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Association of Secondhand Smoke and Infant Lower Respiratory Tract Infection Severity by Familial Atopy Status

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viral lower respiratory tract infection; secondhand smoke exposure; atopic predisposition

INTRODUCTION

Bronchiolitis, a lower respiratory tract infection (LRTI) caused by viruses such as RSV and human rhinovirus, is associated with significant acute and chronic morbidity.^{1–9} Each year, an estimated 20–30% of otherwise healthy, infants develop bronchiolitis, and up to 3% of them are admitted to the hospital.^{2;3;7} Of infants hospitalized for bronchiolitis, up to 30% subsequently develop recurrent wheezing and/or asthma, at least within the first decade of life.^{4–6} Prematurity, chronic lung disease, and congenital heart disease are well-established risk factors for severe bronchiolitis.¹⁰ However, 50% of infants hospitalized with bronchiolitis are term infants in whom risk factors include male gender, birth early in the RSV season, siblings, lower birth weight, secondhand smoke (SHS) exposure, and a family history of asthma and atopy.^{2;11;12}

The association of viral LRTIs, such as bronchiolitis, in infancy and subsequent asthma has resulted in many studies investigating whether a familial atopic predisposition is also a risk factor for bronchiolitis and/or bronchiolitis severity.^{12–17} While results from previous

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studies have had conflicting results, in a large population-based cohort of infants we have previously found that term, otherwise healthy infants with a history of maternal asthma had an increased incidence and increased severity of bronchiolitis.¹² Children with a history of both maternal asthma and maternal smoking during pregnancy had the highest risk of bronchiolitis.¹² Individuals with an atopic background have an increased risk of developing more severe complications of specific infectious diseases and these individuals may also be particularly susceptible to environmental risk factors, such as SHS, that would increase their risk and/or the severity of their illness.^{18–29} Therefore we hypothesized that the impact of SHS on the severity of viral LRTI would be greater in infants with a familial atopic predisposition. The objectives of this study were to assess whether infants with a familial atopic predisposition were more likely to have more severe viral LRTI when exposed to SHS than infants without a familial atopic predisposition.

METHODS

We conducted a cross-sectional study of 451 mother-infant dyads enrolled in the Tennessee Children's Respiratory Initiative (TCRI).³⁰ The TCRI is a longitudinal prospective study investigating childhood asthma and atopic disease outcomes associated with viral respiratory infections during infancy and a familial atopic predisposition.³⁰ Subjects were enrolled at the time of the infant's presentation to a single academic medical center with an acute respiratory infection (ARI) during respiratory viral seasons September through May 2004–2008.³⁰ Subjects were recruited during an acute visit (outpatient clinic, emergency room, hospitalization) for viral LRTI, such as bronchiolitis, or upper respiratory tract infection (URI). Infants less than 1 year of age who were term (>37 weeks estimated gestational age), of birth weight >2275 grams, and otherwise healthy were eligible for study inclusion as previously described.³⁰ Written informed consent was obtained from study women for herself and the infant. The protocol was approved by the Institutional Review Board of Vanderbilt University.

At study enrollment, trained research nurses conducted an interview with the mother using a structured questionnaire. Information collected included demographics, current medical symptoms, past medical history, infant feeding method, detailed family history of asthma and atopic diseases, home environmental exposures including secondhand smoke, number of siblings, and daycare attendance.³⁰ A structured chart abstraction form was used to collect information from the child's electronic medical record including current weight, confirmation of birth weight, length of stay (LOS) in the hospitalized infants, and information about the course of the index illness.³⁰

Primary predictor variables

The main predictor variables were secondhand smoke exposure (SHS) and two measures of a familial atopic predisposition. Self-reported maternal atopic disease was ascertained by women reporting a history of asthma, allergic rhinitis, or atopic dermatitis based on responses to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. In addition, we assessed for evidence of allergen-sensitization preferentially by skin prick testing to 8 aeroallergens common in the geographic region.³⁰ For instances in which skin prick testing was contraindicated or the results uninterpretable, we tested for allergen-specific sensitization by multi-allergen screen which was measured on the ImmunoCAP250 (Phadiatop, Phadia, Kalamazoo, MI).³⁰ Using the self-reported atopic disease and results of allergen sensitization studies we classified women by whether they had both self-reported atopic disease based on the ISAAC questionnaire (asthma, allergies, and/or atopic dermatitis) and allergen sensitization. A detailed family history of atopic disease (asthma, allergic rhinitis, atopic dermatitis) in all first degree relatives was obtained

from the infant's mother.³⁰ Detailed SHS data was collected through maternal questionnaire, and this study included current household smoke exposure.

Primary outcome variables

Infant viral LRTI severity was determined using both the physician discharge diagnosis and post-discharge chart review as previously described.^{30;31} We measured our primary outcome variables, viral LRTI severity, using the ordinal bronchiolitis severity score (BSS) and LOS in days for the hospitalized infants.^{32;33} BSS was determined by trained research nurses through chart abstraction of admission information on respiratory rate, presence of flaring or retractions, room air oxygen saturation, and presence or absence of wheezing.³⁰ The BSS ranges from 0–12 (12 being most severe). For hospitalized patients, length of stay was measured in days.

Covariates for adjustment

We obtained other variables of interest from the enrollment questionnaire including maternal age, infant race/ethnicity, infant insurance status (Tennessee Medicaid, private or none), infant gestational age, infant birth weight (grams), infant sex, infant age at enrollment (weeks), daycare exposure, prior history of breastfeeding, and number of siblings.

Statistical analysis

We compared the baseline characteristics by infant SHS exposure using the Wilcoxon rank-sum test for continuous variables and Chi-square test for categorical variables. We examined the relationship between viral LRTI severity and secondhand smoke exposure in infants with and without a familial predisposition to atopy, using our two pre-specified measures of a familial atopic predisposition separately.

For both measures of a familial atopic predisposition, we conducted multivariable regression models to test for differential effect of SHS by familial atopic predisposition on bronchiolitis severity (as ascertained by either the BSS or LOS). We included an interaction term for SHS exposure and the respective measure of a familial atopic predisposition. We used a proportional odds model for the ordinal BSS and a multiple linear regression model for LOS. Length of stay was log transformed in the model to meet assumption of normality of multivariable regression. Covariates in the regression models included infant gestational age, infant age at study enrollment, infant birth weight, infant gender, infant race, infant insurance, maternal age, daycare exposure, any prior history of breastfeeding, and number of siblings in the home. All analyses were performed with R version 2.12.1 (www.r-project.org, R Development Core Team (2009); Vienna, Austria).

RESULTS

A total of 451 mother-infant dyads in which the infant had a viral LRTI were included in the study. Secondhand smoke (SHS) exposure was reported for 57% of the subjects (Table 1). Overall, 36% of infants had a mother with both atopic disease and evidence of allergen sensitization and 68% of infants had a first degree relative with atopy (familial atopy). Characteristics of infants with SHS exposure compared to those without included lower median birth weight (3246 vs. 3345 grams, $p=0.032$), less likely to have received any breastfeeding before study inclusion (47% vs. 65%, $p<0.001$), and more likely to be enrolled in Medicaid (72% vs. 48%, $p<0.001$). Mothers of infants with SHS exposure compared to those without were more likely to be white (75% vs. 56%, $p<0.001$), and have fewer median years of education (12 vs. 13, $p<0.001$). Infants with SHS exposure were not statistically significantly more likely to have a mother with atopic disease and evidence of allergen sensitization (39% vs. 33%, $p=0.19$) or have familial atopy in a first degree relative (67% vs.

69%, $p=0.57$) than infants without SHS. In infants with SHS exposure vs. those without there were no statistically significant differences detected in infant estimated gestational age, gender, infant age at enrollment, history of daycare attendance, presence of other children in the home, and exposure to sick contacts prior to admission (Table 1).

In univariate analyses, secondhand smoke exposure was associated with more severe bronchiolitis as measured by both BSS and median LOS. BSS was higher in the SHS group (median BSS 7.0 [4.5,9]) than the group without SHS (median 6.0 [IQR:3.5,8]), $p=0.016$. In the hospitalized subset ($n=392$), infants with SHS exposure had difference in LOS distribution (3.0 days [IQR:2,5]) than infants without (3 days [IQR:2,4]), $p=0.054$.

Maternal atopic disease and allergic sensitization

We assessed for the association of secondhand smoke with bronchiolitis severity using two measures of a familial atopic predisposition: maternal atopic disease with allergic sensitization and family history of atopic disease for stratification or interaction analysis. We did not detect a statistically significant difference in BSS with SHS exposure in the groups with or without maternal atopic disease and allergic sensitization (SHS median 7.0 [5.0,9.0] vs. no SHS exposure median 6.0 [4.0,7.5] $p=0.061$) and (SHS median 6.50 [4.50,9.00] vs. non SHS median 6.50 [3.62, 8.50] $p=0.176$), respectively. In the hospitalized subset we did not detect a statistically significant difference in LOS by SHS exposure in the groups with or without maternal atopic disease and allergic sensitization, (SHS median 3 [2,5.75] vs. no SHS median 3 [2,4] $p=0.155$) and (SHS median 3 [2,5] vs. no SHS median 3 [2, 4] $p=0.59$), respectively. In a multivariable analysis including a cross-product of SHS and maternal atopic disease and allergic sensitization, there was not statistical significance for interaction effect on BSS (p for interaction=0.64) or LOS (p for interaction=0.55).

Familial atopy

Next we investigated the association of SHS and familial atopy on viral LRTI severity. We did not detect a statistically significant difference in BSS by SHS exposure in the groups with familial atopy (SHS median 7.00 [4.50, 9.0] vs. no SHS median 6.50 [4.0, 8.38] $p=0.098$) or without familial atopy (SHS median 6.50 [4.62, 9.0] vs. no SHS median 5.00 [2.88, 8.0] $p=0.056$), nor was there an interaction detected in multivariable regression (p for interaction=0.51). Regarding LOS among infants with familial atopy, those with SHS exposure had increased LOS (median 3.0 days [IQR:2,6]) compared to those without SHS exposure (median 2.5 days [IQR:2,4]), $p=0.006$. There was not a statistically significant difference detected by SHS exposure in the group without familial atopy (SHS median 3 [2,4] vs. no SHS exposure median 3 [2,4] $p=0.686$). In a multivariable analysis there was a statistically significant interaction (p for interaction=0.004) for LOS. Among infants with a history of familial atopy there was 23% increased LOS in infants with SHS exposure versus those without SHS exposure ($p=0.025$). This relationship was not seen in the group without familial atopy ($p=0.069$), Figure 1.

DISCUSSION

Bronchiolitis, a viral LRTI, affects an estimated 20–30% of infants and is the most common cause of hospitalizations in infants.^{1–3,7} Of infants hospitalized for bronchiolitis, up to 30% will develop recurrent wheezing or asthma in early childhood.^{4–6} In this investigation we studied the influence of two important risk factors, familial atopic predisposition and SHS exposure on severity of viral LRTI during infancy.^{12–15} As previous work has shown an increased risk of a familial predisposition to atopy in children with bronchiolitis and individuals with an atopic background have greater burden and morbidity from specific viral and bacterial infections, we hypothesized that infants with a family history of atopy would

have more severe bronchiolitis associated with SHS exposure than infants without this history.^{18–25} In our study which investigated two measures of a familial atopic predisposition, maternal atopic disease with allergen sensitization and familial atopy, we found that in hospitalized infants with familial atopy, SHS exposure was associated with a longer length of stay, and this relationship was not seen in infants with no family history of atopy.

The association of SHS exposure with enhanced respiratory viral illness has been well recognized, with several studies having previously reported a positive association between SHS exposure and increased bronchiolitis severity.^{16;34;35} We hypothesized that those infants with an atopic predisposition would be more susceptible to environmental exposures, particularly SHS, and thus we investigated whether the impact of SHS exposure on bronchiolitis severity, was modified by familial atopic predisposition. While the immunologic mechanisms responsible for the association of SHS and bronchiolitis severity have not been fully delineated, recent work has shown alterations in the innate and adaptive immune response to infecting virus.^{36–39} In addition, a recent study demonstrated that human epithelial cell (HEC) exposure to both cigarette smoke extract and human rhinovirus (HRV), a common etiology of viral LRTI among children with an atopic predisposition, resulted in suppression of genes, including some genes involved in antiviral activity and inflammation, that were expressed when the HEC were exposed to HRV alone.⁴⁰ This has interesting implications as to whether SHS exposure can impair the antiviral response which could potentially influence susceptibility to and severity of viral infections. The particular research question studied in this current investigation included whether the association of smoking and viral LRTI severity was enhanced by a familial predisposition to atopy.

We focused on two important measures of a familial atopic predisposition and found that in infants with familial atopy, SHS exposure was associated with one measure of viral LRTI severity. Individuals with atopy or a familial predisposition have an increased risk of developing or having more severe infectious diseases.^{12;18;19;25} For example, individuals with asthma have an increased burden or severity of illnesses such as influenza and invasive pneumococcal disease.^{12;18} In addition, some but not all studies have found that infants with a familial atopic predisposition have a higher risk or severity of bronchiolitis during infancy.^{12;16} Several studies shed light on the mechanisms explaining how atopy may modify SHS effects on viral infection severity. Apoptosis is an innate antiviral defense activity that serves to limit the extent and severity of viral infections.³⁹ Groskreutz et al. found that human tracheobronchial epithelial cells incubated with cigarette smoke extract (CSE) prior to RSV inoculation demonstrated less apoptosis and more cellular necrosis than cells exposed to RSV alone.³⁹ Interestingly, in airway epithelial cells from individuals with asthma compared to controls, Wark et al found decreased apoptosis in response to rhinovirus infection with associated increased viral replication.⁴¹ Therefore, it is possible that SHS results in impaired viral-induced apoptosis in individuals predisposed to develop asthma. Another potential mechanism stems from impairment in T-helper 1 (Th1) immunity in neonates, such as reduced interferon (IFN) gamma production. In an unselected cohort, cord blood from infants with atopic mothers demonstrated decreased IFN-gamma secretion, in a separate cohort a lower percentage of cord blood IFN-gamma producing CD4⁺ T cells was associated with subsequent atopic disease, and in a high-risk asthma cohort decreased IFN-gamma production from stimulated cord blood monocytes was associated with increased viral infections and wheezing episodes during infancy.^{42–45} Therefore individuals at high-risk for atopy could be more susceptible to the adverse effects of SHS which may also adversely affect INF-gamma dependent antiviral defense mechanisms and potentially lead to more severe viral infection.³⁷

Supporting the hypothesis that SHS exposure would be particularly important in individuals with an atopic predisposition, in an animal model, Singh et al. found prenatal SHS, and to a lesser extent post-natal SHS exposure, to be associated with increased allergen-induced T helper cell type 2 polarization in the lung and increased total serum IgE.⁴⁷ Interestingly, in a mouse model Min et al. found that while the sole exposure of chronic environmental tobacco smoke (ETS) was not associated with allergic airway remodeling, exposure to both chronic ETS and ovalbumin (OVA) sensitization resulted in enhanced airway remodeling.²¹ We tested the hypothesis that infants with a predisposition to asthma or atopy would be particularly vulnerable to the impact of SHS exposure on LRTI severity. Although familial atopy was not associated with infant LRTI severity as measured by the BSS, it was differentially associated with longer length of hospital stay in children with SHS exposure compared to those without familial atopy, which may have implications regarding the pace of recovery from the acute infection.^{25;29;46} Lastly, we did not detect interaction between maternal atopy and SHS exposure on severity of infant LRTI. This could be because no true interaction exists, because of misclassification, or paternal atopy, which was only assessed by questionnaire.

There are limitations to consider. As previously described, the TCRI cohort is composed of a convenience sample of mother-infant dyads in which the infants were enrolled at the time of an unscheduled visit for a viral respiratory infection.³⁰ However, our study cohort included infants enrolled across 4 different respiratory viral seasons which should strengthen generalizability. We studied maternal-reported total household SHS exposure and did not include a biomarker of SHS, such as urine cotinine. Our study had a high prevalence of household SHS exposure (57%), however a degree of non-differential misclassification because of underreporting is possible that would result in an underestimation of effects detected. Maternal and family history of an atopic disease was determined by self-report by the mother. In addition, methods used to determine maternal allergen-sensitization did not include all potential relevant allergens, such as dog hair allergen in skin prick testing, and we did not capture all potential environmental exposures such as wood stoves. We also had limited sample size and power for our effect modification analysis and results need to be confirmed in independent data sources and larger samples. Lastly, we cannot completely rule out the possible influence of unknown or unmeasured potential confounding factors as with all observational studies.

In summary, SHS exposure is an established risk factor for infant LRTI severity and we sought to investigate whether this relationship was modified by familial atopic predisposition. We found that in infants with familial atopy, SHS exposure was associated with a longer length of infant hospital stay for LRTI, which was not the case in those without this family history. Future longitudinal investigations will be able to assess the consequences of these findings with subsequent asthma outcomes in the children.

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Figure 1. The association of secondhand smoke exposure and hospital length of stay for viral LRTI in infants with familial atopy versus those without (p for interaction=0.004), Tennessee Children's Respiratory Initiative, 2004–08.

Table 1

Infant and Maternal Characteristics by Secondhand Smoke Exposure among Dyads Enrolled in the Tennessee Children's Respiratory Initiative, 2004–08

Characteristic	No Secondhand Smoke Exposure N=194	Secondhand Smoke Exposure N=257	All N=451
Median EGA *, weeks [IQR] †	39 [38,40]	39 [38,40]	39 [38,40]
Median infant birth weight, grams [IQR] †	3345 [3062,3657]	3246 [2970,3572]	3289 [3005, 3629]
Infant sex, n (%)			
Male	116 (60)	136 (53)	252 (56)
Median infant age, weeks [IQR] ‡	9 [5,19]	11 [6,22]	11 [6,21]
Any breastfeeding, n (%)	127 (65)	119 (47)	246 (55)
Infant insurance, n (%)			
Private	88 (45)	52 (20)	140 (31)
Medicaid	94 (48)	184 (72)	278 (62)
None	12 (6)	21 (8)	33 (7)
Day care attendance, n (%)	41 (21)	62 (24)	103 (23)
Other children in home, n [IQR]‡	1 [1,2]	1 [1,2]	1 [1,2]
Maternal atopic disease and allergen sensitization, n (%) N=405	57 (33)	88 (39)	145 (36)
Familial atopy, yes	134 (69)	171 (67)	305 (68)
Median maternal age, years[IQR] *	28 [24,32]	24 [21,28]	26 [22,30]
Maternal race, n (%)			
White	109 (56)	192 (75)	301 (67)
African-American	36 (19)	48 (19)	84 (19)
Latino	41 (21)	12 (5)	53 (12)
Other	8 (4)	5 (2)	13 (3)
Median maternal education, years[IQR] (N=357)	13 [12,16]	12 [11,13]	12 [12,14]

* infant estimated gestational age

†, interquartile range