Severity of Respiratory Syncytial Virus Bronchiolitis Is Affected by Cigarette Smoke Exposure and Atopy

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ABSTRACT. *Objective.* **Respiratory syncytial virus (RSV) bronchiolitis is a common cause of hospitalizations in children and has been increasingly identified as a risk factor in the development of asthma. Little is known about what determines the severity of RSV bronchiolitis, which may be helpful in the initial assessment of these children.**

Design. **We evaluated a variety of environmental and host factors that may contribute to the severity of RSV bronchiolitis in the RSV Bronchiolitis in Early Life prospective cohort study. Severity of bronchiolitis was based on the quantization of lowest O_2 saturation and the length of stay. These factors included the child's and family's demographics, presence of household allergens (dust mite, cat, dog, and cockroach), peripheral blood eosinophil count, immunoglobulin E level, infant feeding, prior illnesses, exposure to intrauterine and postnatal cigarette smoke, and family history of atopy.**

Patients. **We prospectively enrolled 206 hospitalized infants, all under 12 months old (4.0 ± 3.3 months old), with their first episode of severe RSV bronchiolitis (mean O_2 saturation: 91.6 ± 7.3%; length of stay: 2.5 ± 2.5 days; presence of radiographic opacities: 75%). Patients were excluded for a variety of reasons including previous wheezing, regular use of bronchodilator or antiinflammatory medications, any preexisting lung disease including asthma, chronic lung disease of prematurity/bronchopulmonary dysplasia, or cystic fibrosis; gastroesophageal reflux disease on medical therapy; or congenital anomalies of the chest or lung.**

Results. **Age was found to be a significant factor in the severity of infection. The younger an infant was, the more severe the infection tended to be as measured by the lowest oxygen (O_2) saturation. We also found that infants exposed to postnatal cigarette smoke from the mother had a lower O_2 saturation than those not exposed. However, there was no significant difference in RSV bronchiolitis severity between infants exposed only to intrauterine smoke and those infants never exposed to cigarette smoke. Infants with a family history of atopy, especially a maternal history of asthma or hay fever, had a higher O_2 saturation. Although a history of maternal atopy seemed to be protective, there was no association between allergens and bronchiolitis severity, although 25% of households had elevated allergen levels. Black infants demonstrated less severe RSV bronchiolitis than their white counterparts. Multivariate analysis revealed age, race, maternal atopy, and smoking to be associated with severity of RSV bronchiolitis.**

Conclusion. **The severity of RSV bronchiolitis early in life seems modified by postnatal maternal cigarette smoke exposure and atopy and age of the infant, not by levels of allergens in the home environment.** *Pediatrics* **2005;115:e7–e14. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0059; *RSV, bronchiolitis, asthma.***

ABBREVIATIONS. RSV, respiratory syncytial virus; RBEL, RSV Bronchiolitis in Early Life; ED, emergency department; BPD, bronchopulmonary dysplasia; O_2, oxygen; CXR, chest radiograph; IgE, immunoglobulin E.

Respiratory syncytial virus (RSV) infection is very common in early life: >95% of children have been infected by 2 years of age. RSV infections are responsible for ~100 000 hospital admissions in the United States annually, mostly affecting infants.[1] Of RSV-related admissions, 7% to 21% will require ventilatory support because of respiratory insufficiency.[2–4] Therefore, RSV infection imposes a significant burden on children early in life.

Furthermore, previous case-controlled studies have demonstrated that severe RSV bronchiolitis is associated with an increased risk of development of childhood asthma by 12-fold.[5] A recent study from the Tucson Children's Respiratory Study found that outpatient RSV lower respiratory tract infection was associated with frequent wheezing at 6 and 11 years old, but this effect was no longer significant at 13 years.[6] Given that the results from the Tucson study indicated that wheezing occurred after outpatient infection with RSV, it is important to measure the effects from a severe episode of RSV bronchiolitis on the subsequent development of asthma. The relationship between viral infections and the subsequent development of asthma and atopy is complex and seems to depend in part on the pathogen and severity of the initial infection.

Therefore, to evaluate the link between RSV infection and asthma, we enrolled 206 infants hospitalized with their first episode of RSV bronchiolitis into the RSV Bronchiolitis in Early Life (RBEL) prospective cohort study. The data presented here represent the baseline cross-sectional data of the cohort immediately after hospitalization. We proposed that exposure to indoor allergens as well as second-hand cigarette smoke would worsen the severity of infection

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with RSV. Moreover, we hypothesized that infants with a family history of atopy would have a significantly more severe infection of RSV bronchiolitis.

METHODS

Study Group

All infants with a positive nasopharyngeal swab for RSV (n = 1222) at St Louis Children's Hospital from 1998 to 2001 were screened to determine if they met our inclusion criteria (Fig 1). We included infants in the RBEL prospective cohort study if they were ≤12 months old, had a first episode of wheezing (documented by the primary physician) and bronchiolitis severe enough to require emergency department (ED) care or hospitalization, and had a positive nasopharyngeal swab confirming infection with RSV. A positive RSV swab was determined by an RSV enzyme immunoassay (Directigen RSV assay, Becton-Dickinson, Franklin Lakes, NJ), direct fluorescent antibody assay (Light Diagnostics Simulfluor RSV/FluA or RSV Immunofluorescence assay, Chemicon, Temecula, CA), or viral culture. Informed consent was obtained from the parent/legal guardian, and the Washington University School of Medicine Institutional Review Board approved the study.

Infants were excluded on the basis of having any 1 of the following criteria: previous wheezing, regular use of bronchodilator or antiinflammatory medications, any preexisting lung disease including asthma, chronic lung disease of prematurity/bronchopulmonary dysplasia (BPD), or cystic fibrosis; gastroesophageal reflux disease on medical therapy; or congenital anomalies of the chest or lung (Fig 1).

After enrollment, a cross-sectional analysis of potential environmental and host factors was performed. During the index hospitalization, concentration and duration of oxygen (O_2) supplementation, the lowest O_2 saturation recorded, length of stay, and the presence of infiltrates or hyperinflation on chest radiograph (CXR) were all abstracted from the medical record. During the conduct of this study, there was no defined care path or treatment for RSV bronchiolitis, and all children were treated by different providers. The decision to use supplemental O_2 and when to discharge the child was decided by the primary attending physician, independent of the study. A detailed questionnaire containing information regarding the child's and family's demographics, perinatal history, infant feeding, prior illnesses, and family history for atopic disorders (asthma, hay fever, eczema or allergies: a nonspecific category) was administered to the parent(s) by a study coordinator. Blood was obtained for measurement of peripheral blood eosinophil counts and total serum immunoglobulin E (IgE) levels.

Environmental samples from the home were obtained from each infant enrolled into the RBEL cohort. Specific areas of the home (infant's mattress, infant's bedroom carpet or floor, a major piece of upholstered furniture in the family or living room, the family room or living room carpet or floor adjacent to the upholstered furniture, and the kitchen floor) had dust collected from them using a vacuum cleaner attached with collection bags provided by the Dermatology, Allergy, and Clinical Immunology laboratory at Johns Hopkins Asthma and Allergy Center (Baltimore, MD). The dust was sieved, frozen, and then analyzed at the Dermatology, Allergy, and Clinical Immunology laboratory. The methods for dust collection and allergen level analysis have been described.[7,8] The samples were analyzed for the presence of 5 allergens: cat (Fel d1), dog (Can f1), house dust mite (Der p1 and Der f1), and cockroach (Bla g1).

Data Acquisition and Analysis

Descriptive analyses were conducted to characterize the population and assess the severity of RSV bronchiolitis infections. Categorical variables included gender, race, marital status, annual household income, employment status, complications during pregnancy or delivery, presence of hyperexpansion or opacities on CXR, presence of asthma, eczema, hay fever, or allergies in the parents and immediate family members, intrauterine and postnatal smoking exposure, and presence of pets or pests in the home. Continuous variables included age of the infant, duration of pregnancy, birth weight and height, IgE level, percent eosinophils, lowest O_2 saturation, and length of hospital stay. Continuous and dichotomous allergen levels were analyzed: 8000 ng/g of dust for both Fel d1 and Can f1, 2000 ng/g for Der p1 and Der f1, and 1 U/g of dust for Bla g1, based on published sensitization levels.[8] These analyses included frequency distributions for the categorical variables and means with SDs for continuous variables. Comparisons between continuous variables were assessed by using

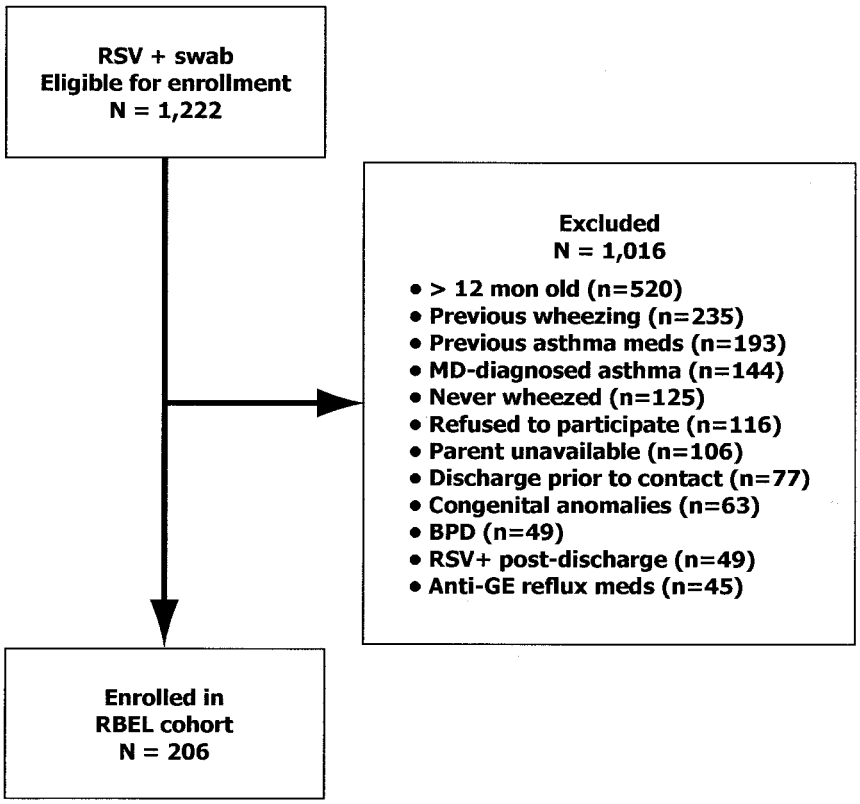

Fig 1. RBEL cohort flow diagram.

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Student's t test (2-tailed), and comparisons among dichotomous categorical variables were assessed by using Pearson's χ^2, with both performed by using SAS version 8.0 (SAS Institute, Inc, Cary, NC). Univariate and multivariate linear regressions also were performed by using SAS. These regressions were used to evaluate the relationships between predictor variables (independent variables) and the dependent variable "lowest O_2 saturation." An α level of .05 was used to determine statistical significance.

RESULTS

Study Population

We enrolled 206 children with their first episode of RSV bronchiolitis into the RBEL cohort (Fig 1). The overall characteristics of the RBEL cohort are summarized in Table 1. The mean age of the infants at enrollment was 4.0 ± 3.3 months, and 58.7% were males. Nonwhite ethnic groups represented 46.5% of the cohort. Sixty-one percent of the respondents reported a combined yearly family income ≥$20 000.

We excluded 1016 infants with positive RSV assay/culture for the following reasons: >12 months old (n = 520), previous episodes of wheezing (n = 235), bronchodilator/antiinflammatory medications (n = 193), physician-diagnosed asthma (n = 144), never wheezed (n = 125), parental refusal (n = 116), parent unavailable (n = 106), discharged early before contact by study coordinator (n = 77), congenital anomalies (n = 63), positive RSV culture after discharge (n = 49), BPD (n = 49), and taking anti–gastroesophageal reflux medications (n = 45) (Fig 1).

Many of the infants enrolled in this study came from atopic families (Table 2). Forty-five percent of infants had at least 1 first-degree relative with allergies, and 43% of infants had at least 1 first-degree relative with a history of asthma. These findings are similar to a previous study of RSV bronchiolitis that demonstrated 45% of the children had a positive family history for asthma.[5] Twenty-seven percent of infants had at least 1 first-degree relative with a history of eczema, and 21% of the RBEL infants had at least 1 first-degree relative with a history of hay fever.

TABLE 2. Family History of Asthma or Atopic Disorders

Atopic Disorder	Father	Mother	First-Degree Relative
Allergies,* n (%)	35 (17.0)	58 (28.2)	92 (44.7)
Asthma, n (%)	28 (13.6)	38 (18.4)	88 (42.7)
Eczema, n (%)	5 (2.4)	14 (6.8)	55 (26.7)
Hay fever, n (%)	18 (8.7)	41 (19.9)	43 (20.9)

* "Allergies" is a nonspecific term referring to the presence of any of the above disorders reported by the caregiver.

Environmental Exposures

Many of the RBEL infants had exposure to cigarette smoke either during pregnancy or continued exposure during infancy (Table 3). Twenty-five percent (N = 50) of mothers smoked cigarettes during pregnancy (intrauterine cigarette smoke exposure), and 28% (N = 56) of mothers were smoking at the time of enrollment (postnatal cigarette smoke exposure). Other individuals living in the household exposed 40% of infants to second-hand cigarette smoke.

Allergen levels within the home environment of RBEL infants were above the threshold for allergic sensitization[8] in approximately one quarter of homes, with the exception of roach allergen, which was found in 11.5% of homes (Table 3). There was a strong association between the report of a pet or pest in the home with the presence of a high level of allergens: cat, $P < .001$; dog, $P < .001$; and cockroach, $P = .02$.

TABLE 1. Baseline Characteristics of the RBEL Cohort

Characteristics	Included (n = 206)	Ranges
Age,* mo	4.0 ± 3.3	0–13
Male, %	58.7	
Race/ethnicity, %		
White	53.5	
Black	45.5	
Other	1.0	
Parent marital status, %		
Single	49.3	
Married	46.9	
Separated/divorced	3.8	
Annual household income ≥$20 000, %	60.6	
At least 1 parent employed, %	90.3	
Pregnancy history		
Duration of pregnancy,* wk	38.5 ± 2.1	28–47
Birth weight,* kg	3.19 ± 0.56	1.0–4.7
Birth length,* cm	77.1 ± 350.4	35.6–57.1
Medical problems during pregnancy, %	27.1	
Complications during delivery, %	22.7	
IgE level (N = 180),* IU/mL	21.6 ± 42.3	6.0–278
Eosinophils (N = 153),* %	1.8 ± 2.5	0–18
Bronchiolitis severity, index hospitalization		
Lowest O_2 saturation (N = 190),* %	91.6 ± 7.3	50–100
Length of stay (N = 198),* d	2.5 ± 2.5	
Presence of hyperexpansion on CXR (N = 131), %	63.4	0–17
Presence of opacities on CXR (N = 152), %	75.0	

* Values are means ± SD.

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TABLE 3. Characteristics of the Home Environment

Characteristic	%
Tobacco smoke	
Mother's smoking habits	
During pregnancy	25.1
Currently smoking cigarettes	28.0
Others in household currently smoking tobacco	40.4
Animals	
Pets/Pests in the home (observed or self-report)	
Cats	22.7
Dogs	33.8
Rodents	4.8
Roaches	9.0
Allergen levels (n = 130)	
Fel d1 > 8000 ng/g	23.1
Can f1 > 8000 ng/g	27.7
Bla g1 > 1 U/g	11.5
Der f1 and Der p1 > 2000 ng/g	25.0

Severity of RSV Bronchiolitis

Infants in the RBEL cohort had severe bronchiolitis at entry into the study as demonstrated by a low O_2 saturation (91.6% ± 7.3%), a length of hospital stay (2.5 ± 2.5 days), and radiographic evidence of lower respiratory tract disease as demonstrated by opacities on CXRs in 75% of the cohort (Table 1). The lowest O_2 saturation was recorded on either room air (N = 177) or supplemental O_2 (N = 13; average inspired O_2 concentration: 28% ± 9%). Black infants had a higher O_2 saturation during hospitalization than white infants (93.2% ± 4.9% vs 90.2% ± 8.8%; P = .004; Fig 2) and a shorter length of hospital stay (1.9 ± 1.7 vs 2.9 ± 3.0 days; P = .006). Black children were no more likely to present earlier for admission after the onset of respiratory symptoms (3.44 vs 3.46 days; P = .78). There was no significant effect of gender or socioeconomic status on RSV severity.

Those infants in the RBEL cohort exposed to second-hand maternal cigarette smoke had a significantly lower O_2 saturation during hospitalization than those not exposed: 89.8% ± 8.3% vs 92.2% ± 6.9% (P = .01; Fig 2). However, when we evaluated those infants with only smoke exposure during pregnancy (intrauterine cigarette smoke exposure) and not postnatal exposure (N = 10) versus those without intrauterine or postnatal exposure (N = 136), we found no effect on RSV bronchiolitis severity: the O_2 saturation was 95.0% ± 5.4% vs 92.0% ± 7.0%, respectively (P = .09). Another measure of RSV severity (length of stay) was also not significantly different: 2.3 ± 2.9 days vs 2.5 ± 2.4 days (P = .68). Therefore, this suggests that the postnatal cigarette smoke exposure in our cohort was more important in terms of RSV severity than the intrauterine exposure. Furthermore, we found a weak positive correlation between the age of the infant and the lowest O_2 saturation during hospitalization (r = 0.15, P = .04; Fig 3 A), whereas a strong negative correlation existed between the length of stay and the lowest O_2 saturation (r = −0.55, P < .001; Fig 3 B).

We then sought to evaluate those environmental factors that may be contributing to the severity of RSV bronchiolitis at entry into the study. We found no significant association between bronchiolitis severity and exposure to allergens in the child's home. This lack of association with RSV bronchiolitis was noted whether the allergen levels were evaluated in a linear fashion (eg, levels of Bla g 0.3–8.8 U/g) or as dichotomous levels (eg, above or below threshold for sensitization, for Bla g 1 U/g).

Infants with a family history of atopy had a higher O_2 saturation during hospitalization (Table 4 and Fig 4). Those maternal atopic disorders found to be significant were asthma (94.2% ± 4.0% vs 91.0% ± 7.7%; P = .001) and hay fever (94.3% ± 3.9% vs. 91.0% ± 7.8%; P < .001). Moreover, the presence of ≥1 immediate family member with asthma (93.3% ± 4.8% vs 90.4% ± 8.5%; P = .003) or hay fever (93.7% ± 4.8% vs 90.9% ± 7.9%; P = .004) was associated with a significantly higher O_2 saturation. An analysis of the time of onset of respiratory symptoms to the date of admission revealed no significant effect of maternal allergies, asthma, eczema, or rhinitis (3.23 vs 3.33 days; P = .87).

Multivariate regression analysis determined that, after controlling for multiple factors, age, race, and maternal asthma and smoking were all associated with the severity of RSV bronchiolitis based on O_2 saturation. The independent effect of each variable on O_2 saturation is depicted in Table 5. For example,

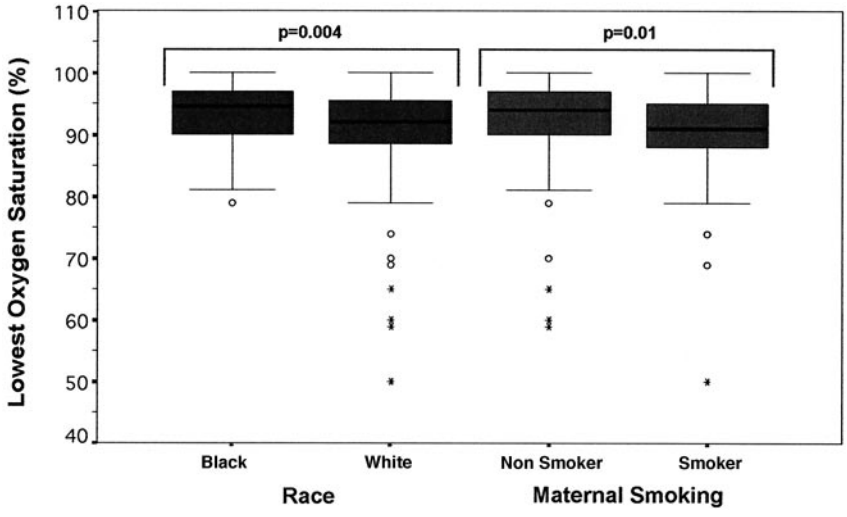

Fig 2. Lowest O_2 saturation during RSV bronchiolitis: effect of race and cigarette smoking. Box plots demonstrating the range, median, and 95% confidence intervals are shown. The circles represent outliers (cases with values between 1.5 and 3 box lengths from the upper or lower edge of the box), and the stars represent extreme outliers (>99th percentile).

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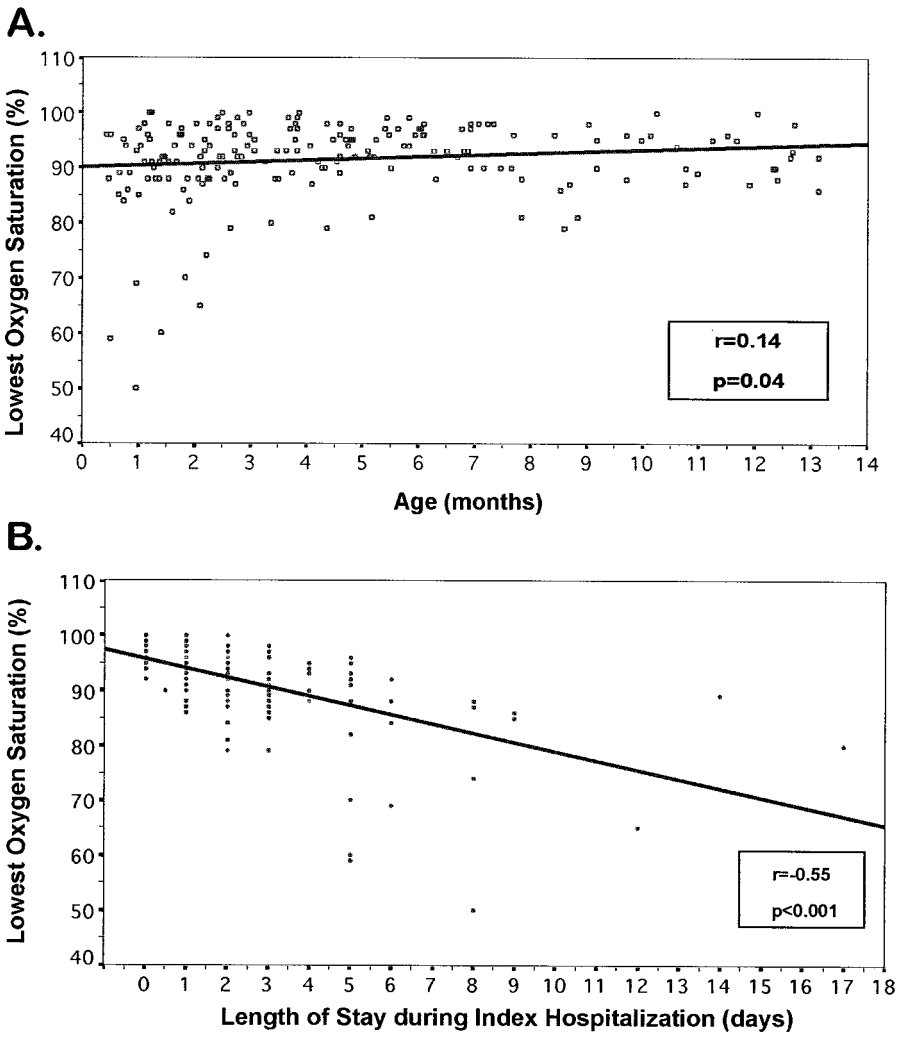

Fig 3. Lowest O_2 saturation during RSV bronchiolitis: relationship to age and length of stay. A, Linear regression model of lowest O_2 saturation during RSV bronchiolitis by age at enrollment. B, Linear regression model of lowest O_2 saturation during RSV bronchiolitis by the length of stay.

TABLE 4. Comparison of Atopic Disorders to RSV Bronchiolitis Severity

Atopic Disorder	O_2 Saturation, %	*P* Value	Length of Stay, d	*P* Value
Maternal allergy*				
Yes	92.3 ± 7.0	.42	2.4 ± 2.4	.79
No	91.3 ± 7.4		2.5 ± 2.6	
Maternal asthma				
Yes	94.2 ± 4.0	.001	2.6 ± 2.8	.66
No	91.0 ± 7.7		2.4 ± 2.4	
Maternal eczema				
Yes	92.5 ± 5.5	.54	1.9 ± 1.0	.11
No	91.5 ± 7.4		2.5 ± 2.6	
Maternal hay fever				
Yes	94.3 ± 3.9	<.001	2.0 ± 2.2	.18
No	91.0 ± 7.8		2.6 + 2.6	
Immediate family allergy*				
Yes	92.2 ± 6.8	.27	2.6 ± 2.8	.62
No	91.1 ± 7.7		2.4 ± 2.3	
Immediate family asthma				
Yes	93.3 ± 4.8	.003	2.3 ± 2.3	.44
No	90.4 ± 8.5		2.6 ± 2.6	
Immediate family eczema				
Yes	93.6 ± 4.7	.01	1.7 ± 1.3	.003
No	91.1 ± 7.8		2.6 ± 2.7	
Immediate family hay fever				
Yes	93.7 ± 4.8	.004	2.1 ± 2.3	.22
No	90.9 ± 7.9		2.6 ± 2.6	

Values are means ± SD.
* "Allergy" is a nonspecific term referring to the presence of any of the above disorders reported by the caregiver.

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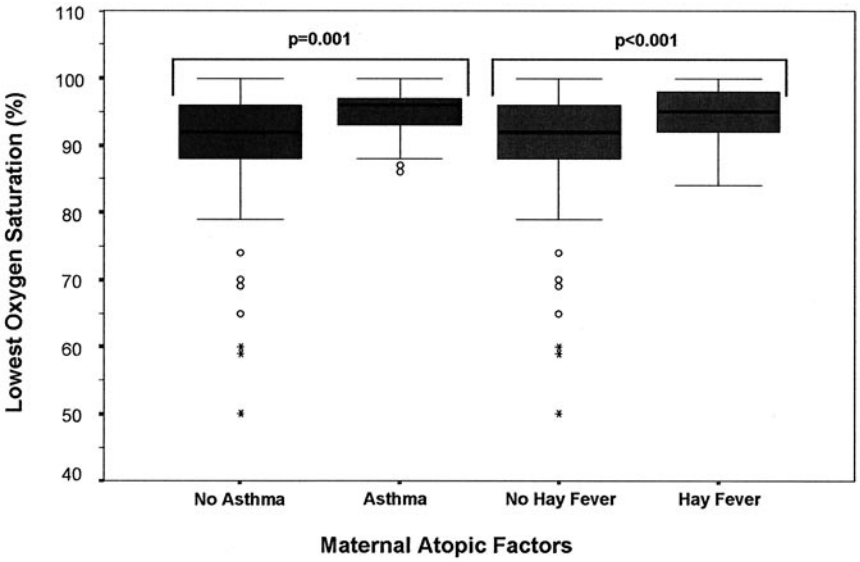

Fig 4. Lowest O_2 saturation during RSV bronchiolitis: effect of maternal asthma and hay fever. Box plots demonstrating the range, median, and 95% confidence intervals are shown. The circles represent outliers (cases with values between 1.5 and 3 box lengths from the upper or lower edge of the box), and the stars represent extreme outliers (>99th percentile).

TABLE 5. Independent Predictors of Reduced O_2 Saturation

Predictor Variable	Predicted Decrease in O_2 Sat	95% Confidence Interval of Decrease in O_2 Sat	*P* Value
Younger age, mo	0.41*	0.09–0.73	.01
White race	2.47	0.31–4.63	.02
Absence of maternal asthma	2.75	−0.05–5.55	.05
Maternal smoking	2.30	−0.05–4.66	.05

* Each month of younger age is associated with a predicted reduction of 0.41% in O_2 saturation.

each month of younger age in a child enrolled in the RBEL cohort was associated with a predicted reduction of 0.41% in the O_2 saturation. The maternal asthma β parameter was −2.75, corroborating the negative correlation found between maternal asthma and O_2 saturation in univariate regression analysis. The *r* square value for the multivariate model indicated that 10% of the variance in O_2 saturation was due to the independent variables tested, and the *P* value for the entire model was $P < .001$.

DISCUSSION

Given the impact that RSV bronchiolitis has on infants and the risks associated with this disease, it is important to try to understand those factors that may contribute to the severity of such an infection. Moreover, one may be able to gain a better understanding of how this common infection may lead to the development of asthma. Our analysis of risk factors in the RBEL cohort demonstrates that cigarette smoking exposure and the younger age of the infant are associated with increased severity of bronchiolitis, whereas maternal atopy and race may be protective.

Maternal smoking exposure has been shown to reduce lung function in children, and several studies suggest that this effect on lung function is attributable primarily to exposure during pregnancy (intrauterine cigarette smoke exposure).[9–14] Maternal smoking during pregnancy may impair in utero airway development or alter lung elastic properties. In addition, intrauterine smoking exposure may increase the risk for the development of asthma; however, postnatal smoking exposure is considered to induce wheezing in children with asthma.[15–19] Furthermore, Singh et al[20] demonstrated in an animal model that intrauterine cigarette smoke exposure decreased cyclic adenosine monophosphate levels and increased phosphodiesterase-4 enzymatic activity, resulting in increased airway hyperresponsiveness, which may explain the potential mechanism by which intrauterine smoke exposure decreases lung function and leads to the development of asthma.

The current study reveals that maternal cigarette smoking, especially postnatal, compounds the severity of RSV bronchiolitis infection in infants. Lanari et al[21] demonstrated that exposure to cigarette smoke, in general, seems to worsen the severity of the bronchiolitis. Moreover, a study by Gurkan et al,[22] in which cotinine levels were measured at index of hospitalization, showed that infants admitted to the hospital with severe RSV bronchiolitis were exposed more recently to cigarette smoke than infants hospitalized for nonrespiratory diseases. According to a 1997 economic analysis of the medical effects of smoking on children, 22000 hospitalizations and 1100 deaths from RSV occur every year due to parental second-hand smoke.[23] Thus infants exposed to second-hand cigarette smoke seem to have a predisposition to developing severe bronchiolitis after infection with RSV.

Analysis of the RBEL prospective cohort suggests that children with atopy in the family, especially the mother, had, on average, less severe RSV infection, which is in contrast to a study conducted by La Via et al,[24] in which they determined that a family history of asthma, although very common throughout

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their study (35%), did not significantly affect the length of stay or any other complications due to RSV. However, their results were based on overall family history of asthma, whereas our results show that maternal atopy in the form of asthma and allergies actually was associated with less severe infection. It is unclear why a maternal history of atopy would be associated with less severe RSV, although we postulated that the mother may be more attentive to respiratory infections if she herself has asthma or allergies and therefore presents her child sooner for evaluation. However, an analysis of the time of onset of respiratory symptoms to the date of admission revealed no significant effect of maternal asthma or allergies. Alternatively, the immunologic response of the child to RSV may be altered by the mother's atopic T helper 2 predisposition. We are currently evaluating the T cell profile of each infant in the RBEL cohort at the time of RSV infection to further understand the relationship between cytokine production in infancy and the development of asthma.

In our study, RSV bronchiolitis seems to be more severe in white children than black children. This finding seems to be unique to our study. Although La Via et al[24] showed that hospitalization with the infection was skewed toward minorities, there seems to be no evidence in the study that these minorities had any more or less severe infections than their white counterparts. We and others have shown that black asthmatics tend to be hospitalized more often for their asthma.[25] In addition, black people experience more episodic rather than routine care for respiratory problems.[26] Black children may demonstrate a less severe RSV bronchiolitis in our study due to more prompt use of the health care system or a certain protective genetic effect; however, the exact cause of this finding is not known. An analysis of the time of onset of respiratory symptoms to the date of admission revealed no significant effect of race.

It is interesting to note that we found that the levels of common allergens within the home environment, although significantly elevated in 25% of the homes, seemed to have no effect on the severity of RSV bronchiolitis. This is in contrast to animal models, which demonstrated that mice presensitized to allergens were more likely to develop a severe form of RSV bronchiolitis.[27] In addition, it has been shown that certain allergens may play a role in the child's immune response and subsequent development of asthma.[28] Others have suggested that those infants deemed to have a severe form of the bronchiolitis may go on to develop sensitization to the allergens.[29] It may be that the infants in our cohort, given their young age, have not yet developed a sensitization to the allergens. Additional follow-up with allergen skin-prick tests will be used to determine the effect of severity of RSV bronchiolitis on subsequent allergic sensitization. Furthermore, a limitation of the present study is that the allergens were collected in dust samples after the RSV infection (within 12 months) and may not reflect the levels before RSV infection.

In addition, we found that younger infants had a lower O_2 saturation and more severe disease than older children, which is similar to a previous study that demonstrated that infants <6 weeks old had lower O_2 saturation and more prolonged hospitalization than older children.[30] This finding is substantiated further by the fact that infants with a higher O_2 saturation spent less time in the hospital than infants with a lower O_2 saturation. Presumably, the airways of the older infants have had more time to mature and enlarge, enabling older infants to better handle this severe respiratory infection.

The Tucson Children's Respiratory Study indicated that children who experienced even a mild episode of RSV bronchiolitis may go on to develop wheezing indicative of asthma later in life.[6] However, the association between wheezing and infection dropped off at age 13. The loss of a significant association between RSV and wheezing later in life may be more related to lost follow-ups, the small number of children at age 13 with previous RSV infection ($n = 49$), and, more importantly, the fact that these children had mild RSV infection not requiring hospitalization. In contrast, our RBEL study investigated only those infants with a severe RSV infection. The RBEL study will continue until all children have turned 6 years old to ascertain potential genetic, biological, and immunologic predictors of recurrent wheezing and asthma.

Potential limitations of our study include the fact that it is a cross-sectional evaluation of a cohort presenting to the ED or hospital for acute care. Ideally, one would like to evaluate the determinants of severe RSV bronchiolitis in an unaffected cohort and evaluate them prospectively. However, this is not feasible, given that nearly all children are exposed to RSV by 2 years of age and only 1% are hospitalized. Therefore, the results of this study may not be generalizable to all children affected with varying severities of RSV infection. Another limitation of our study is that we did not prospectively obtain information on why the child with RSV presented to the ED or was hospitalized. This additional information may have provided insight into why certain covariates, such as race or maternal atopy, influenced the severity of RSV bronchiolitis.

CONCLUSIONS

We found that age, race, smoking, and maternal atopy are all independently associated with the severity of RSV bronchiolitis in the RBEL cohort. Younger infants with lower respiratory tract infection symptoms during the RSV season should be promptly assessed for RSV. Furthermore, it is important for family physicians and pediatricians to inform parents of the risks involved with second-hand smoking exposure, especially in young infants. Hopefully, the RBEL cohort will continue to provide us with valuable insights into the genetic, biological, and immunologic determinants of asthma so that early-intervention strategies can be developed for children exposed to serious RSV infection.

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