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Authors

Rodeghier, Mark
Strunk, Robert
Bacharier, Leonard
et al.

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Aeroallergen Sensitization Predicts Acute Chest Syndrome in Children with Sickle Cell Anemia

Shaina M Willen, MD¹, Mark Rodeghier, PhD², Robert C. Strunk, MD³, Leonard B. Bacharier, MD³, Carol L. Rosen, MD⁴, Fenella J. Kirkham, FRCPCH, MD, res⁵, Michael R. DeBaun, MD, MPH¹, and Robyn T Cohen, MD, MPH⁶

¹Department of Pediatrics, Division of Hematology/Oncology, Vanderbilt-Meharry Center for Excellence in Sickle Cell Disease, Vanderbilt University Medical Center, Nashville, TN, USA

²Rodeghier Consultants, Chicago, IL, USA

³Department of Pediatrics, Division of Allergy, Immunology, and Pulmonary Medicine, Washington University School of Medicine, St Louis, MO, USA

⁴Department of Pediatrics, Division of Pediatric Pulmonary, Allergy/Immunology and Sleep, University Hospitals-Cleveland Medical Center, Rainbow Babies and Children's Hospitals, Cleveland OH, USA

⁵Developmental Neurosciences Unit, UCL Great Ormond Street, Institute of Child Health, London, United Kingdom

⁶Department of Pediatrics, Division of Pediatric Pulmonary & Allergy, Boston University School of Medicine, Boston, MA, USA

Summary

Asthma is associated with higher rates of acute chest syndrome (ACS) and vaso-occlusive pain episodes among children with sickle cell anemia (SCA). Aeroallergen sensitization is a risk factor for asthma. We hypothesized that aeroallergen sensitization is associated with an increased

Correspondence to: Robyn Cohen, MD, Department of Pediatrics, Division of Pediatric Pulmonary & Allergy, Boston University School of Medicine, 850 Harrison Ave, Boston, MA, USA 02118, Phone : (617) 414-4841, robyn.cohen@bmc.org.

Contributions: Dr. Willen and Dr. Cohen had full access to all of the data in the study and take responsibility for the integrity of the data, the accuracy of the data analysis, and the work as a whole. Dr. Willen (Clinical Fellow, Department of Pediatrics, Division of Hematology/Oncology, Vanderbilt University School of Medicine, Nashville, TN) interpreted the data, created the initial draft, and finalized the manuscript for submission; Dr. Rodeghier (Independent statistician, Chicago, Illinois) developed the statistical approach, performed those analyses, reviewed the integrity of those analyses, reviewed and revised the manuscript; Dr. Strunk (Division of Allergy, Immunology, and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine, St Louis, MO) was the co-principal investigator for the SAC study, contributed to the development of the SAC project, study concepts, and procedures, and conceptualized the manuscript; Dr. Bacharier (Division of Allergy, Immunology, and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine, St Louis, MO) interpreted the results, reviewed and revised the manuscript; Dr. Rosen (Department of Pediatrics, Case Western Reserve University School of Medicine, Rainbow Babies and Children's Hospitals, University Hospitals Cleveland Medical Center, Cleveland, OH) contributed to the development of the SAC project, study concepts and procedures, and reviewed and helped revise the manuscript; Dr. Kirkham (UCL Great Ormond Street, London Institute of Child Health) was the site investigator for one site, helped develop the concepts for the SAC project and reviewed and revised the manuscript; Dr. DeBaun (Department of Pediatrics, Division of Hematology/Oncology, Vanderbilt and Meharry Center for Excellence in Sickle Cell Disease, Vanderbilt University Medical Center, Nashville, TN) was the principal investigator for the SAC project, helped design the concepts for SAC and this manuscript, interpreted the results, and reviewed and revised the manuscript; Dr. Cohen (Department of Pediatrics, Boston University School of Medicine, Boston, MA) interpreted the data, developed the initial draft, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

incidence of hospitalizations for ACS and pain. Participants in a multicenter, longitudinal cohort study, ages 4–18 years with SCA, underwent skin prick testing to ten aeroallergens. ACS and pain episodes were collected from birth through the end of the follow-up period. The number of positive skin tests were tested for associations with prospective rates of ACS and pain. Multivariable models demonstrated additive effects of having positive skin tests on future rates of ACS (incidence rate ratio (IRR) for each positive test 1.23, 95% CI 1.11–1.36, $p < 0.001$). Aeroallergen sensitization was not associated with future pain (IRR 1.14, 95% CI 0.97–1.33, $p = 0.11$). Our study demonstrated that children with SCA and aeroallergen sensitization are at increased risk for future ACS. Future research is needed to determine whether identification of specific sensitizations and allergen avoidance and treatment reduce the risk of ACS for children with SCA.

Keywords

Allergy; Atopy; Sickle cell anemia; Acute chest syndrome; Asthma

Introduction

Sickle cell anemia (SCA) is the most common inherited blood disease in the United States. The most common complications for patients with SCA include acute vaso-occlusive pain (herein referred to as “pain”) and acute chest syndrome (ACS) (Platt *et al*, 1994; Castro *et al*, 1994). Previous studies have demonstrated that children with SCA and asthma have increased rates of ACS and pain and increased risk for premature death compared to those without asthma (Boyd *et al*, 2007; Bernaudin *et al*, 2008). Atopy is the most significant risk factor for the development of childhood asthma in the general population, with an increased risk of 10–20 fold (Burrows *et al*, 1989). Previous studies in children with SCA have demonstrated associations between markers of atopy (positive allergy skin tests (Knight-Madden, 2005; Strunk *et al*, 2014) and elevated total IgE (An *et al*, 2011)) and a history of *prior* ACS.

Given previous evidence suggesting that indicators of atopy may be associated with greater morbidity among children with SCA, we sought to further characterize this relationship. We hypothesize that aeroallergen sensitization is associated with an increased incidence of ACS episodes in children with SCA. The objectives of the current study were: 1) to determine the prevalence of aeroallergen sensitization among an unselected cohort of children with SCA using skin prick testing; 2) to examine associations between aeroallergen sensitization and prospective rates of pain and ACS; and 3) to explore whether scores on a composite index of atopy features (herein termed the “Atopy Index”) would be associated with prospective morbidity in children with SCA.

Methods

Study Design

Data were collected as part of the prospective, observational Sleep and Asthma Cohort (SAC) study. From 2005–2011, children ages 4 to 18 years with SCA (hemoglobin SS or

S β ⁰) were enrolled at three clinical centers (in St. Louis, MO, Cleveland, OH and London, UK) without regard to previous morbidity or diagnosis of asthma. Serum IgE and complete blood count were obtained at study entry. Percentage of blood eosinophils was determined using standard techniques at each clinical center. Medical records of participants were reviewed to obtain the number of hospitalizations for pain and ACS episodes both retrospectively (from birth whenever possible) and prospectively until the end of the study period in 2013 or until participants were lost to follow-up. Medical records of participants were also reviewed in order to determine asthma history. Asthma was defined in our cohort as a physician diagnosis of asthma in the medical record plus a prescription for an asthma medication such as short-acting beta agonist (SABA) and/or inhaled corticosteroid (ICS) (Strunk *et al*, 2014). Children were ineligible for the study if they were receiving chronic transfusion therapy or participating in a clinical trial evaluating hydroxyurea therapy at the time of recruitment. However, if participants were subsequently prescribed chronic transfusions or hydroxyurea therapy during the follow-up period, they were able to continue their participation. Participating sites had institutional approval. Written informed consent was obtained from parents and assent was obtained from children at enrollment according to institutional policies.

Allergy Skin Testing

Participants underwent allergy skin prick testing at study entry performed by SAC-certified technicians using the Multi-test II (Lincoln Diagnostics, Decatur, IL). Ten aeroallergens (Greer Laboratories, Lenoir, NC) were used for skin testing including: *Aspergillus fumigatus*, house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), cockroach (American and German), cat (standardized), dog (mixed breeds), mouse, *Alternaria alternata*, grass (standardized southern mix), tree (eastern 8 tree mix), and weed (national mix). Skin tests were administered with histamine (positive) and saline (negative) controls. Tests were considered positive when the mean diameter of the wheal was ≥ 3 mm. Wheal reactions were traced onto translucent acetate paper and measured centrally by a single investigator (R.C.S.) for quality control of the results.

Definition of vaso-occlusive pain episode and acute chest syndrome

ACS was defined as a new radiographic pulmonary infiltrate in the context of an acute respiratory illness with symptoms such as cough, wheezing, rales, chest pain, decreased oxygen saturation $>2\%$ from baseline, use of accessory muscles of respiration, or increased respiratory rate, with or without fever. Pneumonia was considered an ACS episode. A pain episode was defined as a hospitalization for SCA-associated pain, excluding headaches, and requiring opioid treatment. Headaches were excluded from this definition because of the presumed difference in pathophysiology (Dowling *et al*, 2014). All ACS and pain episodes were reviewed by a single investigator at each participating site with over-reading by the principal investigator (M.R.D), to ensure uniform definitions of ACS and pain episodes in this multi-center study.

Atopy Index

The Atopy Index is a novel evaluation tool created for the purpose of this investigation and was based on 4 factors and their known associations with atopy in children as well as a

potential association with SCA related morbidity and included: aeroallergen sensitization (Lipozen *i* & Wolf, 2010; Strunk *et al*, 2014), serum IgE level (An *et al*, 2011), peripheral blood eosinophils (Canalli *et al*, 2004), and a history of asthma in either parent (Strunk *et al*, 2014). Z-scores for IgE levels were calculated for our cohort using normative data from race-, age-, and gender-matched controls from National Health and Nutrition Examination Survey (NHANES) III 2005–2006 participants (Hyattsville, 2005; Centers for Disease Control and Prevention (CDC), 2008). The Atopy Index score for each SAC participant ranged from 0–4: at least one positive aeroallergen skin test (+1), IgE Z score in the upper quartile ($Z > 0.67$) (+1), peripheral blood eosinophils $> 4\%$ (+1), and a history of asthma in either parent (+1).

Statistical Analysis

The number of positive skin tests (out of a possible 10) was used as a continuous variable; however, because of low numbers, individuals with 6 or more positive tests were grouped together. Associations between the number of positive skin tests and prospective rates of ACS and pain after the date of skin testing were tested with negative binomial regression models. Analyses were limited to participants with ACS and pain data from birth and a minimum of 12 months of prospective follow-up after skin testing. Multivariable models were built in two steps. Potential covariates were included in a screening model. In addition to the number of positive skin tests, covariates we considered to be potentially associated with prospective rates of ACS included sex, ACS prior to 4 years of age (DeBaun *et al*, 2014), white blood cell count, IgE level (An *et al*, 2011), fractional exhaled nitric oxide (FeNO), asthma diagnosis (Boyd *et al*, 2006), parental asthma (Strunk *et al*, 2014), and history of wheezing leading to shortness of breath (DeBaun *et al*, 2014). Covariates considered for inclusion in the model for prospective rates of pain were gender, age, white blood cell count, history of wheeze leading to shortness of breath (Glassberg *et al*, 2006), and hemoglobin. Following analyses with the number of positive skin tests, we constructed additional models to test associations between the score on the Atopy Index and prospective rates of ACS and pain. All covariates with $p < 0.20$ in screening models were included in the final ACS and pain models. Models for the Atopy Index were compared to models for positive skin tests alone using the Likelihood test. Analyses were conducted using Stata statistical software (Version 12, College Station, TX: StataCorp LP) and IBM SPSS Statistics (Version 22, Chicago, IL, IBM).

Results

Recruitment and Demographics

Of the 252 SAC participants, 188 had morbidity data available from birth and 165 had acceptable allergy skin test data, with a mean of 5.0 years (SD 1.2 years) of prospective follow-up after skin testing. Ninety eight participants (59%) did not have aeroallergen sensitization, while 67 participants (41%) had at least one positive skin test (Figure I). Clinical characteristics of the cohort are summarized in Table I. Children with at least one positive skin test had higher IgE levels than those who did not ($p = 0.01$). Individuals were also more likely to have a positive skin test if they had a parent with asthma ($p = 0.01$). The participants excluded from the analysis due to missing or invalid allergy skin test data were

older (mean age 10.0 years compared to 13.8 years, $p<0.01$) and had a slightly higher IgE level (median 51.5 IU/ml compared to 27.0 IU/ml, $p=0.05$) compared to those who were included. These comparisons are summarized in Supplementary Table I. A total of 163 participants had complete data on all covariates used in our models and were therefore included in the analysis.

Positive skin test is predictive of future ACS rate but not future pain

Multivariable models demonstrated additive significant effects of having positive skin tests on future rates of ACS such that each increase of 1 positive test was associated with a 23% increased rate of future ACS episodes (95% CI 11–36%, $p<0.001$) (Table II). In a multivariable model, aeroallergen sensitization was not a significant predictor of pain incidence rates (IRR 1.14, 95% CI 0.97–1.33, $p=0.11$).

Allergy skin testing provides additional information beyond asthma diagnosis

Aeroallergen sensitization does not appear to be simply a proxy for asthma status in our cohort. Although more children with asthma had at least one positive skin test compared to children without asthma, (50% vs. 36%), this difference was not statistically significant ($p=0.09$). Additionally, in analyses stratified by asthma status, among children without asthma the number of positive skin tests was significantly associated with increased rates of ACS, but not among children with a diagnosis of asthma (Table III).

Atopy index is not more predictive of future ACS than allergy skin testing alone

Within our cohort, 132 participants had complete data for all four variables included in the Atopy Index. The Atopy Index was a significant predictor of future rates of ACS (IRR 1.44, 95% CI 1.17–1.76, $p<0.001$) (Table IV), but was not associated with future rates of pain (IRR 1.14, 95% CI 0.82–1.58, $p=0.43$). Using the likelihood test to compare models, the Atopy Index did not perform better than having at least one positive skin test in predicting future episodes of ACS (likelihood test p value=0.22), demonstrating that having a positive skin test was the critical covariate in the index.

Discussion

Asthma in SCA is a known risk factor for increased acute vaso-occlusive pain, ACS, and earlier death. However, the diagnosis of asthma is difficult in children with SCA, particularly because many features of asthma occur in individuals with SCA that do not have asthma, such as cough, wheezing, and airway hyperreactivity. Our study demonstrates for the first time that even a single positive skin test confers a significantly increased risk for future ACS, and more importantly, that increasing numbers of positive skin tests are associated with increased rates of prospective ACS. Furthermore, aeroallergen sensitization also seems to be the most significant indicator of atopy associated with SCA-related morbidity. The addition of other manifestations of atopy, including elevated IgE levels, eosinophilia, and parental asthma, to having a positive skin test did not improve our ability to predict ACS.

While there is strong evidence that a physician diagnosis of asthma is a risk factor for ACS (Boyd *et al*, 2007; Cohen *et al*, 2011; Knight-Madden *et al*, 2005; Sylvester *et al*, 2007),

aeroallergen sensitization does not seem to be merely a marker of asthma status among children with SCA. In our cohort, we demonstrated a significant impact of aeroallergen sensitization on future ACS episodes in children *without* a doctor diagnosis of asthma. One potential explanation for this finding is that for children with SCD *and* asthma, the airways are already primed for exaggerated inflammatory response to a multitude of triggers – allergic, infectious, or other. In those children, a history of early life ACS is the best predictor of future ACS. In contrast, for non-asthmatic individuals whose airways aren't as hyperresponsive to other triggers, exposure to an allergic trigger in the setting of aeroallergen sensitization is a significant factor associated with acute respiratory episodes including ACS (DeBaun & Strunk, 2016). Furthermore, our data demonstrates a nearly 2-fold increase in the risk of future ACS episodes with a history of ACS prior to age 4 years in those participants with asthma compared to those without an asthma diagnosis (Table III). In children with SCA without asthma, there may be more unexplained variation that allows detection by other covariates, such as the number of positive aeroallergen skin tests. Our results differ from a prior study of 340 children with SCA in the Silent Cerebral Infarct Transfusion (SIT) trial which found that having a positive serum allergen-specific IgE test to *Alternaria*, cockroach (*B. germanica*) or dust mite (*D. pteronyssinus*) was not associated with increased risk of ACS or pain episodes (An *et al*, 2011). However, the SIT Trial only included a limited panel of antibody testing to 3 aeroallergens. Serum aeroallergen-specific IgE testing to expanded panels of indoor (i.e., cat, dog, mouse, dust mite, cockroach, indoor molds) and outdoor (i.e., tree and grass pollens, ragweeds, outdoor molds) allergens are widely available, results are not invalidated when a patient is taking antihistamines, and only require a simple blood draw. Further research is needed to determine whether an expanded panel of aeroallergen-specific IgE testing, which is likely more feasible for providers caring for children with SCA, represents a satisfactory alternative to skin testing in this population.

Studies from transgenic sickle cell disease (SCD) mouse models offer a proposed mechanism for the connection between atopy and increased incidence of ACS episodes. Ovalbumin sensitized sickle mice have increased IL-5 levels and increased airway resistance compared to HbA mice (Pritchard *et al*, 2012), and when exposed to additional aerosolized ovalbumin, sickle mice have increased histologic evidence of airway and vascular inflammation, and increased risk of death compared to control mice (Nandedkar *et al*, 2008). Andemariam *et al.* has also demonstrated increased ovalbumin-induced allergic airway inflammation in sickle mice compared to wild type mice including increased BAL leukocytosis and eosinophilia, increased ovalbumin-specific serum IgE levels, and altered inflammatory cytokine profiles in SCD mice compared to control mice (Andemariam *et al*, 2015). These findings suggest that the pro-inflammatory state of SCD may prime the immune system to be hyper-responsive to inhaled allergens, and thus may help explain the high morbidity seen in patients with asthma and SCD. Mpollo *et al.* examined whether placental growth factor (PGF), a member of the vascular endothelial growth factor family known to be increased among patients with SCD, may be a potential mediator on the pathway between allergic sensitization and SCD morbidity (Eiyomo Mwa Mpollo *et al*, 2016). In a series of experiments, they demonstrated that PGF knockout (*Pgf⁻*) mice have significantly less airway resistance, airway hyperresponsiveness, circulating IgE, airway eosinophilia, and goblet cell hyperplasia compared to wild type *Pgf⁺* mice. Furthermore,

these investigators found that intratracheal exposure to house dust mite allergen extract was associated with upregulation of plasma PGF levels in wild type mice. When the investigators then examined sickle mice, they noted exaggerated responses to house dust mite airway exposure in terms of airway hyperresponsiveness, and this finding was mediated by PGF through a leukotriene-dependent pathway. When sickle mice were treated with PGF antibodies and with zileuton (a leukotriene synthesis inhibitor) house dust mite-exposure-induced airway reactivity was significantly decreased (Eiyimo Mwa Mpollo *et al*, 2016). Taken together, these data strongly suggest that individuals with SCD and asthma have airways that may be primed for an exaggerated response to a trigger, such as a viral respiratory infection in young children. This offers a mechanism for the high predictability of an ACS episode prior to age 4 years predicting future episodes of ACS. Additionally, the airways of children with SCD may have a predisposition to airway inflammation that is primed for aeroallergen sensitization leading to future ACS events. Furthermore, a single center study by Glassberg *et al*. demonstrated a benefit of daily inhaled corticosteroids in non-asthmatic adult patients with SCD (Glassberg *et al*, 2017).

Strengths of the current study include the rigorous data collection methods. All SCA-related morbidity data and allergy skin tests were reviewed by a study principal investigator to ensure a uniform definition across multiple sites. In contrast to the prior study about IgE levels in children with SCA in which IgE values from the SIT trial participants were stratified into elevated and non-elevated using comparison data from predominantly Caucasian cohorts (An *et al*, 2011), we standardized IgE levels into Z-scores using population-based data matched for age, gender, and race prior to incorporation into the Atopy Index. Limitations of the study are inclusion of only children with SCA; therefore our results cannot be generalized to children with other SCD genotypes (i.e. hemoglobin SC, S β + thalassemia). The number of children with SCA and a positive allergy skin testing in our cohort is comparable to what has been demonstrated in other studies. NHANES III data from 5,640 participants show that 52.7% age 6–19 years had at least one positive skin test. The prevalence of having at least one positive skin test among children 6–19 years of age with asthma was 78% (Arbes *et al*, 2007). Furthermore, participants were from three distinct regions: St. Louis, Missouri; Cleveland, Ohio; and London, United Kingdom. Although this increased generalizability, regional differences and genetic admixture may have contributed to heterogeneity in our results. Our definition of asthma may have underestimated the number of children who actually had asthma because our definition required a physician of diagnosis of asthma with a prescription of asthma medication. A more liberal diagnosis of asthma commonly used in large epidemiologic studies is a physician only diagnosis of asthma (von Mutius *et al*, 2001; Subramanian & Kennedy, 2009; DeBaun & Strunk, 2016).

The results of the current study provide additional evidence that determination of aeroallergen sensitization, as detected by skin testing, is an objective strategy for identifying a subgroup of children at increased risk of developing ACS episodes. These results, coupled with other studies from the same cohort, demonstrate that aeroallergen sensitization, wheezing causing shortness of breath, and an ACS event prior to age 4 years, are easily identifiable risk factors for future ACS events in children with SCA (DeBaun *et al*, 2014). Additional studies are needed to determine if identifying children with SCA and allergic sensitization, along with strategies aimed at minimizing exposures to and maximizing

treatment of the manifestations of aeroallergen sensitization, can decrease rates of future ACS episodes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

SCA	sickle cell anemia
SCD	sickle cell disease
ACS	acute chest syndrome
SAC	Sleep and Asthma Cohort
SIT	Silent Cerebral Infarct Transfusion Trial
HU	Hydroxyurea

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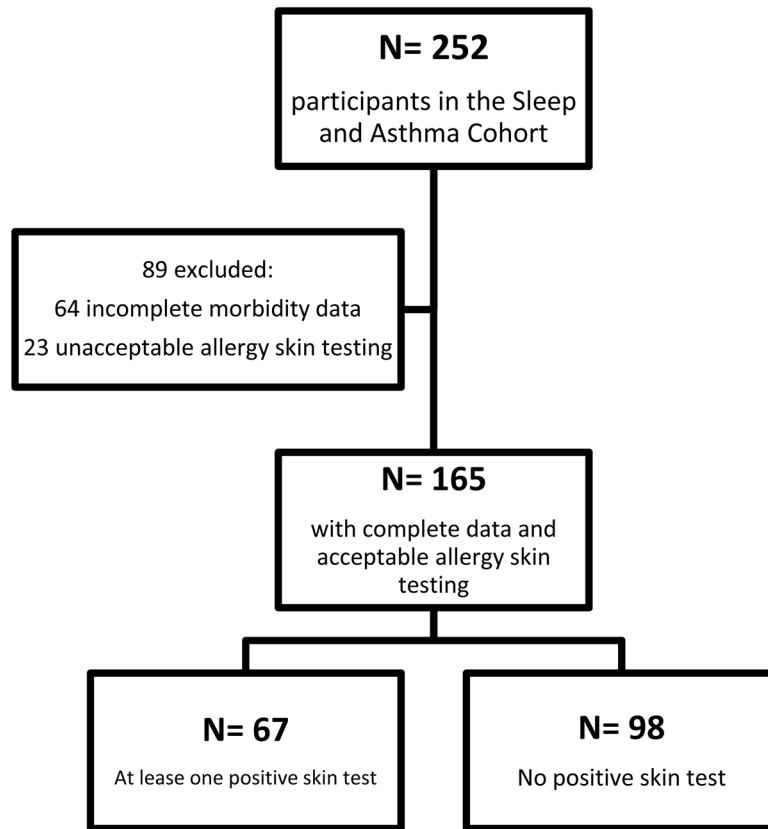


Figure I.
Selection of participants for evaluation and allergy skin testing

Table I

Characteristics of the study population (N=165)*

	All patients N=165	No positive skin tests N= 98 (59%)	At least one positive skin test N= 67 (41%)	P Value [‡]
Characteristic				
Age, years (mean, SD)	10.0 (4.0)	9.6 (4.2)	10.7 (3.8)	0.08
Male (%)	54.5	57.1	50.7	0.42
Total follow up time from birth, years (mean, SD)	14.9 (4.4)	14.4 (4.4)	15.7 (4.2)	0.06
Total follow-up time after study entry, years (mean, SD)	4.9 (1.3)	4.8 (1.2)	5.0 (1.4)	0.32
Hemoglobin, g/l (mean, SD)	83 (12)	82 (11)	84 (13)	0.34
White blood cell count, 10 ⁹ /L (mean, SD)	12.1 (3.9)	12.3 (3.8)	11.9 (3.9)	0.55
Wheezing caused shortness of breath (%)	24.2	22.4	26.9	0.52
Eosinophils, × 10 ⁹ /l (median, IQR) (n=163)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)	0.75 [#]
IgE, g/l (median, IQR) (n=156)	51500 (13550)	33000 (12590)	91600 (13690)	0.01 [#]
Bronchodilator response 12% (%) (n=150)	20.7	22.1	18.8	0.62
Asthma diagnosis (%) (n=163)	32.5	27.6	40.0	0.10
Any parent has asthma (%) (n=140)	24.3	17.2	35.8	0.01
Retrospective rate of pain episodes per year (median, IQR)	0.27 (0.70)	0.26 (0.55)	0.27 (0.99)	0.30 [#]
Retrospective rate of ACS episodes per year (median, IQR)	0.13 (0.42)	0.07 (0.39)	0.24 (0.49)	0.01 [#]
ACS before age 4 (%)	40.5	35.7	47.7	0.13
Prospective rate of pain episodes per year (median, IQR)	0.34 (1.13)	0.26 (0.81)	0.68 (1.15)	<0.01 [#]
Prospective rate of ACS episodes per year (median, IQR)	0.16 (0.35)	0.0 (0.24)	0.27 (0.61)	<0.01 [#]

Abbreviations: SD=standard deviation; IQR=interquartile range; ACS=acute chest syndrome

* Means and SD are presented for normally distributed variables, Medians and IQR's are presented for non-normally distributed variables

[#] Mann-Whitney U test[‡]T-test for means and chi-square test for percentages unless otherwise noted

Table IIFinal multivariable model of prospective rate of ACS in Children with SCA^a (N= 163)

Covariate	IRR	95% CI	P value
Male gender	0.70	0.46–1.05	0.080
History of wheezing leading to shortness of breath	1.95	1.22–3.13	0.006
History of an ACS episode prior to 4 year of age	2.41	1.62–3.59	<0.001
Number of positive aeroallergen skin tests	1.23	1.11–1.36	<0.001

Abbreviations: ACS=acute chest syndrome; SCA=sickle cell anemia; IRR=incidence rate ratio; CI=confidence interval^aNegative binomial regression models with adjustment for over-dispersion, using robust standard errors. Two-tailed significance values.

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Final multivariable model^a of prospective rate of ACS in Children with SCA, Stratified by Asthma Status**Table III**

Covariate	No Asthma (N=110)			Asthma (N=53)		
	IRR	95% CI	P value	IRR	95% CI	P value
Male gender	0.79	0.46–1.36	0.393	0.56	0.31–0.99	0.047
Shortness of breath	1.99	0.91–4.36	0.087	1.78	1.04–3.06	0.037
History of an ACS episode prior to 4 year of age	1.79	1.05–3.05	0.031	3.60	2.00–6.52	<0.001
Number of positive aeroallergen skin tests	1.41	1.19–1.68	<0.001	1.06	0.93–1.21	0.362

^aNegative binomial regression models with adjustment for over-dispersion, using robust standard errors. Two-tailed significance values

Table IV

Final model for ACS in Children with SCA with atopic index (N=163)

Covariate	IRR	95% CI	P value
Male gender	0.78	0.49–1.23	0.286
History of wheezing leading to shortness of breath	1.81	1.11–2.93	0.017
History of an ACS episode prior to 4 year of age	2.53	1.64–3.90	<0.001
Atopic Index score	1.44	1.17–1.76	<0.001

Abbreviations: ACS=acute chest syndrome; SCA=sickle cell anemia; IRR=incidence rate ratio; CI=confidence interval^aNegative binomial regression models with adjustment for over-dispersion, using robust standard errors. Two-tailed significance values.

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