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Wheezing symptoms and parental asthma are associated with a doctor diagnosis of asthma in children with sickle cell anemia

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Abstract

Objective—To identify factors associated with asthma associated with increased sickle cell anemia (SCA).

Study design—Children with SCA (n=187; mean age 9.6 years, 48% male) were classified as having “asthma” based on parent report of doctor diagnosis plus prescription of asthma medication (n=53) or “no asthma” based on the absence of these features (n=134). Pain and acute chest syndrome (ACS) events were collected prospectively.

Results—Multiple variable logistic regression model identified three factors associated with asthma: parent with asthma (p=0.006), wheezing causing shortness of breath (p=0.001), and wheezing after exercise (p < 0.001). When two or more features were present, model sensitivity was 100%. When none of the features were present, model sensitivity was 0%. When only one feature was present, model sensitivity was also 0% and presence of 2 or more positive allergy skin tests, airway obstruction on spirometry, and bronchodilator responsiveness did not improve

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* A list of members of the Sleep Asthma Cohort Investigative Team is available at www.jpeds.com (Appendix).

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clinical utility. ACS incident rates were significantly higher in individuals with asthma than those without asthma (IRR 2.21, CI 1.31-3.76); pain rates were not (IRR 1.28, CI 0.78-2.10).

Conclusions—For children with SCA, having a parent with asthma and specific wheezing symptoms are the best features to distinguish those with and without parent report of a doctor diagnosis of asthma and identify those at higher risk for ACS events. The value of treatment for asthma in prevention of SCA morbidity needs to be studied.

Keywords

Parental history of asthma; Wheezing symptoms; Allergy to aeroallergens

Asthma in a child with sickle cell anemia (SCA) is associated with an increased rate of pain and acute chest syndrome (ACS) ¹²³⁴⁵⁶⁷⁸ and premature death ⁹. Thus, determining the clinical symptoms and historical and laboratory features associated with a doctor diagnosis of asthma within the context of SCA would be important to identify patients at increased risk for complications. Reports that have demonstrated the association between a doctor diagnosis of asthma and increased morbidity in children with SCA have not provided details of symptoms or other clinical factors that were associated with a doctor's diagnosis of asthma.

Our primary objective was to determine whether clinical and laboratory features could distinguish children with SCA and a doctor diagnosis of asthma from children with SCA without such a diagnosis. We used data from the Sleep and Asthma Cohort (SAC) study, a multicenter prospective cohort focused on assessing the long term-complications of asthma and sleep disordered breathing in children with SCA sponsored by the National Heart, Lung and Blood Institute (NHLBI). We tested the hypothesis that among children with SCA, respiratory symptoms, parental history of asthma, evidence of atopy (elevated levels of total serum IgE and peripheral blood eosinophil counts and positive results of epicutaneous skin tests to aeroallergens), and presence of bronchodilator responsiveness and/or evidence of airway obstruction would be associated with a parent report of a doctor's diagnosis of asthma and prescription of anti-asthma therapy. We also examined the impact of asthma on rates of pain and ACS episodes collected prospectively over almost 5 years of follow-up.

Methods

The current study uses data collected at baseline and prospectively as part of our observational cohort study of children with SCA, either hemoglobin SS (Hgb SS) or sickle-beta⁰-thalassemia (Hgb Sβ⁰), enrolled from 4 to 18 years of age (mean 9.6) at three clinical centers and followed for 4.61 ± 1.16 years. Children were enrolled without regard to past morbidity or doctor diagnosis of asthma, but those on chronic transfusion or participating in a clinical trial evaluating hydroxyurea therapy were not eligible. Institutional approval was obtained from participating sites: Washington University School of Medicine in St. Louis, Missouri; Case Western Reserve University in Cleveland, Ohio; and University College London in London, UK (which recruited from three London hospitals); and from the Coordinating Center at Vanderbilt School of Medicine in Nashville Tennessee. Informed written parental consent was obtained, and children were consented or assented on enrollment according to institutional policies of each institution.

During initial interviews parents were asked if a doctor had ever diagnosed their child with asthma, what medications their child was currently using [using a list that included asthma relievers (e.g., albuterol) and controllers (e.g., inhaled corticosteroid and leukotriene modifier)], and to answer the American Thoracic Society Division of Lung Disease (ATS/DLD) questionnaire ¹⁰ regardless of asthma status. Spirometry before and after

bronchodilator (4 inhalations of albuterol, 90 mcg/inhalation, via a valved holding chamber), allergy skin tests using the prick puncture technique with the multi-test (Lincoln Diagnostics) to nine aeroallergens (*Aspergillus* and *Alternaria* molds, cat, dog, dust mite, and cockroach, and site specific tree, grass, and weed pollens), and methacholine challenges were performed as previously reported¹¹¹²¹³. Total serum IgE and a complete blood count with determination of white blood cell count and percentage of eosinophils were performed using standard techniques in each clinical center.

Definitions of vaso-occlusive pain episode and acute chest syndrome

A vaso-occlusive pain episode was defined as bone pain in chest, extremities, or other areas (not headaches only) directly associated with SCA that required hospitalization for treatment with opioids. Acute chest syndrome was defined as an episode of acute respiratory distress with at least a new radiodensity on chest roentgenogram, temperature greater than 38⁰ Celsius and increased respiratory effort, with a decrease in oxygen saturation or increased respiratory rate documented in the medical record. To ensure a uniform definition of pain and ACS in this multi-center study, all ACS and vaso-occlusive pain episodes requiring hospitalization were reviewed by a single investigator at each participating site, with over reading by the principal investigator (MBD). Concerns about the assignment of the diagnosis raised by the principal investigator were discussed with the site investigators and consensus reached.

Classifications as asthma and non-asthma

Two-hundred and fifty-two subjects were enrolled with a diagnosis of SCA, 95% with Hgb SS and 5% with Hgb Sβ⁰ (Figure). Subjects were classified as having asthma, based on a doctor diagnosis of asthma and current prescription of an asthma medication, or as no asthma, based on having neither a doctor diagnosis of asthma nor an asthma medication (Figure).

Participants did not meet our criteria for “asthma” if they either had a doctor diagnosis but no asthma medication (n=15) or albuterol prescribed without a doctor diagnosis (n=10). These participants were not included in the analysis so as to have the classifications of asthma and non-asthma discrete for purposes of understanding the characteristics of asthma among children with SCA.

Of the 227 subjects with an asthma classification, 40 had missing data on at least one of the 8 covariates in the model (Figure). Rates of missing data for each group ranged from 0.4% for wheeze causing shortness of breath, wheeze without colds, wheeze with colds, and wheeze after exercise, to 0.9% for cough without colds and phlegm without colds, to 3.1% for does mother have asthma, to 14.5% for does either parent have asthma and 15.4% for does father have asthma. These 40 subjects were not included in the initial logistic regressions to maintain a consistent case basis for the models; a process of data imputation was not used because there were no other variables that would reliably predict maternal and paternal asthma. An analysis of the differences between subjects with and without missing data showed no large or consistent differences.

Statistical Analyses

All data from subjects in the asthma and no asthma study groups were combined and continuous variables were assessed for normality. Analyses were conducted using Stata statistical software (StataCorp LP, Version 12, College Station, Texas) and IBM SPSS Statistics (IBM, Version 20, Chicago, Illinois). Continuous data that were normally distributed were analyzed using t-tests, skewed data were analyzed with the Mann-Whitney

Wilcoxon test, and categorical data were analyzed using chi-squared tests. Variance is reported using standard deviation or inter-quartile ranges.

A multivariable logistic regression was performed using characteristics postulated to be relevant to a diagnosis of asthma that could be readily available to a clinician conducting an initial interview using the ATS/DLD questionnaire with a patient and family: wheeze, cough, and phlegm production without colds; wheeze after exercise; wheeze causing shortness of breath; and either mother and father with asthma or either parent with asthma. Due to collinearity between mother and father with asthma, each had to be assessed separately. Because both allergy skin test results and spirometry variables of bronchodilator response (BDR) and percentage of those with an forced expiratory volume in one second/forced vital capacity (FEV₁/FVC) ratio below the lower limit of normal (LLN) were significantly different between the asthma and no asthma groups, these variables were used subsequently to determine if they added any explanatory power to the results of the logistic regression analyses. Relationships between asthma diagnosis and prospective rates of pain and ACS were examined using multivariable negative binomial regressions, controlling for features known to affect pain and ACS outcomes: sex, WBC, hemoglobin, and age ¹.

Results

Of the 187 subjects included in the analysis, 53 (28.3%) were classified as having asthma and 134 (71.7%) were classified as “no asthma” (Figure). Sex and age at entry into the study were not different between those with and without asthma (Table I). The proportions having a father with asthma or either parent with asthma were higher in the asthma group.

Children with asthma had significantly more affirmative responses to each of the wheezing symptoms associated with asthma than children without asthma (Table I). Overall, 88.7% of children with asthma had at least one of these symptoms: wheeze causing shortness of breath, wheeze apart from colds, wheeze with colds, and wheeze after exercise. While those classified as not having asthma had significantly fewer wheeze symptoms overall, 47.8% had a least one wheezing symptom. Thus, in our cohort wheezing alone is necessary, but not sufficient, for making a physician diagnosis of asthma that also required prescription of an asthma medication.

The number of positive skin tests and percent of children with 2 or more positive tests were both significantly higher in the asthma group (Table II); the percentage of children with a positive reaction to the individual skin tests ranged from 7.5 (dog) to 34.0 (grass) for asthma and 1.7 (dog) to 11.3 (grass) for no asthma, with differences significant for 7 of the 9 allergens (not for dog, $p=0.055$, and mite, $p=0.168$).

There was no significant difference in baseline values for FVC, FEV₁, and FEV₁/FVC between children with and without asthma, although those with asthma had a greater increase in FEV₁ after administration of albuterol (bronchodilator response, BDR) when compared with the children without asthma, 7.7% and 4.5%, respectively, and had a greater percentage FEV₁/FVC below the lower limit of normal, 24.0% and 11.0%, respectively (Table II). Methacholine challenge was originally scheduled for all participants, but was stopped prematurely in the study because a study participant had a severe vaso-occlusive pain episode that was temporally associated with this procedure ¹⁴. Among the subset of 79 children (55% with asthma and 37% without) who underwent methacholine challenge, no significant difference occurred in the concentration needed to reduce FEV₁ by 20% from the baseline (PC₂₀) according to asthma status (Table II). Inflammatory markers, white blood count, eosinophil count as percentage of total white blood count, and total serum IgE, did not differ between the asthma and no asthma groups (Table II).

Multiple Variable Analyses of Factors Distinguishing Children with Asthma and No Asthma

The multivariable logistic regression was conducted in two steps. First, all characteristics in Table I, with the exception of age, sex, and those associated with a cold, were used in a model to screen for those with significance of $p < 0.20$. Then a second model was run with the screened set of characteristics.

In the first stage, four characteristics met the screening criterion: having a parent with asthma ($p=0.055$), wheeze without colds ($p=0.086$), wheeze causing shortness of breath ($p=0.006$), and wheeze after exercise ($p<0.001$). In the reduced model with only these four characteristics, three remained significantly associated with asthma (model chi square = 65.1, 3 df, $p < 0.001$): having a parent with asthma (OR 3.41, 95% CI 1.43-8.15, $p=0.006$), wheeze after exercise (OR 7.68, (95% CI 3.44-17.16, $p < 0.001$), and wheeze causing shortness of breath (OR 4.38, 95% CI 1.89-10.19, $p=0.001$). The model sensitivities and specificities are shown in Table III.

In terms of model probabilities, when none of the characteristics was present, asthma probability was predicted to be only 0.07. In contrast, presence of any two characteristics had a predicted probability of 0.68, and the presence of all three characteristics had a predicted probability of 0.90. However, predicted probability of asthma with only 1 characteristic present was 0.29, and so no prediction of asthma was made, but 29.6% of these children had an asthma diagnosis.

Given that the model probabilities for the presence of only 1 of 3 predictive characteristics were not useful clinically, additional logistic regression models were performed to determine the added value of the presence of 2 or more positive allergy skin test results in this subset. Addition of the skin test variable to the model was significant ($p < 0.001$), increasing sensitivity from 0% but only to 18.8%, indicating that in subjects with minimal historical evidence of asthma the skin test variable may be only minimally useful as a diagnostic aid. A 12% or greater increase in FEV₁ in response to bronchodilator¹⁵ or an FEV₁/FVC ratio below the lower limits of normal, were not significant when added to the model, with p values of 0.535 and 0.492, respectively.

Relationship between asthma diagnosis and SCA morbidity

Patients were followed prospectively for 4.61 ± 1.16 years, for a total of 857 patient years for occurrence of pain and ACS episodes. A negative binomial regression was used to determine the effect of asthma diagnosis used in this study on prospective pain and ACS episodes, controlling for age, sex, hemoglobin, and white blood cell count (one case was unavailable for this analysis because of missing data on covariates). The asthma diagnosis was associated statistically with ACS occurring after entry into the study, IRR=2.21: 95% CI 1.31-3.76. No other variable was significant ($p>0.05$). There was no association between asthma and pain occurring after entry, IRR=1.28: 95% CI 0.78-2.10. Both WBC (IRR=1.06; 95% CI 1.01-1.13) and age (IRR=1.09; 95% CI 1.04-1.15) were associated with pain ($p<0.05$).

Discussion

Given that asthma in SCA is associated with increased morbidity and mortality, identifying characteristics of children who should be considered to receive a diagnosis of asthma is clinically relevant. The combination of three characteristics identified in this study, a parental history of asthma and two historical wheeze symptoms (wheezing after exercise and wheezing causing shortness of breath), distinguished children with SCA as having asthma from children classified as having no asthma. Previous descriptions of asthma in children with SCA have used parent report of a doctor diagnosis or chart audit of presence of

physician diagnosis¹²³⁴⁶⁷⁸. However, none of these studies provide historical and laboratory features associated with the diagnoses of asthma.

The importance of wheeze symptoms in SCA is similar to the general population, in that almost all children with asthma had at least one wheeze symptom. However, unlike the general population, children with SCA can have wheeze associated with their primary disease, an association reported during episodes of ACS¹⁶ and well recognized in adults¹⁷¹⁸. Based on our results and others, we believe that at least in children with SCA, wheezing is a necessary, but not sufficient component to make the diagnosis of asthma.

The relevance of the criteria for asthma presented here is emphasized by the prediction of future ACS episodes in those with this diagnosis. This result is consistent with several other studies that have found an association of asthma diagnosis with higher rates of ACS¹¹⁹⁴²⁰⁸⁶²¹. Criteria from our analysis can now be applied to facilitate diagnosis of asthma. In contrast to other studies¹²¹, the diagnosis of asthma in SAC patients was not associated with future pain events. In this study the cumulated number of patient years was 857, whereas in the Boyd et al.¹ and An et al.²¹ articles the patient years that contributed to the analyses were approximately 4000 and 3000, respectively. Possibly, increasing patient years in follow-up for the study cohort might have demonstrated an association between asthma and pain. Based on our results and others, there is clearly a stronger relationship between asthma and increased ACS incidence rate¹¹⁹⁴²⁰⁸⁶²¹ than asthma and increased pain incidence rate^{1, 21}.

The model with three characteristics was accurate in predicting asthma at the extremes, i.e., presence of 2 or 3 characteristics had high sensitivity in predicting asthma, with a high specificity for no asthma when none were present. The knowledge of aeroallergen sensitivity, specifically the presence of two or more positive tests, statistically increased the accuracy of detecting asthma with only 1 characteristic present, however, the sensitivity was less than 20%. An FEV₁/FVC ratio indicative of airway obstruction and increased reactivity to bronchodilator were both significantly different between the asthma and no asthma populations, but did not add to the discriminative capacity when only 1 of the 3 characteristics was present. In addition, in contrast to the general population a methacholine challenge was not useful in discriminating children with asthma from those without asthma.

The finding that spirometry could not discriminate between those that have asthma from those that do not has important clinical implications, as clinicians without spirometry available to them can still diagnose an SCA patient with asthma. If asthma is diagnosed in children with SCA, we recommend following the NHLBI guidelines for the management of the asthma that does include regularly scheduled spirometry evaluations. Furthermore, spirometry may still play a role in identifying airway obstruction²² and restrictive lung disease²³, both of which are common in children with SCA and may be important in morbidity outcomes.

Aeroallergen sensitivity by skin testing was statistically associated with an improved sensitivity to identify asthma. However, these results may have limited clinical utility because adding skin testing to identify individuals with 1 of 3 characteristics associated with asthma only increased the sensitivity from 0% to 18%. Knight-Madden et al²⁰ found that atopic asthma was more common among children with recurrent episodes of ACS than those with only single or no episodes, suggesting that aeroallergen sensitivity may play a role in SCA outcomes.

Several limitations exist in the current study. Asthma is a subjective diagnosis. Based on the challenges with an asthma diagnosis particularly in children with SCA, we deliberately selected the most conservative asthma diagnosis, a physician diagnosis of asthma coupled

with prescription of an asthma medication. We also elected for the asthma negative group to be those with neither a physician diagnosis of asthma nor prescription of an asthma medication. The presence of asthma in those with a doctor diagnosis is supported by 83% (44 of 53) having been prescribed either an inhaled corticosteroid or a leukotriene modifier, as well as a bronchodilator. Parents of children with a co-morbid condition of asthma may under report symptoms to their physician because they have accommodated to them, or their sickle cell disease physician may be unaware of the possibility that asthma might be present when wheezing occurs. In both these situations, children with asthma would have been classified as no-asthma, diminishing differences between the two groups. Another limitation is the lack of uniform diagnosis of asthma in the three clinical sites. However, we did routinely ascertain from parental reports a doctor diagnosis of asthma, and report of symptoms was recorded uniformly in all participants regardless of a parental report of a doctor diagnosis of asthma. The lack of common clinical definition of asthma at the three sites would have only contributed to an increase in the variability in the asthma diagnosis. Despite this variability, we were able to demonstrate that a set of wheezing questions plus parental asthma results may help clinicians distinguish between those with and without asthma.

Although this study cannot provide evidence of the value of asthma treatment, a trial of such treatment could be conducted based on the predicted probabilities obtained in these analyses. Medicine recommended in the NHLBI guidelines to control and prevent chronic respiratory symptoms in children with asthma (bronchodilators and inhaled steroids and/or leukotriene modifiers) may ameliorate morbidity in children with SCA. After initiation of such therapy, a child should be re-evaluated within 1-2 months to determine the benefit and/or burden of therapy. Systemic corticosteroids, which are commonly used in the setting of acute asthma, should probably be used with caution in children with SCA as several retrospective studies have demonstrated an association with adverse consequences for children with SCA when used in the setting of ACS ²⁴²⁵²⁶²⁷²⁸²⁹.

In summary, having a parent with asthma and wheezing symptoms are the best features to distinguish those with from those without a parent report of a doctor diagnosis of asthma receiving asthma therapy and to identify those at higher risk for ACS events. The value of treatment for asthma in prevention of SCA morbidity needs to be studied.

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Appendix

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References

1. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. *Blood*. 2006; 108:2923–2927. [PubMed: 16690969]
2. Leong MA, Dampier C, Varlotta L, Allen JL. Airway hyperreactivity in children with sickle cell disease. *J Pediatr*. 1997; 131:278–283. [PubMed: 9290616]
3. Glassberg J, Spivey JF, Strunk R, Boslaugh S, DeBaun MR. Painful episodes in children with sickle cell disease and asthma are temporally associated with respiratory symptoms. *J Pediatr Hematol Oncol*. 2006; 28:481–485. [PubMed: 16912587]
4. Glassberg JA, Chow A, Wisnivesky J, Hoffman R, Debaun MR, Richardson LD. Wheezing and asthma are independent risk factors for increased sickle cell disease morbidity. *Br J Haematol*. 2012; 159:472–479. [PubMed: 22966893]
5. Anim SO, Strunk RC, DeBaun MR. Asthma morbidity and treatment in children with sickle cell disease. *Expert Rev Respir Med*. 2011; 5:635–645. [PubMed: 21955234]
6. Poulter EY, Truszkowski P, Thompson AA, Liem RI. Acute chest syndrome is associated with history of asthma in hemoglobin SC disease. *Pediatr Blood Cancer*. 2011; 57:289–293. [PubMed: 21671365]
7. Newaskar M, Hardy KA, Morris CR. Asthma in sickle cell disease. *Scientific World Journal*. 2011; 11:1138–1152. [PubMed: 21623460]
8. Sylvester K, Patey R, Broughton S, et al. Temporal relationship of asthma to acute chest syndrome in sickle cell disease. *Pediatric Pulmonology*. 2007; 42:103–106. [PubMed: 17186507]
9. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with increased mortality in individuals with sickle cell anemia. *Haematologica*. 2007; 92:1115–1118. [PubMed: 17650441]
10. Ferris B. Epidemiology Standardization Project. *Am Rev Respir Dis*. 1978; 118:1–120. [PubMed: 742764]
11. Field JJ, Stocks J, Kirkham FJ, Rosen CL, Dietzen DJ, Semon T, et al. Airway hyper-responsiveness in children With sickle cell anemia. *Chest*. 2011; 139:563–568. [PubMed: 20724735]
12. Miller M, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005; 26:319–338. [PubMed: 16055882]
13. Kirkby J, Bonner R, Lum S, Bates P, Morgan V, Strunk RC, et al. Interpretation of pediatric lung function: Impact of ethnicity. *Pediatr Pulmonol*. 2012; 1002/ppul.22538
14. Knight-Perry JE, Field JJ, Debaun MR, Stocks J, Kirkby J, Strunk RC. Hospital admission for acute painful episode following methacholine challenge in an adolescent with sickle cell disease. *Pediatr Pulmonol*. 2009; 44:728–730. [PubMed: 19504562]
15. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005; 26:948–968. [PubMed: 16264058]
16. Vichinsky EP, Styles LA, Colangelo LH, Wright EC, Castro O, Nickerson B, et al. Acute chest syndrome in sickle cell disease: clinical presentation and course. Cooperative Study of Sickle Cell Disease. *Blood*. 1997; 89:1787–1792. [PubMed: 9057664]
17. Cohen R, Madadi A, Blinder M, DeBaun M, Strunk R, Field J. Recurrent, severe wheezing is associated with morbidity and mortality in adults with sickle cell disease. *Am J Hematol*. 2011; 86:756–761.

18. Glassberg J, Chow A, Wisnivesky J, Hoffman R, DeBaun M, Richardson L. Wheezing and asthma are independent risk factors of increased sickle cell disease morbidity. *Brit J Haematology*. 2012; 159:472–479.
19. Bernaudin F, Strunk RC, Kamdem A, Arnaud C, An P, Torres M, et al. Asthma is associated with acute chest syndrome, but not with an increased rate of hospitalization for pain among children in France with sickle cell anemia: a retrospective cohort study. *Haematologica*. 2008; 93:1917–1918. [PubMed: 18815195]
20. Knight-Madden JM, Forrester TS, Lewis NA, Greenough A. Asthma in children with sickle cell disease and its association with acute chest syndrome. *Thorax*. 2005; 60:206–210. [PubMed: 15741436]
21. An P, Barron-Casella EA, Strunk RC, Hamilton RG, Casella JF, DeBaun MR. Elevation of IgE in children with sickle cell disease is associated with doctor diagnosis of asthma and increased morbidity. *J Allergy Clin Immunol*. 2011; 127:1440–1446. [PubMed: 21388662]
22. Boyd JH, DeBaun MR, Morgan WJ, Mao J, Strunk RC. Lower airway obstruction is associated with increased morbidity in children with sickle cell disease. *Pediatr Pulmonol*. 2009; 44:290–296. [PubMed: 19205057]
23. MacLean JE, Atenafu E, Kirby-Allen M, MacLusky IB, Stephens D, Grasemann H, et al. Longitudinal decline in lung volume in a population of children with sickle cell disease. *Am J Respir Crit Care Med*. 2008; 178:1055–1059. [PubMed: 18776149]
24. Darbari DS, Castro O, Taylor JGt, Fasano R, Rehm J, Gordeuk VR, et al. Severe vaso-occlusive episodes associated with use of systemic corticosteroids in patients with sickle cell disease. *J Natl Med Assoc*. 2008; 100:948–951. [PubMed: 18717146]
25. Bernini JC, Rogers ZR, Sandler ES, Reisch JS, Quinn CT, Buchanan GR. Beneficial effect of intravenous dexamethasone in children with mild to moderately severe acute chest syndrome complicating sickle cell disease. *Blood*. 1998; 92:3082–3089. [PubMed: 9787142]
26. Sobota A, Graham DA, Heeney MM, Neufeld EJ. Corticosteroids for acute chest syndrome in children with sickle cell disease: variation in use and association with length of stay and readmission. *Am J Hematol*. 2010; 85(1):24–28. [PubMed: 19957348]
27. Huang JC, Gay R, Khella SL. Sickling crisis, fat embolism, and coma after steroids. *Lancet*. 1994; 344:951–952. [PubMed: 7934359]
28. Johnson K, Stastny JF, Rucknagel DL. Fat embolism syndrome associated with asthma and sickle cell-beta(+)-thalassemia. *Am J Hematol*. 1994; 46:354–357. [PubMed: 8037190]
29. Strouse JJ, Hulbert ML, DeBaun MR, Jordan LC, Casella JF. Primary hemorrhagic stroke in children with sickle cell disease is associated with recent transfusion and use of corticosteroids. *Pediatrics*. 2006; 118:1916–1924. [PubMed: 17079562]
30. Quanjer P, Stojanovic S, Cole T, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012; 40:1324–1343. [PubMed: 22743675]

List of abbreviations

SCA	Sickle cell anemia
HgBSS	Sickle cell hemoglobin
Hgb Sβ°	Sickle-beta $^{\circ}$ -thalassemia
ATS/DLD	American Thoracic Society/Division of Lung Diseases
LLN	Lower limit of normal
FVC	forced vital capacity
FEV₁	Forced expiratory volume in one second
FEV₁/FVC	ratio between FEV1 and FVC
BDR	bronchodilator response

IRR

incident rate ratio

Figure 1.
Consort diagram of population studies

Table 1

Demographic, parental characteristics, and responses to ATS/DLD questionnaire for children with SCA without asthma (neither a doctor diagnosis of asthma nor prescribed asthma medication) and with asthma

Variable	No Asthma N=134	Asthma N=53	p-value
Demographics			
Sex, % male	45.5	54.7	0.259
Age, years, median(SD)	9.0 (4.2)	11.0(4.3)	0.117
Parental History, % with Yes answer			
Father with asthma, %	6.0	20.8	0.002
Mother with asthma, %	11.9	22.6	0.065
Either parent has asthma	16.4	39.6	<.001
Responses to ATS/DLD questionnaire, % with Yes answer			
Any wheezing symptom	47.8	88.7	<.001
Wheeze causes shortness of breath	12.7	52.8	<.001
2 or more wheezing episodes that caused shortness of breath	7.5	47.2	<.001
Wheeze apart from colds	7.5	47.2	<.001
Wheeze with colds	38.8	73.6	<.001
Wheezing attack after exercise	17.2	67.9	<.001
Cough with colds	75.4	86.8	0.087
Cough apart from colds	29.9	54.7	0.001
Phlegm with cold usually	53.7	69.8	0.045
Phlegm apart from cold	9.7	28.3	0.001

Results presented as proportions (median for age).

ATS/DLD – American Thoracic Society/Division of Lung Diseases

Table 2

Results of allergy skin tests, lung function tests, and inflammatory markers in children with SCA without asthma (either no doctor diagnosis of asthma or no prescribed asthma medication) and with asthma.

	No Asthma	Asthma	p-value
Allergy skin tests			
Number of positive skin tests (of 9 tested) [†]	0.0(1.0)	1.0(3.0)	<.001
Percent with ≥2 positive skin tests (of the 9 tested)	14.8	45.3	<.001
Lung function tests			
Baseline FEV ₁ % Predicted	89.8(13.6)	85.9(12.4)	0.136
Baseline FVC % Predicted	93.8(14.3)	94.0(13.9)	0.764
Baseline FEV ₁ /FVC % Predicted	96.5 (6.3)	94.4 (8.2)	0.030
% below LLN for baseline FEV ₁ /FVC	11.0	24.0	0.031
Airway lability			
% increase in FEV ₁ after albuterol [†]	4.5 (8.8)	7.7 (9.4)	0.004
PC ₂₀ ^{* †}	3.1 (36.9)	2.9(36.5)	0.932
BD Response ≥12%	16.1	28.0	0.079
Inflammatory markers			
WBC, unt/microL)×10 ³	11.5(3.8)	12.1 (3.3)	0.158
Eosinophils, % WBC [†]	3.0(3.0)	3.0(3.0)	0.155
IgE, IU/ml [†]	43.0(135.0)	58.2(145.3)	0.587

Presented as median (SD) for normally distributed continuous variables and proportions for the categorical variables.

[†] Presented as median (interquartile range) for skewed continuous variables.

Spirometry results were expressed as percent predicted based on recently published all age multi-ethnic reference equations ²⁹, using the 5th percentile as the lower limit of normal for the set of equations derived for Black individuals ²⁹.

* The provocative concentration of methacholine reported is the concentration that resulted in a 20% fall in FEV₁ (PC₂₀). Seventy-nine were tested, 50 without asthma (37% of the non- asthmatics in the cohort) and 29 with asthma (55% of the cohort with asthma). The percentage of children with negative challenges (a PC₂₀ >12.5 mg/ml) was 30% in the no asthma group and 31% in the asthma group, whereas severe hyper-responsiveness (PC₂₀ <2 mg/ml) was observed in 50% of those with no asthma and 41% of those with asthma.

Table 3

Performance of the model in predicting asthma

Number of Positive Factors	Number of Subjects	Percent with Asthma	Model Sensitivity	Model Specificity
0	91	7.7%	0.0%	100.0%
1	54	29.6%	0.0%	100.0%
2	33	63.6	100.0%	0.0%
3	9	100.0%	100.0%	NA
Total	187	28.4%	56.6%	91.0%