

Recurrent respiratory tract infections during the first 3 years of life and atopy at school age

Nystad W, Skrondal A, Njå F, Hetlevik Ø, Carlsen K-H, Magnus P.
Recurrent respiratory tract infections during the first 3 years of life and atopy at school age.

Allergy 1998; 53: 1189–1194. © Munksgaard 1998.

Background The hypothesis that infections reduce the risk of atopy was investigated by estimating the association between recurrent respiratory tract infections during the first 3 years of life and atopy at school age.

Methods According to surveys in three different areas of Norway, children were classified into three groups: asthma, wheeze without asthma (wheeze), and no asthma/no wheeze. The skin prick test (SPT) was conducted on a stratified random sample of children ($n=502$). The outcome was at least one positive SPT. The exposure variable was retrospective parental report of respiratory tract infections during the first 3 years of life.

Results Infections were negatively associated with atopy, crude odds ratio (cOR)=0.3, 95% confidence interval (95% CI) 0.1–0.7, in the asthma group. A similar association was present in children with wheeze cOR=0.4 (95% CI 0.1–1.2). The number of siblings was not associated with atopy in any group. Infections remained negatively associated with atopy in children with asthma, aOR=0.3 (95% CI 0.1–0.7), in a logistic regression model adjusting for confounding factors. A similar pattern was present in the wheeze group.

Conclusions Recurrent respiratory tract infections during the first 3 years of life are negatively associated with atopy at school age in children with asthma.

W. Nystad^{1,2}, A. Skrondal¹, F. Njå³,
Ø. Hetlevik⁴, K.-H. Carlsen⁵,
P. Magnus¹

¹Section of Epidemiology, Department of Population Health Sciences, National Institute of Public Health, Oslo; ²Laboratory of Sport Medicine, Norwegian University of Physical Education and Sport, Oslo; ³Geilomo Children's Hospital for Asthma and Allergy, Geilo; ⁴Community GP, Odda; ⁵Voksentoppen Centre of Asthma and Allergy, University Hospital, Oslo, Norway

Key words: atopy, infection.

Wenche Nystad
Section of Epidemiology
Department of Population Health Sciences
National Institute of Public Health
Postboks 4404 Torshov
N-0403 Oslo
Norway

Accepted for publication 30 July 1998

The hypothesis that early infection may reduce the risk of allergic sensitization is based on the idea that infections strongly promoting Th1 immunity may inhibit atopic disorder by the suppression of Th2 immunity (1). The results of several studies may support the theory (2–4). An inverse association between number of siblings and the prevalence of hay fever has been reported in young British adults (5). Since the effect was stronger for subjects with older than with younger siblings, the author suggested that factors such as viral infections may influence the results. Other studies have confirmed that sibship size is inversely associated with atopy in European adults and children (6–10).

However, it is still unknown whether the apparent effect of the number of siblings is due to an increase in respiratory infections or reflects other underlying variables not yet discovered. The

objective of the present study was to estimate the association between parental report of recurrent respiratory tract infections during the first 3 years of life and atopy at school age in three different groups of children: those reporting neither asthma nor wheeze, those reporting wheeze without asthma, and those reporting asthma.

Material and methods

Subjects

In 1994, 7–16-year-old schoolchildren were enrolled in a cross-sectional study of asthma and allergy in three areas of Norway; the city of Oslo ($n=2188$), the municipality of Odda ($n=831$), and the urban area of Hallingdal ($n=1177$) (11). The parents completed the ISAAC questionnaire and other

questions previously used in studies of childhood asthma (12, 13). The methods and results of the present study are presented elsewhere (14, 15). Subsequently, a second questionnaire was mailed to the parents of the children. This questionnaire included demographic information, family structure, and early exposures from birth throughout childhood.

According to the parental responses to the first questionnaire, the children were classified into three mutually exclusive groups: asthma, wheeze, and no asthma/no wheeze. "Asthma" was defined by a positive response to the question, "Does the child still have asthma?" "Wheeze" was defined by a positive answer to the question, "Has the child had wheezing or whistling in the chest in the last 12 months?" and a negative answer to the asthma question. "No asthma/no wheeze" was defined by a negative response to both the asthma and wheeze questions. A stratified random sample of children ($n=502$) was drawn for skin prick testing, with group and area serving as strata. In Oslo, the sampling probability was 0.66 in the asthma group, 0.58 in the wheeze group, and 0.04 in the no asthma/no wheeze group. In Hallingdal and Odda, all children with asthma and wheeze were included, whereas the sampling probabilities in the no asthma/no wheeze group were 0.11 in Hallingdal and 0.10 in Odda. We obtained complete data for 86% of the children in Oslo, 88% in Odda, and 83% in Hallingdal.

Variables

Atopy. The sensitivity to nine prevalent allergens was assessed by skin prick test (SPT) according to the Nordic guidelines (16, 17). The allergen extracts used were all Soluprick SQ 10 HEP (ALK A/S, Hørsholm, Denmark): hen's egg white, cow's milk, house-dust mite (*Dermatophagoides pteronyssinus*), *Cladosporium herbarum*, dog and cat dander, birch and timothy pollen, and mugwort (*Artemisia vulgaris*) pollen. Saline (saline/glycerol 50/50) was used as negative control, and histamine (10 mg/ml Soluprick) as positive control. The size of the reactions was measured 15 min after testing. The histamine wheal size was recorded as the sum of the longest plus the midpoint orthogonal diameters divided by 2. A child was considered atopic to a specific allergen if the average diameter of the wheal was at least half of that produced by a 10 mg/ml solution of histamine, and with an average diameter of the wheal due to histamine of at least 3 mm. Atopy was defined as having at least one positive SPT.

Recurrent respiratory tract infections. Parents were asked about different infectious diseases (otitis, bronchitis, respiratory tract infections, and pneumonia) diagnosed by a physician from birth throughout childhood. The options of time periods given to the respondents were 0–11 months, 1–2 years, 3–4 years, and 5–6 years. The exposure variable in the present analyses was parental retrospective report of physician diagnoses of recurrent respiratory tract infections during the first two time periods (during the first 3 years of life).

Background variables. In the analyses, we adjusted simultaneously for a set of background variables including sex, year of birth, number of siblings, maternal and paternal education, family history of atopic diseases, day-care attendance, and area (Oslo, Odda, and Hallingdal). Day-care attendance was scored dichotomously with home care as the reference category. The other variables were defined as follows: year of birth was classified into three groups (1978–81, 1982–4, and 1985–8); number of siblings was divided into four categories, none, 1, 2, and ≥ 3 ; and maternal and paternal education, defined by length of education, was categorized at three levels (< 10 years, 10–14 years, and > 14 years). A family history of atopic diseases was measured in terms of reports of maternal and paternal asthma or hay fever.

Statistical analysis

By logistic regression, crude odds ratios (cOR) and adjusted odds ratios (aOR) with 95% confidence interval (95% CI) were used as measures of association between the exposure variables and the outcome. All analyses were conducted within groups (no asthma/no wheeze, wheeze, and asthma). There was no information on paternal or maternal education for 26 children, and they were assigned the category "unknown" on these variables. The analyses were performed with SPSS for Windows (6.0) (18).

Results

Children in the wheeze and asthma groups were more likely to have had recurrent respiratory tract infections (infections) before 3 years of age and atopy at school age than children in the no asthma/no wheeze group (Table 1). Except for a family history of atopic diseases and sex, the background variables had a similar distribution in the three groups.

The prevalence of infections increased with

Table 1. Presence of atopy, recurrent respiratory tract infections (infections) before 3 years of age, and distribution of background variables in three groups of children undergoing skin prick testing (SPT)

	No asthma/no wheeze <i>n</i> =181 %	Wheeze <i>n</i> =155 %	Asthma <i>n</i> =166 %
Atopy			
No	72.9	58.7	43.4
At least one positive SPT	27.1	41.3	56.6
Infections			
No	95.0	87.1	80.1
Yes	5.0	12.9	19.9
Year of birth			
1985-8	27.1	29.0	28.3
1982-4	37.0	34.8	35.5
1978-81	35.9	36.1	36.1
Number of siblings			
None	11.6	22.6	18.7
1	49.2	44.5	42.8
2	32.0	27.7	32.5
≥3	7.2	5.2	6.0
Sex			
F	51.4	56.8	45.2
M	48.6	43.2	54.8
Paternal education (years)			
<10	24.3	30.3	29.5
10-14	35.4	28.4	32.5
>14	34.8	38.1	31.3
Unknown	5.5	3.2	6.6
Maternal education (years)			
<10	23.2	24.5	30.7
10-14	40.3	37.4	40.4
>14	34.3	36.1	27.1
Unknown	2.2	1.9	1.8
Area			
Oslo	35.4	36.1	39.8
Odda	23.2	20.6	19.3
Hallingdal	41.4	43.2	41.0
Maternal atopic disease			
No	80.7	61.9	61.4
Yes	19.3	38.1	38.6
Paternal atopic disease			
No	78.5	74.8	66.9
Yes	21.5	25.2	33.1
Day care			
Home care	66.9	65.8	63.9
Day-care attendance	33.1	34.2	36.1

increasing numbers of siblings in the asthma group (Table 2). Having attended day care outside home increased the prevalence of infections in all three groups. The prevalence of infections decreased with increasing age in the wheeze group. Children in Hallingdal tended to have the lowest prevalence of infections in all three groups. Other background variables were not associated with infections.

The number of siblings was not associated with atopy in any group (Table 3). In children with no asthma/no wheeze, there was a positive association between maternal atopic diseases and atopy (OR 2.5 [1.1-5.3]). In the wheeze group, paternal atopic diseases tended to be associated with atopy (OR 2.0 [0.9-4.1]). In this group, the prevalence of atopy

Table 2. Prevalence (%) of recurrent respiratory tract infections (infections) before 3 years of age according to number of siblings, day care, and area in three groups of children

	Infections (percentage responding yes)		
	No asthma/no wheeze <i>n</i> =181	Wheeze <i>n</i> =155	Asthma <i>n</i> =166
Number of siblings			
None	4.8	14.3	12.9
1	7.9	11.6	19.7
2	1.7	16.3	22.2
≥3	0	0	30.0
Day care			
Home care	3.3	9.8	17.0
Day-care attendance	8.3	18.9	25.0
Year of birth			
1985-8	10.2	22.2	19.1
1982-4	3.0	11.1	18.6
1978-81	3.1	7.1	21.7
Area			
Oslo	7.8	19.6	22.7
Odda	4.8	15.6	28.1
Hallingdal	2.7	6.0	13.2

was highest in Hallingdal (OR 2.8 [1.3-5.8]). In all three groups, the prevalence of atopy increased with increasing age, and there was no association between atopy and any of the other background variables.

Table 4 presents the adjusted odds ratios for at least one positive SPT by recurrent respiratory tract infections in children with no asthma/no

Table 3. Prevalence (%) of at least one positive skin prick test according to number of siblings, maternal and paternal atopic disease, and area in three groups of children

	At least one positive skin prick test (percentage reporting yes)		
	No asthma/no wheeze <i>n</i> =181 %	Wheeze <i>n</i> =155 %	Asthma <i>n</i> =166 %
Siblings			
None	9.5	42.9	64.5
1	30.3	39.1	50.7
2	27.6	44.2	57.4
≥3	30.8	37.5	70.0
Maternal atopic disease			
No	23.3	39.1	56.2
Yes	42.9	58.8	60.0
Paternal atopic disease			
No	24.6	40.8	54.6
Yes	35.9	66.7	78.6
Year of birth			
1985-8	26.5	28.9	55.3
1982-4	23.9	46.3	54.2
1978-81	30.8	46.4	60.0
Area			
Oslo	25.0	32.1	57.6
Odda	28.6	25.0	43.8
Hallingdal	28.0	56.7	61.8

Table 4. Adjusted odds ratios for at least one positive skin prick test (SPT) by recurrent respiratory tract infections (infections) in children with asthma, wheeze without asthma (wheeze), and neither asthma nor wheeze (no asthma/no wheeze)

		At least one positive SPT		
		No	Yes	aOR* (95% CI)
Infections		<i>n</i>	<i>n</i>	
Asthma	No	50	83	1.0
	Yes	22	11	0.3 (0.1–0.7)
Wheeze	No	76	59	1.0
	Yes	15	5	0.4 (0.1–1.4)
No asthma/ no wheeze	No	127	45	1.0
	Yes	5	4	2.6 (0.5–13.1)

*Adjusted for sex, year of birth, number of siblings, paternal and maternal education, area, day care, and paternal and maternal atopy.

wheeze, wheeze without asthma, and asthma. Infections remained negatively associated with atopy both in children with asthma and in children with wheeze in a logistic regression model adjusting for other variables.

In further analyses, we included breast-feeding, smoking during pregnancy, and having pets during the first year of life as explanatory variables. None of these variables were associated with atopy.

Discussion

The results of the present study suggest that parental reports of physician diagnoses of recurrent respiratory tract infections during the first 3 years of life reduce the risk of developing atopy assessed by SPT in children with asthma. A similar, but not statistically significant association, was found in children with wheeze.

One limitation of the present study is that the exposure variable was retrospective parental report of physician diagnoses of recurrent respiratory tract infections. Mothers with children with no asthma/no wheeze, or wheeze, or asthma may differently report infections. This problem of recall bias is partly obviated by the stratified analysis. It seems more unlikely that mothers with and without children with a positive SPT should report infections differently. A probable information bias may also be reduced by using infections confirmed by a physician. Furthermore, the questionnaire was completed before the parents knew whether their child would take part in any SPT. A family history of atopic diseases was present both in children with and without atopy and probably did not cause misclassification. The prevalence of respiratory infections decreases with increasing age in the no asthma/no wheeze and wheeze groups, a fact which may be a result of recall bias. In contrast, the prevalence of at least one positive SPT increases with increasing age. The SPT procedures were performed in accordance with the same standard-

Table 5. Illustration of possible heterogeneity bias. Hypothetic subgroup I: children with recurrent respiratory tract infections (infections) and less atopy. Hypothetic subgroup II: children with fewer infections and more atopy. Last part of table shows actual observations, which are total of hypothetical observations in subgroups

		At least one positive SPT			OR
		No	Yes		
Infections		<i>n</i>	<i>n</i>		
Hypothetic subgroup I	No	20	5	25	1.0
	Yes	20	5	25	
		40	10	50	
Hypothetical subgroup II	No	30	78	108	1.1
	Yes	2	6	8	
		32	84	116	
All (actual observations)	No	50	83	133	0.3
	Yes	22	11	33	
		72	94	166	

dized method using standardized allergens and should thus not bias our results.

However, one explanation of our finding may be heterogeneity bias, as exemplified in Table 5. Imagine that the asthma group consists of two subgroups. In hypothetical subgroup I, the prevalence of airway infections is 50%, and the prevalence of children with positive SPT is 20%. Within this subgroup, there is no association between infections and SPT positivity (OR = 1.0). In hypothetical subgroup II, the prevalence of infections is 6.9%, and the prevalence of SPT positivity is 72%. No significant association is found in this subgroup either (OR = 1.1). However, when these two subgroups are combined, a negative association appears (OR = 0.3), as shown in Table 5. It is plausible to surmise that some children have asthma symptoms mainly in relation to infections, whereas others have asthma symptoms mainly triggered by allergen exposure. This kind of bias may occur in any population with a mixture of subgroups with unequal prevalence of exposures and disease.

Children in Hallingdal consistently had fewer infections and more SPT positivity than other children, which is an ecologic correlate to our finding that infections may reduce the risk of developing atopy on an individual level. In contrast, Forastiere et al. found that multiple episodes of pneumonia, bronchitis, and bronchiolitis in the first 2 years of life were weakly associated with an increased risk of atopy in their population-based study of 7–11-year-old schoolchildren (10). Furthermore, one study of 212 Finnish 7-year-olds found an excess of allergic diseases among children with a history of fever, gastrointestinal illness, or otitis media in infancy (19). However, the exposure variables and the time

period of exposure were different in these studies and not directly comparable.

It has been postulated that viral and bacterial infections may result in downregulation of IgE production (20, 21). It has also been suggested that respiratory viruses may promote allergic sensitization (22). Thus, in contrast to upper airway infections, one single or a few episodes of severe lower respiratory infections such as bronchitis could have an allergy-promoting effect, as found by Forastière et al. (10). Sigurs et al. have shown that RSV bronchiolitis was an important risk factor for the development of IgE antibodies and asthma (23). In contrast, in support of our finding, alterations of the Th2/Th1 balance may become important only in the presence of continued or recurrent infections (1). The infections must precede the atopy. Furthermore, frequent and long-lasting infections increase the probability that the infection comes in relation to an allergen exposure. This would imply that early and frequent infections during all the first 3 years of life could be sufficient to influence the immune response to airborne allergens. Furthermore, children may respond differently to infections early in life when the immune system is immature and thus more amenable to change (24). Genetic differences may explain an inconsistent effect of infections in the groups with asthma and wheeze compared to that without. Among those in the asthma group, there may be an increased susceptibility to immune system alterations early in life associated with the predisposition to developing allergy. In the present study, the asthma group had a higher prevalence of a family history of atopic diseases than the no asthma/no wheeze group, a fact which might suggest that there are genetic differences between the subgroups. The present study does not allow conclusions on the type of infection(s) that may reduce the risk of atopy.

It has been reported that measles infection may prevent the development of atopy in African children (3), implying that a single measles episode is sufficient to influence the immune response to airborne allergens for many years ahead. Furthermore, an inverse relation with hepatitis A infection suggests that infections transmitted through the fecal-oral route might also reduce the risk of developing atopy (4).

The "infection hypothesis" was based on the observation that having older siblings appeared to exert a stronger protective effect on the development of hay fever than having younger siblings (5). The finding has mainly been examined in young British adults, using a report of hay fever, nasal allergies, and allergic sensitization to common aeroallergens as outcome, and number of siblings

as exposure (7–9, 25). Only two studies have previously estimated the association between number of siblings and atopic status assessed by SPT in schoolchildren (6, 10). A negative association between number of siblings and SPT reactivity was found in pooled data of 9–11-year-old children from the former West and East Germany (6). In an Italian study of children 7–11 years of age, the prevalence of positive SPT decreased with increasing number of siblings (10). In these two studies, a similar pattern in the association between number of siblings and SPT positivity was found. It is noteworthy that the inverse association between the exposure and outcome variable appears for three siblings or more, and that the associations are weak. An interesting question is whether the same results would have been found if the data from West and East Germany had been analyzed separately. Thus, the number of siblings may also reflect the influence of other factors related to birth order than the possibility of cross-infection within families. Having three or more siblings was not common in the present study, resulting in low power to detect association.

The present study is the first study to estimate the association between recurrent respiratory tract infections and SPT positivity in subgroups of schoolchildren. In summary, our results are in accordance with the infection hypothesis, but may also be explained by heterogeneity of subjects within the asthma group.

Acknowledgments

The contribution of Prof. Jouni J. K. Jaakkola, the laboratory assistants, the participating children, their parents, and teachers are gratefully acknowledged. The work was funded by the Norwegian Research Council.

References

1. Cookson WOCM, Moffatt MF. Asthma: an epidemic in the absence of infection? *Science* 1997;**275**:41–2.
2. Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. *Science* 1997;**275**:77–8.
3. Shaheen SO, Aaby P, Hall AJ, et al. Measles and atopy in Guinea-Bissau. *Lancet* 1996;**347**:1792–6.
4. Matricardi P, 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.
5. Strachan DP. Hay fever, hygiene and household size. *BMJ* 1989;**299**:1259–60.
6. van Mutius E, Martinez FD, Fritzsch C, Nicolai T, Reitmeier P, Thieman HH. Skin reactivity and number of siblings. *BMJ* 1994;**308**:692–5.
7. Jarvis D, Chinn S, Luczynska C, Burney P. The association of family size with atopy and atopic disease. *Clin Exp Allergy* 1997;**27**:240–5.

8. Strachan DP, Harkins LS, Golding J. Sibship size and self-reported inhalant allergy among adult women. *Clin Exp Allergy* 1997;**27**:151-5.
9. Strachan DP, Harkins LS, Johnston IDA, Anderson HR. Childhood antecedents of allergic sensitization in young British adults. *J Allergy Clin Immunol* 1997;**99**:6-12.
10. Forastiere F, Agabiti D, Corbo G, et al. Socioeconomic status, number of siblings, and respiratory infections in early life as determinants of atopy in children. *Epidemiology* 1997;**8**:566-70.
11. Nystad W, Magnus P, Gulsvik A, Skarpaas I, Carlsen K. Changing prevalence of asthma in schoolchildren. Evidence for diagnostic changes in asthma in two surveys 13 years apart. *Eur Respir J* 1997;**10**:1046-51.
12. Bråbäck L, Breborowicz A, Dreborg S, Knutsson A, Pieklik H, Björkstén B. Atopic sensitization and respiratory symptoms among Polish and Swedish schoolchildren. *Clin Exp Allergy* 1994;**24**:826-35.
13. Peat J, van den Berg R, Green WF, Mellis C, Leeder S, Woolcock A. Changing prevalence of asthma in Australian children. *BMJ* 1994;**308**:1591-6.
14. Nicolai T, van Mutius E. Respiratory hypersensitivity and environmental factors: East and West Germany. *Toxicol Lett* 1996;**86**:105-13.
15. Nystad W, Magnus P, Røksund O, Svidal B, Hetlevik Ø. The prevalence of respiratory symptoms and asthma among schoolchildren in three different areas of Norway. *Pediatr Allergy Immunol* 1997;**8**:35-40.
16. Aas K, Belin L. Standardization of diagnostic work in allergy. First report from the standardization committee of the Northern Society of Allergology, 1971. *Acta Allergol* 1972;**27**:439-68.
17. Haahtela T. Allergen standardization and skin tests. In: Dreborg S, Frew A, editors. *Skin tests used for epidemiologic studies*. Allergy 1993;**48** Suppl 14:76-80.
18. SPSS for Windows. Chicago, IL: SPSS, Inc., 1994.
19. Backman A, Björkstén B, Ilmonen S, Juntunen K, Suoniemi I. Do infections in infancy affect sensitization to airborne allergens and development of allergic disease?. *Allergy* 1984;**39**:309-15.
20. Romagnani S. Human TH1 and TH2 subsets: regulation of differentiation and role in protection and immunopathology. *Int Arch Allergy Immunol* 1992;**98**:279-85.
21. Maggi E, Parronchi P, Manetti R, et al. Reciprocal regulatory effects of IFN-gamma and IL-4 on the *in vitro* development of human Th1 and Th2 clones. *Immunology* 1992;**148**:2142-7.
22. Busse WW. The relationship between viral infections and onset of allergic diseases and asthma. *Clin Exp Allergy* 1989;**19**:1-9.
23. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Björkstén B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics* 1997;**95**:500-5.
24. Holt PG, Sly PD. Allergic respiratory disease: strategic targets for primary prevention during childhood. *Thorax* 1997;**52**:1-4.
25. Strachan DP, Taylor EM, Carpenter RG. Family structure, neonatal infection, and hay fever in adolescence. *Arch Dis Child* 1996;**74**:422-6.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.