

Original article

Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma

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Background: Severe lower respiratory infections (LRIs) and atopic sensitization have been identified as independent risk factors for asthma.

Objective: The nature of potential interactions between these risk factors was the subject of this study.

Methods: A community-based cohort of 198 children at high atopic risk was followed from birth to 5 years. All episodes of acute respiratory illness in the first year were recorded and postnasal aspirates were collected for viral identification.

History of wheeze and asthma was collected annually, and atopy was assessed at 6 months, 2 years, and 5 years.

Results: A total of 815 episodes of acute respiratory illness were reported, and 33% were LRIs. Viruses were detected in 69% of aspirates, most commonly rhinoviruses (48.3%) and respiratory syncytial virus (10.9%). At 5 years, 28.3% (n = 56) had current wheeze, and this was associated with wheezy [odds ratio (OR), 3.4 (1.2-9.7); *P* = .02] and/or febrile LRI [OR, 3.9 (1.4-10.5); *P* = .007], in particular those caused by respiratory syncytial virus or rhinoviruses [OR, 4.1 (1.3-12.6); *P* = .02]. Comparable findings were made for current asthma. Strikingly these associations were restricted to children who displayed early sensitization (≤ 2 years old) and not observed in nonatopic patients or those sensitized later.

Conclusion: These data suggest viral infections interact with atopy in infancy to promote later asthma. Notably the occurrence of both of these events during this narrow developmental window is associated with maximal risk for subsequent asthma, which suggests a contribution from both classes of inflammatory insults to disease pathogenesis.

Clinical implications: Protection of "high-risk" children against the effects of severe respiratory infections during infancy may represent an effective strategy for primary asthma

prevention. The potential benefits of these strategies merit more careful evaluation in this age group. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Acute respiratory infections, childhood asthma, persistent wheeze, rhinovirus, RSV

Wheezy lower respiratory tract illnesses (wLRIs) are common in early childhood and are often associated with respiratory viruses, particularly respiratory syncytial virus (RSV),^{1,2} and RSV-associated wLRI represents the most common cause of hospitalization among infants in first-world countries.³ The relationship between early wheezing and subsequent development of asthma is controversial. On the one hand, it is clear that, although wheezing in infancy is common, these episodes are often transient in nature and are not, on a population basis, associated with asthma in later life.⁴ However, numerous studies have reported associations between severe RSV bronchiolitis in early childhood and recurrent wheezing and asthma in later childhood,⁵⁻⁹ and it is unclear why such relationships occur in some children but not in the population at large.⁴ The relationship between early childhood RSV infection and atopic sensitization is equally controversial, with published studies available that argue either for⁵ or against⁹ a causal relationship between early infections and subsequent atopy. Additionally, accumulating evidence suggests that susceptibility to viral infection and atopy may derive from a common set of transient developmental defects in cellular immune function(s) operative during early infancy,¹⁰⁻¹² which further complicate considerations of causal versus consequential interactions between these disease processes and how they impact on asthma development.

It is also becoming increasingly evident that viruses other than RSV need to be considered in the context of asthma and atopy pathogenesis in early life. Notably, human rhinoviruses are the most commonly identified virus involved in uncomplicated acute respiratory infections (ARIs) and in asthma exacerbations in older children¹³⁻¹⁵ and adults¹⁶; yet their role as lower respiratory pathogens in infants has frequently been disputed. Children who experienced LRI secondary to rhinovirus infection have been regarded as being at particular risk because of underlying

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Abbreviations used

ARI: Acute respiratory illness
 LRI: Lower respiratory illness
 NPA: Nasopharyngeal aspirate
 OR: Odds ratio
 RSV: Respiratory syncytial virus
 SPT: Skin prick test
 wLRI: Wheezy lower respiratory tract illness

respiratory conditions such as asthma, cystic fibrosis, or other cardiorespiratory problems.^{17,18} More recently, Lemanske et al¹⁹ found symptomatic rhinovirus infections in infancy was a significant risk factor for preschool wheezing in their population of “high-risk” children.

We have recently completed the 5-year follow-up of a community-based cohort of children at high risk of atopy. We have documented the occurrence and severity of viral ARIs in infancy in these subjects, identified the specific viral pathogens responsible for each infectious episode, and determined the nature of the association between these factors and the subsequent development of persistent wheeze and current asthma at 5 years of age. We have previously reported synergistic interactions between atopic sensitization and recurrent respiratory infections in early life on the risk of asthma.²⁰ We therefore hypothesized that this risk would be conferred by sensitization early in life rather than later sensitization.

METHODS

A prospective cohort of 263 children at high risk of atopy (at least 1 parent with a doctor-diagnosed history of hay fever, asthma, or eczema) were recruited prenatally into this birth cohort as previously described.²¹ Parents kept a daily symptom diary and recorded the presence of symptoms of ARI, such as runny/blocked nose, cough, and wheeze as well as presence of fever ($>38^{\circ}\text{C}$). If their child developed any of these symptoms, the study center was contacted within 24 hours and a home visit was arranged (within 48 hours) to collect a nasopharyngeal aspirate (NPA) sample. The method of collection of the NPA samples is included in the electronic repository. Detailed information about each episode of ARI, such as duration of fever, runny nose, cough, or wheeze, was obtained at the home visit and further obtained by follow-up telephone calls every 2 weeks until resolution of the child's symptoms.

NPA samples were frozen and stored at -80°C for future analysis. Two control NPA samples (one in winter and a second in summer) were also collected from each child when the child was well and free of any respiratory symptoms for at least 4 weeks. The NPA samples were analyzed by a panel of reverse transcriptase polymerase chain reactions for rhinoviruses, other picornaviruses (coxsackie, echo, and enteroviruses), coronaviruses 229E and OC43, RSV, influenza A and B, parainfluenza viruses 1-3, adenoviruses, human metapneumovirus, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*. Additional details on viral identification and analysis are included in the electronic repository.²²

The children underwent skin prick tests (SPTs) at 6 months, 2 years, and 5 years of age to a panel of 7 allergens (fresh cow's milk, egg white, rye grass, alternaria, aspergillus, house dust mite, and cat dander). Histamine was used as the positive control and normal saline as the negative control. The wheal size was read after 15 minutes, and

a wheal size ≥ 2 mm (for the tests performed at 6 months and 2 years) or ≥ 3 mm (at 5 years) greater than saline control was considered a positive reaction.

SPTs were performed on the parents with the same panel of allergens and a wheal size of ≥ 3 mm was considered positive.

CLASSIFICATION OF ARI

The study doctor used information collected from the follow-up telephone contacts as well as the diary cards to classify the episodes of ARI as follows.

Upper respiratory tract illness (URI)

Any episode of runny/blocked nose or cough in the absence of other respiratory symptoms (no tachypnoea, difficulty breathing, wheeze, or rattly chest) was classified as an upper respiratory illness.

LRI

Episodes that were associated with wheeze or rattly chest and/or evidence of respiratory distress were considered to be LRIs. Rattle/rattly chest was defined as moist, wet noisy breath sounds from the child's chest. Wheeze was defined as a high-pitched whistling sound heard coming from the chest, on expiration. LRIs were further classified into wLRI and nonwheezy LRI based on the presence of any wheeze reported by the parent or family doctor.

Definitions

Asthma: doctor diagnosis of asthma ever in the 5 years.

Current asthma: asthma and wheeze in the 12 months before the 5-year visit.

Classification of wheeze phenotype

Transient wheeze: wheezing episodes only in the first 3 years of life.

Late-onset wheeze: no wheezing before 3 years of age, but wheeze between 3 and 5 years.

Persistent wheeze: wheezing in the first 3 years as well as wheezing at 4 and 5 years.

Current wheeze: wheeze in the 12 months before the 5-year visit.

Data were tabulated and analyzed using SPSS version 11.5 (SPSS Inc, Chicago, Ill). A χ^2 test was used to estimate odds ratios (ORs) and 95% CIs between categorical variables with $P < .05$ considered a significant association. Logistic regression analysis was used to calculate adjusted ORs and 95% CIs.

Approval for the study was obtained from the ethics committee of King Edward Memorial and Princess Margaret Hospitals in Western Australia. Fully informed parental consent was obtained for all subjects.

RESULTS

Characteristics of the cohort

A total of 263 children were recruited into the study. Of these, 236 remained for the first year and 198 were followed for the full 5 years of the study. Most of the

TABLE I. Pathogens detected in the NPA samples²³

Positive for	Infectious NPA (n = 815) No. (%)	Control NPA (n = 366) No. (%)	URI (n = 548) No. (%)	Nonwheezy LRI (n = 193) No. (%)	wLRI (n = 74) No. (%)	Febrile LRI (n = 68) No. (%)
Any virus	562 (69.0)	88 (24.0)	376 (68.6)	135 (69.9)	51 (68.9)	42 (61.8)
Rhinovirus	394 (48.3)	42 (11.3)	284 (51.8)	76 (39.4)	34 (46.0)	19 (27.9)
RSV	89 (10.9)	18 (4.9)	47 (8.6)	30 (15.5)	12 (16.2)	14 (20.6)
Coronavirus	47 (5.8)	19 (5.2)	34 (6.2)	11 (5.7)	2 (2.7)	1 (1.5)
PIF	44 (5.4)	4 (1.1)	26 (4.7)	12 (6.2)	6 (8.1)	5 (7.4)
Influenza	35 (4.3)	0	24 (4.4)	8 (4.1)	3 (4.1)	6 (8.8)
HMPV	17 (2.1)	1 (0.3)	7 (1.3)	9 (4.7)	1 (1.4)	2 (2.9)
Adenovirus	13 (1.6)	5 (1.4)	9 (1.6)	2 (2.7)	2 (2.7)	3 (4.4)
<i>Mycoplasma pneumoniae</i>	11 (1.3)	8 (2.2)	7 (1.3)	4 (2.1)	0	1 (1.5)
<i>Chlamydia pneumoniae</i>	11 (1.3)	5 (1.4)	7 (1.3)	2 (1.0)	2 (2.7)	0

PIF, Parainfluenza viruses 1-3; HMPV, human metapneumovirus.

children who were excluded or withdrew from the study did so within the first 12 months of the study, with the most common reason for withdrawal being move/transfer away from Western Australia. No significant difference was found in the prevalence of wheeze in the first year or atopic status (SPT performed at 6 months) in these children who did not complete the full 5-year follow-up compared with those who did.

This cohort is at high risk of atopy, with 79.3% of mothers and 80.3% of fathers being atopic and more than half (62.6%) with biparental atopy. A male preponderance exists, with boys comprising 56% of the cohort. Approximately half of the children were first born (52.0%) and lived in a household with a pet (56.6%), most commonly a dog (29.7%). Few attended daycare in the first year of life, only 12.6% were exposed to environmental tobacco smoke, and more than 75% were breastfed for more than 6 months. Overall, 59.6% of the cohort was atopic, defined as having positive SPT results to at least 1 allergen, at any time point (when tested at 6 months, 2 years, or 5 years).

Prevalence of wheeze/asthma

Seventy (35.4%) of the children never wheezed during the first 5 years of life. Sixty-eight (34.3%) were found to have transient wheeze, 19 (9.6%) were late-onset wheezers, and 41 (20.7%) were persistent wheezers. Fifty-three (28.3%) had current wheeze at outcome age. Thirty-seven (18.7%) had current asthma at 5 years.

Prevalence of ARIs and relationship to atopy

A total of 815 episodes of ARI were reported in the first year. Of these, 548 (67.2%) were classified as URI, 193 (23.7%) as nonwheezy LRI, and 74 (9.1%) as wLRI. Approximately half of the infants had between 1 and 3 URI (55.0%) and 51.0% at least 1 nonwheezy LRI in the first year. Almost a third (27.3%) of the cohort had at least 1 wLRI during infancy (see Table E1 in this article's Online Repository at www.jacionline.org).

The presence of atopy did not influence the number of ARIs, URIs, or LRIs reported in the first year. After adjusting for confounding effects of gender, older siblings, daycare attendance, pet ownership, environmental

tobacco smoke exposure, and parental history of asthma, no significant differences were found in the number of URI ($P = .2$), nonwheezy LRI ($P = .2$), and wLRI ($P = .6$) experienced by children who were atopic by 2 years compared with nonatopic children (see Table E1 in this article's Online Repository at www.jacionline.org). No differences were found in the number of febrile ARI experienced by nonatopic versus atopic children ($P = .6$).

Pathogens detected in NPA specimens

These results have previously been published but are included here for completeness.²³ Sixty-nine percent of the NPA specimens collected during ARI episodes were positive for at least 1 virus, with rhinoviruses the most commonly detected (48.3%), followed by RSV (10.9%) (Table I). The percentage of specimens tested positive for a virus was similar for URI (68.6%), nonwheezy LRI (69.9%), wLRI (68.9%), and febrile LRI (61.8%) (Table I). Twenty-four percent (88/366) of the control specimens, collected when the children were free of respiratory symptoms, were virus positive with rhinovirus detected in 11.3% (42/366) and RSV in 4.9% (18/366) of the samples (Table I). Although rhinovirus isolation was more common than RSV in infectious NPA, a higher proportion of RSV infections displayed evidence of spread to the lower respiratory tract (56% vs 30% for rhinovirus; $P < .05$) and a higher proportion of RSV infections resulted in wheeze and/or febrile reactions (29.2% vs 13.4% for rhinovirus; $P < .05$).

Risk factors for asthma/type of wheeze at age 5 years

Wheezy LRI with positive isolates for rhinovirus and RSV were significantly associated with wheeze at outcome age 5 years (Table II). These associations were confirmed for current wheeze and persistent wheeze after adjusting for gender, older siblings, environmental tobacco smoke exposure, breastfeeding, daycare attendance and parental asthma. Although wLRI with positive isolates for rhinovirus and RSV were found to be associated with current asthma, this only reached statistical significance for rhinovirus-positive wLRI (Table II).

TABLE II. Association between type of ARI caused by RSV and rhinovirus and type of wheeze

	Any ARI caused by RSV OR (95% CI) <i>P</i>	Any ARI caused by rhinovirus OR (95% CI) <i>P</i>	Nonwheezy LRI caused by RSV OR (95% CI) <i>P</i>	Nonwheezy LRI caused by rhinovirus OR (95% CI) <i>P</i>	Wheezy LRI caused by RSV OR (95% CI) <i>P</i>	Wheezy LRI caused by rhinovirus OR (95% CI) <i>P</i>
Current asthma	1.5 (0.7-3.2) 0.3	1.1 (0.6-3.2) 0.9	1.1 (0.4-2.9) 0.9	0.7 (0.4-1.3) 0.3	2.1 (0.5-8.1) 0.3	2.9 (1.2-7.1) 0.02
Transient wheeze	1.2 (0.6-2.3) 0.6	1.6 (0.6-3.9) 0.3	1.7 (0.8-4.0) 0.2	1.3 (0.8-1.9) 0.3	1.7 (0.4-6.3) 0.5	0.9 (0.4-2.2) 0.9
Late-onset wheeze	1.5 (0.6-4.1) 0.4	0.8 (0.3-2.9) 0.8	0.6 (0.1-2.8) 0.5	0.6 (0.2-1.5) 0.3	0.7 (0.1-7.0) 0.8	0.7 (0.1-3.2) 0.6
Persistent wheeze	1.1 (0.5-2.4) 0.7	0.8 (0.3-2.1) 0.6	1.1 (0.7-1.6) 0.8	1.1 (0.7-1.6) 0.8	2.7 (0.7-9.8) 0.04	2.9 (1.2-7.0) 0.02
Current wheeze	1.2 (0.6-2.4) 0.6	0.7 (0.3-1.8) 0.5	0.7 (0.3-1.7) 0.4	0.8 (0.5-1.2) 0.3	2.5 (1.0-11.3) 0.05	2.5 (1.1-5.9) 0.03

Data in boldface are statistically significant at the .05 level.

TABLE III. Predictors of current wheeze at 5 years of age in relation to time of atopic sensitization

Type of ARI	Never atopic OR (95% CI) <i>P</i> value	Atopic by age of 2 years OR (95% CI) <i>P</i> value	Atopic after 2 years OR (95% CI) <i>P</i> value
Whole population regardless of ARI history	0.4 (0.2-0.8) 0.006*	3.1 (1.5-6.4) 0.05	2.9 (1.4-5.8) 0.05
Any wheezy LRI in first year	1.4 (0.4-5.1) 0.6	3.4 (1.2-9.7) 0.02	0.5 (0.1-3.5) 0.5
No. of wheezy LRI (<i>linear model</i>)	1.1 (0.5-2.8) 0.8	2.4 (1.2-4.7) 0.01	0.9 (0.2-4.1) 0.9
0	Comparison group	Comparison group	Comparison group
1	1.6 (0.4-6.9) 0.5	1.9 (0.7-5.5) 0.2	(≥1) 0.5 (0.1-3.4) 0.5
≥2	1.0 (0.1-9.1) 1.0	7.1 (1.3-38.4) 0.02	NA
Any febrile infections in first year	1.2 (0.4-3.8) 0.8	1.2 (0.8-1.8) 0.4	1.8 (0.3-9.6) 0.5
Any febrile URI	1.3 (0.4-4.1) 0.7	0.9 (0.5-1.5) 0.9	1.4 (0.3-7.1) 0.7
Any febrile LRI	1.0 (0.2-3.8) 1.0	4.2 (1.5-11.8) 0.006	1.3 (0.2-9.9) 0.8
Any wheezy or febrile LRI	1.0 (0.3-3.4) 1.0	3.9 (1.4-10.5) 0.007	0.7 (0.1-3.9) 0.7
Any wLRI associated with rhinovirus or RSV	0.8 (0.2-4.0) 0.8	4.1 (1.3-12.6) 0.02	0.9 (0.1-6.4) 0.9
Any wLRI associated with rhinovirus	1.6 (0.3-8.7) 0.6	3.2 (1.1-9.5) 0.03	2.1 (0.3-18.5) 0.5
Any wLRI associated with RSV	1.6 (0.3-8.7) 0.6	3.6 (1.0-13.3) 0.06	Insufficient number

NA, Not applicable.

*Data in boldface are statistically significant at the .05 level.

Predictors of current asthma and current wheeze at 5 years according to age of atopic sensitization

Within the population at large, increased risk for wheeze persisting to age 5 years was associated with sensitization by age 2 (OR, 3.1; 95% CI, 1.5-6.4; $P = .05$) or at outcome age (OR, 2.9; 95% CI, 1.4-5.8; $P = .05$) (Table III). Significant associations were also found between type of ARI in the first year and current wheeze at 5 years (Table III). These predictors included any febrile or wLRI, any wLRI associated with rhinovirus or RSV, and any wLRI associated with rhinovirus. Although a trend was found for current wheeze to be associated with wLRI associated with RSV, this association failed to reach statistical significance (OR, 3.6; 95% CI, 1.0-13.3; $P = .06$) (Table III). The association between the risk of current wheeze increased with the number of wLRI. These associations were, however, found only in children who were atopic by the age of 2 years (Table III). Similarly significant predictors for current asthma at 5 years were any wLRI (OR, 2.9; 95% CI, 1.0-8.3; $P = .05$), febrile LRI (OR, 3.6; 95% CI, 1.2-10.7; $P = .02$), wheezy or febrile LRI (OR, 3.8; 95% CI, 1.2-11.6; $P = .02$), and any rhinovirus or RSV associated wLRI (OR, 3.6; 95% CI, 1.1-11.6; $P = .03$). These associations remained after adjustments for gender, parental

atopic disease, pet ownership, older siblings, environmental smoke exposure, and daycare attendance. When rhinovirus and RSV infections were considered separately, a positive association existed between current asthma at 5 years and RSV-associated wLRI (OR, 5.4; 95% CI, 0.8-34; $P = .07$) as well as current asthma and rhinovirus-associated wLRI (OR, 2.8; 95% CI, 0.9-8.6; $P = .07$). These associations were, however, no longer significant after adjusting for the same confounders.

DISCUSSION

The results of the current study from this cohort of children at high risk of atopy demonstrate significant associations between rhinovirus-induced and RSV-induced wLRI in the first year of life and the subsequent development of persistent wheeze at 5 years. Significant associations were also observed between rhinovirus-induced wLRI in the first year of life and current asthma at 5 years. These findings were found to be attributable only to those children who were sensitized early, which makes this study unique. This community study is the first one reported that has ascertained the viral etiology of all respiratory illnesses occurring in the first year of life and that has related it to persistent wheezing and current asthma at 5 years of age. Moreover, this study is the first

one to address the issue of potential differences in susceptibility to viral-induced wheeze and asthma within a pediatric population at uniformly high risk of atopy, comparing children who do versus those who do not develop sensitization during infancy.

Wheeze was common in this cohort, with only 35.4% of the children in the current study never wheezing during the first 5 years of life. An additional 34.3% were transient wheezers and 30.5% were late-onset or persistent wheezers. In contrast, Martinez et al⁴ reported that 51.5% of their community-based cohort had never wheezed and those with late-onset wheezing and persistent wheeze were more likely to be atopic. The higher prevalence of late-onset and persistent wheeze in our study (compared with 28.7% for late-onset and persistent wheeze in the Tucson cohort) is not surprising as our children were selected on the basis of high genetic predisposition to atopy.

Infant wheezing requiring hospitalization has been shown to be a risk factor for asthma or persistent wheezing in the first decade of life.⁶⁻⁸ Most of this work has focused on the role of RSV and has used populations comprising hospitalised children or children from closed communities. Although the importance of RSV as a cause of severe respiratory infections in infancy is undisputed, few studies have looked at the long-term sequelae of LRI caused by other respiratory viruses, including rhinoviruses. A notable exception is the recent study by Lemanske et al,¹⁹ which found the most significant risk factor for preschool wheezing was symptomatic rhinovirus illnesses in infancy. They evaluated wheezing up to 3 years of age, and it is likely that many of these children belong to the group of transient wheezers previously described, with less than half of them likely to have persistence of wheeze or asthma in later life.⁴ Children hospitalized with rhinovirus-associated wLRI have also been reported to have an increased risk of asthma at 6 years of age.²⁴ The latter study also reported that children with atopic dermatitis were more likely to wheeze during rhinovirus infections, which raised the possibility that these children may have been more likely to wheeze at the time of infection because of underlying atopic changes preexisting in the airways. In the current study, we also found significant associations between rhinovirus-associated wLRI in the first year of life and current asthma, current wheeze at 5 years, and persistent wheeze, which confirms the importance of considering viruses other than RSV when determining the viral contribution to the development of persistent asthma in childhood.

The relationship between respiratory infections and induction of asthma and persistent wheezing is complex and likely to involve interactions between host factors such as age and stage of development of innate and adaptive immune mechanisms at the time of infection and pathogenic factors such as the number and severity of infections. Factors related to immune maturation seem to be particularly relevant in this context. Notably, recent evidence suggests that resistance to viral infection and atopic sensitization is dependent on an overlapping series of immune mechanisms that are strongly developmentally

regulated and as a consequence are attenuated in early life, in particular among children at high atopic risk.²⁶ Moreover, viral infections, in general,²⁵ and RSV infection, in particular,^{26,27} have been hypothesized to be capable of modulating the functions of these immune mechanisms during postnatal maturation. Thus, the degree to which atopic risk determines susceptibility to viral infection versus viral infection driving sensitization, and more importantly how these apparently overlapping processes interact in the context of asthma development in early life, is yet to be resolved.

One aspect of this study contributes important new insight into this issue, as follows. Previous cohort studies that have provided the strongest statistical support for a causative role for the cumulative (potentially synergistic) effects of infection-induced and atopy-induced airways inflammation in the etiology of persistent asthma in childhood^{20,25,28} have suffered from the limitation of lack of information on the timing of atopic sensitization among respective study groups. In both cases, these studies have relied on assessment of atopy status at outcome age (5 or 6 years), which is several years beyond the peak period of respiratory viral infections during infancy. This begs the question of whether genetic predisposition to atopy *per se* creates susceptibility to the asthma-promoting effects of viral infection (for example, such subjects may intrinsically develop excessively T_H2-polarized host antiviral responses that are inefficient in viral elimination), or whether active expression of the atopic phenotype during infancy via sensitization to environmental allergen(s) is required. In contrast to the previous studies, in the current cohort we could assess SPT reactivity employing standard criteria²⁸⁻³⁰ to a broad panel of allergens at 6 months and 24 months *en route* to the final assessment at outcome age 5 years. As demonstrated in Table III, stratification of our study population on the basis of time of initial expression of atopy reveals that the association between viral infections during infancy and subsequent development of persistent wheeze and current asthma at 5 years is restricted to the subset of high-risk children manifesting sensitization during the first 2 years of life. Moreover, this association is also restricted to infections that spread to the lower respiratory tract and are of sufficient intensity to trigger severe symptoms in the infants.

These findings are open to 2 broad interpretations. First, and in line with the bulk of currently prevailing opinion in this field, early atopic sensitization and severe LRI in infancy could both be indirect markers of a wheezy (viz. asthmatic) phenotype *per se*, without playing direct causal roles. Arguing against this opinion and in favor of a direct causal relationship, (1) the effects of early wLRI and early sensitization are at least additive in relation to risk for subsequent asthma (Table III; see references^{6,25,26}); (2) wLRI was not associated with transient wheeze (Table II); and (3) febrile nonwheezy LRI show the same association with subsequent asthma as wLRI (Table III), which suggests that infection intensity during infancy is the key factor determining the level of risk associated with individual infections as opposed to whether they trigger wheeze at

the time. Accordingly, we suggest as an alternative interpretation that these findings are consistent with a model we have recently proposed for asthma etiology in early life.^{25,29} In this model, the contemporaneous occurrence of cycles of viral-induced and allergen-induced inflammation in the airways during the period of rapid lung growth and remodeling in infancy interacts synergistically to disrupt underlying tissue differentiation programs. This interaction results in deleterious changes in ensuing respiratory functions, which may then manifest as persistent wheeze and/or asthma.

In summary, the data from the current study show that acute severe LRI caused by rhinovirus or RSV in the first year of life are important contributors to current asthma and persistent wheeze in 5-year-old children, particularly in those who are sensitized during infancy. These findings collectively suggest that development of more effective strategies to shield the growing airways of susceptible subjects against inflammation during a critical window period during infancy may be a valid approach for long-term asthma prevention. Moreover, given the possibility that the viral and atopy-associated inflammation may interact synergistically to drive asthma pathogenesis,^{25,28} effective attenuation of either of these pathways in infants may be sufficient to achieve significant long-term clinical benefits. In this context, it is pertinent to note the recent publication³⁰ indicating that 1 year of treatment of 2- to 3-year-old children at high risk of asthma with inhaled corticosteroids ameliorated symptoms during treatment, but this effect was lost after withdrawal of treatment, which argues against any disease-modifying effects of early treatment with inhaled corticosteroids. However, the current findings suggest that alternative strategies using a broader range of treatment protocols, including different classes of anti-inflammatory drugs or immunomodulatory therapies, may be required to further assess if early intervention can result in disease modification.

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