Moderate-to-severe lower respiratory tract infection in early life is associated with increased risk of polysensitization and atopic dermatitis: Findings from the CHILD Study

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Background: Respiratory infections in infancy are associated with the development of allergic asthma and atopy. Delineating whether symptomatic infections are a marker of atopic predisposition or contribute to atopic development is important for preventive strategies. We hypothesized that early, severe lower respiratory tract infections (LRTIs) may be a risk factor for the development of atopic disease.

Objective: Our aim was to determine whether clinically defined, moderate-to-severe LRTIs in infancy are associated with the development of atopic dermatitis and allergic sensitization at preschool age.

Methods: LRTI timing and severity in the first 18 months of life was defined by using the Canadian Healthy Infant Longitudinal Development study questionnaires. Polysensitization and atopic dermatitis were determined by standardized skin prick testing and structured clinical assessments. Longitudinal associations between LRTI severity and clinical outcomes at ages 3 years and 5 years were determined by adjusted repeated measures generalized estimation equations.

Results: Moderate-to-severe LRTIs were associated with increased odds of polysensitization (odds ratio = 1.91 [95% CI = 1.16-3.15]; $P = .014$) and atopic dermatitis (odds ratio = 2.19 [95% CI 1.41-3.39]; $P < .001$) as compared with the odds in children with no history of LRTI in the first 18 months of life. The association between moderate-to-severe LRTI and polysensitization or atopic dermatitis remained robust after adjusting for sex; study site; breast-feeding duration; and mother, father, or both-parent atopy or asthma.

Conclusions: These results highlight severe infant LRTI as an important risk factor for allergic and atopic disease (ie, polysensitization and atopic dermatitis), and they suggest that this risk is independent of maternal *in utero* environment, both-parent history of asthma, and both-parent genetic predisposition. (J Allergy Clin Immunol Global 2022;1:73-9.)

Key words: *Respiratory infection, pediatrics, atopy, allergy, food allergy, atopic dermatitis*

Atopic diseases such as atopic dermatitis, food allergy, allergic asthma, and allergic rhinitis are among the most frequent health challenges faced by children.[1] Respiratory infections in infancy are associated with the development of atopic and allergic diseases, including asthma,[2-5] recurrent wheezing,[6,7] and allergic sensitization[8-10] in later childhood. Specifically, respiratory syncytial virus (RSV)[6,8,11] and rhinovirus[12-16] infections are strongly associated with the development of asthma and allergy. More recently, associations between respiratory infections and allergy-atopy have been shown for other common childhood viruses,[17,18] indicating that this link may be independent of respiratory virus type.[19]

The association between respiratory viruses and the development of atopic disease is complicated by an uncertainty as to whether atopy is a risk factor for viral disease or whether atopy is a result of the respiratory infection. The observation that essentially all children are infected by a respiratory virus by age 2 years[11] mandates that there be other critical features of viral infections beyond the mere presence or absence of infection. The early timing of respiratory infections is one such feature. The argument that early viral infections drive atopic disease is supported by murine models in which the timing of the first respiratory infection plays an important role in determining the polarity (T_H1 cell vs T_H2 cell) of subsequent immunologic memory.[3] Cohort studies have suggested that in the first 18 months of life there is a critical period for immune priming by respiratory viruses.[4,5]

However, epidemiologic studies do not universally support the association between infection and atopy. Case-control and

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Abbreviations used
CHILD: Canadian Healthy Infant Longitudinal Development
GEE: Generalized estimation equation
LRTI: Lower respiratory tract infection
OR: Odds ratio
RSV: Respiratory syncytial virus
SPT: Skin prick test

matched cohort studies have shown a positive link between respiratory infection and subsequent allergic sensitization,[6,8,20,21] whereas others have found no association.[22-25] Although studies of high–atopic risk birth cohorts such as COAST and COPSAC$_{2000}$ have found that viral infections in the first few years of life are a key risk factor for later wheeze and asthma, no clear association has been seen for atopic sensitization.[13,19,26] However, these findings from high-risk populations might not apply to all infants, and unselected cohorts are required for generalizability.

There is a total of 3 prospective birth cohorts and 1 longitudinal survey–based study of healthy non–high-risk infants that describe the relationship between respiratory infections and atopic sensitization. The Oslo study,[27] which examined a birth cohort of 2540 children, reported increased atopic sensitization, allergic rhinitis, and asthma at age 10 years in children with early respiratory infections before age 1 year. The associations were strongest for lower respiratory tract infections (LRTIs). Second, in the survey-based follow-up study that merged records from the Infant Feeding Practices Study II (IFPS II) and the Year 6 Follow-up (Y6FU) study,[28] it was found that children with RSV infection in infancy were also more likely to develop hay fever, respiratory allergies, and asthma by age 6 years. Third, in the Avon Longitudinal Study of Parents and Children (ALSPAC),[5] which examined a population birth cohort of 13,761 pregnant women, an association was observed between RSV bronchiolitis before 12 months of age and wheezing and asthma but not atopic sensitization at age 7 years. Finally, in the Tucson Children's Respiratory Study, RSV before age 3 years was not associated with atopic sensitization at age 11 years or age 13 years.[23] It has been suggested that the seemingly conflicting data on respiratory infections and atopic sensitization can be largely reconciled by identifying and subsetting out early wheezers who may reveal an atopic predisposition in the absence of LRTI, whereas severe LRTIs may indeed lead to the development of atopy in those not predisposed to atopy.[29]

These studies have many limitations, however. Several studies, including the IFPS II-Y6FU Study and ALSPAC, do not capture early manifestations of atopic disease occurring before age 6 years and assess only sensitization at a single time point.[28] Conversely, despite the positive results of the Oslo study, only a subcohort of the participants were tested with objective measures of allergic sensitization such as skin prick reactivity (n = 1740), thus necessitating further validation and replication.[27] Given these issues, additional birth cohorts are needed to study the complex longitudinal relationship between infant respiratory infections and atopic disease and to reconcile the conflicting results.

Although there is no standardized definition of severe infant LRTIs, there is some consistency in the belief that severity can be defined by effect on the lower airways and the need for medical attention or hospitalization.[6,7,10,19,30-33] Further work is needed to investigate whether severity of LRTI in early life puts infants at greater risk of subsequent atopic disease.

We therefore leveraged the Canadian Healthy Infant Longitudinal Development (CHILD) Cohort Study, a large, general population Canadian birth cohort study to investigate the hypothesis that severe LRTIs occurring in the first 18 months of life are an important risk factor for the development of atopic disease in children. On the basis of the aforementioned observations, we analyzed the role of moderate-to-severe LRTIs in infancy with respect to the development of atopy while aiming to minimize the confounding of atopic predisposition. Our study fills an important gap in the literature by asking the unique question of how the severity of an infection and parental predisposition affects the link between respiratory infections and atopy.

METHODS

Study design and cohort

The CHILD Cohort Study is a multicenter longitudinal Canadian birth cohort of 3454 mothers, fathers, and infants recruited during pregnancy and followed from birth onward. Parent report child health questionnaire surveys and clinical assessments were conducted at regular intervals, including when the children were aged 1, 3 and 5 years. Details of the study design, recruitment, and collected data have been previously published.[34]

Primary exposure: LRTIs

History of LRTI was assessed by parent responses to questionnaires regarding respiratory tract symptoms and health care utilization that were collected when the children were 3, 6, 12, and 18 months of age. An LRTI was defined as the presence, in the past 3 or 6 months of (1) a cold; (2) a fever; and (3) any of the following: cough, congestion, or trouble breathing (see Fig E1 in the Online Repository at www.jaci-global.org). Children with a history of LRTI were further classified into the following LRTI severity groups based of health care utilization: mild LRTI (presented symptoms but did not require health care services), moderate LRTI (required an unscheduled doctor visit), and severe LRTI (required an emergency room visit and/or hospitalization) (see Fig E1).

Our definition was developed through a thorough review of the literature regarding defining severity of LRTI in children. Although there is no standardized questionnaire-based definition for severe infant LRTI, severity of LRTI can be defined by the need for medical attention and hospitalization.[19,30-33] To minimize identification of children already showing signs of propensity to atopy (ie, bronchial hyperresponsiveness), wheeze was not included in the definition of LRTI.

Clinical outcomes: Sensitization and atopic dermatitis

Allergy skin prick tests (SPTs) were performed on all participants at the year 1, year 3, and year 5 study visits. A child was considered sensitized if the SPT showed a 2-mm or larger wheal in response to any of 4 food (peanut, milk, egg white, and soy) or 13 inhalant (*Alternaria tenuis*, cat hair, dog epithelium, house dust mite [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*], cockroach, *Penicillium, Cladosporium*, *Aspergillus fumigatus*, tree, grass, weed, and ragweed) allergens. Details of the SPT procedure have been described previously.[35] Atopic sensitization was defined as being sensitized to at least 1 allergen eliciting a positive response. Polysensitization was defined as being sensitized to 2 or more allergens (sensitization to both dust mite allergens [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*] was counted as 1 positive SPT result).

Atopic dermatitis was defined by an experienced health care professional (pediatrician or study staff member trained and supervised by these physicians) using the UK Working Party definition,[36] which required an itchy skin condition or a parental report of scratching or rubbing in a child, and at least 1 of the following: a history of involvement of the skin creases of elbows,

TABLE I. Characteristics of the overall cohort (n=3272) and for participants in each LRTI severity group

Characteristic	Overall cohort (N = 3272)	Severity group			*P* value*
		No LRTI (n = 1681)	Mild LRTI (n = 1485)	Moderate-to-severe LRTI (n = 106)	
Sex (male), no. (%)	1722 (52.6)	860 (51.2)	802 (54.0)	60 (56.6)	.196
Ethnicity (White), no. (%)	2076 (64.6)	1048 (63.9)	965 (65.6)	63 (60.0)	.382
Study site, no. (%)					**.005**
Edmonton	736 (22.5)	368 (50.0)	351 (47.7)	17 (2.3)	
Toronto	765 (23.4)	438 (57.3)	298 (39.0)	29 (3.8)	
Vancouver	767 (23.4)	380 (49.5)	362 (47.2)	25 (3.3)	
Manitoba	1004 (30.7)	495 (49.3)	474 (47.2)	35 (3.5)	
Annual family income, no. (%)					.618
$0-$49,999	390 (13.6)	191 (13.1)	181 (13.7)	18 (18.9)	
$50,000-99,999	963 (33.6)	492 (33.8)	438 (33.2)	33 (34.7)	
$100,000-$149,999	807 (28.1)	404 (27.8)	382 (29.0)	21 (22.1)	
≥$150,000	708 (24.7)	368 (25.3)	317 (24.1)	23 (24.2)	
Mother BMI (kg/m^2), mean (SD)	25.41 (5.94)	25.48 (5.87)	25.25 (5.89)	26.56 (7.30)	.078
Mother atopy, no. (%)	1780 (57.8)	878 (57.2)	841 (58.3)	61 (58.7)	.822
Mother asthma, no. (%)	672 (21.0)	311 (19.0)	326 (22.5)	35 (33.3)	**<.001**
Father BMI (kg/m^2), mean (SD)	27.37 (4.70)	27.38 (4.55)	27.39 (4.91)	26.98 (3.77)	.745
Father atopy, no. (%)	1712 (67.9)	879 (69.0)	772 (66.1)	61 (76.2)	.079
Father asthma, no. (%)	495 (18.2)	253 (18.2)	226 (18.2)	16 (17.0)	.956
Breast-feeding duration (mo), mean (SD), months	10.40 (6.80)	9.92 (6.68)	10.91 (6.86)	10.23 (7.25)	**<.001**
Vaginal delivery, no. (%)	2408 (74.6)	1239 (74.6)	1090 (74.6)	79 (75.2)	.989

**P* values have been obtained by ANOVA for continuous variables and the chi-square test for categoric variables. Boldface indicates a statistical significance level of .05.

behind the knees, the front of ankles, or around the neck; a history of general dry skin in the past year; and visible flexural eczema or eczema involving the cheeks or forehead and outer limbs. This measure has previously been validated in the CHILD cohort.[37]

Covariates

All of the adjusted models included sex, study site, and breast-feeding duration (months) based on *a priori* assumptions about the exposure and outcomes. To control for family predisposition to allergic disease, all models were additionally adjusted for mother or father atopy or asthma separately. Mother atopy and father atopy were defined as having a positive SPT result for a minimum of 1 allergen. Data on mother asthma and father asthma were obtained from self-report questionnaires asking whether the mother had ever been diagnosed with asthma by a physician.

Statistical analysis

Descriptive statistics are presented as means (SDs) for continuous measures and frequency (%) for categoric measures. *P* values were obtained by using a 2-sample *t* test and chi-square test, where appropriate.

Longitudinal associations between LRTI severity and clinical outcomes at ages 3 years and 5 years were determined by univariate and adjusted generalized estimation equations (GEEs) with repeated measures. To reduce potential bias associated with missing covariate data, adjusted models were performed on multiple imputed data sets for missing data regarding mother and father asthma and atopy (n = 10 imputations). A fully conditional specification method with logistic regression was performed; it included maternal and paternal predictor variables (ethnicity, education level, body mass index, age at the child's birth, and study site). Pooled effect estimates after the multiple imputation are reported. Results from regressions before imputations are included in Fig E1. All statistical analyses were performed using SAS Software, version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Participant characteristics

A total of 3272 participants from the CHILD Cohort Study with available data collected on infant LRTIs were included in the current analysis (Table I). The average breast-feeding duration was 10.40 months (SD = 6.80 months) (Table I), with more than 50% and 19% of mothers breast-feeding exclusively when their children were 3 and 6 months of age (data not shown). Before imputation, mother and father asthma prevalence rates were 21.0% and 18.2%, respectively. History of atopy was present in 57.8% of mothers and 67.9% of fathers. Of the 3272 participants with LRTI data, 2.4% (n = 79) and 5.8% (n = 190) were missing data on mother asthma and atopy, respectively; father missing data was more notable, with 16.9% (n = 552) missing asthma data and 22.9% (n = 751) missing atopy data.

LRTIs

In the first 18 months of life, 1591 children had experienced a LRTI (Fig 1 and Table I). Only 3.1% of the cohort (n = 106) experienced a moderate-to-severe LRTI before 18 months of age. In contrast, 45.4% of participants (n = 1485) reported a mild LRTI (Fig 1 and Table I). The number of participants with a mild first LRTI increased across all time points (from 36 at age 3 months to 1485 at age 18 months) (Fig 1). A similar increasing trend was observed for the number of participants who experienced a first moderate-to-severe LRTI over time (from 2 at 3 months to 106 at 18 months) (Fig 1).

Participant characteristics by LRTI severity group are described in Table I. Mother atopy and mother asthma were highest in the moderate-to-severe subgroup (58.7% and 33.3%, respectively), and then in the mild LRTI subgroup (58.3% and 22.5%, respectively). Father atopy was also higher among the moderate-to-severe LRTI severity group than among the mild LRTI and no-LRTI groups (76.2% vs 66.1% and 69.0%). However, these differences were significant only for mother asthma ($P <$ .001). Significant differences were also observed among the LRTI severity groups by study site and breast-feeding duration. Other characteristics were similar between the LRTI severity groups.

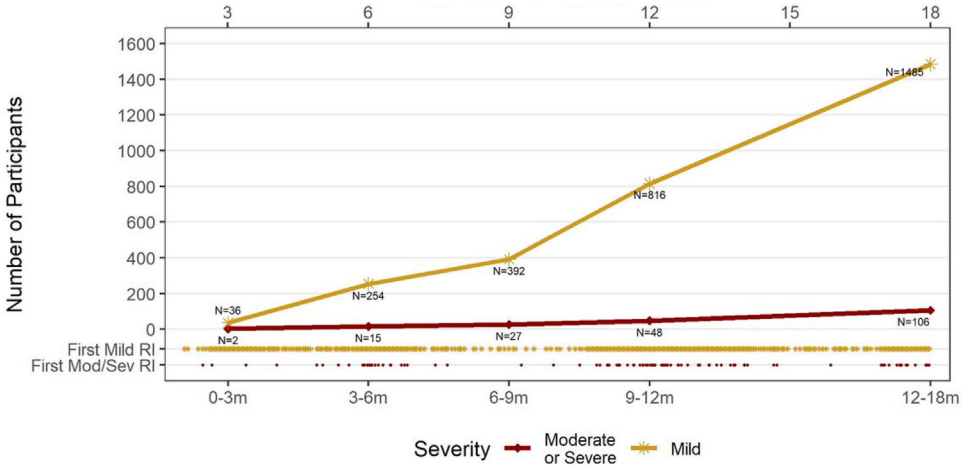

FIG 1. Cumulative number of participants who experienced their first mild or moderate-to-severe LRTI by the age of onset. Age of first LRTI is binned into 0 to 3, 3 to 6, 6 to 9, 9 to 12, and 12 to 18 months.

LRTI severity and sensitization outcomes

At age 1, 13.7% of participants were positive for atopic sensitization, 11.0% were food-sensitized, 4.1% were inhalant-sensitized, and 3.7% were polysensitized (Table II). In children with mild or moderate-to-severe LRTI, the prevalence of atopic sensitization, inhalant sensitization, and polysensitization increased over time (Table II and Fig 2). Food sensitization was an exception to this trend in children without LRTI, with the prevalence decreasing from 11.0% at 1 year of age to 6.2% and 5.4% at ages 3 and 5 years (Table II).

The moderate-to-severe LRTI group had higher proportions of participants with sensitization (atopic, food, and inhalant sensitization, as well as and polysensitization) at all time points than the mild LRTI and no-LRTI groups (Table II and Fig 2). However, the difference in proportion of sensitization by severity group was only significant at age 5 years.

The association between LRTI severity during infancy and sensitization outcomes was first assessed by unadjusted GEE models (see Table E1 in the Online Repository at www.jaci-global.org). Moderate-to-severe LRTIs were associated with higher odds of sensitization outcomes than the no-LRTI group (Table III). Moderate-to-severe LRTIs from age 0 months to 18 months were associated with 84% higher odds of food sensitization (odds ratio [OR] = 1.84 [95% CI = 1.00-3.39]; $P = .050$) and 91% higher odds of developing polysensitization (OR = 1.91 [95% CI = 1.16-3.15]) at age 5 years.

The association between moderate-to-severe LRTIs and polysensitization remained significant after adjustment for mother asthma or atopy (Table III), father asthma or atopy, or both-parent asthma or atopy (Table IV). Associations with food sensitization became nonsignificant after these same adjustments.

Finally, there were no associations found between any sensitization outcome and the mild LRTI group versus the no-LRTI group.

Association of LRTI severity and atopic dermatitis

Atopic dermatitis was observed in 12.0% of participants at age 1, 12.2% at age 3, and 13.8% at age 5 (Table II). Atopic dermatitis prevalences were not statistically different between LRTI severity groups at age 1 (11.7%, 12.3%, and 13.2% for the no-LRTI, mild LRTI, and moderate-to-severe LRTI groups, respectively) (Table II). However, at ages 3 and 5 years, the moderate-to-severe LRTI group had significantly higher prevalence of atopic dermatitis ($P = .001$ and $P = .006$, respectively). Atopic dermatitis prevalence was very similar in the no-LRTI and mild LRTI groups at age 1 (11.7% and 12.3%), age 3 (11.2% and 12.1%), and age 5 years (13% and 14%) (Table II).

The moderate-to-severe LRTI before age 18 months subgroup was positively associated with atopic sensitization. Unadjusted GEE regression models revealed that the odds of developing atopic dermatitis were more than double in the moderate-to-severe LRTI group (OR = 2.19 [95% CI = 1.41-3.39] [see Table E1]) than in the no-LRTI group. These odds were maintained after adjustment for all parental factors, including mother asthma (OR = 2.07 [95% CI = 1.33-3.22]), mother atopy (OR 2.15 [95% CI = 1.38-3.34]), father asthma (OR = 2.16 [95% CI = 1.4-3.35]), father atopy (OR = 2.14 [95% CI = 1.38-3.31]), both-parent asthma (OR = 2.07 [95% CI = 1.33-3.23]), or both-parent atopy (OR = 2.15 [95% CI = 1.38-3.34]) (Tables III and IV). No significant associations were observed between mild LRTIs and atopic dermatitis.

DISCUSSION

In this large, healthy birth cohort, infants with a history of moderate-to-severe LRTIs that occurred before 18 months of age and necessitated an unscheduled doctor visit or health care utilization were at higher odds of atopic disease as defined by atopic dermatitis and polysensitization at preschool age. Notably, mild LRTIs that did not require health care utilization were not associated with these atopic manifestations. These results were robust for polysensitization and atopic dermatitis after controlling for multiple child and parental factors related to predisposition to atopic disease.

In this analysis we focused on minimizing the possibility that those infants with severe LRTI were at an elevated intrinsic risk of atopy. The CHILD Cohort Study is a large, unselected,

TABLE II. Frequency of study outcomes at ages 1, 3, or 5 years in the overall cohort and in participants by LRTI severity subgroup

Study outcome (N = 3272)		LRTI severity group			*P* value*
		None (n = 1681)	Mild (n = 1485)	Moderate-to-severe (n = 106)	
Age 1, no. (%)					
Atopic sensitization	408 (13.7)	206 (14.3)	185 (12.9)	17 (16.3)	.405
Inhalant sensitization	121 (4.1)	57 (4.0)	59 (4.1)	5 (4.8)	.906
Food sensitization	326 (11.0)	171 (11.9)	139 (9.7)	16 (15.4)	.060
Polysensitization	122 (3.7)	70 (4.2)	46 (3.1)	6 (5.7)	.067
Atopic dermatitis	358(12.0)	168 (11.7)	176 (12.3)	14 (13.2)	.808
Age 3 y, no. (%)					
Atopic sensitization	396 (14.3)	192 (14.2)	187 (14.2)	17 (17.9)	.601
Inhalant sensitization	316 (11.4)	149 (11.0)	155 (11.8)	12 (12.6)	.769
Food sensitization	164 (6.0)	83 (6.2)	73 (5.6)	8 (8.5)	.457
Polysensitization	239 (7.3)	117 (7.0)	112 (7.5)	10 (9.4)	.348
Atopic dermatitis	343 (12.2)	158 (11.4)	161 (12.1)	24 (24.2)	**.001**
Age 5 y, no. (%)					
Atopic sensitization	513 (19.5)	250 (19.5)	238 (18.9)	25 (26.9)	.169
Inhalant sensitization	459 (17.4)	220 (17.2)	217 (17.2)	22 (23.7)	.272
Food sensitization	141 (5.4)	68 (5.4)	62 (5.0)	11 (11.8)	**.019**
Polysensitization	388 (11.9)	187 (11.1)	180 (12.1)	21 (19.8)	**.001**
Atopic dermatitis	376 (13.8)	173 (13.0)	181 (14.0)	22 (22.9)	**.025**

*P values have been generated for categoric variables by chi-square test of independence. Boldface indicates statistical significance.

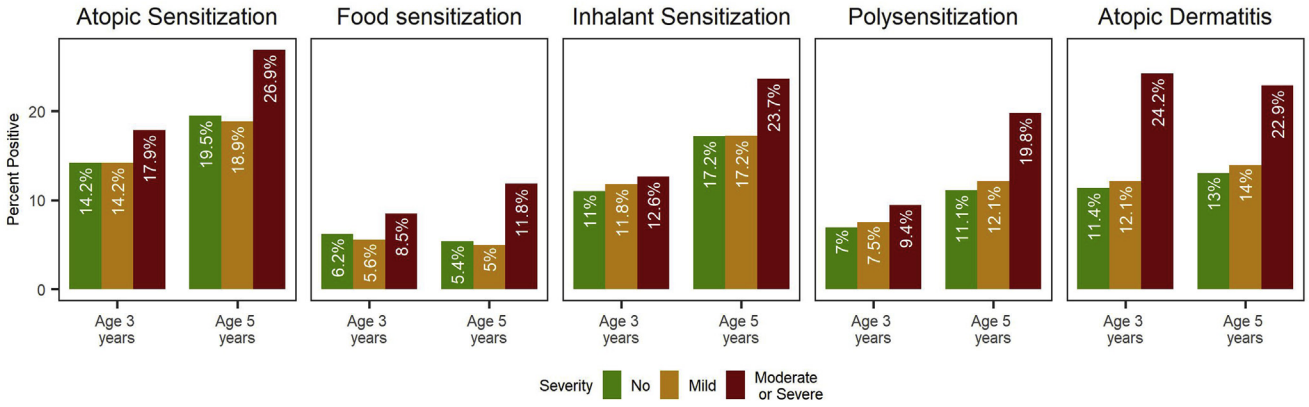

FIG 2. Prevalence of sensitization or atopic dermatitis at ages 3 and 5 years in each LRTI severity group (no-LRTI, mild LRTI, or moderate-to-severe LRTI) between birth and 18 months of age.

TABLE III. ORs, 95% CIs, and *P* values for study outcomes in each LRTI severity group from unadjusted univariate GEE models and models adjusted for sex, study site, breast-feeding, and mother or father asthma or atopy

Study outcome	LRTI severity group	Mother asthma OR (95% CI)	*P* value	Mother atopy OR (95% CI)	*P* value	Father asthma OR (95% CI)	*P* value	Father atopy OR (95% CI)	*P* value
Atopic sensitization	Mild	0.99 (0.83-1.18)	.876	0.99 (0.83-1.17)	.869	0.99 (0.83-1.18)	.890	1 (0.84-1.19)	.975
	Moderate-to-severe	1.41 (0.91-2.17)	.124	1.41 (0.91-2.19)	.129	1.42 (0.93-2.19)	.108	1.4 (0.91-2.16)	.126
Inhalant sensitization	Mild	1.04 (0.86-1.25)	.688	1.04 (0.87-1.25)	.672	1.04 (0.87-1.25)	.673	1 (0.84-1.19)	.975
	Moderate-to-severe	1.32 (0.84-2.06)	.223	1.33 (0.84-2.09)	.222	1.35 (0.86-2.1)	.187	1.4 (0.91-2.16)	.126
Food sensitization	Mild	0.93 (0.69-1.26)	.651	0.93 (0.69-1.25)	.619	0.93 (0.69-1.26)	.653	0.94 (0.7-1.27)	.705
	Moderate-to-severe	1.84 (0.99-3.42)	.054	1.8 (0.97-3.35)	.064	1.83 (0.99-3.37)	.054	1.77 (0.96-3.28)	.068
Polysensitization	Mild	0.87 (0.68-1.11)	.275	0.88 (0.68-1.14)	.342	0.88 (0.68-1.14)	.349	0.89 (0.69-1.16)	.397
	Moderate-to-severe	**1.84 (1.11-3.07)**	**.018**	**1.94 (1.14-3.29)**	**.014**	**1.97 (1.18-3.3)**	**.010**	**1.94 (1.16-3.26)**	**.012**
Atopic dermatitis	Mild	1.12 (0.92-1.35)	.259	1.12 (0.92-1.35)	.253	1.12 (0.93-1.36)	.231	1.13 (0.93-1.37)	.209
	Moderate-to-severe	**2.07 (1.33-3.22)**	**.001**	**2.15 (1.39-3.34)**	**.001**	**2.16 (1.4-3.35)**	**.001**	**2.14 (1.38-3.31)**	**.001**

Missing parent asthma or atopy data were imputed by using multiple imputed data sets (n = 10). The reference group was no LRTI. Boldface indicates statistical significance.

prospective birth cohort of healthy mothers, fathers, and infants rather than a cohort enriched for atopy. We defined LRTIs as being independent of wheezing and having allergic outcomes that were unrelated to lung measures. With this definition of LRTI, mother and father atopy were not significantly more frequent in those infants with moderate-to-severe LRTI (Table I). Moreover, the atopic outcomes were not documented in a higher proportion of infants with moderate-to-severe LRTI at age 1 year; rather,

TABLE IV. ORs, 95% CIs, and *P* values for study outcomes in each LRTI severity group from GEE models adjusted for sex, study site, breast-feeding, and both-parent asthma or both-parent atopy

Study outcome	LRTI severity group	Both-parent asthma OR (95% CI)	*P* value	Both-parent atopy OR (95% CI)	*P* value
Atopic sensitization	Mild	0.99 (0.83-1.18)	.896	0.99 (0.83-1.18)	.940
	Moderate-to-severe	1.41 (0.92-2.18)	.119	1.39 (0.89-2.16)	.143
Inhalant sensitization	Mild	1.04 (0.86-1.25)	.685	1.05 (0.87-1.26)	.621
	Moderate-to-severe	1.32 (0.85-2.07)	.219	1.32 (0.84-2.08)	.235
Food sensitization	Mild	0.94 (0.7-1.27)	.683	0.94 (0.69-1.27)	.673
	Moderate-to-severe	**1.87 (1.00-3.48)**	**.049**	**1.76 (0.94-3.29)**	**.075**
Polysensitization	Mild	0.89 (0.69-1.15)	.357	0.89 (0.69-1.15)	.383
	Moderate-to-severe	**1.96 (1.17-3.3)**	**.011**	**1.92 (1.13-3.25)**	**.016**
Atopic dermatitis	Mild	1.12 (0.92-1.35)	.248	1.12 (0.92-1.36)	.248
	Moderate-to-severe	**2.07 (1.33-3.23)**	**<.001**	**2.15 (1.38-3.34)**	**<.001**

Boldface indicates statistical significance.

differences between the LRTI severity groups were apparent later (at ages 3 and 5 years), supporting the suggestion that early LRTI identifies a group at later risk of atopy.

Maternal history of atopy and asthma has been shown to skew the development of the fetal-infant immune response toward a T_H2 cell allergic phenotype.[38] We controlled for mother asthma as a proxy for the maternal environment during pregnancy and parental history of atopy to control for genetic atopic predisposition. After adjusting for these significantly associated parental factors, we demonstrated that the effect of severe LRTI in infancy on atopic dermatitis and polyallergic sensitization was robust to controlling for maternal environment or genetic predisposition from mothers or fathers.

Our sensitization results support the results of Sigurs et al, who found that a severe RSV infection increased the risk of clinical allergy and allergic sensitization at ages 7, 13, and 18 years.[6,8,20] Our results differ in that we identified a statistically significant increased odds of polysensitization rather than aeroallergen sensitization. Our study found that infants with moderate-to-severe LRTI continued to develop atopic manifestations over time (Table II). At age 3 years they had significantly higher odds of atopic dermatitis, and then at age 5 years they had significantly higher odds of atopic dermatitis, food sensitization, and polysensitization. The increasing development of sensitizations in the infants with moderate-to-severe LRTIs is consistent with the "atopic march."[39-41] Although the atopic march is no longer thought of as a linear path, atopic dermatitis and food sensitizations are important clinical markers for children who are at risk of developing further atopic disease, including aeroallergen sensitization and asthma.[42] Within the CHILD Cohort Study, atopic dermatitis and sensitization to allergens identified by using SPTs are key predictors of the development of clinical allergic disease.[37] This is echoed by other cohort studies reporting that atopic sensitization at age 4 years tends to be persistent and predictive of additional sensitization.[43,44]

Our study does have some limitations. The incidence of moderate-to-severe LRTI was relatively low given that this is a healthy birth cohort. Second, we did not determine the etiology of each LRTI by using nasopharyngeal aspirates. It is possible that particular viruses are more relevant to the development of atopic disease. For example, as was recently reviewed,[45] RSV may be linked more to the development of atopy than to development of rhinovirus. Despite this limitation, clinical campaigns such as Choosing Wisely have reduced viral identification at the point of care,[46] and so it is relevant to define LRTIs independently of the viral agent; our definition of LRTI is widely applicable and lends to wide generalizations of our findings. Furthermore, it is also possible that the children experiencing our definition of moderate-to-severe LRTI did not have a LRTI but instead had an early respiratory manifestation of atopic disease. To minimize this possible misclassification of LRTI, we did not include wheeze in the definition of LRTI and required the presence of a fever. Additionally, the questionnaires used in the CHILD Study introduces the risk of recall bias, which was minimized by frequent surveys and by including health care and/or physician utilization in the classification.

A limitation of our atopic outcomes is that food sensitization was not clinically confirmed by oral food challenge testing. Furthermore, in this analysis, we focused on controlling for atopic predisposition and not for other factors that may be related to LRTIs such as antibiotics. Finally, any associations found in this work cannot directly imply a causal relationship.

Having established that this definition of LRTI identifies infants at risk of atopic disease in the CHILD Cohort Study, as the participants are followed over time, we will determine whether further atopic associations will appear; specifically, we will determine whether the observed link between early-life severe LRTI and sensitization and atopic dermatitis remains and whether a link to inhalant sensitization will develop. We also plan to broaden our analysis to allergic rhinitis and allergic asthma. Finally, we hope to investigate whether antibiotic use and the microbiome may play a mediating role in the association between severe LRTI and atopic disease.

These results highlight the fact that moderate-to-severe infant LRTI is an important risk factor for atopic disease. Children with moderate-to-severe LRTIs in infancy represent a higher-risk category for polysensitization and atopic dermatitis in later childhood. Whether LRTI alone can cause the onset of such diseases is yet to be confirmed.

Conclusion

We have reported a significant association between infant LRTI that necessitated health care utilization and atopic outcomes (SPT-confirmed sensitization and atopic dermatitis) at preschool age. These associations remained significant for polysensitization and atopic dermatitis after controlling for sex; study site; breast-feeding duration; and mother, father, or both-parent atopy or

asthma. Infants with moderate-to-severe LRTIs may be a particular group for targeted interventions and monitoring.

Clinical implications: Moderate-to-severe respiratory infections before 18 months of age are associated with polysensitization and atopic dermatitis independent of their atopic genetic predisposition or both parents' history of asthma.

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