | 44 (56%) | |
| Male | 31 (50%) | 34 (44%) | |
| Race | - | - | *NA* |
| African American | 58 / 59 (98%) | 64 / 70 (91%) | |
| African/Native American | 0 / 59 (0%) | 1 / 70 (1%) | |
| White | 1 / 59 (2%) | 0 / 70 (0%) | |
| Other | 0 / 59 (0%) | 5 / 70 (7%) | |
| Not specified | 3 (5%) | 8 (10%) | |
| Ethnicity | - | - | *NA* |
| Hispanic/Latino | 1 / 56 (2%) | 3 / 67 (4%) | |
| Non-Hispanic/ Latino | 55 / 56 (98%) | 63 / 67 (94%) | |

| | | | |
|---|---|---|---|
| Other | 0 / 56 (0%) | 1 / 67 (1%) | |
| Not specified | 6 (10%) | 11 (14%) | |
| Smoker in Household | - | - | .383 |
| No | 23 / 28 (82%) | 25 / 35 (71%) | |
| Yes | 5 / 28 (18%) | 10 / 35 (29%) | |
| Not specified | 34 (55%) | 43 (55%) | |

Descriptive statistics are reported as event count (percentage of total) or as median (IQR). Adjusted sample size values are reported for variables with missing observations. P-values are computed using Mann-Whitney U tests for continuous data or Fisher's exact test for categorical data. NA = data not available.

* Median household incomes were obtained from the 2017 U.S. Census Bureau American Community Survey (ACS) 5-year estimates. To account for uncertainty in ZIP-code–level income estimates, we conducted a Monte Carlo sensitivity analysis. Across 1,000 iterations, ZIP-code median incomes were randomly sampled from normal distributions parameterized by the ACS-reported median and its associated 90% margin of error. The resulting distribution of between-group income differences was summarized by the simulated median difference and a 90% simulation interval, representing the range of plausible group differences attributable to uncertainty in ZIP-code–level income estimates.