ORIGINAL ARTICLE

Airway infections in infancy and the presence of allergy and asthma in school age children

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11 November 2002**Aim:** To investigate the association between a history of otitis media and respiratory tract infections in infancy and allergic sensitisation and asthma in school age children of atopic and non-atopic parents.**Methods:** Based on a survey of 4585 schoolchildren, three groups of children aged 6–16 years were selected, of whom 502 were eligible with complete data: (1) diagnosed asthma ($n = 166$); (2) wheeze within past 12 months ($n = 155$); and (3) no asthma/no wheeze ($n = 181$). This study population was further analyzed by subgroups of children with or without parental atopy. Main outcome measures were allergic sensitisation verified by skin prick test and asthma.**Results:** Children of atopic parents had a reduced risk of developing allergic sensitisation in school age if they had a combined history of both otitis media and lower respiratory tract infections during infancy (adjusted odds ratio (aOR) 0.13, 95% CI 0.03 to 0.50) or a history of otitis media (aOR 0.31, 95% CI 0.12 to 0.83). A history of lower respiratory tract infections in infancy increased the risk of asthma in children of non-atopic parents (aOR 4.21, 95% CI 1.68 to 10.57).**Conclusion:** In the present study population, a history of otitis media in infancy seems to be negatively associated with allergic sensitisation in school age children of atopic parents, whereas a history of lower respiratory tract infections was positively associated with asthma in children of non-atopic parents.

The "hygiene hypothesis" was proposed to explain some of the increase in allergic diseases observed in the industrialised "western world" in recent years.¹ Improved hygiene and reduced family size resulting in reduced microbiological exposure has been considered to influence development of the immune system.^{2,3} The natural development of the immune system is thought to be partly dependent on environmental microbiological factors, which may influence the relation between the Th-1 and Th-2 system into Th-1 response, with a subsequent reduced risk of allergy.⁴ Lipopolysaccharide capsid antigens from bacteria interfere with cytokine expression of T cells and are suggested to disturb the Th1 differentiation process.⁵ Exposure of endotoxin or other bacterial components has been proposed to protect against the development of allergy in children raised in farmers' homes compared to schoolmates from non farming homes.⁶ Studies on respiratory tract infections (RTI) in early life, being mostly of viral origin, have given diverging results regarding later development of allergy,^{7,8} while studies on RTI as a risk for asthma seem more consistent,^{9,10} especially for the respiratory syncytial virus.¹¹ Otitis media (OM) is common in early childhood, especially in children with a family history of atopy, and often appears in combination with RTI.¹²

We have previously reported, based on the same population of schoolchildren, that recurrent RTI (RRTI) in the first three years of life protects against the development of atopy in school age children with a diagnosis of asthma.¹³ Since the immune system might be more susceptible and more easily influenced by infective agents during the first year of life,¹⁴ our aim was to assess whether or not a history of OM and RTI was associated with allergic sensitisation and asthma in school age children.

PATIENTS AND METHODS

Study design

A survey among 4585 schoolchildren aged 6–16 years living in Oslo, Hallingdal, and Odda using the ISAAC questionnaire

(International Study of Asthma and Allergies in Childhood) was performed in 1994.¹⁵ In Oslo, all children in a random sample of school classes ($n = 2577$) were selected. All schoolchildren in Hallingdal, a mountainous area in mid-south Norway ($n = 1177$), and Odda, an industrial area on the western coast of Norway ($n = 831$), participated. A subsequent clinical part of the study comprised a second questionnaire of early exposures and different health outcomes, and clinical examinations of skin prick test (SPT) sensitisation. Skin prick test was performed out of the pollen season.

Patients

All children from Hallingdal and Odda whose parents had reported either diagnosed asthma or wheeze within the past 12 months but without an asthma diagnosis, were invited, while the recruitment was randomly selected from Oslo. Recruitment to the control group was randomly selected from all three areas, among children whose parents had reported neither asthma nor wheeze during the past 12 months. Randomisation details and sampling probability have been described previously.¹³ Of the study population comprising 570 children, 502 (88%) were eligible with complete data and consisted of the following three diagnostic groups:

- Group 1 ($n = 166$); 134 children with current asthma (reported asthma symptoms the previous 12 months), and 32 children with previous, but no current asthma (comprising 16 children from Hallingdal and 16 children from Odda)
- Group 2 ($n = 155$); children with wheeze within the past 12 months, but no asthma diagnosis
- Group 3 ($n = 181$); children with no asthma/no wheeze.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio; OM, otitis media; RTI, respiratory tract infection; LRTI, lower respiratory tract infection; RRTI, recurrent respiratory tract infection; SPT, skin prick test

Table 1 Demographic details of study population and distribution of background variables in children of atopic and non-atopic parents

Variables	Children of atopic parents (n=270)	Children of non-atopic parents (n=232)	p value
Gender male, %	51.7	46.7	NS
Mean age in years (SD)	12.7 (2.5)	12.7 (2.6)	NS
Skin prick test positive, %	49.3	31.9	<0.001
Breast feeding, %	96.2	92.1	NS
Mothers smoking during infancy, %	24.4	30.2	NS
Mothers smoking during pregnancy, %	32.6	34.9	NS
Day care attendance, %	11.1	8.6	NS
Group 1 (asthma)	104 (62.7%)	62 (37.5%)	<0.001
Group 2 (wheeze)	95 (61.3%)	60 (38.7%)	<0.001
Group 3 (no asthma/no wheeze)	71 (39.2%)	110 (60.8%)	<0.001
Area			
Oslo	106	80	NS
Hallingdal	108	102	NS
Odda	56	50	NS

The regional distribution of the children was 186, 210, and 106 from Oslo, Hallingdal, and Odda, respectively. The children were further divided into two groups: children with (n = 270) and without (n = 232) parental atopy. Parental atopy was defined by parental report of either asthma, allergic rhinoconjunctivitis, or atopic dermatitis in at least one of the parents in the supplementary record form. Table 1 shows demographic data.

Variables

Health outcomes

The main outcome was allergic sensitisation verified by SPT. The SPT was performed according to the Nordic guidelines,¹⁶ using the following nine prevalent allergens: house dust mite (*Dermatophagoides pteronyssinus*), mould (*Cladosporium herbarum*), animal dander (dog and cat), birch pollen, grass (timothy) pollen, mugwort pollen, cows' milk, and hens' egg (Soluprick, ALK, Copenhagen, Denmark). A histamine dihydrochloride solution (10 mg/ml) was used as a positive control, and the allergen diluent as a negative control. Wheal size was measured after 15 minutes, and the histamine induced wheal recorded as half the sum of the largest plus the perpendicular diameter. A wheal size corresponding to the histamine wheal was considered as 3+, wheals of half of that size were given the value 2+. A subject was considered to be sensitised if at least one allergen was $\geq 2+$. We also applied a more strict definition using a cut off level of $\geq 3+$.

The other outcome was parental report of bronchial asthma diagnosed by a physician.

Exposures

The exposures were otitis media and respiratory tract infections. The recall of OM and RTI during infancy comprised only doctor diagnosed diseases as response to the question "Has a physician said that your child ever had otitis (the Norwegian expression of OM) during infancy?". Further, "Has a physician said that your child ever had recurrent respiratory tract infections during infancy?" did not discriminate how many infections the child had experienced (but ≥ 3 episodes/year are commonly applied as "recurrent"), and could include both upper RTI and lower RTI (LRTI). However, we asked separately for a diagnosis of bronchitis, bronchiolitis, and pneumonia, all which were included in the term LRTI, as applied in the present paper.

Respiratory tract infections were categorised into five subcategories: 1, no RRTI/no LRTI/no OM; 2, RRTI/no LRTI/no OM; 3, RRTI/LRTI/no OM; 4, RRTI/LRTI/OM; 5, no RRTI/no LRTI/OM. About one third of children reporting RRTI and

LRTI had also reported OM; the children with OM were therefore separated regarding reported RTI or not.

Covariates

We obtained information on covariates and potential confounders from the questionnaires.

Maternal smoking during pregnancy, infancy, and breast feeding were dichotomised (yes versus no). The mean period of breast feeding was 8.9 months (range 1–40 months), and 95.2% of the mothers breast fed for at least three months. Day care attendance was defined by kindergarten or private home care. The effects of number of siblings and maternal education (in years of education) were also explored in the models.

The Regional Medical Ethics Committee approved the study, and signed, informed consent was obtained from the child and his/her parents prior to inclusion in the sample population.

Statistics

Statistical analyses were performed using the following tools: Statistical Package for the Social Sciences (SPSS, release 8.0 for Windows; SPSS Inc., Chicago, IL, USA, 1998). Demographic data are given by percentage or as mean with standard deviation (SD); differences between groups were analysed by independent sample *t* test. The χ^2 test was used to compare categorical variables between groups. Statistical significance was defined as $p \leq 0.05$. Multiple logistic regression analysis was applied to estimate the association between the explanatory variables and the outcomes (allergic sensitisation and asthma). The results are presented as crude (c) and adjusted (a) odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

The prevalence of allergic sensitisation was different in children of atopic (49.3%) and non-atopic parents (31.9%) ($p < 0.001$). The prevalence decreased to 40.7% and 25.0%, respectively, using a more strict definition ($\geq 3+$). Table 1 shows the prevalence of parental atopy within the diagnostic groups. The prevalence of OM was 8.0% and 7.4% in children of atopic and non-atopic parents, respectively.

The association between OM with and without RTI during infancy and allergic sensitisation in school age in children of atopic parents was aOR 0.13 (95% CI 0.03 to 0.50) and 0.31 (95% CI 0.12 to 0.83), respectively (table 2). There was no such association in children of non-atopic parents, but in this group there was a significant association between a history of RRTI (without OM) and allergic sensitisation, aOR 0.10 (95% CI 0.01 to 0.92). Subsequent allergic sensitisation was not

Table 2 The prevalence and risk of allergic sensitisation (at least one positive skin prick test) and asthma by respiratory tract infections among children of parents with (n=270) and without (n=232) atopy

		Allergic sensitisation			Asthma		
Respiratory tract infections	n	Yes %	cOR	aOR (95%)*	Yes %	cOR	aOR (95% CI)†
1. Children with parental atopy (n=270)							
No	197	53.8	1.00	1.00	35.5	1.00	1.00
Recurrent	13	53.8	1.00	0.98 (0.30 to 3.13)	46.1	1.56	1.62 (0.51 to 5.09)
Recurrent and lower	20	50.0	0.86	0.62 (0.23 to 1.65)	55.0	2.22	2.19 (0.85 to 5.63)
Recurrent, lower, and otitis	16	18.8	0.20	0.13 (0.34 to 0.50)‡	50.0	1.81	1.67 (0.59 to 4.72)
Otitis	24	29.2	0.35	0.31 (0.12 to 0.83)‡	37.5	1.09	0.95 (0.39 to 2.32)
2. Children without parental atopy (n=232)							
No	158	33.5	1.00	1.00	21.5	1.00	1.00
Recurrent	12	8.3	0.18	0.10 (0.01 to 0.92)‡	33.3	1.82	2.02 (0.55 to 7.47)
Recurrent and lower	25	32.0	0.93	0.80 (0.30 to 2.14)	48.0	3.37	4.21 (1.68 to 10.57)‡
Recurrent, lower, and otitis	17	41.2	1.39	1.05 (0.35 to 3.17)	41.2	2.55	2.71 (0.93 to 7.84)
Otitis	20	25.0	0.66	0.77 (0.24 to 2.45)	25.0	1.22	1.30 (0.45 to 4.26)

Percentage of the children with allergic sensitisation and asthma within the subgroups are indicated.

*Adjusted for age, gender, area (Oslo, Hallingdal, Odda), and group (asthma, wheeze, no asthma/no wheeze).

†Adjusted for age, gender, and area.

‡Statistical significance.

associated with LRTI, and there was no difference between children of atopic and non-atopic parents.

The association between RTI and asthma in school age depended on whether or not LRTI was included. In children of non-atopic parents a history of RRTI/LRTI was significantly associated with a history of asthma, aOR 4.21 (95% CI 1.68 to 10.57), whereas such an association was not present in children of atopic parents (table 2). Possible confounding factors such as having siblings, day care attendance, maternal education, breast feeding, and maternal smoking during pregnancy and infancy were not associated with the health outcomes and did not influence the associations between the exposures and health outcomes. The associations between the exposures and the outcome was further explored using a more strict definition of allergic sensitisation ($\geq 3+$), which gave similar results. We also used place of living as strata. The results were consistent regarding the association between OM and allergic sensitisation. The association between RRTI/LRTI and asthma differed by place of living with a stronger but not significant association in Odda compared to Oslo and Hallingdal (data not shown). These results are most likely influenced by low statistical power.

Subanalysis on the associations between the parents different atopic diseases and allergic sensitisation and asthma in school age children showed that fathers' asthma was negatively associated with later asthma (OR 0.42, 95% CI 0.22 to 0.82). Fathers' atopic eczema was positively associated with later allergic sensitisation (OR 3.80, 95% CI 1.6 to 8.98). There was no influence of mothers' atopic diseases or fathers' rhinoconjunctivitis when analysed separately.

DISCUSSION

The present study on selected diagnostic groups of asthmatic, wheezy, and healthy children indicates that children of atopic parents who suffered from OM in infancy are less frequently sensitised to common allergens during school age, compared to children who did not have early OM. Asthma diagnosis during school age was positively associated with LRTI in infancy only in children of non-atopic parents.

The finding of less allergic sensitisation in children who had suffered from OM in infancy has to our knowledge not been shown previously. In a study from Oxfordshire no negative association was found between early infections, such as otitis media, tonsillitis, or upper and lower respiratory tract infections, and later development of hay fever, eczema, or asthma.¹⁷ Stratified analysis on parental atopy was, however,

not presented for these infections, but increasing use of antibiotics in the first two years of life was found to increase later atopy. No objective diagnosis of atopy was recorded, which might have influenced the result. In a Swedish study on 7 year old children, there was an increased risk of a positive SPT (OR 1.43, NS) and "any atopy diagnoses by a physician" (OR 2.65, $p < 0.001$) among children with otitis media in infancy.¹⁸ About 38% of the Swedish children had a family history of atopy, but no stratified analysis was presented. The authors concluded that, in contradiction to the working hypothesis of the study (performed before "the hygiene hypothesis" was introduced), infections in infancy did not facilitate the development of hypersensitivity to allergens and atopic disease. Any protective effect was, however, not found. In a recent published birth cohort study (longitudinal multicentre allergy study), Illi *et al* did not find any association between a group of bacterial infectious diseases (including OM plus 10 additional bacterial diseases) in infancy and atopic sensitisation at the age of 1, 3, and 5 years.¹⁴ The authors did not present results showing how each infectious disease was associated with the outcome, and the children were younger in this study. However, children who experienced two or more episodes of rhinitis in infancy without LRTI were less likely to be sensitised to inhalant allergens before the age of 5 years.¹⁴ Our finding of less allergic sensitisation after RRTI in infancy in the group of children of non-atopic parents supports these results, but the number of children in our groups was too small to be of scientific importance.

Other specific infections, such as hepatitis A and viral infections of the herpes type in early life, seem to be negatively related to later atopic diseases.¹⁴⁻¹⁹ Martinez *et al* found persistently lower serum IgE levels in children who had experienced non-wheezing respiratory infections in early life.⁸ Lower prevalence of atopic diseases was found in a study among children in an anthroposophic milieu in Sweden compared to a non-anthroposophic population.²⁰ The authors suggested that this could be a result of less vaccination as well as less use of antibiotics, and daily use of fermented foods. Recent theories suggest that microbial products, such as lipopolysaccharides from capsid antigens, via CD14 receptors affects the maturation of T cells in the Th1 direction, and that attenuation of this stimulus, either by defects in the gene of CD14 or lack of microbial stimulus, might drive the immune system in the Th2 direction.⁵ Otitis media infections are often of bacterial origin or develop into a bacterial stage, and therefore might induce a T cell response away from the Th2 direction towards a Th1 like response in susceptible infants. The results of the present study support this concept.

Our subanalysis of parental atopy showed that father's asthma was negatively associated with later asthma in the offspring. Previous studies have reported that paternal asthma was more closely related to childhood asthma than was maternal asthma in 9–11 year old children,²¹ and in children below 5 years of age.²² However, children's asthma above 5 years of age had a similar influence to fathers' and mothers' asthma²³; the same observation was seen in studies of older children and young adults.^{23–24} We have no clear explanation for the observed negative association between paternal and their offspring's asthma. Under-diagnosis of asthma among fathers is possible, which would underestimate an association between asthma in fathers and offspring. However, it is unlikely that this could explain the finding since fathers' reported atopic eczema was positively associated with later allergic sensitisation. In the Boston study, a similar influence was found for mothers' and fathers' eczema on the children's eczema, but no association was found in relation to hay fever (SPT not performed).²² It is more likely that some (but not all) of these differences could be attributed to the selection of subjects based on diagnostic groups in the present study.

Since the reports of RTI and OM in infancy were retrospectively done by the parents, there is a risk of preferential recall. However, since we asked for a doctor diagnosis of the diseases, the risk of not separating OM from "the common cold" was reduced. On the other hand, some under-reporting of RTI might be expected since episodes of mild diseases did not necessarily result in a doctor's consultation. If the infants, however, showed symptoms of OM or LRTI, most of the parents would probably have consulted a doctor. Parents with atopic diseases might be more aware of symptoms and illnesses, and subsequently more frequently seek medical advice than non-atopic parents, resulting in recall bias. Asthma development in infants often starts with recurrent wheeze; thus reported LRTI could represent early asthma disease, and thereby bias the association with asthma diagnosis. Furthermore, the sample size is small in our study, and the findings need to be replicated in a prospective study.

Our study showed that the strongest association between later asthma and early childhood infections was found among non-atopic children. Nafstad *et al* found in a Norwegian population that RRTI in early life was associated with increased risk of asthma development at 4 years of age,¹⁰ but no subgroup analyses of parental atopy were performed. However, the findings of the present study are in accordance with those of a German study where repeated fever episodes in the first year of life and antibiotic treatment during the first three years of life were strongly associated with later asthma prevalence in school age, most clearly observed among non-atopic children and within the asthmatic children there was a strong negative association with later atopy prevalence, most clearly observed among non-atopic children.⁹ Since most of the children with asthma came from the non-atopic population, this finding indicates a susceptible subgroup of asthmatics without known risk factors. A prospective birth cohort investigating the relation between indoor allergen exposure and the development of asthma supports this hypothesis; Lau *et al* found that the induction of specific IgE responses and the development of childhood asthma are probably determined by independent factors.²⁵

Conclusion

A diagnosis of OM in infancy was negatively associated with allergic sensitisation in school age children with atopic parents. Lower respiratory tract infections during infancy in children with non-atopic parents were positively associated with asthma diagnosis during school age. Thus, it is likely that different respiratory tract infections during the first year of life may have different bearings on later atopic sensitisation and asthma.

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