

Sickle-Cell Trait and Atopic and Inflammatory Disease in Children

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Roughly 9% of African-Americans carry 1 copy of the sickle β -globin allele [sickle-cell trait (SCT)]. The sickle allele may affect the host responses in a way that protects against sequelae of malaria. Besides the association with sporadic episodes of erythrocyte sickling, acute chest syndrome, and sudden death, the SCT is generally regarded as asymptomatic. Separately, and for unclear reasons, the African-Americans have an elevated risk compared to whites for several immune-mediated diseases, including asthma, eczema, and other respiratory conditions. We propose to determine whether the SCT contributes to the elevated risk of these inflammatory conditions. We performed a retrospective cohort study of children with and without the sickle trait to assess the risk for common immune-mediated conditions. The cohorts were individually matched, and multiple logistic regression was used with variables selected using a backward stepwise approach. A second approach (case-control design) assessed the odds of the SCT among African-Americans with and without asthma. We found 2,481 children with and 4,962 matched patients without the SCT in the cohort design. The sickle trait was associated with greater odds for several immune-mediated conditions in a multivariable analysis, but not associated with asthma (odds ratio, OR=1.10, $P=0.212$). In an adjusted case-control analysis ($n=20,000$), the sickle trait was weakly associated with asthma [adjusted odds ratio (aOR)=1.46, 1.01–2.13]. In both the designs and in all statistical models used, we found that the SCT was associated with bronchitis (aOR=1.71, 1.09–2.67) and eczema (aOR=1.74, 1.23–2.46). The SCT may contribute to an increased risk for eczema and asthma-like symptoms in the African-American children.

Introduction

African-Americans appear to be at a higher risk for developing several common inflammatory conditions, including asthma,¹ pneumonia,² and eczema.³ The African-American asthmatics suffer a greater disease severity compared to the Whites.^{1,4} The underlying mechanisms for these observations remain poorly defined.^{2,5–7} People of the African ancestry have a higher prevalence of the sickle-cell β -globin allele (S) compared to the Whites.⁸ Homozygotes for the sickle allele (SS) develop sickle-cell disease (SCD), characterized by hemoglobin polymerization, erythrocyte sickling, reduced erythrocyte survival,^{9,10} and a greater risk for airway reactivity,¹¹ physician-diagnosed asthma,^{12,13} acute chest syndrome, pneumonia, and chronic lung disease.^{14–16} Around 300 million people worldwide (and around 8%–10% of African-Americans) carry 1 the sickle allele (AS)—known as the sickle-cell trait (SCT).¹⁷ Although AS is typically asymptomatic,¹⁸ it has been associated with sickling

episodes,^{19,20} thrombosis,^{21,22} acute chest syndrome,^{19,23–27,28} and sudden death.^{29–31} Despite its deleterious effects, the S allele has likely been conserved, because it may confer a selective advantage in the malarial regions due to its effect on inflammatory and immune responses to the malaria parasite.

Since the African-Americans are at a greater risk for both the AS genotype and certain inflammatory disorders, and since the AS genotype is associated with an altered immune response to the *Plasmodium falciparum* parasite, it is rational to hypothesize that AS may promote the risk for other inflammatory conditions, as stated above. This question has been not been studied extensively. Palma-Carlos found the prevalence of asthma higher among 66 patients with milder hemoglobinopathies (predominantly the β -thalassemia carriers) compared to the controls.³² Data from a second very small cohort suggested that AS was associated with asthma.³³ Utilizing a large multicenter electronic health record (EHR) database and 2 separate design approaches, we sought to

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determine if the SCT is associated with physician-diagnosed asthma, bronchitis, eczema, pneumonia, and sleep apnea.

Materials and Methods

This study was approved by the Nemours Florida Institutional Review Board [No. 183481-3]. We used a large EHR database involving Nemours hospitals and subspecialty clinics at and around Jacksonville, FL, Orlando, FL, Pensacola, FL, and Wilmington, DE, to construct a retrospective cohort study and a case-control study to determine the association between the SCT and select inflammatory conditions.

Study I: retrospective cohort design

Subject selection. We identified all patients seen between May, 2000, and December, 2010, at any of the 4 Nemours Children's Clinic outpatient sites with an International Classification of Disease (ICD)-9 diagnosis code 282.5 (SCT) in EHR diagnosis, problem list, medical history, or physician billing charge field (Epicare, Summer 2009, IU3, Epic Systems Corporation, Verona, WI). We excluded the patients who had an accompanying diagnosis code of 282.x (SCD, Sickle Cell- β -Thalassemia, and other Sickle Cell hemoglobinopathies) to target the patients likely to have the SCT. The SCT group was considered the exposure cohort (exposed to the S sickle allele). We collected data on race, ethnicity (Hispanic/non-Hispanic), age, Medicaid status, presence or absence of supplemental private insurance (as of November, 2010), and the clinic location. We categorized participants by age groupings: 0-4, 5-8, 9-12, 13-17, and 18 years and up.

We then created a matching no-exposure (non-SCT) group. These non-SCT patients were individually matched for the age group, sex, race, ethnicity, clinical location, Medicaid status, and supplemental insurance status. We randomly selected 2 controls for each SCT patient from a pool of non-SCT and non-SCD patients having the appropriate matching demographic profiles.

For both groups (SCT and non-SCT), we determined the cumulative incidence and odds of physician-diagnosed asthma, sinusitis, bronchiolitis, bronchitis, pneumonia, allergic rhinitis, snoring, sleep-disordered breathing, and obstructive sleep apnea (see the supplementary data section for ICD-9 codes) using the EHR diagnosis and billing field.

Statistical analysis. We compared the baseline characteristics between the exposed and unexposed groups and used chi-square for any categorical outcome variables. We used Student's *t*-test, ANOVA, or Wilcoxon-Mann-Whitney *U* Rank-Sum test to compare the means or medians of continuous variables, as appropriate. SAS (SAS Institute, Cary, NC) and SPSS 11.0 (SPSS, Inc., Chicago, IL) were used for all computations.

We calculated the risk ratios and unadjusted odds ratios (ORs) for each diagnosis. We used multivariable logistic regression that included all variables associated with the SCT in a bivariate analysis. These included asthma, eczema, allergic rhinitis, sleep apnea, bronchitis, bronchiolitis, sinusitis, and snoring. A second model was used that involved variables selected by a stepwise backward selection in a simultaneous model. Multiple logistic regression models adjusted for multiple covariables to

assess the influence of the SCT on individual odds of an inflammatory disease.

Study II: case-control design

Subject selection. We performed a second data query of African-American children, identifying all incident cases seen over the same period (May, 2000, through December, 2010) with an ICD-9 code of 493.x (Asthma) in the EHR diagnosis field, problem list field, medical history field, or physician billing field. We excluded the patients who also had a diagnosis code consistent with SCD, sickle-cell thalassemia, and other sickle-cell hemoglobinopathies/HbSC (282.41-282.42 and 282.6), so that we specifically identified the patients most likely to either have the SCT or be homozygous wild type (hemoglobin AA). Therefore, African-Americans with asthma constituted our case group. We collected information on ethnicity (Hispanic/non-Hispanic), age, Medicaid status, presence or absence of supplemental private insurance (as of November, 2010), and the most recently visited clinical location.

We then created a control group of African-American children without asthma based on individual matching. Controls could be either hemoglobin AS (SCT) or AA (non-SCT), but similar to cases, could not have any of the sickle-related hemoglobinopathies (SS, β S, or SC). We collected an individually matched control patient with the same characteristics for age group, gender, race, ethnicity, clinical location, Medicaid status, and supplemental insurance status. We randomly selected the controls from the pool of EHR patients without asthma and with the appropriate matching demographic profile.

Then for all cases and controls, we determined the prevalence and odds of having the SCT (282.5) documented among the EHR diagnosis field, problem list field, medical history field, or physician billing-charge field. In addition, we collected information on the presence or absence of sinusitis, bronchitis, pneumonia, eczema, allergic rhinitis, snoring, sleep-disordered breathing, and obstructive sleep apnea among the same EHR fields. See the supplementary data section for ICD-9 codes.

Statistical analysis. We used stepwise logistic regression modeling to choose the predictor variables associated with increased odds of the SCT. Eligible predictor variables included the presence of sinusitis, bronchitis, pneumonia, allergic rhinitis, pneumonia, snoring, sleep-disordered breathing, obstructive sleep apnea, and eczema. We calculated the odds of having the SCT according to the asthma status. We created an adjusted multivariable logistic model that included bronchitis, eczema, body-mass index (BMI)-z score, and asthma status to assess the odds of the SCT.

Results

Table 1 lists the baseline characteristics for both the SCT and non-SCT cohorts from Study I. Because of individual matching, all characteristics between the 2 groups are similar and therefore are shown together. The exception was height and weight. Participants with the SCT were significantly shorter and weighed less despite being similar in age and sex. The mean heights [standard deviation (SD)] for the sickle trait group versus controls were 102.8 cm (32.8) and 107.2 cm (32.3), respectively, whereas the mean weights (SD) for the sickle trait group and controls were 22.7 kg (19.9) and 25.4 kg (22.1), respectively ($P < 0.001$ for both comparisons).

TABLE 1. PATIENT CHARACTERISTICS AMONG SICKLE-CELL CARRIERS AND MATCHED CONTROLS

Characteristic	Sickle carrier	Control	P value ^a
N	2,481	4,962	
Percent female	46.6	46.6	>0.9
Age, (years), mean (SD)	8.55 (5.91)	8.61 (6.12)	0.664
Weight (kg), mean (SD)	22.65 (19.91)	25.35 (22.08)	<0.001
Height (cm), mean (SD)	102.75 (32.81)	107.17 (34.27)	<0.001
BMI (kg/m ²), mean (SD)	18.19 (7.92)	18.32 (5.81)	0.473
BMI-z score, mean (SD)	0.395 (1.49)	0.398 (1.74)	0.960
Age groups			>0.9
0–4	30.8	30.8	
5–8	24.1	24.1	
9–12	20.0	20.0	
13–17	16.2	16.2	
18 and up	9.0	9.0	
Race			0.001
Black	74.5	74.5	
White	6.4	6.4	
Asian	0.1	0.1	
Native American	0.1	0.1	
Hawaiian/Pacific Islander	0.04	0.04	
Other	6.4	4.4	
Not available/Refused	12.4	14.37	
Percent Hispanic	5.0	5.0	>0.9
Medicaid	59.9	59.9	>0.9
Private insurance	29.0	29.0	>0.9
Clinical Site			>0.9
Jacksonville	12.3	12.3	
Orlando	13.7	13.7	
Pensacola	4.8	4.8	
Wilmington	69.2	69.2	

^aP value comparing the sickle carrier cohort to noncarriers. P values were determined by chi-square or independent samples Student's *t*-test as appropriate.

SD, standard deviation; BMI, body-mass index.

Risk of respiratory disease in children by the sickle-allele status: Study I

Prevalences of any diagnosis of asthma, persistent asthma, and moderate or severe persistent asthma are shown in Table 2. Risk estimates for asthma, eczema, allergic rhinitis, obstructive sleep apnea, bronchiolitis, bronchitis, sleep-disordered breathing, snoring, and sinusitis were significantly elevated among children with the SCT (Table 2). In the adjusted models, we found significantly increased odds for eczema, allergic rhinitis, bronchitis, bronchiolitis, and sinusitis Table 3. The risk for persistent asthma was the same between the SCT and non-SCT patients ($P=0.804$). The relative risk and odds for all incident diagnoses were similar when we evaluated the African-Americans only and after adjusting for height, weight, and the BMI.

The number of clinical follow-up visits was similar among the SCT-versus-matched control patients ($P>0.05$, data not shown).

Odds of the SCT in African-Americans with asthma: Study II

We found more than 27,000 separate African-American children with asthma within our EHR database. Table 4 describes the background characteristics for the asthmatic cases and nonasthmatic controls combined. The baseline characteristics are shown combined, because cases and controls were matched for age group, gender, race, ethnicity, clinical location, Medicaid status, and supplemental insurance status. The groups were very similar due to the matching design; however, we found that the asthma group had a significantly higher BMI percentile and BMI-z score (data not shown, $P<0.001$ for both comparisons). Simple logistic regression showed several conditions, including physician-diagnosed asthma, bronchitis, eczema, sinusitis, and pneumonia, which were associated with increased odds of the SCT (Table 5). When we adjusted for these covariables, we found that only bronchitis and eczema were significantly associated with the SCT (Table 6). The point estimate of the OR for asthma was 1.20; however, this did not reach statistical significance in the multivariable model.

Discussion

Our study suggests that children who have the SCT (β -globin genotype AS) may be at an increased risk for developing physician-diagnosed bronchitis and eczema, the 2 common inflammatory diseases of childhood. In both of the studies conducted, we saw a significantly increased risk estimate for bronchitis and eczema among children with the sickle trait compared to matched children without the SCT. In the cohort study (Study I), we assessed all physician visits involving children reporting to have the SCT. We performed a similar assessment on individually matched patients without the SCT. In both groups, we collected data on the physician diagnosis of asthma, bronchitis, eczema, and 6 other common inflammatory conditions. In 2 separate multivariable models, we found that eczema, bronchitis, bronchiolitis, allergic rhinitis, and sinusitis were more commonly diagnosed in the SCT group. In the second design (Study II), using a case-control approach, we found that only eczema and bronchitis were significantly associated with the SCT in the 2 separate multivariable models used. In total, we evaluated the data from more than 27,000 children from more than 10 sites in the Southeastern and mid-Atlantic regions of the United States. These epidemiologic data suggest the possibility of an association between the SCT and increased diagnosis of the inflammatory conditions, eczema, and bronchitis.

There are several limitations to the current study that must be considered carefully. It is important to note that this study merely suggests an epidemiologic link, and is far from establishing the causality or specific mechanisms linking the SCT with an immune or inflammatory dysfunction. Because these data were not collected prospectively and were not originally collected for the purpose of research, there exists the considerable possibility of bias and confounding. Bias commonly occurs in epidemiologic studies due to flawed measurement techniques, differential recall, and poor comparison group selection. An important limitation of the current study is the reliance on the EHR data that were created

TABLE 2. STUDY VARIABLE CHARACTERIZATION BY THE SICKLE-CELL-TRAIT STATUS

	SCT n=2,481 (%)	No SCT n=4,962 (%)	OR (95% CI)	P value
Asthma				
No asthma	1,931 (77.8)	4,200 (84.6)	Referent	—
Intermittent	320 (12.9)	445 (8.9)	1.57 (1.34, 1.82)	<0.001
Persistent	230 (9.3)	317 (6.4)	1.50 (1.25, 1.79)	<0.001
Mild	147 (5.9)	195 (3.9)	1.64 (1.32, 2.05)	<0.001
Moderate	78 (3.14)	112 (2.3)	1.52 (1.13, 2.03)	0.006
Severe	5 (0.2)	10 (0.2)	1.09 (0.37, 3.19)	1.00
Eczema	635 (25.6)	693 (14.0)	2.12 (1.88, 2.39)	<0.001
Allergic rhinitis	438 (17.7)	539 (10.9)	1.76 (1.54, 2.02)	<0.001
OSA	101 (4.1)	104 (2.1)	1.98 (1.50, 2.62)	<0.001
Bronchiolitis	252 (10.2)	309 (6.2)	1.70 (1.43, 2.03)	<0.001
Bronchitis	110 (4.4)	93 (1.9)	2.43 (1.84, 3.22)	<0.001
Pneumonia	38 (1.5)	63 (1.3)	1.21 (0.81, 1.81)	0.358
SDB	169 (6.8)	203 (4.1)	1.71 (1.39, 2.11)	<0.001
Snoring	74 (3.0)	84 (1.7)	1.79 (1.30, 2.45)	<0.001
Sinusitis	306 (12.3)	358 (7.2)	1.81 (1.54, 2.13)	<0.001
Median height (cm)	114.8 (45.0, 193.0)	115.57 (45.4, 192.0)	0.999 (0.997, 1.001)	0.278
Median weight (kg)	21.40 (2.3, 187.35)	22.20 (2.55, 156.60)	0.998 (0.996, 1.001)	0.156
Mean age, years (SE)	6.71 (0.11)	6.91 (0.09)	0.992 (0.982, 1.003)	0.169
Median age, years	5.54 (0.01–19.97)	5.78 (0.01–19.97)		
Age-adjusted height			1.002 (0.997, 1.008)	0.415
Age-adjusted weight			0.999 (0.994, 1.004)	0.654

OR, odds ratio (unadjusted); CI, confidence interval; OSA, obstructive sleep apnea; SDB, sleep-disordered breathing; SE, standard error; SCT, sickle-cell trait.

during the routine clinical care. For both the retrospective cohort analysis and the case-control analysis, the sickle trait status was not determined by genotyping or hemoglobin electrophoresis, but instead was determined by physician documentation of the SCT most likely coming from parental

recall. There is some confusion among laypersons about the distinction between disease versus carrier status, and between different hemoglobinopathies that may have created a misclassification bias with regard to the risk group in the cohort study (and the exposure variable in the case-control study). Therefore, the risk-group (SCT versus normal) misclassification could have been present; however, the presence of a differential misclassification bias seems unlikely. The incident diseases in the cohort analysis were detected by a physician diagnosis documented in the EHR. These

TABLE 3. ASSOCIATION OF THE SICKLE-CELL TRAIT WITH COMMON INFLAMMATORY CONDITIONS IN SIMULTANEOUS MULTIVARIATE MODELS

	Model One ^a		Model Two ^b	
	OR (95% CI)	P value	OR (95% CI)	P value
Asthma		0.533		
Intermittent	1.14 (0.96, 1.34)	0.136		
Persistent				
Mild	1.09 (0.86, 1.38)	0.492		
Moderate	0.96 (0.70, 1.31)	0.783		
Severe	.71 (0.24, 2.14)	0.545		
Eczema	1.79 (1.57, 2.04)	<0.001	1.81 (1.59, 2.06)	<0.001
Allergic rhinitis	1.24 (1.05, 1.46)	0.009	1.27 (1.09, 1.48)	0.002
OSA	1.43 (0.93, 2.17)	0.100	1.84 (1.39, 2.45)	<0.001
Bronchiolitis	1.26 (1.05, 1.52)	0.016	1.32 (1.10, 1.58)	0.003
Bronchitis	1.65 (1.23, 2.21)	0.001	1.68 (1.25, 2.25)	0.001
Sinusitis	1.20 (1.00, 1.44)	0.047	1.23 (1.03, 1.47)	0.024
SDB	1.29 (0.93, 1.77)	0.128		
Snoring	1.21 (0.86, 1.68)	0.271		

^aAll significant variables in the bivariable analysis (asthma, eczema, allergic rhinitis, OSA, bronchitis, bronchiolitis, SDB, snoring, and sinusitis) were used in the model. When asthma (presence/absence) was used in model one (instead of asthma severity), the OR (95% CI) was 1.10 (0.95, 1.26), *P* value=0.212.

^bModel includes all significant variables selected by stepwise backward logistic regression in a simultaneous model (and included eczema, allergic rhinitis, OSA, bronchiolitis, bronchitis, and sinusitis).

TABLE 4. PATIENT CHARACTERISTICS AMONG AFRICAN-AMERICAN CHILDREN WITH AND WITHOUT ASTHMA

Characteristic	Asthma	No asthma	P value ^a
N	10,000	10,000	
Females, n (%)	4,082 (40.82)	4,082 (40.82)	1.0
Age, mean (SD)	9.93 (5.62)	9.91 (6.11)	0.8032
BMI-z score, mean (SD)	0.601 (1.30)	0.472 (1.29)	<0.001
BMI-percentile, mean (SD)	65.19 (30.17)	62.34 (30.88)	<0.001
Black	10,000 (100)	10,000 (100)	1.0
Percent Hispanic	152 (1.52)	152 (1.52)	1.0
Medicaid	6,395 (63.95)	6,395 (63.95)	1.0
Private insurance	3,401 (34.01)	3,401 (34.01)	1.0
Clinical site			1.0
Jacksonville	1,482 (14.82)	1,482 (14.82)	
Orlando	513 (5.13)	513 (5.13)	
Pensacola	405 (4.05)	405 (4.05)	
Wilmington	7,600 (76.00)	7,600 (76.00)	

^a*P* value comparing the asthmatics versus nonasthmatics. *P* values were determined by chi-square or independent-sample Student's *t*-test as appropriate.

TABLE 5. ASSOCIATIONS WITH THE SICKLE-CELL TRAIT AMONG ASTHMATICS AND MATCHED CONTROLS^a

	No SCT n=19,857 (%)	SCT n=143 (%)	OR (95% CI)	P value
Asthma	9,905 (49.9)	95 (66.4)	1.99 (1.40–2.82)	<0.001
Bronchitis	1,691 (8.5)	31 (21.7)	2.97 (1.99–4.44)	<0.001
Eczema	4,839 (24.4)	66 (46.2)	2.66 (1.91–3.70)	<0.001
Sinusitis	2,700 (13.6)	34 (23.8)	1.98 (1.35–2.92)	0.001
Pneumonia	332 (1.7)	7 (4.9)	3.03 (1.41–6.52)	0.005
Allergic rhinitis	4,909 (24.7)	41 (28.7)	1.22 (0.85–1.76)	0.276
Snoring	503 (2.5)	7 (4.9)	1.98 (0.92–4.26)	0.080
SDB	1,266 (6.4)	8 (5.6)	0.87 (0.43–1.78)	0.703
OSA	847 (4.3)	6 (4.2)	0.98 (0.43–1.78)	0.703
Medicaid	12,700 (64.0)	90 (62.9)	0.96 (0.68–1.35)	0.800
Private Insurance	6,747 (34.0)	55 (38.5)	1.21 (0.87–1.73)	0.260
Male	11,760 (59.2)	76 (53.1)	0.78 (0.56–1.09)	0.142
Hispanic	302 (1.5)	2 (1.4)	0.92 (0.23–3.73)	0.905
BMI-z score: <i>n</i> , mean (SD) ^{b,c}	15,272, 0.55 (1.30)	138, 0.57 (1.25)	1.02 (0.89–1.16)	0.778
Age (years): <i>n</i> , mean (SD)	19,857, 9.93 (5.88)	143, 8.38 (5.33)	0.95 (0.92–0.98)	0.002

^aAssociations with SCT among 10,000 asthmatic children and 10,000 nonasthmatics matched by race, age, sex, and insurance status.

^bCalculation for BMI-z score OR included 15,410 observations.

^cThe variable BMI-z has 4,590 missing values.

diagnoses also likely involved some degree of diagnostic misclassification, though differential diagnostic misclassification bias between the risk groups (SCT versus normal) again seems unlikely. Bias in this study was reduced by the use of an individual matching scheme that created near-identical control populations (for both study designs) in terms of race, age, sex, and access to healthcare. Potential factors of access to medical care, housing quality, and socioeconomic status should have been adequately controlled for and equal between the risk groups.

Replication of these findings is needed in other datasets and optimally in a prospective study that utilizes laboratory-based determination of the SCT status and supplemental testing to assess the markers of atopy and lung function. In addition, future studies using ancestral markers may be needed to reduce possible confounding by the African ancestry. Despite several methodologic limitations in the current study, there are several supporting lines of evidence that suggest that the links between the SCT and inflammatory conditions may be real. First, it is well established that SCD is a risk factor for small-airway obstruction,^{34,35} bronchial hyperresponsiveness,¹¹ and recurrent asthma-like symptoms.^{12,13,36,37} Since there are many reports of some children with the SCT displaying milder phenomena that are characteristic of true SCD (sickling and thrombosis), it would not be unexpected for the SCT to be associated with some ele-

ment of airway dysfunction. Second, the few studies that have tried to evaluate the risk of asthma in the SCT have found results consistent with an epidemiologic link,^{32,33} although these studies have been small and could represent reporting bias and spurious findings.

Lastly, it is important to note that there is biologic plausibility to the SCT, promoting inflammatory disease. *In vitro* evidence suggests that the SCT may affect immunoglobulin, T-lymphocyte, and eosinophil functioning, all of which are components of asthma pathogenesis.^{38–46} In the malaria endemic regions, the SCT genotype appears to lessen the severity of malaria,^{38,39} possibly through accelerated antibody production,⁴⁰ enhanced antibody and complement binding,⁴¹ and immune-mediated parasite clearance.⁴² The SCT has been associated with upregulation of certain cell-mediated immune responses,^{43,44} eosinophilia,⁴⁵ and enhanced immune recognition of *P. falciparum*-infected RBCs.⁴⁶ It is possible that the heightened immune responses seen in the setting of endemic *P. falciparum* malaria may also contribute to altered inflammatory responses. One study looking at the SCT in a *P. falciparum* endemic region found no altered risk for upper- or lower-respiratory-tract infections.⁴⁰ However, within a nonendemic malarial region, Poehling found that children with the SCT may be at a greater risk for invasive pneumococcal disease, including blood, spinal, and parapneumonic infections.⁴⁷

TABLE 6. ASSOCIATIONS WITH THE SICKLE-CELL TRAIT IN MULTIVARIABLE LOGISTIC REGRESSION MODELS

	Variables selected in a stepwise backward model selection		Variables selected in a stepwise backward model selection (BMI-z score included in the model)	
	OR (95% CI)	P value	OR (95% CI)	P value
Asthma	1.46 (1.01, 2.13)	0.045	—	
Bronchitis	1.72 (1.09, 2.72)	0.019	1.71 (1.09, 2.67)	0.020
Pneumonia	2.07 (0.95, 4.50)	0.067	2.10 (0.97, 4.55)	0.061
Eczema	2.05 (1.44, 2.92)	<0.001	1.74 (1.23, 2.46)	0.002
Private Insurance	1.34 (0.95, 1.89)	0.093	—	
Age (years)	0.97 (0.934, 0.998)	0.040	0.97 (0.93, 1.00)	0.079

A variable is removed from the model if the probability of the likelihood-ratio statistic using the conditional parameter estimates is >0.10.

The SCT has also been associated with reductions in somatic growth among children⁴⁸ and among newborns delivered by the SCT carriers.⁴⁹ Subsequent data have cast a doubt on whether the SCT truly affects somatic growth,^{50,51} and indeed, we also found that the SCT was not associated with somatic growth. Reduced somatic growth in early life (and subsequent reduced lung growth), therefore, is an unlikely explanation for our findings of greater bronchitis symptoms. Sensitive evaluations of the lung mechanics in children with the SCT may uncover growth alterations; however, research in this area is lacking. Similarly, it is rational to hypothesize that alterations in the immune function seen with the SCT in the context of parasitic infection may also be present during viral and bacterial infections that are common in early childhood. Immune modulation may be a mediating factor between the SCT and the risk for eczema and asthma-like symptoms. Since bronchitis in children lacks a clear set of diagnostic criteria, it is hard to know if the link with bronchitis represents some degree of misclassified asthma. Further prospective analysis with detailed phenotyping is needed to answer this question.

In summary, it remains unclear why African-American children (an ancestral group with a high S-allele frequency) have a higher prevalence for eczema, asthma symptoms, and respiratory infections. These common infectious and immune-related pediatric conditions represent a large burden to the primary care and acute care systems in the United States and worldwide. It is possible that a contributing factor is the S allele. The current study has significant limitations due to its retrospective design using EHR data, but it signals the need for more and higher-quality investigation, including a genotype-stratified cohort study prospectively after the relative incidence of asthma, bronchitis, and eczema.

Authors' Contributions

Dr. Lang has made substantial contributions to conception, design, and acquisition of data for this study. He contributed to the analysis and interpretation of data. He drafted the submitted article. Dr. Lang also vouches for the integrity of the data and accuracy of the data analysis. He is a guarantor of the article, taking responsibility for the integrity of the work as a whole, from inception to the final manuscript.

Dr. Hossain has made substantial contributions to the analysis and interpretation of data; He has revised the article critically for important intellectual content.

Dr. Blake made substantial contributions to the design and acquisition of data for this study. She helped critically to edit the manuscript for important intellectual content.

Amel Mercado made substantial contributions to the design and acquisition of data for this study. He helped critically to edit the manuscript for important intellectual content.

Dr. Lima has made substantial contributions to the conception, design, and acquisition of data for this study. He contributed to the analysis and interpretation of data. He helped draft the submitted article and revised it critically for important intellectual content.

Author Disclosure Statement

The authors have no financial relationships or conflicts of interest relevant to this article to disclose.

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Supplementary Data

Online Web Repository

ICD-9 codes used for physician diagnoses for Study I (cohort study)

Diagnosis by subsequent office visits was captured from either the electronic health record (EHR) diagnosis field or physician billing charges using the following International Classification of Disease (ICD)-9 codes: asthma (ICD-9 493.x), sinusitis (461.0, 461.1, 461.9, 473.x), bronchiolitis (466.11), bronchitis (466.0, 490), pneumonia (480.x, 481.x, 482.x, 483.x), allergic rhinitis (477.x), snoring (464.4), sleep-disordered breathing (327.x), and obstructive sleep apnea (327.23).

ICD-9 Codes used for physician diagnoses for Study II (case-control study)

Then for all cases and controls, we determined the prevalence and odds of having the sickle cell trait (282.5) documented among the EHR diagnosis field, problem list field, medical history field, or physician billing charge field. In addition, we collected information on the presence or absence of sinusitis (461.0, 461.1, 461.9, 473.x), bronchitis (466.0, 490), pneumonia (480.x, 481.x, 482.x, 483.x), eczema (691.8), allergic rhinitis (477.x), snoring (464.4), sleep-disordered breathing (327.x), and obstructive sleep apnea (327.23) among the same EHR fields.