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ACUTE RESPIRATORY INFECTIONS IN EARLY CHILDHOOD AND RISK OF ASTHMA AT AGE 7 YEARS

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Young children experience frequent acute respiratory infections (ARIs). Of these, lower respiratory tract infections are associated with an increased risk of developing childhood asthma. The association between upper respiratory infections and subsequent childhood asthma is not yet equally well understood.

In this study, 923 children were followed with symptom diaries for ARIs from birth until two years of age. During ARIs, nasal swabs for respiratory viruses were acquired. Primary outcome was a diagnosed asthma in electronic medical records or a prescription for an inhalation corticosteroid at 6.5 to 7.5 years of age. The association between ARIs and the risk of asthma was evaluated using binary logistic regression analysis.

Electronic prescriptions and medical records were available for 910 (99%) children. A total of 8795 ARIs were recorded, with a mean number of 6.2 (95% confidence interval [CI] 6.0-6.4) per child per year. Asthma was documented at age 7 years in 75 (8%) children. Increased number of ARIs (≥9/year vs <5/year) during 0-2 years of age was associated with an increased risk of asthma at age 7 (adjusted odds ratio 7.20, 95% CI 2.49–20.88), as were more severe and prolonged ARIs. Children who developed asthma had more days with ARI symptoms per year before 2 years of age than other children (mean 65 vs 50, p=0.01).

We found an association between early childhood ARIs and later childhood asthma. This association may stem from common pathophysiologic mechanisms, or ARIs in early childhood may be a predisposing factor to the development of asthma.

Asiasanat: astma, lapset, hengitystieinfektiot

Acute respiratory infections in early childhood and risk of asthma at age 7 years

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Conflicts of Interest

The authors have no conflicts of interest relevant to this article to disclose.

Capsule Summary

In this population-based birth cohort study, increased number of acute respiratory infections in the first 24 months of life was associated with an increased risk for asthma at 7 years of age, suggesting shared pathophysiologic mechanisms.

Key words

asthma; children; infant; respiratory infections; respiratory syncytial virus; rhinovirus; STEPS Study; wheeze; wheezing

To the Editor:

Early lower respiratory tract infections are associated with an increased risk of developing childhood asthma.[1] Young children experience frequent acute respiratory infections (ARIs) of which the vast majority are upper respiratory infections. While the research has mainly focused on lower respiratory infections, limited data exist on the association of all early ARIs and development of asthma. Results from previous studies are inconsistent[1-6] and population-based data are sparse. We conducted a prospective, population-based birth cohort study to investigate the association between ARIs during the first 24 months of life and asthma at 7 years of age.

Details of the methods and data analysis may be found in the **Online repository**. Briefly, in the STEPS study, 923 Finnish children were followed intensively for upper and lower ARIs from birth to 24 months of age.[7] Data were collected with daily symptom diaries, study clinic visits, and from medical records. Nasal swab samples for respiratory viruses were taken at the onset of respiratory symptoms. Asthma diagnoses and medications were retrieved from medical records and electronic prescriptions at 7 years of age. Parents of participating children gave their written, informed consent.

The primary outcome was physician-diagnosed asthma at 7 years of age, based on a diagnosis of asthma in the medical records or an electronic prescription of inhaled corticosteroids for asthma when the child was 6.5-7.5 years of age. Children who completed the follow-up on ARIs for ≥12 months were included in the analyses. Risk of asthma at 7 years of age was analyzed by binary logistic regression analysis.

Thirteen children withdrew from the study. Medical records and electronic prescriptions were reviewed for 910 (99%) children. Characteristics of the children are shown in **Table E1**. Altogether 781 (86%) children completed the follow-up on ARIs for ≥12 months and the median completed follow-up time was 24.0 months (IQR, 20.2-24.0).

A total of 8795 ARIs were recorded with a mean frequency of 6.2 (95% CI, 6.0-6.4) per child per year. Altogether 273 doctor-diagnosed wheezing illnesses were documented in 135 (17%) children and 46 (17%) led to hospitalization. Diagnosis of asthma was documented in 75 (8%) of 910 children at 7 years of age. A prescription for inhaled corticosteroids for asthma was documented in 70 (93%) of these children.

Children with asthma at 7 years of age had higher annual numbers of days with ARI symptoms, lower respiratory tract infections, physician visits, and antibiotics for ARIs at 0-23 months of age as compared to children without asthma, and were more frequently hospitalized for ARI at 0-23 months of age (**Table I**). The median duration of ARIs at 0-23 months of age was longer in children with asthma at 7 years of age than in those without later asthma (8.0 [IQR 5.0-12.0] vs. 7.0 [IQR, 4.0-12.0] days, P=0.04) and ARIs in children with later asthma were more severe, but the virus etiology did not differ (**Table E2**).

Numbers of ARIs and days with ARI symptoms per year at 0-23 months of age were associated with an increased risk of asthma at 7 years of age (**Table II**). Compared to children with <5 ARIs/year at 0-23 months of age, children with ≥9 ARIs/year had a higher risk of asthma at 7 years of age (adjusted OR, 7.20; 95% CI, 2.49-20.88). Recurrent doctor-diagnosed wheezing illnesses, hospitalization for wheezing, and wheezing caused by either RV or RSV at 0-23 months of age were associated with an increased risk of asthma. Association of background variables with asthma is shown in **Table E3**.

In this population-based child cohort, we report that children with high frequency of early ARIs had an increased risk for asthma at 7 years of age. There are limited earlier data about the association of all ARIs –including also upper ARIs– at early age and later asthma in a population-based setting and earlier results are inconsistent.[1-6] In line with our results, some earlier prospective studies have found that an increased number of all ARIs associate with the development of asthma.[2, 3] Some previous studies have found no[1, 4, 5] or even negative[6] association between early upper ARIs and later asthma. However, many previous studies have assessed ARIs as a dichotomous variable, and frequently recurring infections, which in our study were associated with the development of asthma, have not been investigated.[1, 4, 5] In some studies data have been collected by questionnaires which makes it difficult for parents to recall all past ARIs.[1, 2, 5, 6] These data collection methods may have underestimated the effect of recurrent ARIs on asthma risk. In this study, use of symptom diaries allowed a more precise exposure-response-analysis, which showed a clear increase in the risk of asthma as both the number of ARI episodes and days with ARI symptoms increased.

The mean duration of ARIs was longer and measures of severity were higher in children with asthma at 7 years of age compared with those without asthma. These findings may reflect poorer immunological responses in children who later develop asthma. Although

part of this morbidity is probably caused by wheezing illnesses, it is notable that the vast majority of ARIs presented without wheezing. Similar virus etiology of ARIs in children with and without later asthma is in line with an earlier report[3] and suggests that there is no pathogen-specific immunologic weakness.

Our findings suggest common mechanisms behind susceptibility to ARIs and asthma. Airway hyperreactivity in children who later develop asthma may contribute to prolonging symptoms during ARIs. Altered cytokine responses to respiratory viruses have been detected in children with asthma[8] and could predispose to ARIs. Genetic factors or, as recent data suggest, airway microbiome[9] may play a role in susceptibility to ARIs and asthma. Frequent early ARIs may also play a causative role in the development of asthma by adversely affecting the developing lungs.[8]

There are limitations in this study. Outcome definition based partly on electronic prescriptions of inhaled corticosteroids enabled efficient data collection but it may have led to over- or underreporting of asthma. To avoid overreporting, we included only corticosteroid prescriptions with asthma as the indication of treatment. The follow-up time of early ARIs varied. However, we included in the analyses only children with follow-up of ARIs for ≥12 months.

In conclusion, we found that increased number of ARIs in the first 24 months of life was associated with an increased risk of asthma at 7 years of age. Children who later developed asthma had more prolonged and severe ARIs in the first 24 months of life than other children. These results suggest that susceptibility to ARIs and asthma may share common pathophysiologic mechanisms, or recurrent ARIs in early childhood may predispose child to the development of asthma.

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Table I. Numbers of acute respiratory infections at 0-23 months of age in children with and without asthma at 7 years of age[a]

ARIs at 0-23 mo of age	**Children with asthma at 7 y of age**, n = 63	**Children without asthma at 7 y of age**, n = 718	***P***
No. of ARIs per year, mean (95% CI)	6.8 (6.1-7.7)	6.1 (5.9-6.3)	0.07
No. of ARIs per year, n (%)			0.009
<5	14 (22.2)	261 (36.4)	
5-8	31 (49.2)	347 (48.3)	
≥9	18 (28.6)	110 (15.3)	
No. of days with ARI symptoms per year, mean (95% CI)	64.8 (53.4-78.7)	50.2 (47.5-53.0)	0.01
No. of days with wheezing per year, mean (95% CI)	5.2 (3.0-9.2)	1.6 (1.4-1.9)	<0.001
No. of RV infections per year, mean (95% CI)	2.0 (1.6-2.4)	2.0 (1.9-2.1)	0.94
RSV infection, n (%)	21/60 (35)	201/676 (30)	0.39
No. of physician visits for ARIs per year, mean (95% CI)	4.7 (3.8-5.8)	3.0 (2.8-3.2)	<0.001
Hospitalization for an ARI, n (%)	15 (23.8)	41 (5.7)	<0.001
No. of acute otitis media per year, mean (95% CI)	1.3 (1.0-1.7)	1.0 (0.9-1.0)	0.05
No. of LRTIs per year, mean (95% CI)	0.3 (0.2-0.3)	0.0 (0.0-0.1)	<0.001
No. of wheezing illnesses, n (%)			<0.001
0	29 (46)	617 (86)	
1	11 (18)	66 (9)	
≥2	23 (37)	35 (5)	
RV wheezing illness, n (%)	15/60 (25)	34/676 (5)	<0.001
RSV wheezing illness, n (%)	10/60 (17)	32/676 (5)	<0.001
Pneumonia, n (%)	10 (15.9)	26 (3.6)	<0.001
No. of antibiotic treatments for ARIs per year, mean (95% CI)	1.8 (1.4-2.4)	1.2 (1.1-1.3)	0.008

Abbreviations: ARI, acute respiratory infection; RSV, respiratory syncytial virus; RV, rhinovirus.

[a] In children with ≥12 month follow-up data on ARIs. Categorical data were compared by using the chi-square test or Fisher's exact test. Numbers of ARIs and associated outcomes were compared by using negative binomial regression with the natural logarithm of follow-up time as an offset variable.

Table II. Acute respiratory infections at 0-23 months of age and risk of asthma at 7 years of age[a]

ARIs at 0-23 mo of age	**All children** (n = 781), No.	**Children with asthma at 7 y of age** (n = 63), No. (%)	**Adjusted OR (95% CI)**
No. of ARI episodes per year			1.17 (1.04-1.31)
No. of ARI episodes per year			
<5	275	14 (5.1)	1.00
5-8	378	31 (8.2)	2.80 (1.06-7.42)
≥9	128	18 (14.1)	7.20 (2.49-20.88)
No. of days with ARI symptoms per year, per 10 days			1.12 (1.04-1.22)
No. of RV infections per year			
<2	455	38 (8.4)	1.00
≥2	281	22 (7.8)	0.78 (0.40-1.52)
RSV infection			
0	514	39 (7.6)	1.00
≥1	222	21 (9.5)	1.32 (0.68-2.58)

No. of LRTIs			2.03 (1.62-2.53)
No. of doctor-diagnosed wheezing illnesses			
None	646	29 (4.5)	1.00
1	77	11 (14.3)	2.55 (0.95-6.87)
≥2	58	23 (39.7)	16.91 (7.21-39.67)
Age at first wheezing episode, mo			
0-11	76	17 (22.4)	1.00
12-23	59	17 (28.8)	1.33 (0.51-3.46)
Etiology of wheezing illnesses[b]			
No wheezing	603	27 (4.5)	1.00
Wheezing, no detected RV or RSV	44	13 (29.5)	6.89 (2.45-19.32)
At least 1 RSV+ wheezing, no RV	32	5 (15.6)	4.90 (1.53-15.69)
At least 1 RV+ wheezing, no RSV	42	9 (21.4)	5.13 (1.76-14.94)
Both RSV+ and RV+ wheezing	15	6 (40.0)	13.93 (3.88-50.08)
Severity of wheezing illnesses			
No wheezing	646	29 (4.5)	1.00
Wheezing illness without hospitalization	104	21 (20.2)	5.29 (2.46-11.38)
Hospitalized for a wheezing illness	31	13 (41.9)	14.93 (4.99-44.63)
Hospitalization for an ARI			
No	725	48 (6.6%)	1.00
Yes	56	15 (26.8%)	5.46 (2.27-13.14)
No. of antibiotics for ARIs			1.20 (1.09-1.34)

Abbreviations: ARI, acute respiratory infection; CI, confidence interval; LRTI, lower respiratory tract infection; OR, odds ratio; RSV, respiratory syncytial virus; RV, rhinovirus.

[a] Risk of asthma was calculated by using multivariable binomial logistic regression analysis in children with ≥12 month follow-up data on ARIs. Sex, birth by cesarean section, child's atopy at 13 month of age, parental asthma, and parental smoking were used as covariates. Results of unadjusted analyses are shown in Table E4. Association between ARIs at 0-11 months of age and risk of asthma are shown in Table E5.

[b] Virus diagnostics was performed during 164 (60.1%) episodes of the total of 273 doctor-diagnosed wheezing illness. RV was detected in 77 (47.0%) episodes of doctor-diagnosed wheezing illness, RSV in 47 (28.7%), and other virus in 9 (5.5%) episodes.

ONLINE REPOSITORY

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Supplemental Methods

SUPPLEMENTAL METHODS

Study design

In the STEPS observational prospective birth cohort study, 1827 children born in 2008-2010 in the Hospital District of Southwest Finland are followed from pregnancy or birth to early adulthood.[1] An intensive follow-up of acute respiratory infections (ARIs) from birth to 24 months of age of the child was offered to these families, and 923 children were enrolled.[2] The children were followed for ARIs through daily symptom diaries and the families were encouraged to visit the study clinic if they felt that an evaluation by a physician was needed. At the onset of respiratory symptoms, nasal swab samples were taken at the study clinic by a study physician, or at home by the parents and sent to the study clinic as previously described.[2, 3] Background data was collected by structured questionnaires. Data on emergency room visits, hospitalizations, and outpatient visits at the hospitals for ARIs at 0-23 months of age and asthma diagnoses until 7.5 years of age were retrieved from medical records of the Hospital District of Southwest Finland. Asthma medications until 7.5 years of age were retrieved from electronic prescriptions. 3, The electronic prescription was introduced in Finland in 2010, and all public health care providers had taken it in use latest in 2013 and private health care providers by 2015. All pharmacies have been able to deliver electronic prescriptions since 2011. Electronic prescription became the main form of prescription in the beginning of 2017, and paper or phone prescriptions have been allowed only in exceptional situations.

The Ministry of Social Affairs and Health and the Ethics Committee of the Hospital District of Southwest Finland approved the STEPS Study. Parents of participating children gave their written, informed consent.

Respiratory virus detection

The nasal swab samples were stored at -80°C before analysis. Swabs were suspended in phosphate buffered saline and nucleic acids were extracted by NucliSense easyMag (BioMerieux, Boxtel, Netherlands) or MagnaPure 96 (Roche, Penzberg, Germany) automated extractor. Extracted RNA was reverse transcribed and the cDNA was amplified using real-time, quantitative PCR for RV, human enteroviruses and RSV as described earlier.[4, 5] All specimens collected during influenza seasons were analyzed by reverse transcription PCR for influenza A and B viruses.[6] For samples collected in January 2009 or later, laboratory

developed antigen detection tests were performed for influenza A and B viruses, parainfluenza type 1, 2, and 3 viruses, RSV, adenovirus, and human metapneumovirus (89% of samples).

Outcome definition

The primary outcome was physician-diagnosed asthma at 7 years of age, based on a diagnosis of asthma in the medical records, or a prescription of inhaled corticosteroids for asthma, when the child was 6.5-7.5 years of age. All asthma diagnoses and corticosteroid prescriptions were made by physicians. An acute respiratory infection (ARI) was defined as presence of rhinitis or cough, with or without fever or wheezing, documented in the symptom diary by the parents, or as an ARI diagnosed by a physician. The duration of 97.2% of ARIs was ≤ 30 days. To account for overlapping infections, the length of an ARI was limited to 30 days and longer ARIs (2.8%) were calculated as separate episodes with a maximum duration of 30 days. Wheezing illnesses (e.g., bronchiolitis, recurrent wheezing, or acute exacerbation of asthma) were diagnosed by a physician based on expiratory wheezing and other signs and symptoms. If there were repeated diagnoses of acute otitis media, wheezing illness, pneumonia, or laryngitis during continuous respiratory symptoms, diagnoses within 14 days were calculated as one episode. Recurrent wheezing was defined as ≥ 2 doctor-diagnosed wheezing illnesses at 0-23 months of age. Children who completed the follow-up on respiratory infections until at least 12 months of age were included in the analyses on the association between ARIs at 0-23 months of age and asthma at 7 years of age.

Statistical analysis

Categorical data were compared by using the chi-square test or Fisher's exact test. Continuous data were described by using means and 95% confidence intervals (CI) or medians and interquartile ranges (IQR) as appropriate. Skewed data were compared by using Mann Whitney *U* test. Generalized linear models were used for describing and analyzing numbers of ARIs and associated outcomes. Outcome counts were analyzed by using negative binomial distribution and log link with natural logarithm of follow-up time as an offset variable. Numbers of ARIs and associated outcomes were compared by using negative binomial regression. Risk of asthma at 7 years of age was first analyzed by unadjusted binary logistic regression analysis. Adjusted binary logistic regression analyses were performed with background variables based on clinical plausibility and with P values < 0.10 in the univariate analyses included in the final model (sex, birth by cesarean section,

child's atopy at 13 months of age, parental asthma, and parental smoking at child's age of 24 months). Unadjusted and adjusted odds ratios (OR) with 95% CIs were determined. *P* values < 0.05 were considered statistically significant.

The data were analyzed with the use of SPSS software, version 24.0 (IBM SPSS Statistics for Macintosh, Armonk, NY, USA: IBM Corp.), and SAS software for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

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Table E1. Characteristics of the study children

Characteristic	**All children**, n (%) (N = 910)
Female	430 (47.3)
Premature (gestational age <37 wk)	37 (4.1)
Birth by cesarean section	121 (13.3)
Birth weight, kg	
<2.5	25 (2.7)
2.5-4.5	866 (95.2)
>4.5	19 (2.1)
Older siblings	373 (41.0)
Maternal asthma	71/909 (7.8)
Paternal asthma	57/853 (6.7)
Parental asthma	120/909 (13.2)
Maternal atopic eczema, allergy, or allergic rhinitis	320/879 (36.4)
Paternal atopic eczema, allergy, or allergic rhinitis	201/853 (23.6)
Parental atopic eczema, allergy, or allergic rhinitis	411/884 (46.5)
Maternal smoking during pregnancy after 1st trimester	47/906 (5.2)
Parental smoking at child's age of 24 mo	102/628 (16.2)
Maternal educational level at least professional	569/882 (64.5)
Indoor pets at 3 or 24 mo of age	223/567 (39.3)
Breast-fed for at least 6 mo	427/708 (60.3)
At outside-home day-care, age	
13 mo	184/775 (23.7)
18 mo	279/676 (41.3)
24 mo	366/674 (54.3)
Atopic eczema at 13 mo of age	128/748 (17.1)
Asthma at 7 y of age	75 (8.2)
ARIs at 0-23 mo of age[a]	
Mean number of ARIs per child per y (95% CI)	6.2 (6.0-6.4)
Mean number of days with ARI symptoms per child per y (95% CI)	51.3 (48.6-54.1)
Mean number of LRTIs per child per y (95% CI)	0.1 (0.1-0.1)
Wheezing illness	135/781 (17.3)
Recurrent wheezing illness (≥2)	58/781 (7.4)
No. of wheezing illnesses	
0	646/781 (82.7)
1	77/781 (9.9)
2-3	36/781 (4.6)
≥4	22/781 (2.8)
RV wheezing illness	49/736 (6.7)
Recurrent RV wheeze (≥2)	15/736 (2.0)
RSV wheezing illness	42/736 (5.7)
Age at first wheezing episode, mo	
0-11	76/781 (9.7)
12-23	59/781 (7.6)

Abbreviations: ARI, acute respiratory infection; CI, confidence interval; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus; RV, rhinovirus.

[a] In children with ≥ 12 month follow-up data on ARIs (n=781).

Table E2. Characteristics of acute respiratory infections at 0-23 months of age in children with and without asthma at 7 years of age[a]

Variable	**ARIs in children with asthma at 7 y of age**, n = 800	**ARIs in children without asthma at 7 y of age**, n = 7995	***P***
Median duration of an ARI, days (IQR)	8.0 (5.0-12.0)	7.0 (4.0-12.0)	**0.04**
Symptoms during an ARI, No. (%)			
Fever	253/705 (35.9)	2268/6979 (32.5)	0.07
Cough	469/705 (66.5)	3935/6979 (56.4)	**<0.001**
Wheezing	158/705 (22.4)	580/6979 (8.3)	**<0.001**
Rhinorrhea	642/705 (91.1)	6448/6979 (92.4)	0.21
Child absent from day care during an ARI, No. (%)[b]	60/116 (51.7)	647/1783 (36.3)	**0.001**
Parent absent from work during child's ARI, No. (%)[b]	49/116 (42.2)	529/1783 (29.7)	**0.004**
Physician visit during an ARI, No. (%)	387/800 (48.4)	3178/6979 (39.7)	**<0.001**
Hospitalization during an ARI, No. (%)	26/800 (3.3)	52/6979 (0.7)	**<0.001**
Diagnoses during an ARI, No. (%)			
Acute otitis media	157/800 (19.6)	1249/6979 (15.6)	**0.003**
Wheezing illness	97/800 (12.1)	174/6979 (2.2)	**<0.001**
Laryngitis	19/800 (2.4)	125/6979 (1.6)	0.09
Pneumonia	10/800 (1.3)	26/6979 (0.3)	**0.001**
Antibiotic treatment during an ARI, No. (%)	200/800 (25.0)	1530/6979 (19.1)	**<0.001**
Virus detections during an ARI, No. (%)			
Virus positive	269/384 (70.1)	2945/4151 (70.9)	0.71
RV	219/384 (57.0)	2452/4151 (59.1)	0.47
RSV	23/384 (6.0)	228/4151 (5.5)	
Other virus	24/384 (6.3)	199/4151 (4.8)	
Co-detection	3/384 (0.8)	66/4151 (1.6)	

Abbreviations: ARI, acute respiratory infection; IQR, interquartile range; RSV, respiratory syncytial virus; RV, rhinovirus.

[a] In children with ≥12 month follow-up data on ARIs. Categorical data were compared by using the chi-square test or Fisher's exact test. Median durations of ARIs were compared by using Mann Whitney *U* test.

[b] Calculated among children at outside home day care at the time of ARI.

Table E3. Baseline risk factors for asthma at 7 years of age

Characteristic	**All children** (n = 910), No.	**Children with asthma at 7 y of age,** No. (%)	**Univariate,** OR (95% CI)[a]	**Multivariate,** OR (95% CI)[b]
Sex				
Female	430	27 (6.3)	1.0	1.0
Male	480	48 (10.0)	1.66 (1.02-2.71)	2.28 (1.17-4.41)
Birth by cesarean section				
No	789	60 (7.6)	1.0	1.00
Yes	121	15 (12.4)	1.72 (0.94-3.14)	1.10 (0.47-2.59)
Older siblings				
No	537	46 (8.6)	1.0	
Yes	373	29 (7.8)	0.90 (0.55-1.46)	
Child's atopy at 13 mo of age				
No	620	37 (6.0)	1.0	1.0
Yes	128	23 (18.0)	3.45 (1.97-6.05)	3.24 (1.66-6.33)
Indoor pets				
No	344	31(9.0)	1.0	
Yes	223	16 (7.2)	0.78 (0.42-1.46)	
Maternal asthma				
No	838	56 (6.7)	1.0	
Yes	71	19 (26.8)	5.10 (2.83-9.22)	
Paternal asthma				
No	796	60 (7.5)	1.0	
Yes	57	13 (22.8)	3.62 (1.85-7.10)	
Parental asthma				
No	789	47 (6.0)	1.0	1.0
Yes	120	28 (23.3)	4.81 (2.87-8.05)	6.49 (3.31-12.76)
Maternal smoking during pregnancy				
No	859	70 (8.1)	1.0	
Yes	47	5 (10.6)	1.34 (0.51-3.50)	

Parental smoking at child's age of 24 mo				
No	526	39 (7.4)	1.0	1.0
Yes	102	14 (13.7)	1.99 (1.04-3.81)	2.06 (0.99-4.29)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Risk of asthma was calculated by using binomial logistic regression analysis.

[b] Sex, birth by cesarean section, child's atopy at 13 mo of age, parental asthma, and parental smoking as covariates.

Table E4. Full results of analysis of association between acute respiratory infections at 0-23 months of age and risk of asthma at 7 years of age[a]

ARIs at 0-23 mo of age	**All children** (n = 781), No.	**Children with asthma at 7 y of age** (n = 63), No. (%)	**Univariate,** OR (95% CI)	**Multivariate,** OR (95% CI)
No. of ARI episodes per year			1.09 (0.99-1.19)	1.17 (1.04-1.31)
No. of ARI episodes per year				
<5	275	14 (5.1)	1.0	1.0
5-8	378	31 (8.2)	1.67 (0.87-3.19)	2.80 (1.06-7.42)
≥9	128	18 (14.1)	3.05 (1.47-6.35)	7.20 (2.49-20.88)
No. of days with ARI symptoms per year, per 10 days			1.11 (1.03-1.18)	1.12 (1.04-1.22)
No. of RV infections per year				
<2	455	38 (8.4)	1.00	1.00
≥2	281	22 (7.8)	0.93 (0.54-1.61)	0.78 (0.40-1.52)
RSV infection				
0	514	39 (7.6)	1.00	1.00
≥1	222	21 (9.5)	1.27 (0.73-2.22)	1.32 (0.68-2.58)

No. of LRTIs			1.90 (1.60-2.25)	2.03 (1.62-2.53)
Doctor-diagnosed wheezing illnesses				
None	646	29 (4.5)	1.00	1.00
1	77	11 (14.3)	3.55 (1.69-7.43)	2.55 (0.95-6.87)
≥2	58	23 (39.7)	13.98 (7.34-26.64)	16.91 (7.21-39.67)
Age at first wheezing episode, mo				
0-11	76	17 (22.4)	1.00	1.00
12-23	59	17 (28.8)	1.41 (0.64-3.07)	1.33 (0.51-3.46)
Etiology of wheezing illnesses[b]				
No wheezing	603	27 (4.5)	1.00	1.00
Wheezing, no detected RV or RSV	44	13 (29.5)	8.95 (4.21-19.01)	6.89 (2.45-19.32)
At least 1 RSV+ wheezing, no RV	32	5 (15.6)	3.95 (1.41-11.06)	4.90 (1.53-15.69)
At least 1 RV+ wheezing, no RSV	42	9 (21.4)	5.82 (2.53-13.37)	5.13 (1.76-14.94)
Both RSV+ and RV+ wheezing	15	6 (40.0)	14.22 (4.72-42.84)	13.93 (3.88-50.08)
Severity of wheezing illnesses				
No wheezing	646	29 (4.5)	1.00	1.00
Wheezing illness without hospitalization	104	21 (20.2)	5.38 (2.94-9.87)	5.29 (2.46-11.38)
Hospitalized for a wheezing illness	31	13 (41.9)	15.37 (6.87-34.36)	14.93 (4.99-44.63)
Hospitalization for an ARI				
No	725	48 (6.6%)	1.00	1.00
Yes	56	15 (26.8%)	5.16 (2.67-9.98)	5.46 (2.27-13.14)
No. of antibiotics for ARIs			1.14 (1.06-1.24)	1.20 (1.09-1.34)

Abbreviations: ARI, acute respiratory infection; CI, confidence interval; LRTI, lower respiratory tract infection; OR, odds ratio; RSV, respiratory syncytial virus; RV, rhinovirus.

[a] Risk of asthma was calculated by using unadjusted and multivariable binomial logistic regression analysis in children with ≥12 month follow-up data on ARIs. In multivariable analyses, sex, birth by cesarean section, child's atopy at 13 month of age, parental asthma, and parental smoking were used as covariates.

[b] Virus diagnostics was performed during 164 (60.1%) episodes of the total of 273 doctor-diagnosed wheezing illness. RV was detected in 77 (47.0%) episodes of doctor-diagnosed wheezing illness, RSV in 47 (28.7%), and other virus in 9 (5.5%) episodes.

Table E5. Acute respiratory infections at 0-11 months of age and risk of asthma at 7 years of age[a]

ARIs at 0-11 mo of age	**All children** (n = 781), No.	**Children with asthma at 7 y of age** (n = 63), No. (%)	**Univariate,** OR (95% CI)	**Multivariate,** OR (95% CI)
No. of ARI episodes			1.07 (0.99-1.16)	1.10 (1.00-1.22)
No. of days with ARI symptoms, per 10 days			1.08 (1.01-1.16)	1.10 (1.02-1.19)
No. of RV infections				
<2	336	24 (7.1)	1.00	1.00
≥2	400	36 (9.0)	1.29 (0.75-2.20)	1.29 (0.65-2.53)
RSV infection				
0	588	46 (7.8)	1.00	1.00
≥1	148	14 (9.5)	1.23 (0.66-2.31)	1.22 (0.58-2.58)
No. of LRTIs			2.12 (1.56-2.87)	2.12 (1.46-3.08)
No. of doctor-diagnosed wheezing illnesses				
None	705	46 (6.5)	1.00	1.00
1	51	10 (19.6)	3.49 (1.65-7.42)	3.33 (1.33-8.38)
≥2	25	7 (28.0)	5.57 (2.21-14.02)	4.70 (1.37-16.15)
Hospitalization for an ARI				
No	745	54 (7.2)	1.00	1.00
Yes	36	9 (25.0)	4.27 (1.91-9.53)	6.72 (2.36-19.16)
No. of antibiotics for ARIs			1.21 (1.03-1.41)	1.25 (1.04-1.50)

Abbreviations: ARI, acute respiratory infection; CI, confidence interval; LRTI, lower respiratory tract infection; OR, odds ratio; RSV, respiratory syncytial virus; RV, rhinovirus.

[a] Risk of asthma was calculated by using multivariable binomial logistic regression analysis in children with ≥12 month follow-up data on ARIs. Sex, birth by cesarean section, child's atopy at 13 month of age, parental asthma, and parental smoking were used as covariates.