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Original Contribution

Longitudinal Associations Between Respiratory Infections and Asthma in Young Children

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We examined temporal dependencies between repeated assessments of respiratory tract infections (RTIs) and asthma in children in the Leicester Respiratory Cohort, Leicestershire, United Kingdom. Information associated with asthma (i.e., doctor diagnosis, health care visits, wheeze frequency) and RTIs (i.e., cold duration and frequency, cough with colds, ear infections) in the previous 12 months was assessed repeatedly at ages 1, 4, and 6 years for children born between April 1996 and April 1997. We determined associations between contemporaneous and lagged measures of asthma and RTIs, using structural equation modelling. In 1,995 children, asthma was positively associated with contemporaneous infections. Asthma at age 6 years was positively associated with asthma at age 4 years (regression coefficient = 0.87; 95% confidence interval (CI): 0.76, 0.97), but not with asthma at age 1 year (regression coefficient = −0.01; 95% CI: −0.14, 0.11). We found no evidence for direct protective effect of infections at age 1 year on asthma either at age 4 (regression coefficient = −0.20; 95% CI: −0.51, 0.10) or 6 (regression coefficient = 0.24; 95% CI: −0.04, 0.52) years. Adjusting for potential confounders did not qualitatively change those relationships. Based on our findings, we suggest that asthma at age 6 years is directly influenced by asthma history and only indirectly, if at all, by earlier infection episodes. We found little support for a protective effect of preschool infections on asthma at early school age.

asthma in children; longitudinal structural equation modeling; respiratory infections

Abbreviations: CI, confidence interval; RTI, respiratory tract infection; RSV, respiratory syncytial virus; SEM, structural equation modelling.

Respiratory tract infections (RTIs) and asthma are major components of acute and chronic morbidity in childhood, and they place a considerable burden on children, their families, and society (1, 2). Asthma has multiple causes, including genetic predisposition, environmental exposures, and interactions between these factors and a child's developmental stage (3). Although a strong association between microbial (including viral) infections and asthma in children from infancy to school age has been shown in studies (4, 5), the direction of causation is unclear and may be bidirectional (3). Several pathways from microbial infections to atopic conditions have been proposed: Microbial infections can have protective effects (the hygiene hypothesis) (6, 7) or be provocative (8–12) of subsequent asthma. A reverse causation mechanism has also been proposed in which atopic conditions increase the susceptibility to infections (3, 13–15). The association between infections and childhood asthma also may not be causal; rather it may be due to shared genetic components that induce susceptibility to both (16).

Research on asthma is hampered by the complexity of asthma presentation; asthma is particularly difficult to assess in children younger than age 6 years (17). The interpretation of results from observational studies is not straightforward because, at an early age, asthma symptoms are often not easily distinguished from those of RTIs (18, 19), which are the most frequent trigger of wheezing in early childhood (20). In addition, because many studies include large proportions of children at high risk of atopy (11, 12), doubt is cast on the generalizability of the conclusions. Associations between asthma and RTIs are likely to vary with age (5, 9), but associations at different ages in the same cohort have been compared systematically in few studies (21, 22).

In this study, we quantified the relationships between assessments of RTIs and asthma repeated from infancy to school age

in a large, population-based cohort to assess the plausibility of the following 4 hypotheses about contemporaneous and lagged associations: 1) asthma and infections are highly correlated at each age, 2) asthma and infections longitudinally track throughout childhood, 3) infections in preschool children modify later risk of asthma developing by either reducing the risk (protective effect) or increasing the risk (provocative effect), and 4) wheezing infants are more susceptible to RTIs later in childhood.

METHODS

Study population

We used data from a population-based cohort of children of Leicestershire, United Kingdom. For all children, we obtained routine data, including demographic and perinatal data from the Leicestershire Health Authority Child Health Database (Table 1). Questionnaires with detailed questions on upper and lower respiratory symptoms, treatments and health care use, family history of respiratory and atopic diseases, socioeconomic and demographic factors, and environmental exposures were mailed to parents. Relevant exposures and outcome measures for this study are summarized in Table 2.

We included 1,995 children born between April 21, 1996, and April 30, 1997, for whom surveys were returned in each of 3 years: 1998 (mean age = 1.5 years, range, 1.0–1.99, standard deviation, 0.3), 2001 (mean age = 4.8 years, range, 3.9–5.6, standard deviation, 0.3), and 2003 (mean age = 6.5 years, range, 6.0–7.5, standard deviation, 0.3). We refer to these as the 1-year, 4-year, and 6-year age groups. Response rates were 78%, 60%, and 49% for the respective groups in 1998, 2001, and 2003. The Leicester cohorts are described in detail elsewhere (23). The study protocol was approved by the Leicestershire Health Authority Research Ethics Committee.

Table 1. Baseline Characteristics at 1 Year of Age of the 1,995 Children Born Between April 1996 and April 1997, Leicester Respiratory Cohort, Leicestershire, United Kingdom, 1998–2003

Characteristic	No.	%
Male sex	1,049	53
South Asian ethnicity	308	15
Low birth weight[a]	130	7
Preterm birth[b]	121	6
Attended nursery care	574	29
Had older siblings	1,082	54
Maternal smoking	234	12
Paternal smoking	414	21
Breastfed	1,283	64
History of parental wheeze or asthma[c]	335	17
Higher parental educational level[c,d]	932	47
Higher deprivation categories[e]	475	24

[a] Birth weight <2,500 g.
[b] Gestational age <37 weeks.
[c] Either mother or father.
[d] Age at the end of education was >16 years.
[e] Higher deprivation categories consist of deprived and more deprived categories based on the following ranges of Townsend Deprivation scores: more affluent (−6.222 to −2.635), affluent (−2.615 to −0.707), average (−0.705 to 1.859), deprived (1.861 to 5.147), and more deprived (5.160 to 11.072).

Data on asthma and RTIs

From each survey, we derived the following information relating to asthma during the previous 12 months: diagnosis of asthma, asthma-related health care visit to general practitioner or accident/emergency department, episodes of wheeze (current wheeze), number of wheeze attacks (0, 1–3, 4–12, or >12), and use of anti-asthma medication (short- and long-acting β_2-agonists, inhaled corticosteroids). We collected information on infections during the previous 12 months, including frequency and duration of colds, cough with colds, and ear infections (see Web Appendix 1, available at https://academic.oup.com/aje).

All variables with more than 2 response categories were recoded as binary variables. We used thresholds that identified approximately the 10%–20% most severe cases for wheeze and infections at each survey (Table 2). We defined frequent wheeze as 4 or more attacks of wheeze, frequent colds as 7 or more episodes, colds of long duration as colds lasting 2 or more weeks, and frequent ear infections as 2 or more ear infections in the past 12 months.

Statistical analyses

We used longitudinal structural equation modelling (SEM) to assess associations between repeated assessments of asthma and respiratory infections at ages 1, 4, and 6 years. Longitudinal SEM is a multivariate method that allows modelling of the temporal relationships between unobserved, latent variable constructs derived from observed variables (24). In our model, diagrammed in Web Figure 1, we defined asthma and infections as latent constructs corresponding to the aforementioned observed indicator variables. Effect sizes were modelled as either probit regressions of indicators on latent variables (measurement model), or linear regressions between the latent constructs (structural model). Given the multiplicity of hypotheses, we allowed for all possible paths between latent variables for which cause precedes effect. In the model, bidirectional paths represent bivariate associations and account either for the covariance of contemporaneous latent constructs or for correlations between repeated measurements of indicator variables over time. Additional detail on SEM estimation based on dichotomous data is provided in Web Appendix 2.

We used diagonally weighted least squares to estimate the model parameters with their corresponding 95% confidence intervals. The full weight matrix was used to compute robust standard errors (25). *P* values of path coefficients were obtained by the Wald test and were further corrected for multiple statistical testing by controlling for the false discovery rate at the 5% level using the Benjamini–Hochberg procedure (26).

Interpreting effect sizes in longitudinal SEM is meaningful only if the factors corresponding to the same construct (infections or asthma in our model) have the same meaning over time (i.e., they are time invariant). This can be assessed by establishing the invariance of factor loadings (metric invariance) and factor variances over time (factor variance invariance; Web Appendices 3

Table 2. Prevalence of Asthma/Wheeze and Respiratory Tract Infections for Children Born Between April 1996 and April 1997, Leicester Respiratory Cohort, Leicestershire, United Kingdom, 1998–2003

Indicator Variable	1 Year		4 Years		6 Years	
	No.	%	No.	%	No.	%
Asthma/wheeze indicator variables						
Asthma diagnosis	194	10	402	20	430	22
Current wheeze	611	31	305	15	259	13
Wheeze with colds	591	30	323	16	288	14
Frequent wheeze[a]	201	10	106	5	97	5
Asthma-related health care visit	224	11	132	7	83	4
Bronchodilator use	290	15	314	16	280	14
Inhaled corticosteroid use	100	5	201	10	197	10
Infection indicator variables						
Frequent colds[b]	370	19	124	6	93	5
Long duration of colds[c]	249	12	119	6	103	5
Cough with colds	1,299	65	1,403	70	1,403	70
Frequent ear infections[d]	359	18	220	11	190	10

[a] Frequent wheeze was defined as ≥4 wheeze attacks in past 12 months.
[b] Frequent colds were defined as ≥7 cold episodes in past 12 months.
[c] Long duration of colds was defined as colds lasting ≥2 weeks in the past 12 months.
[d] Frequent ear infections are defined as ≥2 ear infections episodes in past 12 months.

and 4). For model comparison, we considered as acceptable goodness of fit a comparative fit index value of 0.95 or greater and a root mean square error of approximation no greater than 0.06 (27). We also regarded a decrease in a comparative fit index value of 0.01 and an increase of root mean square error of approximation of 0.015, which are more sensitive for detecting lack of invariance in studies with large sample sizes (28), as criteria indicative of unacceptable decrease in (or poorer) model fit.

The baseline SEM model was adjusted for variables that were assessed only at age 1 year, which might have confounded the associations assessed in our model: sex, ethnicity, maternal asthma, maternal smoking during pregnancy, breastfeeding, presence of older siblings, family education, birth season, and economic deprivation (Table 1). We assessed the influence of varying response rates at the 3 survey times on our SEM estimates by doing a sensitivity analysis based on all 1-year-old children who responded at the first survey and keeping those children in the analysis independently of their participation to the subsequent questionnaires. We used a full information maximum likelihood estimation to account for the missing information on outcomes in the SEM procedure (Web Appendix 2) (29). Data were prepared and analyzed using Stata, version 13.1 (StataCorp LP, College Station, Texas). SEM models were implemented with the *lavaan* (25) package (version 0.5-20) in R, version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study population

We analyzed the complete-case data of the 1,995 children who were 1 year old in 1998 whose parents responded to all 3 surveys in 1998, 2001, and 2003 (Table 1). Slightly more than half were boys; 15% were of South Asian ethnic origin, and the others were white.

Prevalence of asthma/wheeze and respiratory infections

Prevalence of an asthma diagnosis doubled from 10% at age 1 year to about 20% at ages 4 and 6 years (Table 2). The use of inhaled corticosteroids increased as well, but bronchodilator use remained constant. Prevalence of current wheeze decreased from 31% at age 1 year to about 13% at age 6 years, whereas asthma-related visits decreased from 11% to 4% over the same period. The prevalence of frequent colds, ear infections, and long-lasting colds also decreased. The prevalence of cough with colds remained high at 65%–70% throughout early childhood (Table 2).

Validation of SEM construct and model fit

The variables wheeze with colds and current wheeze were highly correlated (correlation coefficient $\rho = 0.95$), so only current wheeze was kept for further SEM model building. Measurement invariance of the 2 constructs infections and asthma was confirmed with difference in comparative fit index values of concurrent models less than 0.01 (Web Table 1, Web Appendix 1), suggesting that factor loadings and variances and residual variances of the regressions of indicators on the latent variables can be considered invariant across time (Web Tables 2 and 3). This means the 2 constructs have the same interpretation with respect to the questionnaire items regardless of age at response (30). The baseline model (Web Figure 2) showed an acceptable model fit with a comparative fit index value of 0.995 and root mean square error of approximation of 0.028 (90% confidence interval (CI):

Table 3. Path Coefficients for Pathways Between Asthma and Infection Latent Variables for Children Born Between April 1996 and April 1997, Leicester Respiratory Cohort, Leicestershire, United Kingdom, 1998–2003

Path Direction	Crude Model (n = 1,995)			Adjusted Model[c] (n = 1,807)		
	Estimate[a]	95% CI	*P* Value[b]	Estimate	95% CI	*P* Value
Bidirectional paths between latent variable categories						
Between infections (1 year) and asthma (1 year)	0.27	0.20, 0.34	<0.001[d]	0.29	0.21, 0.36	<0.001[d]
Between infections (4 years) and asthma (4 years)	0.17	0.11, 0.23	<0.001[d]	0.165	0.09, 0.22	<0.001[d]
Between infections (6 years) and asthma (6 years)	0.08	0.04, 0.11	<0.001[d]	0.08	0.04, 0.12	<0.001[d]
Unidirectional paths within latent variable categories						
From infections (1 year) to infections (4 years)	0.36	0.11, 0.61	0.005[d]	−0.04	−0.89, 0.82	0.929
From infections (1 year) to infections (6 years)	0.08	−0.25, 0.41	0.630	−1.06	−3.08, 0.97	0.306
From infections (4 years) to infections (6 years)	0.88	0.45, 1.32	<0.001[d]	1.00	0.48, 1.52	<0.001[d]
From asthma (1 year) to asthma (4 years)	0.68	0.56, 0.81	<0.001[d]	2.17	0.88, 3.46	0.001[d]
From asthma (1 year) to asthma (6 years)	−0.01	−0.14, 0.11	0.824	0.48	−0.24, 1.2	0.192
From asthma (4 years) to asthma (6 years)	0.87	0.76, 0.97	<0.001[d]	0.75	0.59, 0.92	<0.001[d]
Unidirectional paths across latent variable categories						
From infections (1 year) to asthma (4 years)	−0.20	−0.51, 0.10	0.192	−4.13	−7.64, −0.62	0.021
From infections (1 year) to asthma (6 years)	0.24	−0.04, 0.52	0.097	−0.99	−2.77, 0.79	0.276
From infections (4 years) to asthma (6 years)	−0.04	−0.32, 0.24	0.769	0.15	−0.16, 0.47	0.330
From asthma (1 year) to infections (4 years)	0.07	−0.03, 0.17	0.174	0.23	−0.1, 0.56	0.179
From asthma (1 year) to infections (6 years)	0.00	−0.15, 0.16	0.962	0.46	−0.37, 1.29	0.274
From asthma (4 years) to infections (6 years)	−0.01	−0.15, 0.14	0.918	−0.07	−0.3, 0.17	0.581

Abbreviations: CFI, comparative fit index; CI, confidence interval; RMSEA, root mean square error of approximation.

[a] Covariances for bidirectional paths and regression coefficients for unidirectional paths, respectively.

[b] *P* value for testing the null hypothesis that the parameter equals zero in the population using the Wald statistical test.

[c] Model was adjusted for child sex and birth season (September–November, December–February, March–May, June–August), as well as maternal asthma, maternal smoking, breastfeeding, presence of older siblings, level of family education, ethnicity, and socioeconomic level at 1 year of age.

[d] $P < 0.05$ after correction for multiple testing (26).

0.026, 0.030) (27). We show results for this model; all indicator variables had significant loadings on their respective latent variable (Web Table 3).

Relationships between asthma and susceptibility to infections

At each survey, the latent constructs infections and asthma were positively correlated, with covariances of 0.27 (95% CI: 0.20, 0.34) at age 1 year, 0.17 (95% CI: 0.11, 0.23) at age 4 years, and 0.08 (95% CI: 0.04, 0.11) at age 6 years (Web Figure 2; latent construct variances decreased similarly and are reported in Web Table 2). Adjusting the SEM model for confounding variables minimally changed these values (Table 3; Web Table 4).

We found strong evidence for the constructs asthma and infections tracking as children grew older (Table 3; Web Figure 2): Factor scores at age 4 years were strongly and positively related to those at age 1 year, with path coefficients of 0.68 (95% CI: 0.56, 0.81) and 0.36 (95% CI: 0.11, 0.61) for asthma and infections, respectively. Dependence of factor scores at age 6 years on previous corresponding values at age 4 years was even stronger, with path coefficients of 0.87 (95% CI: 0.76, 0.97) for asthma and 0.88 (95% CI: 0.45, 1.32) for infections. There was no evidence of a direct effect from ages 1 to 6 years for both constructs.

We found little evidence of cross-lagged relationships between asthma and infections between ages 1 and 4 years, 4 and 6 years, or 1 and 6 years. In particular, higher infections scores at age 1 year were not associated with higher asthma scores at age 4 (regression coefficient = −0.20, 95% CI: −0.51, 0.10) or at age 6 (regression coefficient = 0.24, 95% CI: −0.04, 0.52) years (Table 3; Web Figure 2). We found no evidence that wheezing infants were more susceptible to respiratory tract infections at ages 4 (regression coefficient = 0.07, 95% CI: −0.03, 0.17) or 6 (regression coefficient = 0.00, 95% CI: −0.15, 0.16) years.

Adjusting the model for potential confounders changed the path between infections at ages 1 and 4 years to a nonsignificant association (regression coefficient = 0.08, 95% CI: −0.79, 0.96; $P = 0.850$) but led to a stronger dependency of asthma at 4 years on asthma at 1 year (regression coefficient = 2.22, 95% CI: 0.83, 3.62; $P = 0.002$) (Table 3). Little evidence of cross-lagged associations between asthma and infections was found, as well, after adjusting for potential confounders. Having more infections at age 1 year was negatively related to asthma at age 4 years

(regression coefficient = −4.26, 95% CI: −8.0, −0.49; P = 0.027), but the protective effect failed to reach significance after accounting for multiple statistical testing (Table 3).

Adjusting the path model for time-invariant confounding variables did not change the relationships among and between the latent constructs to any large extent (Table 3). According to results of these analyses (Web Table 4; Web Appendix 3), male sex and the presence of older siblings were both associated with higher scores for infections at age 1 year, whereas higher scores of asthma at age 1 year were associated with male sex, presence of older siblings, maternal asthma, and not having been breastfed. There was no evidence of associations between any of maternal smoking, family education level, ethnicity, socioeconomic deprivation level, or birth season with the latent constructs infections or asthma at age 1 year. Breastfeeding was associated with a significant reduction of the asthma score (regression coefficient = −0.17, 95% CI: −0.28, −0.06; P = 0.004) but not of the infections score (regression coefficient = −0.03, 95% CI: −0.09, 0.02; P = 0.210) at age 1 year (Web Table 4).

The sensitivity analysis based on all children who participated to the first survey and were 1 year old at the time (n = 3,983) led to a very similar picture of the SEM diagram, except that 1) most coefficients were larger in the complete-case SEM than in the full information maximum likelihood SEM approach, and 2) the path from infections at 4 years to asthma at 6 years became significant in the full information maximum likelihood SEM approach but not in the complete-case SEM (Web Table 5; Web Appendix 5). Yet, the coefficient of this path was small compared to the other significant path coefficients in both SEM models. The model fit of the full information maximum likelihood SEM was poorer than that of the model that included the children who answered the 3 questionnaires.

DISCUSSION

This study's results support hypothesis 1: The risks of respiratory infections and asthma were positively related to each other at each age investigated. In addition, infections in infancy led to more infections in subsequent years, and asthma symptoms in infancy similarly led to more asthma symptoms the following years, which support hypothesis 2. In the unadjusted model, there was little evidence of lagged effects from infections to asthma or from asthma to infections as children grew older. After adjusting for potential confounding factors assessed at baseline, we found a protective effect of early respiratory infections on asthma at early school age, which, however, did not reach significance after adjusting for multiple testing; thus, hypothesis 3 was rejected. Patients with wheeze in early childhood did not appear to be more susceptible to respiratory infections when they reached school age; thus, hypothesis 4 was rejected. Male sex, maternal asthma, and older siblings were associated with high scores for both asthma and infections at age 1 years, whereas breastfeeding was associated with significant reduction in asthma but not infection scores at age 1 year (Web Table 4).

To our knowledge, this study is 1 of the first in which the associations between respiratory infections and asthma symptoms from infancy to early school age were examined using a multivariate approach. Our findings corroborate results from previous, mostly cross-sectional studies in which respiratory infections and asthma were strongly associated (8, 10), and various viral and bacterial agents were shown to have elicited similar asthmatic symptoms in young children (5, 31). Our results also support that the trajectories of wheeze and infection phenotypes remain tightly associated with each other during childhood (18). The tracking of asthma symptoms and respiratory infections from infancy to school age became stronger with age, with stronger relationships found for ages 4–6 years than for ages 1–4 years. This finding may indicate that symptom patterns are more variable in preschool years. We know in particular that the predominant phenotype in preschool children, virus-associated wheeze, tends to remit, whereas schoolchildren more often have persistent wheeze associated with atopy (32–34).

We found no evidence of a direct association between upper and lower RTIs in early childhood and increased asthma at age 6–7 years. This observation does not support the commonly held hypothesis that RTIs in early life can initiate a chronic disease trajectory leading to recurrent wheeze later in childhood, and thus may be responsible, in part, for asthma development (35). It was reported from a prospective cohort study that nearly 50% of children who experienced severe respiratory syncytial virus (RSV) bronchiolitis at 12 months of age or younger received a subsequent asthma diagnosis at age 6 years (36), but the study did not include a control group of infants without severe RSV infections. Therefore, it is difficult to assess the causal relationships between severe RSV bronchiolitis and higher risk of asthma later in life. The numbers of children considered in most previous studies (35) have been rather low, at best consisting of a few hundred participants. In addition, the association between RTI and later asthma sometimes disappeared after adjusting for the frequency of respiratory episodes (4), suggesting nonspecific association between the viral trigger with later asthma development. Researchers concluded from results of a study in a large population-based sample of twins (n > 8,000) conducted in Denmark that severe RSV infections that lead to hospitalization do not cause asthma but may serve as indicator of genetic predisposition to asthma (16). They also noted that models in which asthma "causes" RSV hospitalization fit the data better than did models in which RSV hospitalization "causes" asthma (16). Therefore, higher susceptibility and inflammatory response to RTIs may be related to the fact that patients with asthma have an altered epithelial immune response to viral and bacterial agents and a higher likelihood of lower RTI development in relation to these (3, 37).

Some researchers have suggested that asthma may predispose children to RTIs (38) or colonization by microbes (3, 13–15). This early wheezing–later infections relationship may be related to diminished antiviral activity and a defective immune function against microbes in patients with asthma (3). However, high-risk children with virus-induced wheeze during early childhood have been included in previous studies, which increases the chance of confounding and limits the generalizability of conclusions based on those studies' findings. We did not find that early wheezing is a direct indicator of higher susceptibility to RTIs at school age.

A major strength of our study is its large, population-based sample, which included the full spectrum of disease severity. This afforded the use of a model in which many relationships between repeated assessments of infections and asthma over time were assessed simultaneously. In the first years of life, the distinction between RTIs and asthma symptoms or between upper and lower RTIs is not always clear cut and diagnoses differ according to a

clinician's experience and preferences. In contrast to most previous studies, we used a data-driven approach, by which infection at a specific age was modelled as a continuous latent (unobserved) variable composed of multiple observed indicators of RTIs, each contributing to a different degree, which was determined by fitting the model to the data. This, in turn, allowed us to test several hypotheses in a single multivariate model, which is an approach we have argued should receive greater attention in respiratory research (39). This also helped reduce confounding of, for example, the estimated effect of infections on later asthma without considering earlier asthma, which can easily arise when assessing these relationships separately. Our study was based on a large sample size, with a population that included the full spectrum of disease severity. Infections and asthma were defined as latent constructs on the basis of multiple variables. This enabled us to avoid subjective decisions commonly involved in defining these outcomes. Although participation rates were lower in the second and third surveys, the findings of our sensitivity analysis including all participating 1-year-old children regardless of later participation suggest that selection bias did not materially influence the direction of our findings or the strength of the associations. Therefore, we believe that the results obtained from the subgroup of children who participated in all surveys are robust and can be extrapolated to the entire study population.

The limitations of our study include the fact that all variables in our model were reported by parents and did not include objective measurements. Laboratory measurements were available for only a subset of the cohort participants at 1 time point, so they could not have been used for this longitudinal study. Also, there is no single laboratory parameter that tells us whether a child has had asthma or RTIs in the past year. We also had limited information on severity of infections, and our latent variable infection only partly reflects severity. RSV bronchiolitis, for instance, is a severe infection, but being a disease of infancy, it was only asked about regarding 1-year-old children; thus, we could not use this information to construct a variable reflecting vulnerability to infections with the same meaning in different ages. Thus, for the latent variable infection, we used data that were available in all age groups and that indicated frequent and long-lasting infections rather than single severe episodes. However, all 4 variables used (i.e., frequent colds, long duration of colds, coughing with every cold, repeated ear infections) (Web Table 3) were significantly associated with the likelihood of having a case of bronchiolitis or pneumonia in our study population (data not shown), so that our latent variable infection is, to some degree, also a proxy for severe infections. In addition, in our questionnaires, we mostly targeted RTIs and did not assess other infections such as those of the urinary and gastrointestinal tracts (40, 41). Although the latent constructs took into account different aspects of disease that, for asthma, included physician diagnosis, health care use, asthma medication, and frequency of symptoms, our approach was not entirely free of subjective decisions, because we had to select the variables used to define the constructs. Our latent variable infections, which captured the common variation in the observed indicators of RTIs, explained only a small proportion of the variation in each of the indicator variables, underlining the multidimensional nature of infections variables. We suggest that in future work, different aspects of infections (e.g., different germs, different locations of infections, differences in severity) and their interplay with asthma should be investigated to complement and expand on the findings obtained in this study.

In conclusion, susceptibility to RTIs and to asthma are strongly correlated and track throughout early childhood. According to our study findings, recurrent RTIs at preschool age do not increase the risk for asthma at school age except potentially through an indirect effect mediated by contemporaneous wheezing illness.

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REFERENCES

1. Stevens CA, Turner D, Kuehni CE, et al. The economic impact of preschool asthma and wheeze. *Eur Respir J*. 2003;21(6):1000–1006.
2. Kuehni CE, Davis A, Brooke AM, et al. Are all wheezing disorders in very young (preschool) children increasing in prevalence? *Lancet*. 2001;357(9271):1821–1825.
3. Juhn YJ. Risks for infection in patients with asthma (or other atopic conditions): is asthma more than a chronic airway disease? *J Allergy Clin Immunol*. 2014;134(2):247–257.
4. Bønnelykke K, Vissing NH, Sevelsted A, et al. Association between respiratory infections in early life and later asthma is independent of virus type. *J Allergy Clin Immunol*. 2015;136(1):8.e41–86.e4.
5. Rantala AK, Jaakkola MS, Mäkikyrö EM, et al. Early respiratory infections and the development of asthma in the first 27 years of life. *Am J Epidemiol*. 2015;182(7):615–623.
6. Tantisira KG, Weiss ST. Childhood infections and asthma: at the crossroads of the hygiene and Barker hypotheses. *Respir Res*. 2001;2(6):324–327.
7. Schaub B, Lauener R, von Mutius E. The many faces of the hygiene hypothesis. *J Allergy Clin Immunol*. 2006;117(5):969–977.
8. Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ*. 1995;310(6989):1225–1229.

9. Kusel MM, Kebadze T, Johnston SL, et al. Febrile respiratory illnesses in infancy and atopy are risk factors for persistent asthma and wheeze. *Eur Respir J*. 2012;39(4):876–882.
10. Stensballe LG, Simonsen JB, Thomsen SF, et al. The causal direction in the association between respiratory syncytial virus hospitalization and asthma. *J Allergy Clin Immunol*. 2009; 123(1):131.e1–137.e1.
11. 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(7):667–672.
12. Illi S, von Mutius E, Lau S, et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ*. 2001;322(7283):390–395.
13. Lapin B, Piorkowski J, Ownby D, et al. The relationship of early-life antibiotic use with asthma in at-risk children. *J Allergy Clin Immunol*. 2014;134(3):728–729.
14. Busse WW, Gern JE. Asthma and infections: is the risk more profound than previously thought? *J Allergy Clin Immunol*. 2014;134(2):260–261.
15. Jung JA, Kita H, Yawn BP, et al. Increased risk of serious pneumococcal disease in patients with atopic conditions other than asthma. *J Allergy Clin Immunol*. 2010;125(1):217–221.
16. Thomsen SF, van der Sluis S, Stensballe LG, et al. Exploring the association between severe respiratory syncytial virus infection and asthma: a registry-based twin study. *Am J Respir Crit Care Med*. 2009;179(12):1091–1097.
17. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med*. 2006;355(21):2226–2235.
18. Wickens K, Ingham T, Epton M, et al. The association of early life exposure to antibiotics and the development of asthma, eczema and atopy in a birth cohort: confounding or causality? *Clin Exp Allergy*. 2008;38(8):1318–1324.
19. Ege M, von Mutius E. Microbial airway colonization: a cause of asthma and pneumonia? *Am J Respir Crit Care Med*. 2013; 188(10):1188–1189.
20. Martinez FD. Development of wheezing disorders and asthma in preschool children. *Pediatrics*. 2002;109(2 suppl):362–367.
21. Elliott L, Henderson J, Northstone K, et al. Prospective study of breast-feeding in relation to wheeze, atopy, and bronchial hyperresponsiveness in the Avon Longitudinal Study of Parents and Children (ALSPAC). *J Allergy Clin Immunol*. 2008;122(1):49–54.
22. Matheson MC, Erbas B, Balasuriya A, et al. Breast-feeding and atopic disease: a cohort study from childhood to middle age. *J Allergy Clin Immunol*. 2007;120(5):1051–1057.
23. Kuehni CE, Brooke AM, Strippoli MP, et al. Cohort profile: the Leicester respiratory cohorts. *Int J Epidemiol*. 2007;36(5): 977–985.
24. Little TD, Preacher KJ, Selig JP, et al. New developments in latent variable panel analyses of longitudinal data. *Int J Behav Dev*. 2007;31(4):357–365.
25. Rosseel Y. Lavaan: an R package for structural equation modeling. *J Stat Softw*. 2012;48(2):1–36.
26. Benjamini Y, Hochberg Y. Controlling the false discovery rate – a practical and powerful approach to multiple testing. *J R Stat Soc Series B-Methodol*. 1995;57(1):289–300.
27. Hu Lt, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Struct Equ Modeling*. 1999;6(1):1–55.
28. Meade AW, Johnson EC, Braddy PW. Power and sensitivity of alternative fit indices in tests of measurement invariance. *J Appl Psychol*. 2008;93(3):568–592.
29. Savalei V, Rhemtulla M. On obtaining estimates of the fraction of missing information from full information maximum likelihood. *Struct Equ Modeling*. 2012;19(3):477–494.
30. Vandenberg RJ, Lance CE. A review and synthesis of the measurement invariance literature: suggestions, practices, and recommendations for organizational research. *Organ Res Meth*. 2000;3(1):4–70.
31. Strippoli MP, Spycher BD, Pescatore AM, et al. Exclusive viral wheeze and allergic wheeze: evidence for discrete phenotypes. *Eur Respir J*. 2011;38(2):472–474.
32. Garden FL, Simpson JM, Mellis CM, et al. Change in the manifestations of asthma and asthma-related traits in childhood: a latent transition analysis. *Eur Respir J*. 2016; 47(2):499–509.
33. Henderson J, Granell R, Heron J, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax*. 2008;63(11):974–980.
34. Spycher BD, Silverman M, Brooke AM, et al. Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. *Eur Respir J*. 2008;31(5):974–981.
35. Beigelman A, Bacharier LB. Early-life respiratory infections and asthma development: role in disease pathogenesis and potential targets for disease prevention. *Curr Opin Allergy Clin Immunol*. 2016;16(2):172–178.
36. Bacharier LB, Cohen R, Schweiger T, et al. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. *J Allergy Clin Immunol*. 2012;130(1):91.e3–100.e3.
37. Szefler SJ. Advances in pediatric asthma in 2014: moving toward a population health perspective. *J Allergy Clin Immunol*. 2015;135(3):644–652.
38. Patella V, Bocchino M, Steinhilber G. Asthma is associated with increased susceptibility to infection. *Minerva Med*. 2015; 106(4 suppl 3):1–7.
39. Ramette A, Kuehni CE. Bed-sharing and childhood asthma: from associations to causal modelling. *Eur Respir J*. 2015; 45(3):596–600.
40. Kusumi K, Becknell B, Schwaderer A. Trends in pediatric urolithiasis: patient characteristics, associated diagnoses, and financial burden. *Pediatr Nephrol*. 2015;30(5): 805–810.
41. Lin CH, Wang YC, Lin WC, et al. Neonatal urinary tract infection may increase the risk of childhood asthma. *Eur J Clin Microbiol Infect Dis*. 2015;34(9):1773–1778.