Early Respiratory Infections, Asthma, and Allergy: 10-Year Follow-up of the Oslo Birth Cohort

Per Nafstad, MD, PhD*‡; Bert Brunekreef, PhD‡§; Anders Skrondal, PhD‡; and Wenche Nystad, PhD‡

ABSTRACT. *Objective.* **It has been hypothesized that early infections protect against the development of atopic disease, but there have been few long-term follow-up studies. We estimated the associations between early respiratory infections and doctor-diagnosed asthma, allergic rhinitis, and skin-prick sensitization in children at 10 years of age in the Oslo Birth Cohort, established in 1992–1993. We also considered birth order and attendance at a child care center as proxy measures of increased exposure to infections early in life.**

Methods. **A total of 2540 children were followed from birth to the age of 10 years. Experiences of respiratory infections were recorded in follow-up surveys at 6 and 12 months. At age 10, questions were asked about current symptoms of asthma and allergic rhinitis and about having ever received a doctor diagnosis for these diseases. A subsample (n = 1740) of the cohort was tested for skin-prick test reactivity.**

Results. **Current asthma was related to lower respiratory tract infection (adjusted odds ratio [OR]: 2.1; 95% confidence interval: 1.3–3.0) and croup (adjusted OR: 2.3; 95% confidence interval: 1.3–4.2) in the first year. ORs for allergic rhinitis and skin-prick sensitization were smaller but mainly positive. Birth order and child care attendance at age 1 year were not significantly associated with any of the studied outcomes.**

Conclusions. **Early respiratory infections did not protect against the development of asthma, allergic rhinitis, or sensitization to common allergens during the first 10 years of life but increased the risk for asthma symptoms at age 10 in this population.** *Pediatrics* **2005;116:e255–e262. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2785;** ***children, epidemiology, asthma, allergy, cohort study.***

ABBREVIATIONS. SPT, skin prick test; ETS, environmental tobacco smoke; OR, odds ratio; CI, confidence interval.

Having older siblings has been found to be inversely associated with asthma and other atopy-related disorders.[1–6] Some studies have also shown that these disorders are inversely associated with child care attendance outside the home,[6–10] whereas other studies have not been able to confirm these findings.[11–13] A common interpretation of these results has been that older siblings and child care attendance are indirect measures of early-life infections and that early-life infections have a preventive effect on the development of atopic disorders. A number of studies have also assessed the relation between atopic disorders and direct measures of early-life infections,[11,13–23] but fewer have been able to do this prospectively.[13–15,18–22] Studies that have used direct measures of infections have shown less consistent results than the studies that have used indirect measures, and the inverse relation has often been restricted to subgroups of diseased individuals, mainly those with atopic predisposition. Furthermore, childhood asthma has been found to be more common in children who experienced at least 1 specific type of early respiratory infection, namely respiratory syncytial virus infection.[24–27] The inverse relation between early-life infections and the development of atopic disorders is supported by a plausible biological mechanism, according to which early-life infections stimulate Th1 lymphocytes that may inhibit the proliferation of allergen-specific Th2 lymphocytes and limit the development of allergic diseases.[28,29] Although childhood asthma is considered predominantly an allergic disease, a substantial proportion of children with asthma are not sensitized to common allergens.[17,30] This indicates that there are other mechanisms that could be involved in the development of asthma.[31,32] We used the Oslo Birth Cohort Study to address prospectively the role of several types of early respiratory infections in the development of asthma and allergic rhinitis during the first 10 years of life. We considered both actual infections and factors that are considered as indicators of infectious exposure. We also assessed these factors' association with skin-prick test (SPT) positivity and whether the association between early-life infections and asthma/allergic rhinitis was dependent on children's SPT positivity.

METHODS

Study Population

The source population included children who were born in the 2 main birth clinics in Oslo during a 15-month period in 1992–1993, the Oslo Birth Cohort.[33] At birth, 3754 children were included in the study, and information on the child's health and environmental exposures was collected from parents by questionnaires at birth and when the child was 0.5, 1, 1.5, 2, 4, and 10 years of age. The eligibility criteria and data-collection procedures during the first 2 years of life and at the age of 4 years have been described in detail elsewhere.[13,33,34] During 2001–2002, we con-

From the *Department of General Practice and Community Medicine, Medical Faculty, University of Oslo, Oslo, Norway; ‡Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway; and §Institute for Risk Assessment Sciences, University of Utrecht, Utrecht, Netherlands.
Accepted for publication Feb 28, 2005.
doi:10.1542/peds.2004-2785
No conflict of interest declared.
Address correspondence to Per Nafstad, MD, PhD, Department of General Practice and Community Medicine, Medical Faculty, University of Oslo, Pb 1130 Blindern, 0316 Oslo, Norway. E-mail: per.nafstad@fhi.uio.no

ducted a 10-year follow-up. A similar questionnaire to that used in the 4-year follow-up was mailed to the parents of the children for whom we succeeded to get a correct mailing address (n = 3529). A completed questionnaire was received from 2549 children (72% of those successfully reached by mail). The participants who were living in Oslo or in the vicinity of Oslo (Akershus County) in 2001 (n = 2846) were also invited to participate in a clinical examination. A mobile unit of trained research nurses visited all schools in the area and conducted the examination, which included SPTs, spirometry, and collection of buccal cells for DNA extraction. Of all invited children, 1815 (64%) were examined, and 1740 received a SPT. For safety reasons, children who reported any kind of severe allergic reactions (n = 43) did not receive SPT. Furthermore, 32 children refused to be tested because of anxiety. In the present study, we focused on children with complete information on asthma and other atopic diseases at the age of 10 years. This left 2540 children for the analyses. We also performed analyses of the subsample of children who had received SPT.

Health Outcomes

The primary outcomes were ever and current asthma and allergic rhinitis (allergy from the nose or eyes including hay fever). These outcomes were defined on the basis of answers to the 10-year follow-up questionnaire, and the questions were asked in the same manner as in the 4-year follow-up.[13] The outcomes had to be diagnosed by a physician, and current disease meant that the child had experienced symptoms of the disease during the previous 12 months.

SPT Positivity

The SPTs were performed according the ISAAC phase II protocols.[35] The following standardized allergens were included: cat, dog, birch, grass (timothy), house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), molds (*Cladosporium herbarum* and *Alternaria tenuis*), codfish, and horse (Soluprick SQ; ALK Laboratories, Hørsholm, Denmark). All of the allergens were Soluprick 10 HEP, except for *Cladosporium herbarum* and *Alternaria*, which were presented in a 1:20 dilution. A positive SPT corresponded to a wheal with a mean diameter exceeding the negative control by at least 3 mm.[35] Taking into account skin-test reactivity to histamine,[36] we also and alternatively defined a positive SPT as an average diameter corresponding to at least half of that caused by histamine. Children with at least 1 positive SPT were considered skin-prick positive.

Exposures

Early Respiratory Infections

The determinants of interest were respiratory infections, such as lower respiratory tract infections, otitis media, and croup, during the first year of life and the common cold during the first 6 months of life. Information on these early respiratory infections was registered in the 6- and 12-month follow-up questionnaires. The same determinants have been used for similar analyses of the data obtained at the 4-year follow-up of the cohort.[13] Because almost all children had experienced an episode of the common cold during their first 12 months of life, information on the common cold was restricted to their first 6 months of life.

Indirect Measures of Exposure to Infectious Agents

Indirect measures of exposure to infectious agents were attendance to a child care center at the age of 1 year (measured as the number of hours per week in a child care center at the age of 1 year and categorized as ≥10 hours per week versus <10 hours per week) and having older siblings (measured as birth order when the child was included in the cohort). We did not investigate size of child care facility because, generally, child care centers in Norway were large (>30 children) and small child care centers (eg, home day care) were rarely used.

Covariates

Information on potential confounders was extracted from hospital records and the 6-month and the 1-year questionnaires. The covariates in the present analyses included gender, parental atopy, maternal age at delivery, maternal education, family income, single parenthood, length of breastfeeding, and environmental tobacco smoke (ETS) exposure at birth.[32] Parental atopy was defined as a history of maternal or paternal asthma or hay fever. Length of breastfeeding was categorized into 0 to 6 and >6 months. Exposure to ETS was defined as living together with ≥1 smokers. The categorization of these covariates is presented in Table 1.

Statistical Methods

We used an analytical approach similar to that of the 4-year follow-up of the Oslo Birth Cohort.[13] First, we estimated associations between early respiratory infections and infection indicators and ever and current asthma and allergic rhinitis at the age of 10 years. We also estimated the associations between these exposures

TABLE 1. Characteristics of the Oslo Birth Cohort at Birth and at the 2-, 4-, and 10-Year Follow-up

	At Birth, % (n = 3754)	2-Year Follow-up, % (n = 2967)	4-Year Follow-up, % (n = 2531)	10-Year Follow-up, % (n = 2540)	SPT 10-Year Follow-up, % (n = 1740)
Parental atopy	33.7	34.1	34.6	34.4	36.1
Birth order					
First	51.4	52.3	52.6	51.9	50.6
Second	36.3	36.1	35.7	36.4	37.0
Third or later	12.2	11.6	11.7	11.7	12.5
Breastfeeding after 6 mo		70.1	71.2	70.7	71.9
Maternal age at delivery, y					
<25	12.2	10.5	9.5	10.3	9.0
25–29	36.2	35.7	35.5	35.4	32.6
≥30	51.6	53.8	55.0	54.3	58.4
Maternal education, y					
<12	7.3	5.6	4.7	4.9	4.6
12–15	39.5	37.7	36.4	35.9	34.2
>15	53.2	56.7	58.9	59.2	61.2
Family income per year (NOK)					
<200 000	17.0	14.0	13.2	13.9	13.1
200 000–500 000	64.7	66.9	66.8	65.9	64.4
>500 000	18.3	19.1	20.0	20.2	22.6
Single parenthood (at 6 mo of age)		7.8	7.1	7.3	6.6
Child care outside the home (at 1 y)		15.0	15.0	15.2	16.2
ETS exposure in early life	43.6	41.0	39.8	40.3	40.3
One or more lower respiratory infections		16.8	16.2	17.0	17.3

Maximum number of subjects with missing data in the baseline questionnaire: 78 (family income per year); in the 2-year questionnaire: 101 (breastfeeding); in the 4-year questionnaire: 79 (breastfeeding); in the 10-year questionnaire: 107 (breastfeeding); and among children with an SPT at 10 years: 65 (breastfeeding).

and having ≥1 positive SPT reactions to common Norwegian allergens. In addition, we assessed whether SPT reactivity modified the effects of early-life infections by performing analyses for skin prick–positive and –negative children. The odds ratio (OR) was used as a measure of effect. We calculated adjusted ORs from logistic regression analysis. We always included gender, parental atopy, birth order, child care center attendance, length of breastfeeding, and ETS exposure in the models. Other variables were included only when they significantly modified the ORs (>0.1 or >10% change in OR). We dealt with missing information for covariates by coding a missing category for the corresponding variable in the model. Results of logistic regression analyses with and without the missing category and crude analyses gave consistent results. Only results of the first approach are presented.

RESULTS

Table 1 presents the distributions of some characteristics and early exposures of the children at birth and 2, 4, and 10 years of life and among children who received SPT at the age of 10 years. Compared with the baseline registrations, parental income and maternal education were somewhat higher at all of the follow-ups. The distributions of the other variables were very similar for the variables at the different follow-ups. This was also the case for gender, birth weight, and keeping pets at home when the child was 6 months of age (figures not given). Information on asthma and allergic rhinitis was obtained for 2540 of the 2549 children with questionnaire information at the age of 10 years. Of these children, 292 (11.5%) reported ever having received a diagnosis asthma by a doctor, and 142 (5.6%) had experienced symptoms of asthma during the past 12 months. Corresponding figures for allergic rhinitis were 357 (14.1%) and 302 (11.9%). Among the 1740 children with a valid SPT result, 418 (24%) had a positive SPT, 182 (10.5%) had doctor-diagnosed asthma, and 84 (4.9%) had experienced asthma symptoms the past 12 months. In this group, 247 (14.3%) children had a doctor-diagnosed allergic rhinitis, and 207 (12.0.9%) had experienced symptoms the past 12 months (missing information: 12). A positive SPT was found among 51 (61%) of the children with current asthma, whereas 154 (74%) of the children with current allergic rhinitis had a positive SPT.

Tables 2 and 3 present the risk for a lifetime doctor diagnosis of asthma and allergic rhinitis and the risk for current asthma and allergic rhinitis at the age of 10 years in relation to early respiratory infections, birth order, and attendance to child care centers. All measures of early-life infections were positively associated with doctor-diagnosed asthma ever in life. Current asthma was significantly associated with early lower respiratory tract infections and croup; associations with otitis media and common cold were also positive without reaching statistical significance. Similar associations were found when hospitalization for lower respiratory tract infection was used as exposure (figures not given). For allergic rhinitis, the associations in general were weaker but also mainly positive. The association between early-life otitis media and allergic rhinitis was statistically significant.

Neither birth order nor early-life child care center attendance was associated with asthma or allergic rhinitis. However, there were only a few children (297) who had >1 older sibling, and among these, the ORs for both asthma and rhinitis were less than unity (0.7 and 0.8, respectively), without reaching statistical significance. Stratified analyses of the associations among asthma, allergic rhinitis, and early-life respiratory infections in children with and without parental atopy showed that the associations were not different between these 2 groups (data not shown).

Associations between SPT positivity and early-life

TABLE 2. Risk for Doctor-Diagnosed Asthma During the First 10 Years of Life and With Symptoms at the Age of 10 Years in Relation to Early-Life Respiratory Infections, Birth Order, and Child Care Attendance at the Age of 1 Year

		Doctor-Diagnosed Asthma					
	N	Ever Asthma			Asthma With Current Symptoms		
		Lifetime Prevalence, %	aOR	95% CI	Prevalence, %	aOR	95% CI
Lower respiratory tract infection (first 12 mo)							
No	2031	8.6	1		4.7	1	
Yes	428	25.9	3.3	2.5–4.4	10.0	2.0	1.3–3.0
Otitis media (first 12 mo)							
No	1695	9.8	1		5.1	1	
Yes	585	15.9	1.3	1.0–1.8	7.0	1.2	0.8–1.8
Croup (first 12 mo)							
No	2149	10.7	1		5.2	1	
Yes	131	21.4	2.0	1.3–3.2	12.2	2.3	1.3–4.2
Common cold (first 6 mo)							
No	732	8.7	1		5.1	1	
Yes	1662	12.7	1.4	1.0–1.9	5.8	1.1	0.7–1.6
Birth order							
First	1319	10.8	1		5.7	1	
Second	924	13.4	1.1	0.8–1.5	6.2	1.1	0.7–1.6
Third or later	297	8.4	0.7	0.4–1.2	3.4	0.7	0.4–1.5
Child care center attendance at 1 y							
No	2155	11.2	1		5.6	1	
Yes	385	13.0	1.1	0.8–1.6	5.5	1.0	0.6–1.6

All adjusted ORs (aORs) are controlled for gender, parental atopy, birth order, child care center attendance at 1 year, breastfeeding at 6 months, maternal age, ETS exposure in early life, and pets at the age of 6 months. aORs are additionally controlled for the other infections in the first 6 or 12 months of life. Missing information on 1-year infections from 49 to 169 children.

TABLE 3. Risk for Doctor-Diagnosed Allergic Rhinitis During the First 10 Years of Life and With Symptoms at the Age of 10 Years in Relation to Early-Life Respiratory Infections, Birth Order, and Child Care Attendance at the Age of 1 Year

		Doctor-Diagnosed Allergic Rhinitis					
	N	Ever Allergic Rhinitis			Allergic Rhinitis With Current Symptoms		
		Lifetime Prevalence, %	aOR	95% CI	Prevalence, %	aOR	95% CI
Lower respiratory tract infection (first 12 mo)							
No	2031	14.1	1		11.9	1	
Yes	428	14.0	0.9	0.7–1.3	12.1	0.9	0.6–1.3
Otitis media (first 12 mo)							
No	1695	12.6	1		10.4	1	
Yes	585	19.1	1.4	1.1–1.9	15.4	1.5	1.1–2.0
Croup (first 12 mo)							
No	2149	13.5	1		11.4	1	
Yes	131	19.1	1.5	0.9–2.3	16.8	1.5	0.9–2.4
Common cold (first 6 mo)							
No	732	14.6	1		11.6	1	
Yes	1662	13.8	0.9	0.7–1.1	12.0	1.0	0.7–1.3
Birth order							
First	1319	15.5	1		12.7	1	
Second	924	14.3	0.9	0.7–1.2	11.6	0.9	0.7–1.2
Third or later	297	14.1	0.8	0.5–1.2	9.1	0.8	0.5–1.3
Child care center attendance at 1 y							
No	2155	14.0	1		11.7	1	
Yes	385	14.3	1.0	0.7–1.4	12.7	1.1	0.8–1.5

All aORs are controlled for gender, parental atopy, birth order, child care center attendance at 1 year, breastfeeding at 6 months, maternal age, ETS exposure in early life, and pets at the age of 6 months. aORs are additionally controlled for the other infections in the first 6 or 12 months of life. Missing information on 1-year infections from 49 to 169 children.

respiratory infections, birth order, and child care attendance were weak (Table 4). This was also the case when positive SPT was defined as at least half the size of the histamine reaction and when reaction to pollen (grass/birch) and furred pets (dog/cat) was used as outcome (figures not shown). Of the children who were not tested because of reports of severe allergic reactions, 47% (20 of 43) had asthma and/or allergic rhinitis. Early respiratory infections and indicators of infections did not reduce the chance of asthma and allergic rhinitis among these children either (figures not given).

Table 5 shows associations between early-life respiratory infections and indicators of infections and asthma/allergic rhinitis at the age of 10 years in children with positive and negative SPTs. Several of the ORs were different in children with different SPT reactions. Among children with negative SPTs, the associations between early-life croup (adjusted OR: 4.7; 95% confidence interval [CI]: 1.7–12.7) and both asthma and allergic rhinitis (adjusted OR: 2.7; 95% CI: 1.1–6.6) were positive, whereas among children with a positive SPT, the corresponding ORs were negative (OR: 0.6; 95% CI: 0.1–2.7; OR: 0.8; 95% CI:

TABLE 4. Risk for Allergic Sensitization According to Early-Life Respiratory Infections, Birth Order, and Child Care Center Attendance at the Age of 1 Year

	N	Prevalence, %	Crude OR	aOR	95% CI
Lower respiratory tract infection (first 12 mo)					
No	1398	24.2	1	1	
Yes	292	23.3	1.0	0.8	0.6–1.2
Otitis media (first 12 mo)					
No	1160	22.4	1	1	
Yes	410	27.3	1.3	1.3	1.0–1.7
Croup (first 12 mo)					
No	1477	23.8	1	1	
Yes	93	21.5	0.9	0.8	0.5–1.3
Common cold (first 6 mo)					
No	506	23.5	1	1	
Yes	1139	24.1	1.0	1.0	0.8–1.3
Birth order					
First	880	25.0	1	1	
Second	643	23.3	0.9	0.9	0.7–1.3
Third or later	217	22.1	0.9	1.0	0.6–1.4
Child care center attendance at 1 y					
No	1458	23.7	1	1	
Yes	282	25.9	1.1	1.1	0.8–1.5

All aORs are controlled for gender, parental atopy, birth order, child care center attendance at 1 year, breastfeeding at 6 months, maternal age, ETS exposure in early life, and pets at the age of 6 months. aORs are additionally controlled for the other infections in the first 6 or 12 months of life.

TABLE 5. Relation Between Early Life Respiratory Infections and Indicators of Infections With Asthma, Allergic Rhinitis and SPT Positivity at the Age of 10 Years

	No				Yes					
	SPT+: No, %	SPT+: Yes			SPT+: No			SPT+: Yes		
		%	aOR	95% CI	%	aOR	95% CI	%	aOR	95% CI
Doctor-diagnosed asthma with symptoms past 12 mo	(*n* = 1279)	(*n* = 365)			(*n* = 33)			(*n* = 51)		
Lower respiratory tract infection	17.2	15.0	0.8	0.6–1.1	25.8	1.6	0.6–4.1	27.5	1.3	0.6–2.6
Otitis media	24.7	29.2	1.2	0.9–1.7	22.2	0.7	0.3–1.9	37.5	1.6	0.8–3.1
Croup	5.8	5.6	0.9	0.5–1.6	22.2	4.7	1.7–12.7	4.2	0.6	0.1–2.7
Common cold (6 mo)	69.1	69.6	1.0	0.8–1.4	70.0	0.8	0.3–2.0	69.4	0.9	0.5–1.7
Birth order: second or later	49.8	47.1	0.9	0.7–1.3	57.6	1.7	0.7–4.2	51.0	1.2	0.6–2.3
Child care center attendance at 1 y	16.1	17.0	1.0	0.7–1.4	9.1	0.5	0.2–1.9	21.6	1.3	0.6–2.7
Doctor-diagnosed allergic rhinitis with symptoms past 12 mo	(*n* = 1259)	(*n* = 262)			(*n* = 53)			(*n* = 154)		
Lower respiratory tract infection	17.3	17.3	0.9	0.6–1.3	19.6	1.2	0.6–2.6	15.3	0.8	0.5–1.3
Otitis media	24.5	26.6	1.1	0.8–1.5	28.9	1.2	0.6–2.4	36.5	1.9	1.3–2.8
Croup	5.8	5.6	0.8	0.4–1.6	15.6	2.7	1.1–6.6	5.1	0.8	0.4–1.9
Common cold (6 mo)	68.9	71.3	1.1	0.8–1.5	72.9	0.9	0.4–1.8	66.7	0.8	0.6–1.3
Birth order: second or later	49.5	50.8	1.1	0.8–1.5	62.3	1.6	0.8–3.3	42.2	0.8	0.5–1.2
Child care center attendance at 1 y	16.1	16.8	0.9	0.6–1.4	11.3	0.5	0.2–1.3	18.8	1.2	0.7–1.9

All aORs are controlled for gender, parental atopy, birth order, child care center attendance at 1 year, breastfeeding at 6 months, maternal age, ETS exposure in early life, and pets at the age of 6 months. aORs are additionally controlled for the other infections in the first 6 or 12 months of life. Missing information on otitis media, croup, and common cold from 127 to 209 children.

0.4–1.9; *P* value for differences between the adjusted odds ratio was .02 for asthma and .03 for allergic rhinitis). Differences in ORs for otitis media, birth order, and child care attendance and asthma and allergic rhinitis were also sizable, without reaching nominal statistical significance, however.

Children who had experienced >1 type of early-life respiratory infections (lower respiratory tract infections, otitis media, and croup) had an increased risk for having asthma compared with children who had experienced none or only 1 type of respiratory infection during their first year of life (Table 6). The risk for allergic rhinitis showed a similar but less clear pattern, whereas the risk for being SPT positive did not change substantially.

DISCUSSION

The 10-year follow-up of the Oslo Birth Cohort showed that the risk for doctor-diagnosed asthma before the age of 10 years and having symptoms of asthma at the age of 10 years were positively associated with several types of early-life respiratory infections. For allergic rhinitis, the associations were weaker but in general positive, whereas for skin-prick sensitization, there were no clear associations except for a small increase in the risk related to early-life otitis media.

Childhood asthma is a heterogeneous disease, which can start early or late in childhood and be transient or persistent.[37] A 4-year follow-up of the Oslo Birth Cohort showed that early-life respiratory infections increased the risk for asthma-like disorders in the first 4 years of life.[13] Other studies have found that indicators of infections early in life protect against the development of asthma and other allergic diseases, especially in subgroups of high-risk children. Because the diagnosis of asthma notably is more difficult in young children than in older children, we wanted to study the associations between early respiratory infections and having asthma later in childhood and how these infections were related to other atopy-related disorders.

TABLE 6. Risk for Doctor-Diagnosed Asthma and Allergic Rhinitis With Symptoms at the Age of 10 Years in Relation to the Number of Respiratory Infections (Lower Respiratory Infection, Croup, and Otitis Media) During 1 Year of Life

No. of Respiratory Infections in the First 12 Months of Life	*N*	Prevalence, %	Crude OR	aOR	95% CI
Doctor-diagnosed asthma					
0	1475	4.5			
1	752	6.5	1.5	1.3	0.8–1.9
2	162	11.7	2.8	2.5	1.5–4.4
Doctor-diagnosed allergic rhinitis					
0	1475	11.3			
1	752	12.4	1.1	1.0	0.8–1.4
2	162	16.7	1.6	1.4	0.9–2.4
SPT +					
0	1053	23.6			
1	526	24.0	1.1	0.9	0.7–1.2
2	111	27.9	1.2	1.1	0.7–1.7

All aORs are controlled for gender, parental atopy, birth order, child care center attendance at 1 year, breastfeeding at 6 months, maternal age, ETS exposure in early life, and pets at the age of 6 months.

By design, prospective cohort studies such as ours exclude recall bias as an alternative explanation of the positive associations between early-life infections and asthma that we observed, because information on exposures and potential confounders are measured in time before and independent of the disease outcome measurements. Large cohort studies have to use simple and practical data-collection methods, which may lead to some misclassification of both exposures and outcomes. However, this type of misclassification is most likely nondifferential, which will make associations weaker but not change direction. The distributions of the covariates at the different follow-ups and among children who received SPT do not indicate selective losses to follow-up. The subgroup of children who participated in the clinical examinations reported a somewhat higher occurrence of atopic diseases. We do not see reasons for why this should affect the studied associations, besides reducing statistical power and precision of risk estimates. SPT results for the 43 children who reported severe allergic reactions may have influenced the associations among the children who received SPT. However, analyses among these 43 children did not indicate so. Furthermore, <50% of these children had asthma and/or allergic rhinitis, indicating that some families had considered, for instance, adverse drug reactions as severe allergic reactions.

As we found before for asthma at the age of 4 years,[13] respiratory infections increased the risk for both ever asthma and current asthma at the age of 10 years, and the effect was strongest in children who had experienced >1 type of infection. Associations were strongest for infections that affect the lower parts of the airways, including croup. For the infections that affect the upper part of the respiratory tract, the effect was less clear. This seems reasonable and could indicate that some infections affect the lower part of the airways in a way that increases the risk for developing asthma in the following years. Studies of respiratory syncytial virus infections support this view.[38] As for respiratory syncytial virus infections, croup symptoms may indicate hyperreactivity in the airways, including the lower airways, which may explain the association with asthma.[39,40]

As in other studies,[14,30] we found that asthma had been diagnosed in a substantial proportion of SPT-negative children. Stratified analyses of SPT-positive and -negative children gave no indication of protective effects of early-life infections in either of the 2 groups. It is interesting that early-life experience of croup seemed to have the strongest effect among SPT-negative children.

If early-life infections have effect on the development of allergy in childhood, then one would expect that this would also be the case for other atopy-related disorders. We therefore analyzed associations with allergic rhinitis at the age of 10 years as well. The overlap between current and ever allergic rhinitis was substantial, which indicates that most children who develop allergic rhinitis before the age of 10 years will continue to have symptoms during childhood. The large overlap resulted in similar associations for both ever and current allergic rhinitis. Most children with reported rhinitis were SPT positive. As for asthma, we did not find protective effects of these early-life infections that could indicate immunologic reactions that reduce the risk for allergy development. Early-life otitis media was positively associated with allergic rhinitis, and the effect seemed to have the strongest impact among SPT-positive children. These findings are somewhat in contrast with other findings, including Norwegian studies based on retrospective reporting of infections, which indicate protective effects on sensitization in subgroups of children with asthma.[41,42] Conversely, several studies have indicated a positive link between allergic rhinitis and otitis media, which is what we found in this study.[43,44] As for asthma, early-life experience of croup seems to increase the risk for allergic rhinitis, especially among nonatopic children.

All ORs between early-life respiratory infections and sensitization to common allergens were near 1, with narrow CIs. Thus, this study does not support the view that early respiratory infections protect against sensitization. In fact, the only borderline significant association that was found was a positive association between SPT positivity and early-life otitis media, which further raises the question of how allergy and otitis media are related.

Neither birth order nor child care attendance at 1 year was significantly associated with any of the health outcomes, which is in contrast with findings from several other studies. The finding of protective effects of having older siblings was in fact important for the development of the hygiene hypothesis.[2,3] Our findings seem to be in contrast with these findings. In fact, there was a tendency that second and higher birth order increased the risk for asthma and allergic rhinitis in SPT-negative children. However, the sibling effect mostly has been found in families with many children. In our cohort, there were few large families. It therefore could be argued that we could not address fully the sibling effect in this study and that we in fact had the advantage of addressing the effects of respiratory infections in a population without a strong sibling effect. Child care attendance outside home seldom starts before the age of 1 year in Norway because of a long and fully paid maternity leave. One thus could argue that this ensures that early child care attendance exposure could not affect the results and that our results express a true relation between early-life respiratory infection and atopy-related diseases. A recent, comprehensive review of the literature has argued that it is inappropriate to equate having older siblings or attending a large child care center with increased exposure to infections, in the absence of more direct measures of exposure to infections or microbial agents such as bacterial endotoxin.[45]

Our results do not support the view that early-life respiratory infections, the most common infections in early childhood, cause immunologic reactions that protect against the development of atopic disease, which is in agreement with recent results from a Dutch cohort study.[46] The findings are more in support of the view that certain respiratory infections

affect the airways in a way that increases the risk for developing asthma and that the effect may be different in atopic and nonatopic children. Apart from lower respiratory infections, we found that croup, which often is caused by parainfluenza viruses, was positively associated with asthma and partly with allergic rhinitis. Similar results were also found in the 4-year follow-up of the cohort as well as in some other studies,[13,39,40,47] and the findings indicate that other infectious agents than respiratory syncytial viruses can cause long-term airway effects. Early-life otitis media was positively associated with allergic rhinitis. We even found a weak relation between allergen sensitization and early-life otitis media. The result raises the question of the role of atopy in the pathogenesis of otitis media and vice versa.

We were unable to address microbial exposure of the developing gut in this study. It has been argued that the type of gastrointestinal flora in early life influences the development of the immune system.[48] Also, child care center attendance has long been associated with increased incidence of gastrointestinal infections.[49] Some have suggested that the difference in infection incidence between home child care and attending large child care is restricted to children who are younger than 18 months,[50] which would be in line with the absence of a child care effect in this study in which few children went into child care before 12 months of age. Nevertheless, our study cannot exclude that infections other than respiratory or microbial load in general influence development of sensitization and atopic disorders later in childhood.

ACKNOWLEDGMENTS

This study was supported with grants from the Norwegian Research Council. The Oslo Birth Cohort was initiated in 1992 by the Norwegian Institute of Public Health in cooperation with Aker and Ullevål University Hospitals.

We thank head physician Per G. Lund-Larsen and his staff at the Norwegian Institute of Public Health for conducting excellent data collection at the 10-year follow-up of the cohort.

REFERENCES

1. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? A review. *J Epidemiol Community Health.* 2002;56:209–207
2. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis." *Thorax.* 2000;55(suppl 1):S2–S10
3. Strachan DP. Hay fever, hygiene and household size. *BMJ.* 1989;299:1259–1260
4. von Mutius E, Martinez FD, Frizsch C, Nicolai T, Reitmeir P, Thiemann HH. *Skin test reactivity and number of siblings BMJ.* 1994;308:692–695
5. Matricardi PM, Franzinelli F, Franco A, et al. Sibship size, birth order, and atopy in 11,371 Italian young men. *J Allergy Clin Immunol.* 1998;101:439–444
6. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med.* 2000;343:538–543
7. Haby MM, Marks GB, Peat JK, Leeder SR. Daycare attendance before the age of two protects against atopy in preschool age children. *Pediatr Pulmonol.* 2000;30:377–384
8. Krämer U, Heinrich J, Wjst M, Wichmann HE. Age of entry to day nursery and allergy in later childhood. *Lancet.* 1999;353:450–454
9. Infante-Rivard C, Amre D, Gautrin D, Malo JL. Family size, day-care attendance, and breastfeeding in relation to the incidence of childhood asthma. *Am J Epidemiol.* 2001;53:653–658
10. Celedon JC, Wright RJ, Litonjua AA, et al. Day care attendance in early life, maternal history of asthma, and asthma at the age of 6 years. *Am J Respir Crit Care Med.* 2003;167:1239–1243
11. Nystad W, Skrondal A, Magnus P. Day care attendance, recurrent respiratory tract infections and asthma. *Int J Epidemiol.* 1999;28:882–887
12. Salam MT, Li YF, Langholz B, Gilliland FD. Early-life environmental risk factors for asthma: findings from the Children's Health Study. *Environ Health Perspect.* 2004;112:760–765
13. Nafstad P, Magnus P, Jaakkola JJK. Early respiratory infections and childhood asthma. *Pediatrics.* 2000;106(3). Available at: www.pediatrics.org/cgi/content/full/106/3/e38
14. 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;322:390–395
15. Bodner C, Godden D, Seaton A. Family size, childhood infections and atopic diseases. The Aberdeen WHEASE Group. *Thorax.* 1998;53:28–32
16. Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. *Thorax.* 1998;53:927–932
17. von Mutius E, Illi S, Hirsch T, Leupold W, Keil U, Weiland SK. Frequency of infections and risk of asthma, atopy and airway hyperresponsiveness in children. *Eur Respir J.* 1999;14:4–11
18. Ponsonby AL, Couper D, Dwyer T, Carmichael A, Kemp A. Relationship between early life respiratory illness, family size over time, and the development of asthma and hay fever: a seven year follow-up study. *Thorax.* 1999;54:664–669
19. Williams LK, Peterson EL, Ownby DR, Johnson CC. The relationship between early fever and allergic sensitization at age 6 to 7 years. *J Allergy Clin Immunol.* 2004;113:291–296
20. McKeever TM, Lewis SA, Smith C, Hubbard R. The importance of prenatal exposures on the development of allergic disease: a birth cohort study using the West Midlands General Practice Database. *Am J Respir Crit Care Med.* 2002;166:827–832
21. Benn CS, Melbye M, Wohlfahrt J, Bjorksten B, Aaby P. Cohort study of sibling effect, infectious diseases, and risk of atopic dermatitis during first 18 months of life. *BMJ.* 2004;328:1223
22. Bager P, Westergaard T, Rostgaard K, Hjalgrim H, Melbye M. Age at childhood infections and risk of atopy. *Thorax.* 2002;57:379–382
23. Matricardi PM, Rosmini F, Ferrigno L, et al. Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. *BMJ.* 1997;314:999–1003
24. Sly PD, Hibbert ME. Childhood asthma following hospitalization with acute viral bronchiolitis in infancy. *Pediatr Pulmonol.* 1989;7:153–158
25. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman M, Björksten B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics.* 1995;95:500–505
26. Sigurs N. A cohort of children hospitalised with acute RSV bronchiolitis: impact on later respiratory disease. *Paediatr Respir Rev.* 2002;3:177–183
27. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet.* 1999;354:541–545
28. Romagnani S. Human Th1 and Th2 subsets: regulation of differentiation and role in protection and immunopathology. *Int Arch Allergy Immunol.* 1992;98:279–285
29. Holt PG. Infections and the development of allergy. *Toxicol Lett.* 1996;86:205–210
30. Beasley R, Pekkanen J, Pearce N. Has the role of atopy in the development of asthma been over-emphasized? *Pediatr Pulmonol.* 2001;23:149–150
31. Pohunek P, Roche WR, Turzikova J, Kudrmann J, Warner JO. Eosinophilic inflammation in the bronchial mucosa of children with bronchial asthma. *Eur Respir J.* 1997;10(suppl 25):160s
32. Shaeen SO, Barker DJ, Holgate ST. Do lower respiratory tract infections in early childhood cause chronic obstructive pulmonary disease? *Am J Respir Crit Care Med.* 1995;151:1649–1651
33. Nafstad P, Jaakkola JJK, Hagen JA, Botten G, Kongerud J. Breastfeeding, maternal smoking and lower respiratory tract infections. *Eur Respir J.* 1996;9:2623–2629
34. Nafstad P, Kongerud J, Botten G, Hagen JA, Jaakkola JJK. The role of passive smoking in the development of bronchial obstruction the first 2 years of life. *Epidemiology.* 1997;8:293–297
35. ISAAC Steering Committee. *Phase II Modules of The International Study of Asthma and Allergies in Childhood (ISAAC).* Münster, Germany: Institute of Epidemiology and Social Medicine; 1998
36. Meinert R, Frischer T, Karmaus W, Kuehr J. Influence of skin prick test criteria on estimation of prevalence and incidence of allergic sensitization in children. *Allergy.* 1994;49:526–532
37. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Harlonen M, Morgan WJ. Asthma and wheezing the first six years of life. *N Engl J Med.* 1995;332:133–138

38. Ogra PL. Respiratory syncytial virus: the virus, the disease and the immune response. *Paediatr Respir Rev.* 2004;5(suppl A):S119–S126
39. Van Bever HP, Wieringa MH, Weyler JJ, Nelen VJ, Fortuin M, Vermeire PA. Croup and recurrent croup: their association with asthma and allergy. An epidemiological study on 5–8-year-old children. *Eur J Pediatr.* 1999;158:253–257
40. Castro-Rodriguez JA, Holberg CJ, Morgan WJ, et al. Relation of two different subtypes of croup before age three to wheezing, atopy, and pulmonary function during childhood: a prospective study. *Pediatrics.* 2001;107:512–518
41. Nystad, W, Skrondal A, Magnus P. Recurrent respiratory tract infections during the first 3 years of life and atopy at school age. *Allergy.* 1998;53:1189–1194
42. Nja F, Nystad W, Hetlevik O, Carlsen KCL, Carlsen KH. Airway infections in infancy and the presence of allergy and asthma in school age children. *Arch Dis Child.* 2003;88:566–569
43. American Academy of Family Physicians; American Academy of Otolaryngology Head and Neck Surgery; American Academy of Pediatrics Subcommittee on Otitis Media With Effusion. Otitis media with effusion. *Pediatrics.* 2004;113:1412–1429
44. Doyle WJ. The link between allergic rhinitis and otitis media. *Curr Opin Allergy Clin Immunol.* 2002;2:21–25
45. Stamwell-Smith R, Bloomfield S. The hygiene hypothesis and implications for home hygiene, International Scientific Forum on Home Hygiene, Milan, 2004. Available at: www.ifh-homehygiene.org/2003/2hypothesis/hh.htm
46. Balemans WAF, Rovers MM, Cornelis K. Childhood upper respiratory tract infections are not associated with asthma, hay fever and eczema at adulthood: a birth cohort study [abstract]. *Eur Respir J.* 2004;24(suppl 48):4046
47. Nicolai T, von Mutius E. Risk of asthma in children with a history of croup. *Acta Paediatr.* 1996;85:1295–1299
48. Garofalo RP, Welliver RC, Ogra PL. Clinical aspects of bronchial reactivity and cell-virus interaction. In: Ogra PL, Mestecky J, Lamm ME, Strober W, Bienenstock J, McGhee JR, eds. *Mucosal Immunology*. San Diego, CA: Academic Press; 1999:1223–1238
49. Ferson MJ. Infections in daycare. *Curr Opin Pediatr.* 1993;5:35–40
50. Lu N, Samuels ME, Shi L, Baker SL, Glover SH, Sanders JM. Child day care risks of common infectious diseases revisited. *Child Care Health Dev.* 2004;30:361–368

Early Respiratory Infections, Asthma, and Allergy: 10-Year Follow-up of the Oslo Birth Cohort

Per Nafstad, Bert Brunekreef, Anders Skrondal and Wenche Nystad

Pediatrics 2005;116;e255
DOI: 10.1542/peds.2004-2785

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Early Respiratory Infections, Asthma, and Allergy: 10-Year Follow-up of the Oslo Birth Cohort

Per Nafstad, Bert Brunekreef, Anders Skrondal and Wenche Nystad

Pediatrics 2005;116;e255
DOI: 10.1542/peds.2004-2785