Early Respiratory Infections and Childhood Asthma

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ABSTRACT. *Objective.* **To assess the role of early respiratory infections in the development of bronchial obstruction in the first 2 years of life, and asthma by the age of 4 years in the Oslo Birth Cohort, established in 1992–1993. Having older siblings and attendance to a day care center were also considered as proxy measures of early infections.**

Methods. **A total of 2531 children were followed from birth to 4 years of age. Experiences of respiratory infections were recorded in the follow-up surveys at 6 and 12 months of age, and children with symptoms and signs of bronchial obstruction during the first 2 years of life were identified and examined. The presence of current asthma was recorded when the children were 4 years old.**

Results. **Children with respiratory infections during infancy had a higher risk of having bronchial obstruction during the first 2 years of life and of having asthma at 4 years of age. In logistic regression adjusting for confounders including other infections, the risk of asthma at 4 years of age was related to lower respiratory tract infection (odds ratio [OR]: 3.4; 95% confidence interval [CI]: 2.3–7.0), otitis media (OR: 1.8; 95% CI: 1.2–2.6), croup (OR: 2.1; 95% CI: 1.2–3.7) in the first year and related to the common cold (OR: 2.0; 95% CI: 1.3–3.1) in the first 6 months of life. The risk of current asthma was inversely related to older siblings after controlling for early respiratory infections.**

Conclusion. **Early respiratory infections indicate increased, rather than decreased, risk of developing bronchial obstruction during the first 2 years of life and of having asthma at 4 years of age.** *Pediatrics* **2000;106(3). URL: http://www.pediatrics.org/cgi/content/full/106/3/e38; *childhood, asthma, respiratory infections, cohort.***

ABBREVIATIONS. RSV, respiratory syncytial virus; OR, odds ratio; CI, confidence interval.

Recent epidemiologic studies have shown that children with siblings have a lower prevalence of allergies and asthma than do children without siblings.[1–8] This association has been attributed to a preventive effect of early infections that are suggested to be more common in children with older siblings. This hypothesis is supported by a plausible biologic mechanism, according to which early-life infections stimulate Th1 lymphocytes that may inhibit the expansion of allergen-specific Th2 lymphocytes and may limit the development of allergic diseases.[9,10] In a German cross-sectional study of school children, a history of attendance to day care centers was used as a surrogate measure of early infections.[11] The prevalence of asthma, hay fever, and atopy was higher among children who started day care after the age of 1 year than among those who started at a younger age. This association was present only in small families of up to 3 persons.

Although considered predominantly an allergic disease, childhood asthma has been found to be more common after the experience of at least 1 specific type of early respiratory infection. Two cohort studies indicate that lower respiratory tract infections during infancy caused by respiratory syncytial virus (RSV) are associated with increased risk of asthma in the following years.[12,13] Further, both pneumonia and RSV infection in the lower respiratory tract during the first 3 years of life have been associated with an increased risk of asthma or asthma-like symptoms up to 11 years of age.[14,15]

We used the Oslo Birth Cohort Study to address the role of several types of early infections in the development of bronchial obstruction in the first 2 years of life and the development of asthma by 4 years of age.[16] We focused on infections during infancy and considered actual infections as well as factors increasing the exposure to infectious agents, such as having older siblings or attendance to day care centers. Episodes of lower respiratory tract infections during the first year of life often lead to symptoms of bronchial obstruction. Therefore, we also estimated the effects of early respiratory infections on asthma separately in children who did and who did not experience bronchial obstruction during the first 2 years of life.

METHODS

Study Population

The source population included children born in the 2 main birth clinics in Oslo during a 15-month period in 1992–1993. The eligibility criteria and data collection procedures during the first 2 years of life are described in detail elsewhere.[16,17] Information on the health and environmental exposures of the child was collected from parents by questionnaires at birth and when the child was 6, 12, 18, and 24 months old. The 2-year follow-up rate was 81% (n = 3048).[16] In November 1996, we conducted a 4-year follow-up in connection with a survey directed at all the 4-year-old children living in Oslo and at the members of the birth cohort living outside Oslo.[18] In the present study, we focused only on the 3048 children with information on respiratory health from the first 2 years of life. A correct mailing address was obtained for 2985 of these children,

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and a completed questionnaire was received from families of 2594 (87%) children. Information on current asthma was available for 2531 children, who comprised the study population. These children had a mean age of 4.3 years (standard deviation: .3).

Health Outcomes

The primary outcome was current asthma, which was defined based on answers to the 4-year follow-up questionnaire. Current asthma was defined as a history of asthma diagnosed by a physician and experience of symptoms of asthma during the previous 12 months. The secondary outcome was bronchial obstruction in the first 2 years of life. Bronchial obstruction was defined as 2 or more episodes with symptoms and signs of obstruction or 1 episode lasting >1 month.[16] At least one of the episodes had to be diagnosed by a physician, and the guidelines were that at least 3 of 5 symptoms or signs (wheezing, chest recession, rhonchi during auscultation, forced expiration, and rapid breathing) should be observed.

Early Respiratory Infections and Indirect Measures of Exposure to Infectious Agents

The determinants of interest were respiratory infections, such as lower respiratory tract infections, otitis media, croup, and the common cold, during the first 6 months of life and during the first year of life. The occurrence of these early respiratory infections was asked for in the 6- and 12-month follow-up questionnaires. Lower respiratory tract infection was defined as an episode of bronchiolitis, including RSV infection, bronchitis, or pneumonia. Indirect measures of exposure to infectious agents were attendance to a day care center at the age of 1 year (measured as the number of hours/week in a day care center at the age of 1 year and stratified as 10 or more hours/week or less), and having older siblings (measured as birth order when the child was included in the cohort).

Covariates

Information on potential confounders was obtained from the hospital records and the 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 exposure at birth. Parental atopy was defined as a history of maternal or paternal asthma or hay fever. Length of breastfeeding was categorized into 0 to 6 months and >6 months of age. Exposure to environmental tobacco smoke was defined as living together with 1 or more smokers. The categorization of these covariates is presented in Table 1.

Statistical Methods

We estimated associations between early respiratory infections, bronchial obstruction in the first 2 years of life, and current asthma at the age of 4 years. The odds ratio (OR) was used as a measure of effect. We calculated adjusted ORs from logistic regression analysis. Based on earlier knowledge of the determinants of the outcomes and preliminary data analyses, we always included gender, parental atopy, having older siblings, day care center attendance, length of breastfeeding, and environmental tobacco smoke exposure into the models. Other variables were included only if they had an impact on accuracy (>10% change in OR) and precision of the studied relations. First, we assessed the early respiratory infections, having older siblings, and attendance to day care center as determinants of bronchial obstruction in the first 2 years of life and of asthma at 4 years of age. Second, we elaborated to what extent the effects of early respiratory infections on asthma are mediated through paths other than via episodes of bronchial obstruction during the first 2 years of life by estimating the effects separately in children who did and who did not experience bronchial obstruction.

We dealt with missing information 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 produced quite consistent results. Only results of the first approach are presented.

TABLE 1. Characteristics of the Oslo Birth Cohort at Birth and at Two and Four Years Follow-Up

	At Birth (n = 3754) %	2 Years Follow-Up (n = 2985) %	4 years Follow-Up (n = 2531) %
Gender (male)	51.8	51.3	51.3
Parental atopy	33.7	33.9	34.6
Birth weight			
<3000 g	12.6	12.3	12.0
3000–3499 g	32.4	31.6	31.5
+3500 g	55.1	56.1	56.4
Birth order			
First	51.4	52.6	52.6
Second	36.3	35.7	35.7
Third or later	12.2	11.7	11.7
Breastfeeding after 6 mo		70.1	71.2
Maternal age at delivery			
<25 y	12.2	10.5	9.5
25–29 y	36.2	35.7	35.5
+30 y	51.6	53.8	55.0
Maternal education			
<12 y	7.3	5.6	4.7
12–15 y	39.5	38.0	36.4
>15 y	53.2	56.4	58.9
Family income per year			
<200 000 NOK	17.0	14.1	13.2
200 000–500 000 NOK	64.7	66.8	66.8
>500 000 NOK	18.3	19.1	20.0
Single parenthood (at 6 mo age)		7.7	7.1
Pets at home (at 6 mo age)		20.2	19.9
Day care outside the home (at 1 y)		15.0	15.0
Environmental tobacco smoke exposure in early life	43.6	41.3	39.8
Bronchial obstruction 0–2 y of life		8.8	8.9
1 or more lower respiratory infection first y of life		16.7	16.2

NOK indicates Norwegian Kroner.
Maximal number of subjects with missing data in the baseline questionnaire: 78 (family income per year), in the 2-year questionnaire: 101 (breastfeeding), and in the 4-year questionnaire: 79 (breastfeeding).

RESULTS

The characteristics and early exposures of the children who were followed for 4 years did not differ substantially from those of the baseline and 2-year cohort, as shown in Table 1. The occurrence of lower respiratory tract infections during the first year of life was similar in children followed for 2 and 4 years (16.7% vs 16.2%). A total of 225 children (8.9%) experienced bronchial obstruction during the first 2 years of life, and 164 children (6.5%) had current asthma at 4 years of age. Of the children with current asthma, 66.3% used corticosteroids, and 78.4% had experienced wheeze, 93.9% heavy breathing/chest tightness, and 92.7% nightly cough during the previous 12 months.

Table 2 presents the risk of bronchial obstruction during the first 2 years of life and the risk of asthma at the age of 4 years in relation to early respiratory infections, having older siblings, and attendance to day care centers. The risks of both bronchial obstruction and asthma were consistently higher in children

TABLE 2. Risk of Bronchial Obstruction From Birth to Two Years of Life (n = 225) and Asthma at the Age of Four Years (n = 164) According to Early-Life Respiratory Infections, Birth Order, and Day Care Attendance at the Age of One Year

		Risk of Bronchial Obstruction 0 to 2 years of Life				Risk of Asthma at the Age of 4 Years			
	All n = 2531	Risk	Crude OR	Adjusted OR	95% CI	Risk	Crude OR	Adjusted OR	95% CI
* Respiratory infections in the first 6 mo of life									
Lower respiratory tract infection									
No (reference)	2397	.074				.060			
Yes	134	.358	7.0	6.3	4.2–9.6	.142	2.6	2.3	1.3–3.9
Otitis media									
No (reference)	2278	.078				.058			
Yes	126	.222	3.4	2.3	1.4–3.8	.151	2.9	2.5	1.4–4.3
Croup									
No (reference)	2378	.083				.061			
Yes	26	.346	5.9	4.2	1.6–10.5	.192	3.6	2.9	1.0–8.2
Common cold									
No (reference)	753	.060				.037			
Yes	1651	.098	1.7	1.4	1.0–2.0	.075	2.1	2.0	1.3–3.1
† Respiratory infections in the first 12 mo of life									
Lower respiratory tract infecton									
No (reference)	2121	.040				.047			
Yes	410	.341	12.4	11.6	8.3–16.2	.156	3.7	3.4	2.4–4.9
Otitis media									
No (reference)	1732	.067				.050			
Yes	590	.141	1.4	1.4	1.0–1.9	.103	1.3	1.8	1.2–2.6
Croup									
No (reference)	2189	.079				.058			
Yes	133	.195	1.9	2.3	1.3–3.9	.143	1.7	2.1	1.2–3.7
Common cold									
No (reference)	171	.053				.029			
Yes	2154	.088	1.7	1.5	.7–3.3	.066	2.3	2.3	.9–5.7
† Indicators of exposure to infectious agents									
Birth order									
First (reference)	1332	.059				.067			
Second or later	1199	.123	2.2	1.8	1.3–2.6	.063	.9	.7	.5–1.0
Day care center attendance at 1 y old									
No (reference)	2151	.082				.064			
Yes	380	.129	1.7	1.6	1.1–2.4	.071	1.1	1.0	.6–1.6

All adjusted ORs are controlled for gender, parental atopy, birth order, day care center attendance at 1 year of life, breastfeeding at 6 months of life, maternal age, environmental tobacco smoke exposure in early life, and pets at the age of 6 months.
* Adjusted ORs are additionally controlled for the other infections first 6 months of life.
† Adjusted ORs are additionally controlled for the (other) infections during the first 12 months of life. Missing information on otitis media, croup, and common cold from 127 to 209 children.

who had experienced any of the 4 types of infections than in children who did not have the corresponding infection. Adjustment for a set of the most important determinants of asthma, including the other types of infections, did not change the overall picture. The risk of bronchial obstruction in the first 2 years of life, but not of asthma at the age of 4 years, increased when having older siblings (OR: 1.8; 95% confidence interval [CI]: 1.3–2.6) and attendance to a day care center at the age of 1 year (OR: 1.6; 95% CI: 1.1–2.4). In fact, older siblings seemed to decrease the risk of asthma at the age of 4 years, after controlling for early-life respiratory infections (OR: .7; 95% CI: .5–1.0). Experience of lower respiratory tract infections either during the first 6 months (OR: 6.3; 95% CI: 4.2–9.6) or 12 months of life (11.6, 8.3–16.2) was the strongest determinant of bronchial obstruction.

Experience of bronchial obstruction during the first 2 years of life was a strong determinant of the risk of asthma (OR: 12.9; 95% CI: 9.1–18.2). Of the 225 children who had bronchial obstruction, 76 (33.8%) had symptomatic asthma at the age of 4 years. To elaborate to what extent the effect of early infections is not mediated through bronchial obstruction in early life, we estimated their effect separately in children who experienced bronchial obstruction and in those who did not. The early infections increased the risk of asthma at the age of 4 years both in children who experienced and in those who did not experience bronchial obstruction, as shown in Table 3. In children without bronchial obstruction, birth order higher than 1 decreased the risk of asthma (OR: .5; 95% CI: .3–.8). This effect was also seen after adjusting for early infections (OR: .5; 95% CI: .3–.9).

DISCUSSION

The results of our prospective cohort study show that several types of respiratory infections during infancy increase the risk of developing bronchial obstruction during the first 2 years of life and of devel-

TABLE 3. Risk of Asthma at the Age of Four Years in Children With and Without Bronchial Obstruction From Birth to Two Years of Life According to Early-Life Respiratory Infections, Birth Order, and Day Care Attendance at the Age of One Year

	n	Risk of Asthma	Crude OR	Adjusted OR	95% CI
With bronchial obstruction 0–2 y of life					
Lower respiratory tract infection in the first 12 mo of life					
No (reference)	85	.306			
Yes	140	.357	1.3	2.0	.9–4.3
Otitis media in the first 12 mo of life					
No (reference)	116	.276			
Yes	83	.361	1.5	1.3	.7–2.5
Croup in the first 12 mo of life					
No (reference)	173	.289			
Yes	26	.462	2.1	1.7	.7–4.3
* Common cold in the first 6 mo of life					
No (reference)	45	.222			
Yes	161	.342	1.8	1.8	.8–4.1
Birth order					
First (reference)	78	.346			
Second or later	147	.333	.9	.5	.2–1.1
Day care at the age of 1 y					
No (reference)	176	.364			
Yes	49	.245	.6	.5	.2–1.1
Without bronchial obstruction 0–2 y of life					
Lower respiratory tract infection in the first 12 mo of life					
No (reference)	2036	.036			
Yes	270	.052	1.4	1.3	.7–2.4
Otitis media in the first 12 mo of life					
No (reference)	1616	.033			
Yes	507	.061	1.9	1.9	1.2–3.0
Croup in the first 12 mo of life					
No (reference)	2016	.039			
Yes	107	.065	1.7	1.5	.7–3.4
* Common cold in the first 6 mo of life					
No (reference)	708	.025			
Yes	1490	.046	1.8	1.9	1.1–3.3
Birth order					
First (reference)	1254	.049			
Second or later	1052	.025	.5	.5	.3–.9
Day care center attendance at 1 y					
No (reference)	1975	.037			
Yes	331	.045	1.2	1.1	.6–2.0

Adjusted ORs: controlled for (other) respiratory infections first 12 months of life, gender, parental atopy, birth order, day care center attendance at 1 year of life, breastfeeding at 6 months of life, maternal age, environmental tobacco smoke exposure in early life, and pets.
* Adjusted for other respiratory infections in the first 6 months and not in the first 12 months of life.

oping asthma by 4 years of age. Although experience of bronchial obstruction in the first 2 years of life was a strong determinant of later asthma, only 34% of children who had bronchial obstruction had asthma at the age of 4 years. In young children, the symptoms and signs of bronchial obstruction are similar to those of lower respiratory tract infections. We found that respiratory infections during infancy increased the risk of asthma both in children who experienced bronchial obstruction and in children who did not. This indicates that part of the effect of infections in infancy on the risk of asthma at the age of 4 years is not mediated through early bronchial obstruction. Some of the CIs in the stratified analyses included 1, probably attributable to loss of statistical power. However, the estimated ORs were consistently >1 and in accordance with the unstratified analysis.

A prospective cohort study provides a valid approach for the assessment of the effect of early respiratory infections on the development of asthma in later childhood. Parental reporting of infections in infancy could have led to some misclassification. However, such misclassification should not have introduced a systematic error because the information was collected before the diagnosis of asthma. The early symptoms and signs of bronchial obstruction were recorded carefully during the first 2 years of life.[16] The definition of current asthma was based on a diagnosis of a physician and an experience of asthma-like symptoms during the previous 12 months. The follow-up rate was relatively high and it was not related to the determinants of interest. Thus, selection bias is not a likely alternative explanation for the observed relations between the occurrence of respiratory infections and the risk of asthma.

We focused on respiratory infections in very early life, because it is possible that this period in life is of special importance for later development of asthma and allergy.[11–13,19,20] Two previous longitudinal studies have provided evidence that respiratory infections during infancy increase the risk of asthma in the following years.[12,13] Sly and Hibbert[12] followed 48 infants hospitalized for RSV bronchiolitis for 5 years and reported that 92% of these children had later symptoms suggestive of asthma and that 71% of

the 35 examined children had clinical evidence of asthma. Sigurs and colleagues[13] followed 47 children with RSV bronchiolitis and 93 without such bronchiolitis until the age of 3 years. The prevalence of asthma, defined as 3 or more episodes of bronchial obstruction verified by a physician, was 23% in the bronchiolitis group and 1% in the reference group. Further, a cohort study from Tucson, Arizona showed recently that both an episode of RSV infection in lower respiratory tract and an episode of pneumonia during the first 3 years of life increased the risk of asthma or asthma-like symptoms up to the age of 11 years.[14,15] In the present study of 2531 children, a positive association between respiratory infections in infancy and asthma at the age of 4 years was observed for 4 different types of respiratory infections, including lower respiratory tract infections, croup, otitis media, and the common cold. The risk estimates did not change substantially when all the other infections were included in the logistic regression models. This means that each type of infection had an independent effect on the risk of asthma. The relations were present for respiratory infections during both the first 6 months and the first 12 months of life.

Early respiratory infections and asthma may have several common genetic and environmental determinants, which could explain the observed relations. We adjusted for the best known environmental determinants of asthma, as well as parental atopy as a measure of hereditary propensity to asthma. Thus, the adjusted ORs represent relations that are independent from these controlled covariates. The overall results are consistent with the proposition that early respiratory infections actually increase the risk of having asthma at the age of 4 years. It is not possible to know based on the data to what extent genetic propensity and common environmental exposures contribute to the observed relations. Asthma, particularly childhood asthma, is a heterogeneous disease,[21–23] and the role of early-life infections could be different in subgroups of disease children.[23] The present study indicated a relatively strong effect of early respiratory infections on the risk of asthma. Therefore, a protective effect in any subgroup should be very strong or the subgroup should be large.

Birth order and attendance to a day care center have been used as surrogate measures of early respiratory infections.[5,6,11] We were able to assess their effect with and without taking into account the actual occurrence of early respiratory infections. Having older siblings and attendance to a day care center at the age of 1 year increased the risk of bronchial obstruction. In contrast, older siblings seemed to decrease the risk of asthma at the age of 4 years, when taking into account early respiratory infections. In previous studies, one interpretation of the inverse association between having older sibling(s) and the risk of atopic diseases has been a protective effect of early infections that are more frequent in children with older sibling(s).[1–7] The present findings indicate that early respiratory infections increase, rather than decrease, the risk of asthma at the age of 4 years, but having older siblings has a protective effect on the risk of asthma, which seems independent from experience of infections. Attendance to a day care center had a small crude effect (OR: 1.2) on the risk of asthma that disappeared after taking into account the early respiratory infections (OR: 1.0).

CONCLUSION

The results show clearly that children who experience any respiratory infections during infancy have a higher risk of asthma later in childhood. The observed relations between the occurrence of early respiratory infections and the risk of asthma could have been influenced by common environmental or hereditary factors despite our attempts to control for most of these factors. Exposure to infectious pathogens and a consequent respiratory infection may also represent environmental causes of childhood asthma. The results suggest that having older siblings may decrease the risk of asthma in childhood, but this effect is probably not mediated through a higher frequency of early respiratory infections, because early respiratory infections seem to increase, rather than decrease, the risk of asthma at the age of 4 years.

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