

Relationship of secondhand smoke and infant lower respiratory tract infection severity by familial atopy status

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ABSTRACT

Background: Individuals with atopy have more severe complications of infectious diseases. We hypothesized that the importance of secondhand smoke (SHS) on lower respiratory tract infection (LRTI) severity would be greater in infants with a familial atopic predisposition.

Objective: To determine whether infants with a familial atopic predisposition are more susceptible to adverse effects of SHS, resulting in more severe LRTI.

Methods: We conducted cross-sectional analyses of mother-infant dyads enrolled during 2004 to 2008 during an infant LRTI. Predictor variables were SHS and 2 measures of a familial atopic predisposition (maternal atopic disease with allergen sensitization or familial atopy). LRTI severity was determined by bronchiolitis severity score (BSS) and hospital length of stay (LOS). We conducted multivariable regression analysis to test for a differential relationship between SHS and LRTI severity by measures of familial atopic predisposition.

Results: In 451 dyads, 57% of infants had SHS exposure, 36% had a mother with atopic disease, and 68% had familial atopy. We did not detect differences in BSS or LOS by SHS exposure stratified by history of maternal atopic disease. In bivariate analysis, there was a significant difference in LOS by SHS in those with familial atopy ($P = .006$) but not in those without ($P = .66$). In multivariable analysis, among infants with familial atopy, there was a 23% increased LOS in infants with SHS exposure ($P = .03$), whereas no statistical significance was detected in those without familial atopy ($P = .07$).

Conclusion: In infants with familial atopy, SHS was associated with longer hospital LOS for LRTI but not BSS. Because the effect was seen only among hospitalized infants, confirmation is required.

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Introduction

Bronchiolitis, a lower respiratory tract infection (LRTI) caused by viruses such as respiratory syncytial virus (RSV) and human rhinovirus, is associated with significant acute and chronic morbidity.^{1–9} Each year, an estimated 20% to 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 sex, 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} Although results from previous 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

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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 effect 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 Participants were enrolled at the time of the infant's presentation to a single academic medical center with an acute respiratory infection during respiratory viral seasons September through May 2004 to 2008.³⁰ Participants were recruited during an acute care visit (outpatient clinic, emergency department, or hospitalization) for viral LRTI, such as bronchiolitis, or upper respiratory tract infection. Infants younger than 1 year who were term (estimated gestational age of ≥ 37 weeks), with a birth weight of 2275 g or more, and who were otherwise healthy were eligible for study inclusion as previously described.³⁰ Written informed consent was obtained from study women for themselves and their 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, medical history, infant feeding method, detailed family history of asthma and atopic diseases, and home environmental exposures, including SHS, number of siblings, and daycare attendance.³⁰ A structured medical record 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 SHS and 2 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 multiallergen screen, which was measured on the ImmunoCAP250 (Phadiatop; Phadia, Kalamazoo, Michigan).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, or atopic dermatitis) in all first-degree relatives was obtained from the infant's mother.³⁰ Detailed SHS data were 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 postdischarge medical record 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} The BSS was determined by trained research nurses through medical record 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 to 12 (12 being most severe). For hospitalized patients, LOS 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 (in grams), infant sex, infant age at enrollment (in 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 χ^2 test for categorical variables. We examined the relationship between viral LRTI severity and SHS exposure in infants with and without a familial predisposition to atopy, using our 2 prespecified 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. LOS 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 sex, 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, Vienna, Austria).

Results

A total of 451 mother-infant dyads in which the infant had a viral LRTI were included in the study. Exposure to SHS was reported for 57% of the participants (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 with those without included lower median birth weight (3,246 vs 3,345 g, $P = .03$), less likely to have received any breastfeeding before study inclusion (47% vs 65%, $P < .001$), and more likely to be enrolled in Medicaid (72% vs 48%, $P < .001$). Mothers of infants with SHS exposure compared with those without were more likely to be white (75% vs 56%, $P < .001$) and have fewer median years of education (12 vs 13, $P < .001$). 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%, $P = .19$) or have familial atopy in a first-degree relative (67% vs 69%, $P = .57$) than infants without SHS. In infants with SHS exposure vs those without, no statistically significant differences were detected in infant estimated gestational age, sex, infant age at

Table 1

Infant and maternal characteristics by secondhand smoke exposure among dyads enrolled in the Tennessee Children's Respiratory Initiative, 2004–2008

Characteristic	No secondhand smoke exposure (n = 194)	Secondhand smoke exposure (n = 257)	All (N = 451)
EGA, median (IQR), wk	39 (38–40)	39 (38–40)	39 (38–40)
Infant birth weight, median (IQR), g	3,345 (3,062–3,657)	3,246 (2,970–3,572)	3,289 (3,005–3,629)
Male sex, No. (%)	116 (60)	136 (53)	252 (56)
Infant age, median (IQR), wk	9 (5–19)	11 (6–22)	11 (6–21)
Any breastfeeding, No. (%)	127 (65)	119 (47)	246 (55)
Infant insurance, No. (%)			
Private	88 (45)	52 (20)	140 (31)
Medicaid	94 (48)	184 (72)	278 (62)
None	12 (6)	21 (8)	33 (7)
Day care attendance, No. (%)	41 (21)	62 (24)	103 (23)
Other children in home, No. (IQR)	1 (1–2)	1 (1–2)	1 (1–2)
Maternal atopic disease and allergen sensitization, No. (%) (N = 405)	57 (33)	88 (39)	145 (36)
Familial atopy, yes	134 (69)	171 (67)	305 (68)
Maternal age, median (IQR), y	28 (24–32)	24 (21–28)	26 (22–30)
Maternal race, No. (%)			
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)
Maternal education, median (IQR), y (N = 357)	13 (12–16)	12 (11–13)	12 (12–14)

Abbreviations: EGA, estimated gestational age; IQR, interquartile range.

enrollment, history of daycare attendance, presence of other children in the home, and exposure to sick contacts before admission (Table 1).

In univariate analyses, SHS exposure was associated with more severe bronchiolitis as measured by both BSS and median LOS. The BSS was higher in the SHS group (median BSS, 7.0; interquartile range [IQR], 4.5–9) than the group without SHS (median, 6.0; IQR, 3.5–8; $P = .02$). In the hospitalized subset ($n = 392$), infants with SHS exposure had a difference in LOS distribution (3.0 days; IQR, 2–5 days) than infants without (3 days; IQR, 2–4 days; $P = .05$).

Maternal Atopic Disease and Allergic Sensitization

We assessed for the association of SHS with bronchiolitis severity using 2 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 (median, 7.0; IQR, 5.0–9.0; for SHS exposure vs median, 6.0; IQR, 4.0–7.5; for no SHS exposure; $P = .06$; and median, 6.50; IQR, 4.50–9.00; for SHS exposure vs median, 6.50; IQR, 3.62–8.50; for no SHS exposure; $P = .18$; 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 (median, 3; IQR, 2–5.75; for SHS exposure vs median, 3; IQR, 2–4; for no SHS exposure; $P = .16$; and median, 3; IQR, 2–5; for SHS exposure vs median, 3; IQR, 2–4; for no SHS exposure; $P = .59$; respectively). In a multivariable analysis that included a cross-product of SHS and maternal atopic disease and allergic sensitization, no statistical significance was found for the interaction effect on BSS (P for interaction = .64) or LOS (P for interaction = .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 (median, 7.00; IQR, 4.50–9.0; for SHS exposure vs median, 6.50; IQR, 4.0–8.38; for no SHS exposure; $P = .10$) or without familial atopy (median, 6.50; IQR, 4.62–9.0; for SHS exposure vs median, 5.00; IQR, 2.88–8.0; for no SHS exposure; $P = .06$), and there was no an

interaction detected in multivariable regression (P for interaction = .51). Regarding LOS among infants with familial atopy, those with SHS exposure had increased LOS (median, 3.0 days; IQR, 2–6 days) compared with those without SHS exposure (median, 2.5 days; IQR, 2–4 days; $P = .006$). No statistically significant difference was detected by SHS exposure in the group without familial atopy (median, 3; IQR, 2–4; for SHS exposure vs median, 3; IQR, 2–4; for no SHS exposure; $P = .66$). In a multivariable analysis there was a statistically significant interaction (P for interaction = .004) for LOS. Among infants with a history of familial atopy, there was a 23% increased LOS in infants with SHS exposure vs those without SHS exposure ($P = .03$). This relationship was not seen in the group without familial atopy ($P = .07$) (Fig 1).

Discussion

Bronchiolitis, a viral LRTI, affects an estimated 20% to 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 2 important risk factors, familial atopic predisposition and SHS exposure, on severity of viral LRTI during infancy.^{12–15} Because previous work has reported 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 2 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 without a 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 effect of SHS exposure on bronchiolitis

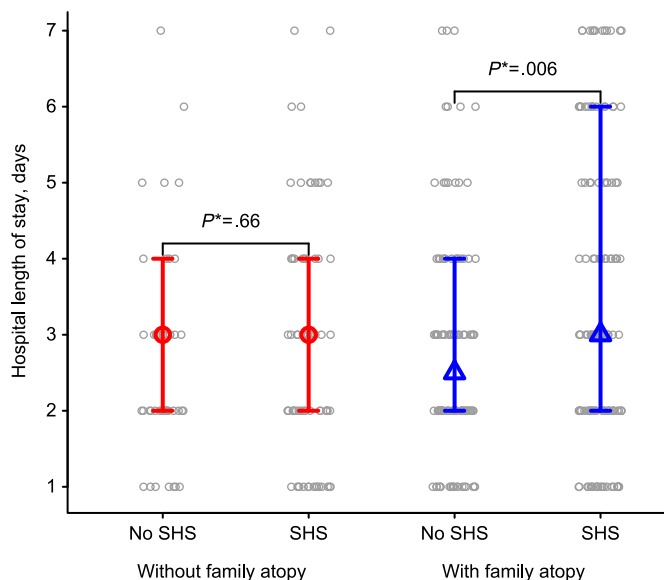


Figure 1. The relationship between secondhand smoke exposure and hospital length of stay for viral lower respiratory tract infections in infants with familial atopy vs those without (P for interaction = .004), Tennessee Children's Respiratory Initiative, 2004–2008.

severity was modified by familial atopic predisposition. Although the immunologic mechanisms responsible for the association of SHS and bronchiolitis severity have not been fully delineated, recent work has found alterations in the innate and adaptive immune response to infecting virus.^{36–39} In addition, a recent study demonstrated that human epithelial cell exposure to both cigarette smoke extract and human rhinovirus, a common cause 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 human epithelial cells were exposed to human rhinovirus alone.⁴⁰ This finding has interesting implications for 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 2 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.^{18,19} 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 that explain 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 al³⁹ found that human tracheobronchial epithelial cells incubated with cigarette smoke extract before RSV inoculation demonstrated less apoptosis and more cellular necrosis than cells exposed to RSV alone. Interestingly, in airway epithelial cells from individuals with asthma compared with controls, Wark et al⁴¹ found decreased apoptosis in response to rhinovirus infection with associated increased viral replication. 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_H1 immunity in neonates, such as reduced interferon γ (IFN- γ) production. In an unselected cohort, cord blood from infants with atopic mothers demonstrated decreased IFN- γ secretion; in a separate cohort, a lower percentage of cord blood IFN- γ -producing $CD4^+$ T cells were associated with subsequent atopic disease, and in a high-risk asthma cohort decreased IFN- γ 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 IFN- γ -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 al⁴⁷ found prenatal SHS, and to a lesser extent postnatal SHS exposure, to be associated with increased allergen-induced T_H2 cell polarization in the lung and increased total serum IgE. Interestingly, in a mouse model Min et al²¹ found that although the sole exposure of long-term environmental tobacco smoke was not associated with allergic airway remodeling, exposure to both long-term environmental tobacco smoke and ovalbumin 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 effect 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 with 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 nondifferential misclassification because of under-reporting 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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References

- [1] Smyth RL, Openshaw PJ. Bronchiolitis. *Lancet*. 2006;368:312–322.
- [2] Carroll K, Gebretsadik T, Griffin M, et al. The increasing burden and risk factors for bronchiolitis-related medical visits in infants enrolled in a state healthcare insurance plan. *Pediatrics*. 2008;122:58–64.
- [3] Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980–1996. *JAMA*. 1999;282:1440–1446.
- [4] Carroll KN, Wu P, Gebretsadik T, et al. The severity-dependent relationship of infant bronchiolitis on the risk and morbidity of early childhood asthma. *J Allergy Clin Immunol*. 2009;123:1055–1061.
- [5] Sigurs N, Gustafsson PM, Bjarnason R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med*. 2005;171:137–141.
- [6] Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet*. 1999;354:541–545.
- [7] Wright AL, Taussig LM, Ray CG, Harrison HR, Holberg CJ. The Tucson Children's Respiratory Study, II: lower respiratory tract illness in the first year of life. *Am J Epidemiol*. 1989;129:1232–1246.
- [8] Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med*. 2008;178:667–672.
- [9] Lemanske RF Jr, Jackson DJ, Gangnon RE, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol*. 2005;116:571–577.
- [10] Boyce TG, Mellen BG, Mitchel EF Jr, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. *J Pediatr*. 2000;137:865–870.
- [11] Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *J Pediatr*. 2003;143:S118–S126.
- [12] Carroll KN, Gebretsadik T, Griffin MR, et al. Maternal asthma and maternal smoking are associated with increased risk of bronchiolitis during infancy. *Pediatrics*. 2007;119:1104–1112.
- [13] Sims DG, Gardner PS, Weightman D, Turner MW, Soothill JF. Atopy does not predispose to RSV bronchiolitis or postbronchiolitic wheezing. *Br Med J (Clin Res Ed)*. 1981;282:2086–2088.
- [14] Pullan CR, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *Br Med J (Clin Res Ed)*. 1982;284:1665–1669.
- [15] Trefny P, Stricker T, Baerlocher C, Sennhauser FH. Family history of atopy and clinical course of RSV infection in ambulatory and hospitalized infants. *Pediatr Pulmonol*. 2000;30:302–306.
- [16] Bradley JP, Bacharier LB, Bonfiglio J, et al. Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy. *Pediatrics*. 2005;115:e7–e14.
- [17] Carroll KN, Gebretsadik T, Minton P, et al. Influence of maternal asthma on the cause and severity of infant acute respiratory tract infections. *J Allergy Clin Immunol*. 2012;129:1236–1242.
- [18] Talbot TR, Hartert TV, Mitchel E, et al. Asthma as a risk factor for invasive pneumococcal disease. *N Engl J Med*. 2005;352:2082–2090.
- [19] Miller EK, Griffin MR, Edwards KM, et al. Influenza burden for children with asthma. *Pediatrics*. 2008;121:1–8.
- [20] Neuzil KM, Wright PF, Mitchel EF Jr, Griffin MR. The burden of influenza illness in children with asthma and other chronic medical conditions. *J Pediatr*. 2000;137:856–864.
- [21] Min MG, Song DJ, Miller M, et al. Coexposure to environmental tobacco smoke increases levels of allergen-induced airway remodeling in mice. *J Immunol*. 2007;178:5321–5328.
- [22] Strulovici-Barel Y, Omberg L, O'Mahony M, et al. Threshold of biologic responses of the small airway epithelium to low levels of tobacco smoke. *Am J Respir Crit Care Med*. 2010;182:1524–1532.
- [23] Kulkarni R, Rampersaud R, Aguilar JL, Randis TM, Kreindler JL, Ratner AJ. Cigarette smoke inhibits airway epithelial cell innate immune responses to bacteria. *Infect Immun*. 2010;78:2146–2152.
- [24] Noah TL, Zhou H, Monaco J, Horvath K, Herbst M, Jaspers I. Tobacco smoke exposure and altered nasal responses to live attenuated influenza virus. *Environ Health Perspect*. 2011;119:78–83.
- [25] James KM, Peebles RS Jr, Hartert TV. Response to infections in patients with asthma and atopic disease: an epiphenomenon or reflection of host susceptibility? *J Allergy Clin Immunol*. 2012;130:343–351.
- [26] Olenec JP, Kim WK, Lee WM, et al. Weekly monitoring of children with asthma for infections and illness during common cold seasons. *J Allergy Clin Immunol*. 2010;125:1001–1006.
- [27] Petruzella FD, Gorelick MH. Duration of illness in infants with bronchiolitis evaluated in the emergency department. *Pediatrics*. 2010;126:285–290.
- [28] Kloepper KM, Olenec JP, Lee WM, et al. Increased H1N1 infection rate in children with asthma. *Am J Respir Crit Care Med*. 2012;185:1275–1279.
- [29] Corne JM, Marshall C, Smith S, et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet*. 2002;359:831–834.
- [30] Hartert TV, Carroll K, Gebretsadik T, Woodward K, Minton P. The Tennessee Children's Respiratory Initiative: objectives, design and recruitment results of a prospective cohort study investigating infant viral respiratory illness and the development of asthma and allergic diseases. *Respirology*. 2010;15:691–699.
- [31] Carroll KN, Gebretsadik T, Larkin EK, et al. Relationship of maternal vitamin D level with maternal and infant respiratory disease. *Am J Obstet Gynecol*. 2011;205:215.e1–215.e7.
- [32] Tal A, Bavilski C, Yohai D, Bearman JE, Gorodischer R, Moses SW. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics*. 1983;71:13–18.
- [33] Goebel J, Estrada B, Quinonez J, Nagji N, Sanford D, Boerth RC. Prednisolone plus albuterol versus albuterol alone in mild to moderate bronchiolitis. *Clin Pediatr (Phila)*. 2000;39:213–220.
- [34] Semple MG, Taylor-Robinson DC, Lane S, Smyth RL. Household tobacco smoke and admission weight predict severe bronchiolitis in infants independent of deprivation: prospective cohort study. *PLoS One*. 2011;6:e22425.
- [35] Jones LL, Hashim A, McKeever T, Cook DG, Britton J, Leonardi-Bee J. Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: systematic review and meta-analysis. *Respir Res*. 2011;12:5.
- [36] Castro SM, Chakraborty K, Guerrero-Plata A. Cigarette smoke suppresses TLR-7 stimulation in response to virus infection in plasmacytoid dendritic cells. *Toxicol In Vitro*. 2011;25:1106–1113.
- [37] Modestou MA, Manzel LJ, El-Mahdy S, Look DC. Inhibition of IFN-gamma-dependent antiviral airway epithelial defense by cigarette smoke. *Respir Res*. 2010;11:64.
- [38] Phaybouth V, Wang SZ, Hutt JA, McDonald JD, Harrod KS, Barrett EG. Cigarette smoke suppresses Th1 cytokine production and increases RSV expression in a neonatal model. *Am J Physiol Lung Cell Mol Physiol*. 2006;290:L222–L231.
- [39] Groskreutz DJ, Monick MM, Babor EC, et al. Cigarette smoke alters respiratory syncytial virus-induced apoptosis and replication. *Am J Respir Cell Mol Biol*. 2009;41:189–198.
- [40] Proud D, Hudy MH, Wiehler S, et al. Cigarette smoke modulates expression of human rhinovirus-induced airway epithelial host defense genes. *PLoS One*. 2012;7:e40762.
- [41] Wark PA, Johnston SL, Bucchieri F, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med*. 2005;201:937–947.
- [42] Herberth G, Heinrich J, Roder S, et al. Reduced IFN-gamma- and enhanced IL-4-producing CD4+ cord blood T cells are associated with a higher risk for atopic dermatitis during the first 2 yr of life. *Pediatr Allergy Immunol*. 2010;21:5–13.
- [43] Schaub B, Liu J, Hoppler S, et al. Impairment of T-regulatory cells in cord blood of atopic mothers. *J Allergy Clin Immunol*. 2008;121:1491–1499.
- [44] Copenhaver CC, Gern JE, Li Z, et al. Cytokine response patterns, exposure to viruses, and respiratory infections in the first year of life. *Am J Respir Crit Care Med*. 2004;170:175–180.
- [45] Gern JE, Brooks GD, Meyer P, et al. Bidirectional interactions between viral respiratory illnesses and cytokine responses in the first year of life. *J Allergy Clin Immunol*. 2006;117:72–78.
- [46] Tang ML, Kemp AS, Thorburn J, Hill DJ. Reduced interferon-gamma secretion in neonates and subsequent atopy. *Lancet*. 1994;344:983–985.
- [47] Singh SP, Gundavarapu S, Pena-Philippides JC, et al. Prenatal secondhand cigarette smoke promotes Th2 polarization and impairs goblet cell differentiation and airway mucus formation. *J Immunol*. 2011;187:4542–4552.