



Original Contribution

Early Respiratory Infections and the Development of Asthma in the First 27 Years of Life

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Previous studies have provided contradictory evidence on the role of early childhood respiratory infections in the development of asthma and other allergic diseases during childhood. We investigated early-life respiratory infections as predictors of the development of asthma in a 20-year prospective cohort study (the Espoo Cohort Study, 1991–2011). Information on upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs) was collected with a parent-administered baseline questionnaire covering the preceding 12 months (part 1; $n = 2,228$), and information on LRTIs leading to hospitalization was obtained from the National Hospital Discharge Registry (part 2; $n = 2,568$). The incidence of asthma was assessed on the basis of 6-year and 20-year follow-up questionnaires. Adjusted hazard ratios were estimated using Cox proportional hazards models. Both URTIs (adjusted hazard ratio (HR) = 1.64, 95% confidence interval (CI): 1.22, 2.19) and LRTIs (adjusted HR = 2.11, 95% CI: 1.48, 3.00) in early childhood were strong predictors of asthma incidence up to young adulthood (ages 20–27 years). A declining age trend was present for both URTIs (P -trend < 0.01) and LRTIs (P -trend < 0.001). In part 2 of our analysis, a significant risk of asthma was found in relation to LRTIs requiring hospitalization (adjusted HR = 1.93, 95% CI: 1.10, 3.38). The results provide new evidence that respiratory tract infections in early life predict the development of asthma through childhood to young adulthood.

asthma; cohort studies; early childhood respiratory infections; hygiene hypothesis; proportional hazards model; respiratory tract

Abbreviations: CI, confidence interval; HR, hazard ratio; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

Currently, 235–300 million people worldwide are affected by asthma, and approximately 346,000 people per year die from it (1, 2). Respiratory tract infections constitute the most common group of acute illnesses occurring during early childhood, with a median of 5 episodes of upper respiratory tract infection (URTI) per year (3), and they remain common later in life as well. The incidence of severe acute lower respiratory tract infection (LRTI) among children in industrial countries has been estimated at 1 episode per 100 person-years (4). Previous studies have provided contradictory evidence on the role of early childhood infections in the development of asthma and other allergic diseases during childhood; some results have been consistent with a protective effect, mainly based on indirect evidence regarding family size or day-care attendance (the original

“hygiene hypothesis”) (5–9), while other researchers have reported an increased risk of asthma (10–19). In a systematic search of the literature, we did not identify any previous population-based longitudinal studies that investigated how childhood infections predict the development of asthma up to adulthood.

The Espoo Cohort Study is a 20-year population-based prospective cohort study implemented to assess the role of early-life exposures in the development of asthma during the first 20–27 years of life. This study offered a unique opportunity to assess the relationship between early respiratory tract infections and the risk of developing asthma prospectively through childhood and up to young adulthood. In addition, we were able to link the study’s data with registry-based information on early infections requiring hospitalization.

METHODS

Study population

The source population included all children in the city of Espoo, Finland, who were born between January 1, 1984, and March 31, 1990. Espoo, located near the western border of Helsinki, is the second largest municipality in Finland, with a population of 265,646 in 2014 (20). A parent-administered baseline questionnaire was distributed in March 1991 to a random sample of children drawn from the roster of Finland's Statistical Center (21). The baseline population included 2,568 children whose parents filled in the questionnaire. In March 1997, we conducted a 6-year follow-up survey of the cohort, with a follow-up rate of 77.3%. The characteristics of the baseline study population and the 6-year cohort have been described in detail elsewhere (21–23). In 2010–2011, we conducted a 20-year follow-up and received 1,623 responses (follow-up rate = 63.2% of the baseline study population). Part 1 of the present analyses was conducted among a cohort of 2,228 subjects (86.8% of the baseline population) who had no asthma at baseline (81 subjects were excluded due to asthma) and who participated in at least 1 follow-up survey (259 were excluded due to nonparticipation). Part 2 was conducted among the whole baseline study population ($n = 2,568$). Figure 1 presents data on participation in the different

phases of the study. The study protocol was approved by the Ethics Committee of Oulu University Hospital (Oulu, Finland).

Health outcome

The outcome of interest was the development of asthma during the follow-up period. In the baseline and 6-year follow-up surveys, this was determined with the question, “Has the child ever had physician-diagnosed asthma?” If the answer was yes, the age at which the asthma had started was requested. The following questions were asked in the 20-year follow-up: “Have you ever had physician-diagnosed asthma? If yes, at what age did it start?” We applied survival analysis in which we used the information on the age of asthma onset.

Respiratory tract infections as determinants of asthma

In part 1 of our analyses, the occurrence of respiratory infections during the 12 months preceding baseline data collection was assessed with the following question: “How often did the child experience the following infections during the past 12 months?” The list of infections included the common cold, tonsillitis, sinusitis, otitis media, acute bronchitis, and pneumonia. To judge the relative frequency of common cold and otitis media, we used the age-specific frequency distribution

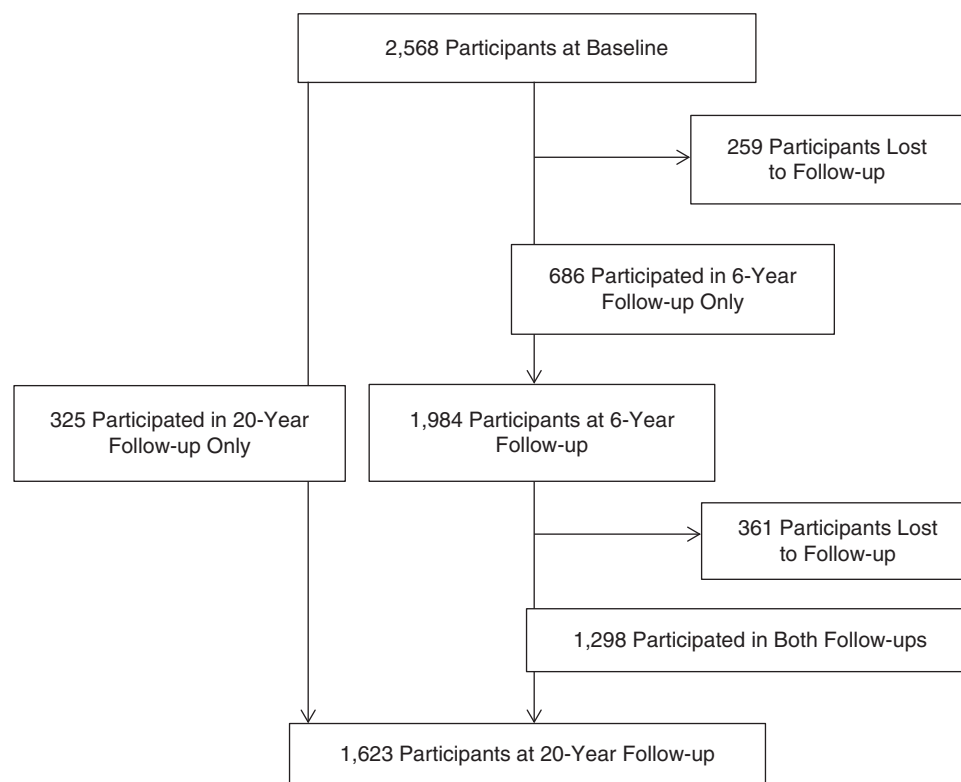


Figure 1. Selection of subjects for the Espoo Cohort Study, 1991–2011. Part 1 of the current analyses included 2,228 subjects after exclusion of those with no follow-up data ($n = 259$; 10.1%) or with previous or current asthma reported at baseline ($n = 81$; 3.2%). Part 2 of our analyses was conducted in the whole study population ($n = 2,568$; 100%). A total of 1,984 (77.3%) subjects participated in the 6-year follow-up, and 1,623 (63.2%) participated in the 20-year follow-up. Altogether, 686 (26.7%) subjects participated only in the 6-year follow-up, 1,298 (50.5%) subjects participated in both follow-ups, and 325 (12.7%) participated only in the 20-year follow-up.

Table 1. Numbers and Incidence Rates of Lower Respiratory Tract Infections Leading to Hospitalization From Birth to the Age of 6 Years (Part 2), The Espoo Cohort Study, 1991–2011^a

Type of Infection	ICD-8 Code (1969–1986)	ICD-9 Code(s) (1987–1995)	No. of Infections	Incidence Rate ^b
Viral pneumonia		4808X, 4809X	6	3.89
Pneumococcal pneumonia		4810A	1	0.65
Other bacterial pneumonia	482.98		1	0.65
Other specific microbial pneumonia		4830A, 4830X	2	1.30
Unspecified pneumonia	486.09	4859X	83	53.87
Unspecified bronchitis	490.99	4900A	5	3.25
Chronic bronchitis	491.09	4911A, 4912A, 4919X	14	9.09
Acute bronchitis	466.99	4660A, 4661A	22	14.28

Abbreviations: ICD-8, *International Classification of Diseases*, Eighth Revision; ICD-9, *International Classification of Diseases*, Ninth Revision.

^a Diagnoses were coded according to the ICD-8 between 1969 and 1986 and the Finnish version of the ICD-9 between 1987 and 1995.

^b Incidence rate per 10,000 person-years.

of each infection in the total study population in defining the exposure and reference categories (the cutoff point was at the 75th percentile). In children under 3 years of age, the exposure category included at least 4 infections and was coded 1, while fewer than 4 infections was used as the reference category (coded 0). For acute otitis media, the corresponding cutoff point was at least 2 infections (coded 1) versus fewer than 2 infections (coded 0). In the older children, the cutoff for common cold was at least 3 infections (coded 1) versus fewer than 3 infections (coded 0), and for acute otitis media it was at least 1 infection (coded 1) versus no infection (coded 0). For tonsillitis, sinusitis, acute bronchitis, and pneumonia, the cutoff point was at least 1 infection (coded 1) versus no infection (coded 0). Respiratory infections were classified as LRTIs (including acute bronchitis and pneumonia) or URTIs (including the common cold, tonsillitis, sinusitis, and otitis media).

Recurrent otitis media before the age of 3 years was defined as at least 3 episodes of acute otitis media during the past 12 months and/or a confirmatory answer to the question, “Has the child had recurrent otitis media?”

In part 2 of our analyses, information on respiratory infections leading to hospitalization from birth to age 6 years was retrieved from the National Hospital Discharge Register using computerized record linkage, with the Finnish personal identification number used as the key. The National Hospital Discharge Register includes the dates and causes of all hospitalizations (hospital admission requiring an overnight stay) of Finnish citizens that have occurred since January 1969. The diagnoses were coded according to the *International Classification of Diseases*, Eighth Revision, between 1969 and 1986 and the Finnish version of the *International Classification of Diseases*, Ninth Revision, between 1987 and 1995.

Respiratory infections requiring hospitalization included all of the main diagnoses of LRTIs, such as pneumonia and bronchitis (Table 1). The subject was recorded as having had an LRTI during a 1-year period if he/she had had at least 1 diagnosis during that year. This was recorded for every

year from birth to age 6 years, and then the sum of the periods with at least 1 infection was calculated for the LRTIs, so that the maximum number of time periods with exposure was 6.

Covariates

The following variables were included in the analyses as potential confounders: age (24), sex (24), family socioeconomic status at baseline (25), duration of breastfeeding (26), second-hand smoke exposure from birth to age 3 years (27), maternal smoking during pregnancy (27), history of pets at home from birth to age 3 years (28), and form of day care (day-care center or family day care vs. home care) (6). Information on the covariates was obtained from the baseline questionnaire and later follow-up surveys. Family socioeconomic status was determined by combining the highest level of parental education with the highest parental occupational level at baseline.

Statistical methods

We assessed the relationships between early respiratory tract infections and risk of developing asthma later in life by comparing the risk of asthma among subjects with LRTIs and/or more than the cutoff point of URTIs (exposure categories) with the risk among subjects with no LRTIs and fewer than the cutoff point of URTIs (reference category), taking into account the age of the child. The analysis was based on the time to onset of asthma, and the ratio of hazard rates—denoted the hazard ratio—was used as the measure of association (29). First, in part 1, we applied 4 overlapping age periods (baseline age to ages 6, 12, 18, and 27 years) to ascertain the influence of respiratory infections on the risk of asthma over time. The trend in the hazard ratio over time (from baseline age to age 27 years) was assessed using the Wald χ^2 test. Second, we evaluated whether the age at which respiratory infections were experienced had any association with the studied hazard ratios by comparing the adjusted hazard ratios for children who had experienced respiratory infections early (1–2 years of age)

Table 2. Personal and Environmental Characteristics of the Baseline Study Population Included in Part 2 of the Current Analyses, Persons Lost to Follow-up, and the Follow-up Population Included in Part 1 of the Current Analyses, The Espoo Cohort Study, 1991–2011

Baseline Characteristic	Study Population					
	Espoo Baseline Population (Used in Part 2)		Lost to Follow-up		Espoo Follow-up Population (Used in Part 1) ^a	
	No. of Persons	% ^b	No. of Persons	% ^b	No. of Persons	% ^b
Total	2,568	100.0	259	10.1	2,228	86.8
Age, years						
1	424	16.5	42	16.2	371	16.7
2	405	15.8	45	17.4	352	15.8
3	411	16.0	37	14.3	367	16.5
4	400	15.6	35	13.5	350	15.7
5	415	16.2	45	17.4	355	15.9
6–7	513	20.0	55	21.2	433	19.4
Sex						
Male	1,311	51.1	147	56.8	1,118	50.2
Female	1,257	49.0	112	43.2	1,110	49.8
Family socioeconomic status						
Low	667	26.1	90	34.9	555	25.0
Medium/high	1,889	73.9	168	65.1	1,662	75.0
Duration of breastfeeding, months						
<4	481	19.3	67	27.4	401	18.5
4 ≤ x < 8	670	26.9	72	29.4	581	26.8
≥8	1,343	53.9	106	43.3	1,189	54.8
Secondhand smoke exposure at ages ≤3 years						
Yes	299	11.6	25	9.7	270	12.1
No	2,269	88.4	234	90.4	1,958	87.9
Maternal smoking during pregnancy						
Yes	364	14.2	56	21.6	298	13.4
No	2,199	85.8	203	78.4	1,925	86.6
Pets in the home at ages ≤3 years						
Yes	457	17.8	12	4.6	431	19.3
No	2,111	82.2	247	95.4	1,797	80.7
Form of day care						
Home care	940	36.6	96	37.0	829	37.2
Day-care center	513	20.0	57	22.0	438	19.7
Family day care	252	9.8	22	8.5	216	9.7
Combination	863	33.6	84	32.4	745	33.4

^a Excludes persons with no follow-up data ($n = 259$) or with previous or current asthma reported at baseline ($n = 81$).^b Percentage of baseline population.

with those of children who had experienced respiratory infections later (3–7 years of age). We tested the statistical significance of the difference between the compared hazard ratios using Q statistics for heterogeneity between the corresponding adjusted hazard ratios (30, 31). In part 2, we applied the corresponding age periods used in part 1, with the exception that instead of using baseline age, we used the subject's date of birth.

The hazard ratio for development of asthma was estimated using Cox's proportional hazards model and adjusting for the covariates mentioned above. The proportionality of all variables was evaluated visually from the survival curves and quantitatively by applying proportionality test measures. The hazard ratios were calculated using the PROC PHREG procedure in SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

Table 3. Adjusted Hazard Ratios for Asthma in Different Age Groups Throughout the 20-Year Follow-up Period in Relation to the Occurrence of Respiratory Infections in the Past 12 Months at Baseline (Part 1), The Espoo Cohort Study, 1991–2011

Type of Infection	No. of Infections	Incidence Rate ^a	Age Period								P Value ^b
			Baseline Age ^c to Age 6 Years		Baseline Age to Age 12 Years		Baseline Age to Age 18 Years		Baseline Age to Age 27 Years		
			HR ^d	95% CI	HR ^d	95% CI	HR ^d	95% CI	HR ^d	95% CI	
LRTIs	541	0.24	3.20	1.54, 6.65	2.80	1.84, 4.28	2.24	1.55, 3.24	2.11	1.48, 3.00	<0.001
Acute bronchitis	465	0.21	2.57	1.12, 5.91	2.66	1.67, 4.24	2.07	1.39, 3.09	1.92	1.31, 2.83	<0.001
Pneumonia	76	0.03	5.96	2.15, 16.54	4.83	2.45, 9.53	3.24	1.69, 6.21	3.51	1.92, 6.41	<0.001
URTIs	8,251	3.70	2.49	1.29, 4.80	2.08	1.45, 2.98	1.75	1.29, 2.38	1.64	1.22, 2.19	<0.01
Common cold	5,826	2.61	2.54	1.24, 5.23	2.08	1.39, 3.12	1.71	1.22, 2.40	1.62	1.18, 2.24	<0.01
Sinusitis	126	0.06	— ^e	—	3.03	1.56, 5.89	2.40	1.32, 4.36	2.29	1.29, 4.07	0.01
Tonsillitis	221	0.10	1.45	0.42, 4.97	1.88	1.04, 3.39	1.56	0.92, 2.64	1.63	1.00, 2.66	0.05
Acute otitis media	2,078	0.93	1.46	0.78, 2.76	1.48	1.02, 2.14	1.28	0.93, 1.77	1.32	0.98, 1.79	0.07
Recurrent otitis media	— ^f	NA	1.94	0.99, 3.78	1.73	1.16, 2.57	1.46	1.03, 2.05	1.38	0.99, 1.91	0.06

Abbreviations: CI, confidence interval; HR, hazard ratio; LRTI, lower respiratory tract infection; NA, not applicable; URTI, upper respiratory tract infection.

^a Incidence rate per person-year.

^b Wald χ^2 test for linear trend in the relationship between experience of infections and asthma onset from baseline age to the end of follow-up (ages 20–27 years).

^c Age at baseline ranged from 1 to 7 years, except in the first age period, where it ranged from 1 to <6 years ($n = 1,803$ in the first age period).

^d Adjusted for age, sex, family socioeconomic status at baseline, duration of breastfeeding, secondhand smoke exposure from birth to age 3 years, maternal smoking during pregnancy, history of pets at home from birth to age 3 years, and form of day care.

^e There were no cases of asthma before the age of 6 years among children with sinusitis.

^f A total of 753 persons experienced recurrent otitis media over time.

RESULTS

Characteristics of the study population

There were no substantial differences between the baseline population (part 2) and the study population of 2,228 subjects (part 1) followed for up to 20 years (Table 2). In addition, the assumption of proportionality held for all variables.

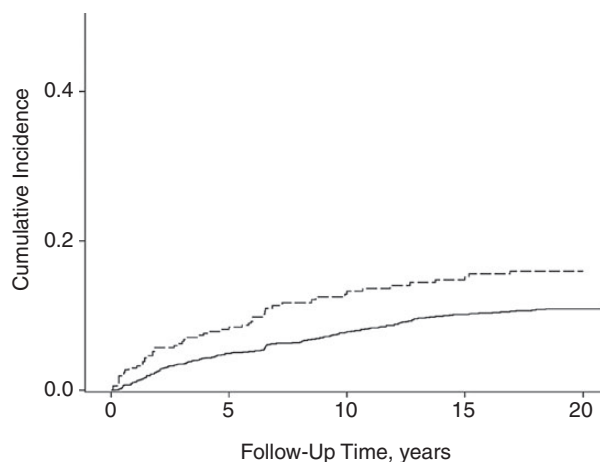


Figure 2. Development of asthma throughout the 20-year follow-up period among children who had had lower respiratory tract infections (LRTIs) during the past 12 months at baseline (broken line) and those with no past-year LRTIs at baseline (solid line), The Espoo Cohort Study, 1991–2011. Follow-up time started at the baseline age of each study subject.

Part 1: respiratory infections during the 12 months preceding baseline data collection and risk of asthma

The estimated incidence rates of respiratory infections occurring during the 12 months preceding baseline data collection are shown in Table 3. A total of 954 persons (42.8%) were categorized as exposed to URTIs and 368 (16.5%) to LRTIs (see Methods). The risk of asthma was consistently

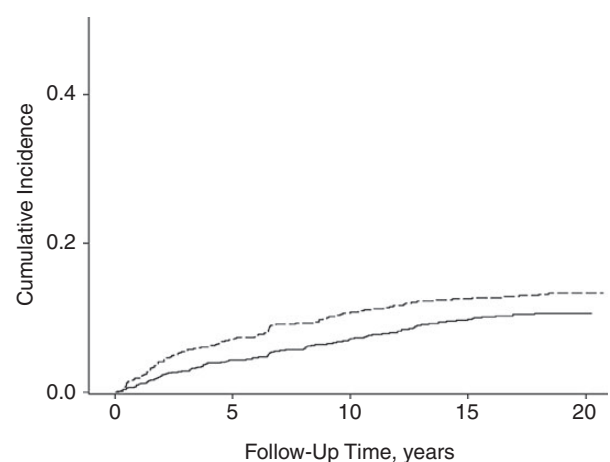


Figure 3. Development of asthma throughout the 20-year follow-up period among children with upper respiratory tract infections (URTIs) during the past 12 months at baseline (broken line) and those with no past-year URTIs at baseline (solid line), The Espoo Cohort Study, 1991–2011. Follow-up time started at the baseline age of each study subject.

Table 4. Adjusted Hazard Ratios for Asthma Throughout the 20-Year Follow-up Period in Relation to the Occurrence of Respiratory Infections in the Past 12 Months at Baseline, According to Age of Occurrence of Infection (Part 1), The Espoo Cohort Study, 1991–2011

Type of Infection	Age Group, years								P for Heterogeneity ^a
	1–2 (n = 723)				3–7 (n = 1,505)				
	HR	95% CI	Adjusted HR ^b	95% CI	HR	95% CI	Adjusted HR ^b	95% CI	
LRTI	2.19	1.36, 3.54	3.18	1.78, 5.69	1.28	0.84, 1.96	1.66	1.04, 2.65	0.09
URTI	1.75	1.11, 2.77	2.49	1.45, 4.29	1.20	0.87, 1.65	1.36	0.96, 1.92	0.06

Abbreviations: CI, confidence interval; HR, hazard ratio; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

^a Heterogeneity in the adjusted hazard ratios for asthma in relation to respiratory infections during the age ranges of 1–2 years and 3–7 years.

^b Adjusted for sex, family socioeconomic status at baseline, duration of breastfeeding, secondhand smoke exposure from birth to age 3 years, maternal smoking during pregnancy, history of pets at home from birth to age 3 years, and form of day care.

increased throughout the 20-year follow-up period in relation to both LRTIs and URTIs. The risk of developing asthma increased significantly in relation to LRTIs throughout the follow-up period, with a slightly decreasing trend in hazard ratios with increasing age periods (adjusted hazard ratio (HR) from baseline age to age 6 years ($HR_{\text{baseline-6}} = 3.20$ (95% confidence interval (CI): 1.54, 6.65); from baseline age to age 12 years, $HR_{\text{baseline-12}} = 2.80$ (95% CI: 1.84, 4.28); from baseline age to age 18 years, $HR_{\text{baseline-18}} = 2.24$ (95% CI: 1.55, 3.24); and from baseline age to age 27 years, $HR_{\text{baseline-27}} = 2.11$ (95% CI: 1.48, 3.00)) (Table 3; see Web Table 1, available at <http://aje.oxfordjournals.org/>, for crude hazard ratios). The relationship between the experience of early LRTIs and the risk of developing asthma decreased monotonically with chronological age, as indicated by a test for a linear trend in the age-specific hazard ratio (Wald χ^2 : $P < 0.001$). Similarly, the risk of developing asthma was related to early URTIs throughout all age periods (adjusted $HR_{\text{baseline-6}} = 2.49$ (95% CI: 1.29, 4.80), $HR_{\text{baseline-12}} = 2.08$ (95% CI: 1.45, 2.98), $HR_{\text{baseline-18}} = 1.75$ (95% CI: 1.29, 2.38), and $HR_{\text{baseline-27}} = 1.64$ (95% CI: 1.22, 2.19)) (Table 3 and Web Table 1), and the decreasing trend was statistically significant (Wald χ^2 : $P < 0.01$). Figure 2 illustrates that subjects with LRTIs during the past 12 months at baseline

developed asthma at an earlier age than those with no LRTIs, and this difference remained throughout the 20-year follow-up period. In Figure 3, a similar pattern is seen in relation to the occurrence of URTIs.

The risk of developing asthma was also increased in relation to specific infections, such as acute bronchitis, pneumonia, common cold, and sinusitis (Table 3). There were 753 persons (35.8%) who had experienced recurrent otitis media as defined in Methods. The risk of developing asthma was related to early recurrent otitis throughout the follow-up period, with a slightly decreasing trend in hazard ratios by age period (adjusted $HR_{\text{baseline-6}} = 1.94$ (95% CI: 0.99, 3.78), $HR_{\text{baseline-12}} = 1.73$ (95% CI: 1.16, 2.57), $HR_{\text{baseline-18}} = 1.46$ (95% CI: 1.03, 2.05), and $HR_{\text{baseline-27}} = 1.38$ (95% CI: 0.99, 1.91)) (Wald χ^2 : $P = 0.06$) (Table 3).

The risk of developing asthma was more strongly associated with LRTIs and URTIs experienced at 1–2 years of age than with infections experienced later in childhood (Table 4).

Part 2: LRTIs leading to hospitalization from birth to age 6 years and risk of asthma

Table 1 shows numbers of participants according to a diagnosis of LRTI leading to hospitalization by the age of 6 years and the corresponding incidence rate. A total of 85 persons (3.3%) were categorized as exposed to LRTIs that required hospitalization (see Methods). The risk of developing asthma was related to early hospitalized LRTI throughout the study period (from birth to age 6 years, adjusted HR = 2.05 (95% CI: 0.70, 6.05); from birth to age 12 years, HR = 1.72 (95% CI: 0.82, 3.63); from birth to age 18 years, HR = 2.09 (95% CI: 1.19, 3.67); and from birth to age 27 years, HR = 1.93 (95% CI: 1.10, 3.38)) (Table 5; see Web Table 2 for crude hazard ratios).

DISCUSSION

Main findings

The results of our population-based, 20-year prospective cohort study show that the occurrence of respiratory tract infections during early childhood predicts the development of asthma up to young adulthood. We were able to utilize both

Table 5. Adjusted Hazard Ratios for Asthma in Different Age Groups Throughout the Follow-up Period in Relation to the Occurrence of Lower Respiratory Tract Infection Leading to Hospitalization (Part 2), The Espoo Cohort Study, 1991–2011

Age Group, years	HR ^a	95% CI
≤6	2.05	0.70, 6.05
≤12	1.72	0.82, 3.63
≤18	2.09	1.19, 3.67
≤27	1.93	1.10, 3.38

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Adjusted for age, sex, family socioeconomic status at baseline, duration of breastfeeding, secondhand smoke exposure from birth to age 3 years, maternal smoking during pregnancy, history of pets at home from birth to age 3 years, and form of day care.

questionnaire data that included information on the occurrence of respiratory infections during the 12 months preceding baseline data collection (part 1) and registry-based data that included information on respiratory infections leading to hospitalization (part 2). In part 1, persons with at least 1 early LRTI had a 2.8-fold incidence of asthma by the age of 12 years and a 2.1-fold incidence by the age of 27 years in comparison with persons without LRTIs. The risk of developing asthma up to young adulthood was also increased in relation to having at least 1 LRTI that required hospitalization by the age of 6 years (part 2), suggesting a 2-fold risk of asthma by the ages of 18 and 27 years in comparison with persons without LRTIs.

Although our results are consistent with the causal hypothesis, there are alternative explanations, such as the presence of one or several common causes for both the studied infections and asthma (genetic, environmental, or their joint effect), which could partially explain the observed association between early infections and the risk of asthma. For example, children with a genetic propensity to asthma could be more prone to frequent and/or severe respiratory infections (32). Even in this case, respiratory infections predict the development of asthma and are likely to be harmful in relation to asthma development.

The risk of asthma had the strongest association with infections occurring before the age of 3 years. The immunological and physiological development of the respiratory system has been found to be fastest during early childhood (33), which could make the respiratory tract more susceptible to the effects of infections at those ages. Respiratory infections at that time may cause permanent changes, which could have an influence on asthma development all the way to adulthood.

Validity of results

The strengths of our study include the prospective follow-up of a large population-based cohort from early childhood to the ages of 20–27 years. The response rate at baseline was high (80.3%). The present study population—including those who participated in either the 6-year follow-up or the 20-year follow-up or both—included 86.8% of the baseline population. There were no substantial differences between the baseline population and the present study population (Table 2), suggesting that any major selection bias was unlikely.

The definition of asthma was based on parent- or self-reported physician-diagnosed asthma assessed at the 6-year and 20-year follow-ups. Using a questionnaire rather than medical records as a source of information on the diagnosis may have introduced some measurement error. We partially evaluated this type of error at baseline by calling all of the parents who had reported that their child had physician-diagnosed asthma. All of the parents verified the information provided, which indicates that they were well informed about the presence of asthma. We think it is reasonable to assume that young adults at the 20-year follow-up were also well aware of their diagnosed asthma. The National Social Insurance Institution partially reimburses patients whose asthma diagnosis fulfills the diagnostic criteria for the cost of asthma medication. The criteria are presented by the personal physician and evaluated independently by a specialist at the National Social Insurance

Institution before approval of the diagnosis. This reduces heterogeneity in diagnostic practice between physicians, but naturally does not eliminate changes in diagnostic practice over time. The Finnish health-care system has broad coverage for the entire population, and the majority of persons with asthma are likely to receive medical attention. Special reimbursement for the cost of asthma medication offered people a strong economic incentive for getting their asthma clinically diagnosed.

In addition, our analysis included information on the age of asthma onset, provided first by the parents and then by the subjects themselves in the 20-year follow-up survey. Pattaro et al. (34) showed that using the age of asthma onset increased the reliability of incidence estimates. Assessment of the age of onset for asthma is problematic both conceptually and empirically. Conceptually, a subject has asthma when the diagnostic criteria are fulfilled, but given the nature of the disease, the diagnosis is always made after some delay. The delay depends, among other things, on the health behavior and activity of the individual and his or her access to health care. After the actual diagnosis, the patient often recalls symptoms and signs that may have started before the physician-made diagnosis. Given these limitations, the results should be interpreted cautiously.

Information on the frequency and type of respiratory infections occurring during the 12-month period in early childhood was based on parents' reporting in the baseline questionnaire. This was a limitation of the study, but it is not likely to have introduced systematic error, because the parents did not know whether their child would develop asthma when reporting about infections at baseline. In addition, we were able to strengthen our findings by using information on hospitalized respiratory infections from the National Hospital Discharge Register database, which has been consistently evaluated to maintain highly complete and reliable data (35, 36). Both of our information sources on infections included strengths and limitations. Reporting in the questionnaire may have included some misclassification. For example, information on recurrent otitis media is susceptible to error, but the error is not likely to be systematic in relation to the development of asthma. Further, the association for recurrent otitis media was greater than for acute otitis media and thus consistent with the hypothesis that the greater the number of ear infections the higher the risk of developing asthma. The hospital diagnoses did not include any information on primary health-care visits, because that information started to be registered in Finland only after 2011. However, we were able to include all hospital diagnoses from birth to the age of 6 years and to estimate the associated risk of developing asthma, whereas in the questionnaire analyses we probably missed infections from the time period before data collection. Since both parts of the analyses were restricted to persons who did not have previous or current asthma at the beginning of follow-up, recall bias was not an issue when the occurrence of infections was assessed.

We adjusted our analyses for a number of potential confounders that represented the most common determinants of asthma.

Synthesis with previous knowledge

The original hygiene hypothesis—based on the results presented in 1989—suggested that early-life infections would

protect against atopic disease (8, 9). However, the results of these studies have been consistent with a protective effect, mainly based on indirect evidence using the number of younger siblings or day-care attendance as proxy measures for the occurrence of respiratory infections (6, 7). In addition, in a prospective birth cohort study, Illi et al. (5) reported that infectious diseases other than LRTIs in the first 3 years of life would reduce the risk of asthma development by the age of 7 years. However, they also presented figures suggesting that LRTIs were actually predictors of asthma risk.

There is also contradictory evidence that childhood respiratory infections are associated with development of asthma and atopy later in childhood, but none of those longitudinal studies covered adulthood (12–19). In 2 prospective birth cohort studies of children selected on the basis of a high risk for asthma (i.e., history of asthma or allergies in at least 1 parent), LRTIs in early life were a significant risk factor for asthma development at age 6–7 years (13, 16). Additionally, Kusel et al. found in a birth cohort that children with acute respiratory illness and atopy by the age of 2 years constituted the highest-risk group for asthma at the ages of 5 (12) and 10 (18) years. In the Oslo Birth Cohort Study—a prospective longitudinal study of 2,540 children—LRTIs (including bronchiolitis, bronchitis, and pneumonia) during the first year of life were determinants of asthma at the ages of 4 (15) and 10 (14) years. URTIs (such as otitis media) in early childhood have also been linked to asthma at the ages of 4–6 years (15, 37). In addition, 2 similar reports on data from the European Community Respiratory Health Survey (20- to 44-year-old subjects), with retrospective collection of information on early respiratory infections during the first 5 years of life, suggested that childhood respiratory infections could influence the risk of asthma in adulthood (38, 39). In our previous population-based incident case-control study among working-age adults (the Finnish Environment and Asthma Study), we found that the occurrence of respiratory infections during the previous 12 months was a strong determinant of adult-onset asthma (40). According to our systematic literature search, ours is the first prospective cohort study to have assessed the relationship between childhood respiratory infections and the development of asthma up to adulthood.

Conclusions

The present results provide new evidence that both URTIs and LRTIs in early life actually predict development of asthma through childhood to young adulthood. These results suggest that preventing respiratory infections in childhood could reduce the development of asthma in childhood as well as in adulthood. These findings also provide evidence to refute the original hygiene hypothesis, according to which early respiratory infections would protect against allergic diseases.

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Web Table 1. Adjusted Hazard Ratios for Asthma in Different Age Groups Throughout the 20-Year Follow-up Period in Relation to the Occurrence of Respiratory Infections in the Past 12 Months at Baseline (Part 1), Espoo Cohort Study, 1991–2011

Respiratory Infection	No. of Infections	IR ^b	Age Period																P Value ^d
			Baseline Age ^a to Age 6 Years				Baseline Age to Age 12 Years				Baseline Age to Age 18 Years				Baseline Age to Age 27 Years				
			HR	95% CI	HR ^c	95% CI	HR	95% CI	HR ^c	95% CI	HR	95% CI	HR ^c	95% CI	HR	95% CI	HR ^c	95% CI	
LRTIs			2.10	1.16, 3.82	3.20	1.54, 6.65	1.84	1.29, 2.63	2.80	1.84, 4.28	1.67	1.21, 2.30	2.24	1.55, 3.24	1.59	1.17, 2.17	2.11	1.48, 3.00	< 0.001
Acute bronchitis	465	0.21	1.59	0.83, 3.05	2.57	1.12, 5.91	1.71	1.18, 2.49	2.66	1.67, 4.24	1.60	1.14, 2.23	2.07	1.39, 3.09	1.50	1.08, 2.07	1.92	1.31, 2.83	< 0.001
Pneumonia	76	0.03	4.07	1.73, 9.56	5.96	2.15, 16.54	3.06	1.66, 5.65	4.83	2.45, 9.53	2.45	1.33, 4.50	3.24	1.69, 6.21	2.71	1.55, 4.74	3.51	1.92, 6.41	< 0.001
URTIs			1.75	0.99, 3.07	2.49	1.29, 4.80	1.64	1.20, 2.26)	2.08	1.45, 2.98	1.47	1.11, 1.94	1.75	1.29, 2.38	1.35	1.04, 1.76	1.64	1.22, 2.19	< 0.01
Common cold	5,826	2.61	1.89	1.08, 3.30	2.54	1.24, 5.23	1.50	1.09, 2.06	2.08	1.39, 3.12	1.45	1.10, 1.91	1.71	1.22, 2.40	1.36	1.04, 1.77	1.62	1.18, 2.24	< 0.01
Sinusitis	126	0.06	— ^e		— ^e		2.40	1.33, 4.33	3.03	1.56, 5.89	2.04	1.18, 3.51	2.40	1.32, 4.36	1.90	1.13, 3.21	2.29	1.29, 4.07	0.01
Tonsillitis	221	0.10	1.11	0.35, 3.58	1.45	0.42, 4.97	1.34	0.77, 2.32	1.88	1.04, 3.39	1.20	0.73, 1.98	1.56	0.92, 2.64	1.26	0.80, 2.00	1.63	1.00, 2.66	0.05
Acute otitis media	2,078	0.93	1.28	0.73, 2.26	1.46	0.78, 2.76	1.16	0.84, 1.60	1.48	1.02, 2.14	1.09	0.82, 1.45	1.28	0.93, 1.77	1.13	0.86, 1.48	1.32	0.98, 1.79	0.07
Recurrent otitis media			1.66	0.94, 2.93	1.94	0.99, 3.78	1.45	1.04, 2.01	1.73	1.16, 2.57	1.30	0.98, 1.74	1.46	1.03, 2.05	1.25	0.95, 1.66	1.38	0.99, 1.91	0.06

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

^a Age at baseline ranged from 1 to 7 years, except in the first age period, when it was 1–<6 years (*n* = 1,803 in the first age period).

^b IR per person-year.

^c Adjusted for age, sex, family socioeconomic status at baseline, duration of breastfeeding, secondhand smoke exposure from birth to the age of 3 years, maternal smoking in pregnancy, history of pets at home from birth to the age of 3 years, and form of day care.

^d Wald χ^2 test for linear trend in the relationship between experience of infections and time to asthma onset from age at baseline to the end of follow-up (ages 20–27 years).

^eThere were no cases of asthma before the age of 6 years among children with sinusitis.

Web Table 2. Hazard Ratios for Asthma in Different Age Groups Throughout the Follow-up Period in Relation to the Occurrence of Lower Respiratory Tract Infection Leading to Hospitalization (Part 2), Espoo Cohort Study, 1991–2011

Type of Infection	Age Group, years															
	≤6				≤12				≤18				≤27			
	HR	95% CI	HR ^a	95% CI	HR	95% CI	HR ^a	95% CI	HR	95% CI	HR ^a	95% CI	HR	95% CI	HR ^a	95% CI
LRTI	1.67	0.62, 4.52	2.05	0.70, 6.05	1.35	0.69, 2.63	1.72	0.82, 3.63	1.64	0.99, 2.69	2.09	1.19, 3.67	1.66	1.03, 2.66	1.93	1.10, 3.38

Abbreviations: CI, confidence interval; HR, hazard ratio; LRTI, lower respiratory tract infection.

^aAdjusted for age, sex, family socioeconomic status at baseline, duration of breastfeeding, secondhand smoke exposure from birth to the age of 3 years, maternal smoking during pregnancy, history of pets at home from birth to the age of 3 years, and form of day care.