Neighborhood Deprivation and Racial Cohesion are Associated with Reduced Acute Chest Syndrome Recurrence in Sickle Cell Disease Children

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Abstract

Background: Acute chest syndrome (ACS) is the leading cause of death for children with sickle cell disease (SCD). Recurrent ACS has detrimental effects on pulmonary health and healthcare costs. Neighborhood characteristics affect the outcomes of many pediatric chronic diseases, but their role in SCD is not well investigated. In this study, we investigated the effects of area-level socioeconomic deprivation and racial composition on the recurrence of ACS. Study design: We performed a retrospective cross-sectional analysis of clinical data from a large pediatric SCD center. Patients' residential addresses were geocoded and linked to a composite Area Deprivation Index (ADI) and percent African American population at the level of Census block groups. The association of recurrent ACS with neighborhood characteristics was evaluated using logistic regression analysis. Results: The sample included 709 children with SCD. Residence in a socioeconomically deprived neighborhood was associated with 27% less risk of recurrent ACS, and residence in a predominantly African American neighborhood was associated with 41% less risk of ACS recurrence. The racial composition explained the protective effect of living in a high-deprivation area after adjusting for sociodemographic and clinical covariates. Demographic and clinical factors associated with recurrent ACS included older age, male gender, asthma, hydroxyurea use, and chronic transfusion therapy. Conclusions: This is the first study to report a protective effect of residing in a predominantly African American community for ACS recurrence. Further prospective studies are needed to confirm the association and to understand the mechanisms of such relationship.

INTRODUCTION

Sickle cell disease (SCD), an inherited red blood cell disorder, affects approximately 100,000 individuals in the United States and 20 million worldwide, most of them of African ancestry.[1] The condition is associated with lifelong fatigue, pain, infections, and diminished quality of life and survival, even in developed countries.[2,3] Since the use of prophylactic antibiotics has reduced infection-related pediatric mortality from SCD, the focus has shifted to acute chest syndrome (ACS), which is currently the leading cause of death in children with SCD in high-income countries.[4] ACS peaks between 2 and 4 years of age and is associated with significant morbidity (an average of 7 days hospital stay for each ACS admission), and even mortality. Approximately half of SCD patients develop at least one episode of ACS, and more than half of those have further recurrences.[5] Repeated ACS is associated with increased lung injury and worsening restrictive pulmonary disease, with a dose-response effect.[6,7] The risk of ACS recurrence is associated with clinical factors such as asthma, degree of anemia, and white blood count.[8]There is some evidence for environmental risks as well, such as tobacco smoke, high ozone levels, and low carbon monoxide exposure.[9,10] The role of neighborhood characteristics in ACS incidence and recurrence has not been explored.

There is a wealth of literature that links socioeconomic conditions with child health outcomes.[11-13] It is also known that African Americans families, even at higher levels of individual socioeconomic status, reside in disproportionately disadvantaged neighborhoods.[14,15] Prior research indicates that the association of neighborhood-level socioeconomic deprivation with health varies by race and ethnicity.[16,17] The mechanism of this relationship is unclear. It is possible that neighborhood racial composition moderates the health effects of neighborhood socioeconomic context. Seeking answers to some of these questions, the current study used area-level and clinical data to evaluate the association between neighborhood socioeconomic deprivation, neighborhood racial composition, and ACS incidence and recurrence in pediatric patients with SCD at a large SCD Center in the Southeastern United States.

METHODS

Study design and participants

This is a retrospective cross-sectional study of pediatric SCD patients managed at Children's of Alabama (the only free-standing pediatric hospital in the state with a large pediatric SCD center) from 2012 to 2018. Clinical and socio-demographic data of the cohort were obtained retrospectively from the electronic medical record throughout the lifetime of each individual through an ongoing protocol approved by the University of Alabama at Birmingham Institutional Review Board (IRB-00000196). Area-level data were obtained by geocoding patients' residential addresses to U.S. Census block groups (the smallest geographic units for which U.S. Census data is available, used as proxies for neighborhoods) and pairing them to existing area-level measures as described further.

Measures

ACS was defined by new chest radiograph infiltrate associated with fever, chest pain, increased work of breathing, or oxygen desaturation. *Single ACS* (Yes/No) was defined as only one admission for ACS throughout the lifetime. *Recurrent ACS* (Yes/No) was defined as at least 2 ACS incidents during the lifetime.*Severe ACS* was defined by admission to the pediatric intensive care or special care units.

Neighborhood deprivation was assessed with the 2015 Area Deprivation Index (ADI) for the State of Alabama. The ADI is an existing factor-based composite measure of socioeconomic deprivation, available in state-specific (1-10 scale) versions, with higher values indicating higher deprivation.[18,19] The ADI is constructed from 17 variables in the domains of income, education, employment, and housing quality collected by the American Community Survey and aggregated to U.S. Census block groups. Neighborhood racial composition is not a component of the ADI. In this study, each patient was assigned a neighborhood ADI value according to the Census block group in which he or she resided based on the current address in their electronic health record. Because the ADI was not normally distributed, we dichotomized it as high (ADI 7-10) vs low (ADI 1-6) socioeconomic deprivation.

Neighborhood racial composition was calculated using the count of African American residents in each Census block group and converting it to a percentage of the total population count in that block group. The measure was not normally distributed and was treated as a categorical variable. As neighborhoods that were [?]90% African American were more prevalent in the sample than any other category, we dichotomized the measure as [?]90% vs <90% African American. Alternative categorization (tertiles and quartiles) produced similar results.

Rurality was assessed with the 2010 Rural-Urban Commuting Area (RUCA) codes, a classification that combines U.S. Census Bureau definitions with commuting information and ranks Census tracts on a scale of 1-10, with higher values indicating higher rurality.[20] We dichotomized the measure as metro vs non-metro (RUCA scores 1-3 vs [?]4).

Covariates included sex (Male/Female), age, health insurance type (Public/Private), body mass index (BMI), chronic transfusions (Yes/No), hydroxyurea (Yes/No), asthma diagnosis (using ICD-10 code or active asthma treatment in the electronic medical records) (Yes/No), and SCD phenotype (SS, SB0, SB+, or SC), which was confirmed by hemoglobinopathy fractionation.

Statistical Analysis

We first characterized data missingness and calculated descriptive statistics for the sample. Patients without a valid street addresses and those with missing clinical data were excluded from the analytical sample. As less than 7% of the sample had missing clinical data, we used listwise deletion to account for missingness. A STROBE diagram of the study population is presented in **Figure 1** .

The distribution of neighborhood-level and patient characteristics was obtained for the overall sample and by recurrent ACS status. Bivariate associations were estimated using simple logistic regression. Models of recurrent ACS were estimated with multiple logistic regression. As 52% of Census block groups included singleton observations with only one individual per block group, we used robust standard errors to account for clustering of individuals within block groups.[21]We estimated generalized linear models to compare recurrent ACS to single and no ACS combined, with results represented as incidence-rate ratios (IRR). We estimated multinomial logistic regression models to compare each category (no ACS/single ACS/recurrent ACS), with results represented as relative risk ratios (RRR). To better understand the contribution of residential characteristics to ACS recurrence, we four separate models were estimated: Model 1 with neighborhood socioeconomic deprivation alone, Model 2 with neighborhood racial composition alone, Model 3 with rurality alone, and Model 4 with all three characteristics together. All four models included the same covariates: age, sex, insurance type, BMI, chronic transfusions, hydroxyurea, asthma, and phenotype. Statistical tests were two-sided and were performed using a 5% significance level (α=0.05). Analyses were performed using Stata software, version 15 (StataCorp, College Station, TX).

RESULTS

The analytical sample included 709 patients. The geographic distribution of the population is visualized in **Figure 2** with wide spread of the subjects and increased concentration around the major cities of north and central Alabama. Characteristics of the sample, overall and by ACS status, are presented in **Table 1** . Median age was 13.6 years, and the majority (72%) had public health insurance. Those who resided in highly deprived areas made up 45% of the sample, while 21% resided in neighborhoods that were [?]90% African American in composition, and 17% resided in rural areas. The most prevalent phenotype was the SS phenotype (54%). When compared to children with non-recurrent ACS (no ACS and single ACS), those with recurrent ACS were older (IRR 1.05, CI 1.02–1.07, p<0.001), more likely to have asthma (IRR 3.93, CI 2.84–5.44, p<0.001), to be a male (IRR 1.91, CI 1.36–2.68, p<0.001), and to be on chronic blood transfusion (IRR 1.78, CI 1.26–2.52, p=0.001) and hydroxyurea (IRR 6.3, CI 4.01–9.91, p<0.001). Recurrent ACS was lower among those living in a highly deprived area (IRR 0.72, CI 0.52–0.99, p=0.044) and in a predominantly African American community (IRR 0.56, CI 0.35–0.90, p=0.017).

To assess the adjusted association between residential characteristics and ACS categories (no ACS, single ACS, any ACS, non-recurrent ACS, and recurrent ACS), we estimated a separate model for each neighborhood characteristic (Model 1: deprivation; Model 2: racial composition; Model 3: rurality) and a full model with all three neighborhood characteristics together (Model 4) **Table 2** . All four models controlled for the same covariates: age, sex, insurance type, BMI, chronic transfusions, hydroxyurea, asthma, and phenotype. Residence in high-deprivation neighborhood was associated with 27% lower risk of recurrent ACS vs non-recurrent ACS, 43% lower risk of recurrent ACS vs single ACS, and 42% lower risk of recurrent ACS vs no ACS (Model 1,**Table 2**). Residence in predominantly African American neighborhood was associated with 43% lower risk of recurrent ACS vs non-recurrent ACS, 57% lower risk of recurrent ACS vs single ACS, and 59% lower risk of recurrent ACS vs no ACS (Model 2, **Table 2**). However, when all residential characteristics were assessed together, area deprivation was no longer significant while neighborhood racial composition remained significant, indicating that the neighborhood's racial composition accounts for the association between socioeconomic deprivation and decreased ACS recurrence (Model 4, **Table 2**). A separate analysis showed that those who reside in a predominantly African American neighborhood are 1.24 times more likely to reside in a socioeconomically deprived neighborhood (CI 1.04–1.48, p=0.016). Rurality was not associated with ACS, neither by itself (Model 3,**Table 2**) nor together with the other neighborhood characteristics (Model 4, **Table 2**). There was no difference in residential characteristics when comparing single ACS to no ACS (**Table 2**).

Multiple regression of recurrent ACS adjusted for all covariates showed that males have nearly two-fold risk of recurrent ACS compared to females **Table 3** . Clinical covariates associated with increased risk of recurrent ACS included asthma (IRR 2.62, CI 1.89–3.63, $p<0.001$) and being on hydroxyurea (IRR 2.89, CI 1.74-4.8, $p<0.001$). In contrast, patients with the SB+ and SC phenotypes had 82% (CI 0.04–0.72, p=0.015) and 66% (CI 0.19–0.61, $p<0.001$) less risk of recurrent ACS compared to those with the SS phenotype. Because asthma was a significant risk factor for recurrent ACS, in a separate analysis we assessed the relationship between living in a highly deprived area and having asthma, but found no significant association (IRR 1.10, CI 0.93–1.30, p=0.28).

Next, we sought to determine if the adverse relationship of neighborhood socioeconomic deprivation with recurrent ACS is explained by access to care. While mild ACS may be managed at home or local hospitals, severe ACS has to be managed in a tertiary pediatric hospital with intensive care unit abilities. We therefore used the medical records to determine the severity of ACS (mild vs severe) and replicated the model build-ups to determine the odds of experiencing severe ACS. These additional analyses found no association between neighborhood characteristics and ACS severity **Supporting Information Table S1** , indicating that the association of neighborhood characteristics with recurrent ACS is not explained by access to care. We also estimated a model of ACS recurrence with distance to the hospital in miles as another marker of access to care, and again found no significant association**Supporting Information Table S2** .

Finally, we performed sensitivity analyses where all area-level measures were treated as continuous variables **Supporting Information Table S2** . These analyses confirmed a dose-response relationship between neighborhood socioeconomic deprivation, neighborhood racial composition, and recurrent ACS. We also tested for interactions between neighborhood socioeconomic deprivation and each of rurality and racial composition**Supporting Information Table S3** . None were found to be significant, suggesting that the likelihood of recurrent ACS does not vary by the relationship between deprivation and rurality or racial composition.

DISCUSSION

We conducted a cross-sectional analysis of data from a large pediatric SCD Center in the Southeastern U.S. to quantify the contributions of neighborhood socioeconomic deprivation and racial composition to ACS recurrence. Our results show that children with SCD residing in socioeconomically deprived neighborhoods have fewer occurrences of ACS, and this association is accounted for by the predominantly African American make-up of the community. This is the first report documenting a relationship between community characteristics and risk of ACS recurrence in pediatric SCD population in the United States.

Area deprivation is a well-documented risk factor for chronic diseases and their exacerbations in adult[22-24] and pediatric populations.[25] However, research has been conducted in predominantly White or racially mixed populations. In contrast, our sample comprises exclusively African American children with SCD living in the state of Alabama. In our study, neighborhood socioeconomic deprivation was associated with less recurrent ACS, and this effect was explained by the racial composition of the community. It is possible that the area deprivation index used in this analysis, which has been developed for the general population, does not work well when applied to a racially homogeneous African American sample.[14,15]Race-specific area-level measures may be needed for accurate assessment of the role of socioeconomic environment in child health.

Our results show that residence in a predominantly African American neighborhood substantially reduces the risk of ACS recurrence. A number of previous studies have reported a positive health effect of residence in racially or ethnically homogenous areas, or the so-called "ethnic density effect."[26,27] The health benefits of ethnic density have been attributed to the buffering effect of neighborhood cohesion, enhanced social support, and a stronger sense of community.[27-29] Ethnic density may provide opportunities to engage with others who share similar cultural or ethnic background, and these supportive interactions may confer social advantages that facilitate recovery from life stressors.[30] These effects are further strengthened after controlling for area deprivation.[31] For example, previous research has documented that neighborhood cohesion offsets the adverse health effects of neighborhood socioeconomic disadvantage, likely through minimizing stress related to living in mixed neighborhood.[32] This interpretation is plausible in the context of SCD, as stress is a known risk factor for systemic inflammation, which is associated with worse SCD outcomes, including recurrent ACS.[33,34] Family stress may negatively affects offspring which was suggested by reports associating parental stress with life quality scores in children with SCD.[35]

Environmental exposures, whether indoor or outdoor, have been shown to affect SCD outcomes. A recent study from the Southern United States showed that higher levels of ambient carbon monoxide are associated with increased ED visits for SCD, with particularly strong effects among children.[36] Epidemiologic studies in Europe reported that high levels of ozone, nitric oxide, and wind speed; and low levels of carbon monoxide and nitrous oxide are associated with increased ED admissions for SCD crises, including ACS.[10,37] These environmental factors may have contributed to the risk of ACS recurrence in our cohort.

Previous studies have linked ACS risk with public insurance[38] and rural residence.[39]Such associations were not observed in our data. Access to care, measured by distance to the hospital and by the severity of the ACS episode, was also not associated with ACS recurrence in our sample. Our study corroborates previous reports of increased ACS in SCD patients with asthma[40,41] and SS phenotype.[8]As well, ACS in our sample was more prevalent in males, confirming a reported association between male sex and increased risk of ACS.[42,43]

Despite an increased scientific interest in the role of socio-environmental factors for SCD outcomes, medical records rarely include sufficient patient-level socioeconomic data. This study demonstrates that area-level measures can be used as a proxy of patient-level socioeconomic data. It also highlights the opportunity for expanding health records with publicly available area-level information that is relevant for clinical decision-making. Small-area measures can be a clinically useful tool for identifying high-risk SCD patients who may benefit from ACS prevention approaches.

The current study has several limitations. Our data does not include individual-level socioeconomic characteristics such as household income and parent education. Therefore, we cannot determine if the observed neighborhood effects vary by individual-level socioeconomic position. We also do not have measures of environmental exposures related to their residence that can affect their lung health. The reported associations may not be applicable to adult SCD populations or patients living in different regions. Finally, the cross-sectional design, with its inherent information bias and inability to control for all confounders, prevents us from making causal inferences about the observed relationships between neighborhood socioeconomic deprivation, racial composition, and ACS.

Our results indicate that children with SCD living in socioeconomically deprived neighborhoods have lower risk of recurrent ACS due to the protective effect of African American neighborhood composition. These results provide initial evidence for the role of neighborhood environment for ACS risk in pediatric patients with SCD. Future research should investigate these associations in a SCD sample from multiple U.S. regions. Neighborhood characteristics and area-level exposures may also be incorporated in ACS risk prediction models.

Our study sheds light on the role of community characteristics for SCD outcomes and highlights the potential role of neighborhood cohesion and social support in reducing ACS recurrence. However, these health-conferring characteristics must be interpreted in the socio-political context that reproduces concentrated socioeconomic disadvantage in areas of high racial density. Addressing the inequitable distribution of socioeconomic resources by race is critical for improving health and reducing inequalities. Futures studies in this population should attempt to collect prospective individual-level data in order to examine more precisely the effects of racial composition and socioeconomic deprivation on SCD complications.

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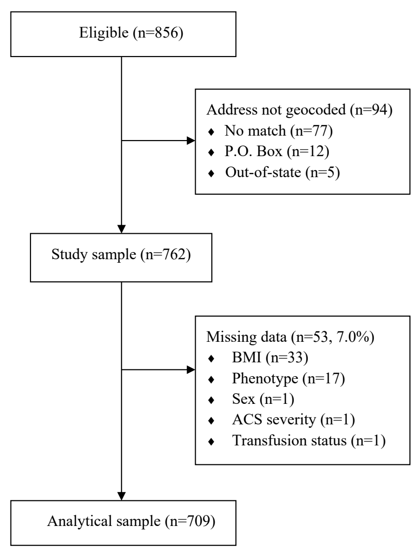
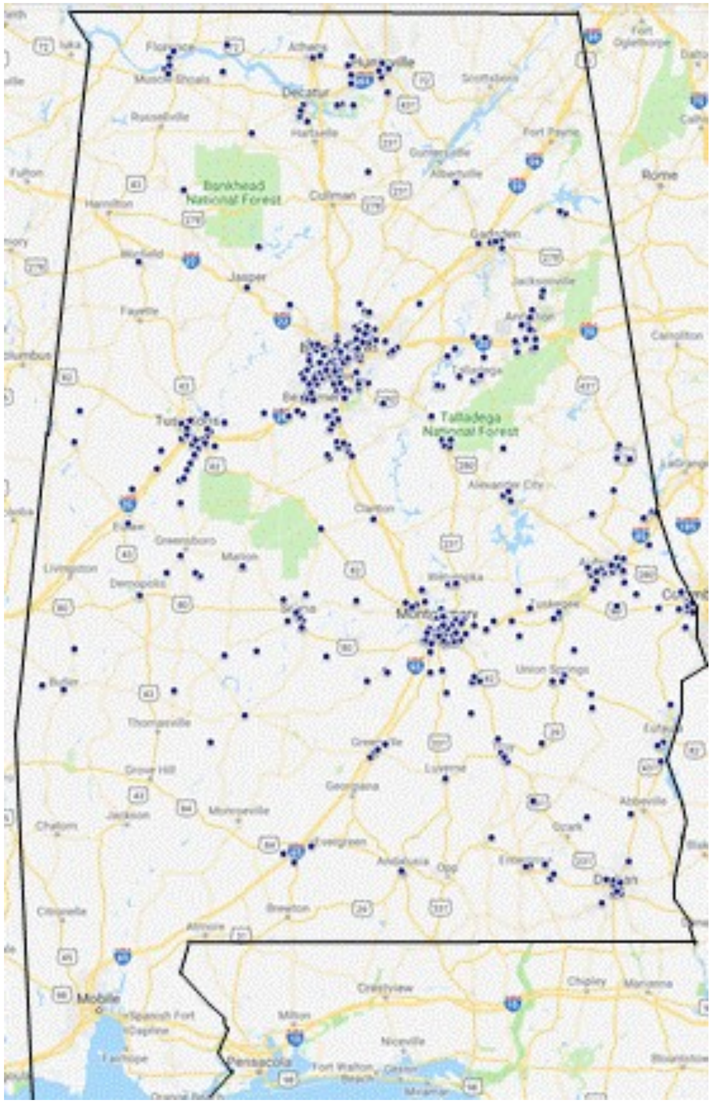
LEGENDS

Figure 1. STROBE Diagram of the Study Population

Figure 2. Geographic Distribution of the Study Population

Figure 1. STROBE Diagram of Study Population





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