

Original article

Rhinoconjunctivitis in 5-year-old children: a population-based birth cohort study

Background: There is a paucity of data on the prevalence, risk factors and natural history of rhinitis in early childhood.

Objective: Within the context of a whole-population birth cohort we investigated the prevalence of and risk factors for current rhinoconjunctivitis (CRC) at age 5 years.

Methods: Children were followed prospectively to age 5 years [questionnaires ($n = 815$), skin testing ($n = 717$), specific immunoglobulin E ($n = 478$), lung function ($n = 711$), dry air challenge ($n = 556$)]. Endotoxin and allergen exposures were measured in dust samples.

Results: The prevalence of rhinitis ever, current rhinitis and rhinoconjunctivitis was 28.2%, 26.1%, and 12.1%, respectively. Asthma, wheeze and eczema coexisted with CRC ($P \leq 0.01$). In a multivariate model, maternal asthma (OR 2.38, 95% CI: 1.30–4.38, $P = 0.005$), paternal hay fever (1.96, 1.11–3.46, $P = 0.02$) and sensitization to grass (3.46, 1.86–6.42, $P < 0.001$) and cat (2.42, 1.14–5.18, $P = 0.02$) remained significant and independent associates of CRC. Whilst almost half of children with CRC were nonatopic, there was little difference in risk factors between atopic and nonatopic CRC. Amongst children with current wheeze, the presence of concurrent CRC had no effect on either severity or frequency of wheezy episodes. There was no difference in specific airway resistance, forced expiratory volume in 1 second (FEV₁) or airway reactivity between children with and without CRC after adjustment for the presence of wheeze.

Conclusion: Family history of allergic disease and sensitization to inhalant allergens are risk factors for rhinoconjunctivitis in preschool children. In this age group, there is no association between the presence of rhinoconjunctivitis and severity of wheeze, increased airway reactivity and reduced lung function.

S. Marinho, A. Simpson, L. Lowe, P. Kissen, C. Murray, A. Custovic

University of Manchester, Academic Division of Medicine and Surgery, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK

Key words: allergy; childhood; epidemiology; rhinitis; rhinoconjunctivitis.

Susana Marinho MD
North West Lung Centre
University of South Manchester NHS Foundation Trust
Manchester M23 9LT
UK

Accepted for publication 10 November 2006

Rhinitis is a global health problem (1–4) and one of the most common chronic conditions in children (5). Several studies have provided compelling evidence that the prevalence of rhinitis is increasing, especially in children and young adults (1–4). Rhinitis is often undiagnosed (6), its prevalence underestimated and many patients fail to seek medical assistance.

Although usually not a severe disease, rhinitis may significantly impair the quality of life of patients (1, 7). It affects school performance, work productivity and has been recognized as a cause of absenteeism (1, 8, 9). Asthma and rhinitis are common co-morbidities amongst adults and older children, and are linked by epidemiological and patho-physiological characteristics and a common therapeutic approach (1).

Despite the recognition that rhinitis affects an increasing proportion of the paediatric population, at present there is a paucity of epidemiological data regarding its distribution, risk factors and natural history. Thus, in the current study we aimed to investigate the prevalence of

symptoms suggestive of allergic rhinitis [using current rhinoconjunctivitis (CRC) as a marker] in preschool children in an epidemiological setting, within the context of a large prospective birth cohort study. In addition, we evaluated risk factors associated with the development of this phenotype during the first 5 years of life, its association with symptoms suggestive of other allergic diseases, and relationship with the objective measures of lung function and airway reactivity in preschool age.

Methods

Manchester Asthma and Allergy Study (MAAS) is an unselected population-based birth cohort study, described in detail elsewhere (10, 11). Subjects were recruited during the first trimester of pregnancy. Both parents completed a questionnaire regarding allergic diseases and skin prick testing (SPT) to common inhalant allergens. Children were followed prospectively and attended review clinics at ages 3 and 5 years (± 4 weeks). The study was approved by the Local Research Ethics Committee. Written informed consent was

obtained from subjects' parents/guardians, and children gave their assent.

Outcomes

Symptoms. A validated questionnaire (12) was interviewer-administered to collect information on parentally reported symptoms, doctor-diagnosed illnesses and treatments received. Rhinitis was defined at age 5 years as a 'sneezing or a runny or blocked nose when the child DID NOT have a cold or chest infection'. Questions included the presence of symptoms during lifetime (rhinitis ever) and in the past 12 months (current rhinitis [CR]).

Amongst children with current rhinitis, CRC was defined as a positive answer to the question 'In the past 12 months, has this nose problem been accompanied by itchy watery eyes?' The severity of CRC was assessed by its interference in daily activities.

According to parentally reported history of wheeze at two follow ups, children were assigned to the following wheeze phenotypes (13): *No wheezing* – no wheeze during the first 3 years of life, no wheezing ever by age 5; *Transient early wheezing* – wheezing during the first 3 years, no wheezing in the previous 12 months at age 5 years; *Late-onset wheezing* – no wheeze during the first 3 years, wheezing in the previous 12 months at age 5; *Persistent wheezing* – wheezing during the first 3 years, wheezing in the previous 12 months at age 5. The severity of wheezing symptoms was assessed by several parameters including sleep disturbance, speech limitation, use of medication, frequency of wheeze and the number of school days missed, emergency visits and hospital admissions.

Eczema was defined as an itchy rash which was coming and going for at least 6 months.

Lung function was assessed at age 5 using plethysmography (specific airway resistance, sR_{aw} ; 14) and spirometry (using incentive animation software). Spirometry was repeated at 30-s intervals until three technically acceptable traces were obtained [the highest forced expiratory volume in 1 second (FEV_1) was recorded].

Airway reactivity was assessed by eucapnic voluntary hyperventilation (EVH-dry air) challenge (15). Subjects hyperventilated gas containing 21% O_2 , 5% CO_2 , remainder N_2 with a water content of < 10 mg/l for 6 min at a ventilation rate of 75% of maximum voluntary ventilation. The highest sR_{aw} value measured at 2, 5 or 10 min after challenge was recorded, and the response was expressed as per cent change in sR_{aw} . Positive EVH challenge was defined as > 60% increase in sR_{aw} .

Allergic sensitization. We performed SPT at age 5 years (*Dermatophagoides pteronyssinus*, cat, dog, mixed grasses, mixed moulds, milk and egg; Bayer, Elkhart, IN, USA), and defined sensitization as a mean wheal diameter at least 3 mm greater than that of the negative control. Total and specific serum immunoglobulin E (IgE; *D. pteronyssinus*, cat, dog, grass, milk, egg and peanut) was measured by ImmunoCAP® (Phadia, Uppsala, Sweden). Sensitization was defined as specific IgE concentration > 0.2 kU_A/l.

Environmental exposures

We collected information on environmental tobacco smoke (ETS) exposure, pet ownership and contact, childcare arrangements and vaccination uptake by questionnaires.

We visited homes immediately after the child's birth and at the age of 3 and 5 years. Dust samples from the child's bed, the child's bedroom floor, the parental bed and the lounge floor were collected by vacuuming 1 m² areas for 2 min in a standardized fashion. Mite, cat and dog allergens were assayed using enzyme-linked immunoassays (16). We estimated cumulative allergen exposure over the

first 5 years of life as a sum of allergen levels in four sites at three time points (allergen concentration – µg/g). Endotoxin content in the dust collected at the age of 5 was measured by a kinetic limulus assay (EU/mg; 17).

Statistical analysis

Statistical analysis was carried out using SPSS 13.0. Endotoxin and allergen data were subject to a log_e-transformation; the results are presented as geometric mean (GM) and 95% confidence intervals (CI). The sR_{aw} measurements were subject to a log_e-transformation prior to analysis. FEV_1 data followed a normal distribution.

Appropriate univariate tests (*t*-test and chi-square test) were used to investigate the differences between children with and without symptoms. Further analysis was carried out using logistic regression (univariate, followed by a forward stepwise multivariate analysis). The size of the effect was measured using the odds ratio (OR) and 95% CI.

Results

The study profile is illustrated in Fig. 1. We reviewed 1025 children at age 5 years, of which 122 randomized to an environmental intervention (11) and 88 with incomplete data were excluded. Questionnaire data were available on 815 children (54.7% boys), skin tests on 717, IgE on 478 (470 with both skin tests and IgE) and lung function on 711 children.

Rhinitis ever was reported by 230 (28.2%), CR by 213 (26.1%), CRC by 99 (12.1%) and doctor-diagnosed allergic rhinitis/hay fever by 43 (5.3%) of participants. Amongst children with CRC, the symptoms did not

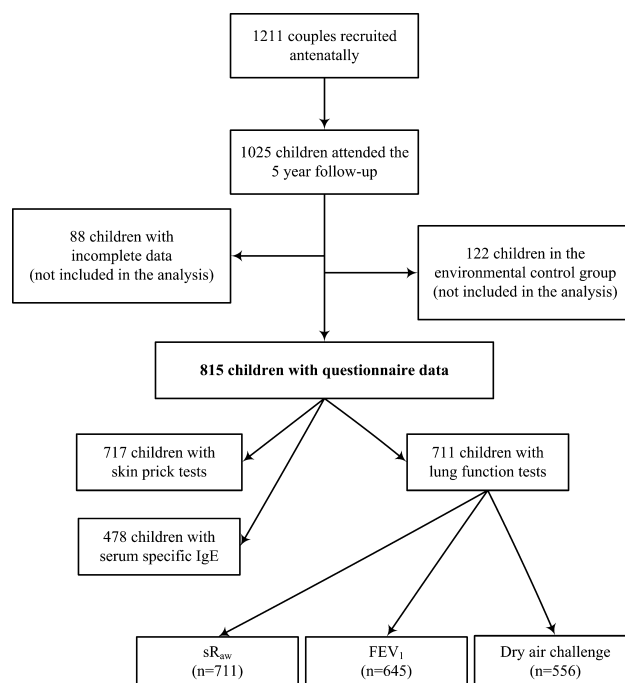


Figure 1. Study profile.

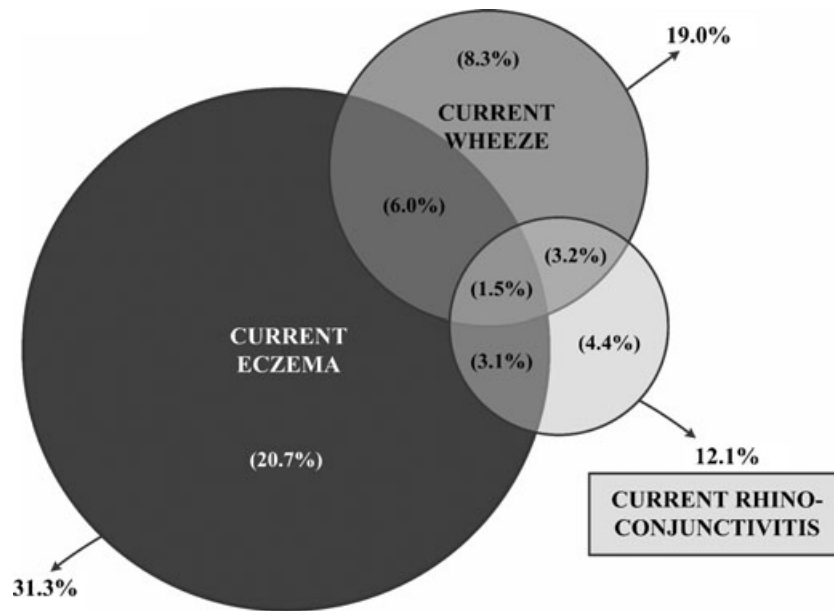


Figure 2. Prevalence of current rhinoconjunctivitis, wheeze and eczema in the study population.

interfere with their activities in 38.4%, interfered a little in 42.4%, moderately in 14.1% and a lot in 5.1%. The prevalence and co-morbidity of CRC, wheeze and eczema in the study population is illustrated in Fig. 2. In the whole population, 26.8% children were sensitized to at least one allergen on skin test and 34.9% on IgE.

Factors associated with current rhinoconjunctivitis

Results of the univariate analysis are presented in Table 1. Wheeze and eczema in the first year of life were associated with an increased risk of CRC. Children with parental atopy and a family history of allergic diseases were more likely to have CRC. There was no effect of gender, position in sibship, parental smoking, breastfeeding, pet ownership or contact, childcare arrangements or season of birth (even amongst pollen-sensitized children). Cumulative mite allergen exposure was significantly and inversely associated with CRC. When adjusting for mite sensitization, this effect was only observed amongst nonsensitized children (OR 0.78, 95% CI: 0.63–0.96, $P = 0.02$). There was no association between cat and dog allergen exposure and CRC, with or without adjustment for specific sensitizations. We found no association between CRC and endotoxin exposure.

Allergic sensitization. The analysis of the association between sensitization to each of the allergens tested (either on IgE or SPT) and rhinoconjunctivitis is shown in Table 1. When skin test results were used, CRC was significantly associated with sensitization to grass pollen, mite, cat and dog, but not to mould or food allergens (Table 1); similar results were obtained for specific IgE,

with significant associations with all the inhalant allergens, peanut and milk, but not egg (Table 1).

Multiple logistic regression analysis

We performed multiple logistic regression analysis including all the factors associated with CRC in the univariate analysis in two separate models, considering sensitization on either SPT or IgE. The factors identified as independently associated with CRC were maternal asthma, paternal hay fever and sensitization to grass pollen and to cat (the size of their effect varied slightly depending on whether we used SPT or IgE data), as shown below:

Model 1 (SPT).

- Maternal asthma: adjusted OR 2.38, 95% CI: 1.30–4.38, $P = 0.005$
- Paternal hay fever: adjusted OR 1.96, 95% CI: 1.11–3.46, $P = 0.02$
- Sensitization to grass pollen: adjusted OR 3.46, 95% CI: 1.86–6.42, $P < 0.001$
- Sensitization to cat: adjusted OR 2.42, 95% CI: 1.14–5.18, $P = 0.02$

Model 2 (IgE).

- Maternal asthma: adjusted OR 3.19, 95% CI: 1.60–6.36, $P = 0.001$
- Paternal hay fever: adjusted OR 2.04, 95% CI: 1.02–4.05, $P = 0.04$
- Sensitization to grass pollen: adjusted OR 2.28, 95% CI: 1.07–4.84, $P = 0.03$
- Sensitization to cat: adjusted OR 3.35, 95% CI: 1.36–8.25, $P = 0.009$

Table 1. Risk factors for current rhinoconjunctivitis: univariate analysis

	Current rhinoconjunctivitis		OR	95% CI	P-value
	Yes, n (%)	No, n (%)			
Male gender	60/99 (60.6)	386/716 (53.9)	1.32	0.86–2.02	0.21
One or both parents atopic	91/99 (91.9)	567/716 (79.2)	2.99	1.42–6.29	0.004
Maternal atopy	64/99 (64.6)	368/716 (51.4)	1.73	1.12–2.68	0.01
Paternal atopy	65/99 (65.7)	390/716 (54.5)	1.60	1.03–2.48	0.04
Maternal hay fever	32/99 (32.3)	156/716 (21.8)	1.71	1.09–2.71	0.02
Paternal hay fever	31/99 (31.3)	148/716 (20.7)	1.75	1.10–2.78	0.02
Maternal asthma ever	29/99 (29.3)	129/716 (18.0)	1.89	1.18–3.03	0.009
Paternal asthma ever	17/99 (17.2)	82/716 (11.5)	1.60	0.91–2.84	0.11
Maternal eczema	16/99 (16.2)	108/716 (15.1)	1.09	0.61–1.93	0.78
Paternal eczema	13/99 (13.1)	59/716 (8.2)	1.68	0.89–3.20	0.11
First born	52/99 (52.5)	342/716 (47.8)	1.21	0.79–1.84	0.38
Age started at nursery					
Home	19/83 (22.9)	146/606 (24.1)		Reference group	
0–6 months	7/83 (8.4)	61/606 (10.1)	0.88	0.35–2.21	0.78
7–12 months	6/83 (7.2)	47/606 (7.8)	0.98	0.37–2.60	0.97
After 12 months	51/83 (61.4)	352/606 (58.1)	1.10	0.64–1.95	0.71
Never breastfed	23/94 (24.5)	193/682 (28.3)	1.22	0.74–2.01	0.44
Cat ownership	27/99 (27.3)	177/716 (24.7)	1.14	0.71–1.83	0.58
Dog ownership	19/99 (19.2)	138/716 (19.3)	1.00	0.58–1.70	0.99
Maternal smoking	11/99 (11.1)	92/716 (12.8)	0.85	0.44–1.65	0.63
Paternal smoking	27/99 (27.3)	181/716 (25.3)	1.11	0.69–1.78	0.67
Asthma ever	31/99 (31.3)	124/716 (17.3)	2.18	1.37–3.47	0.001
Wheeze ever	58/99 (58.6)	234/716 (32.7)	2.91	1.90–4.48	<0.001
Phenotypes of wheeze					
Wheeze never	32/85 (37.6)	388/644 (60.2)		Reference group	
Transient early wheeze	19/85 (22.4)	156/644 (24.2)	1.48	0.81–2.68	0.20
Late-onset wheeze	9/85 (10.6)	33/644 (5.1)	3.31	1.46–7.51	0.004
Persistent wheeze	25/85 (29.4)	67/644 (10.4)	4.52	2.52–8.11	<0.001
Current wheeze	38/99 (38.4)	117/716 (16.3)	3.19	2.03–5.01	<0.001
Wheeze in the first year of life	31/91 (34.1)	153/678 (22.6)	1.77	1.11–2.84	0.02
Eczema ever	55/99 (55.6)	299/716 (41.8)	1.74	1.14–2.66	0.01
Current eczema	37/98 (37.8)	218/716 (30.4)	1.39	0.89–2.15	0.15
Eczema in the first year of life	40/92 (43.5)	214/678 (31.6)	1.67	1.07–2.60	0.02
Sensitization to any allergen					
SPT	47/88 (53.4)	145/629 (23.1)	3.83	2.42–6.05	0.001
IgE	37/63 (58.7)	130/415 (31.3)	3.12	1.81–5.37	<0.001
Sensitization to mite					
SPT	22/88 (25.0)	83/627 (13.2)	2.19	1.28–3.73	0.004
IgE	20/63 (31.7)	67/415 (16.1)	2.42	1.34–4.36	0.003
Sensitization to cat					
SPT	20/88 (22.7)	40/628 (6.4)	4.32	2.39–7.82	<0.001
IgE	15/63 (23.8)	28/415 (6.7)	4.32	2.16–8.66	<0.001
Sensitization to dog					
SPT	12/88 (13.6)	24/629 (3.8)	3.98	1.91–8.28	<0.001
IgE	13/63 (20.6)	33/415 (8.0)	3.01	1.49–6.10	0.002
Sensitization to grass pollen					
SPT	36/88 (40.9)	84/629 (13.4)	4.49	2.77–7.28	<0.001
IgE	23/63 (36.5)	64/415 (15.4)	3.15	1.77–5.62	<0.001
Sensitization to mould*					
SPT	2/88 (2.3)	10/613 (1.6)	1.40	0.30–6.51	0.67
Sensitization to peanut†					
IgE	11/63 (17.5)	22/415 (5.3)	3.78	1.73–8.24	0.001
Sensitization to milk					
SPT	1/88 (1.1)	3/614 (0.5)	2.34	0.24–22.76	0.46
IgE	14/63 (22.2)	43/413 (10.4)	2.46	1.26–4.82	0.009
Sensitization to egg					
SPT	2/88 (2.3)	10/614 (1.6)	1.41	0.30–6.52	0.66
IgE	8/63 (12.7)	36/415 (8.7)	1.53	0.68–3.47	0.31

Table 1. Continued

	Current rhinoconjunctivitis		OR	95% CI	P-value
	Yes, n (%)	No, n (%)			
Cumulative Der p 1 exposure ($\mu\text{g/g}$; GM and 95% CI)	25.53 (18.17–35.87)	41.68 (37.34–46.53)	0.81	0.68–0.98	0.03
Cumulative Fel d 1 exposure ($\mu\text{g/g}$; GM and 95% CI)	29.96 (18.17–49.90)	28.22 (23.57–34.12)	1.02	0.91–1.13	0.79
Cumulative Can f 1 exposure ($\mu\text{g/g}$; GM and 95% CI)	27.11 (17.12–42.95)	21.76 (18.54–25.53)	1.03	0.91–1.17	0.63
Endotoxin load (U/mg; GM and 95% CI)	14.88 (12.18–18.36)	16.44 (14.88–17.99)	0.94	0.78–1.13	0.50

GM, geometric mean; CI, confidence interval; IgE, immunoglobulin E; SPT, skin prick test; OR, odds ratio.

* Specific IgE to mould not measured at age 5.

† Children not skin tested to peanut at age 5.

Atopic vs nonatopic rhinoconjunctivitis

Almost half of the children with CRC were not atopic. We compared children with atopic CRC (symptoms and positive SPT; $n = 47$) and nonatopic CRC (symptoms and negative SPT; $n = 41$) to ascertain whether there were any differences in risk factors between these groups. The prevalence of current eczema was higher in atopic than nonatopic CRC (47.8% vs 26.8%, $P = 0.05$). There was a trend towards more boys in the atopic CRC group ($P = 0.07$). We found no other significant differences between these groups (Table 2), in particular, there was no difference in the severity or seasonal pattern of symptoms.

Current rhinoconjunctivitis and severity of lower airway disease

Using never wheezers as a reference, CRC was significantly more prevalent amongst the persistent and late-onset, but not transient early wheezers (Table 1).

Amongst the group of children with current wheeze ($n = 155$), the presence of concurrent CRC had no effect on either severity or frequency of wheezy episodes (Table 3). Similarly, amongst the 99 children with CRC, the presence of wheeze did not influence the severity of rhinoconjunctivitis symptoms [some interference with daily activities: 60.5% vs 62.3%, wheezers ($n = 38$) vs nonwheezers ($n = 61$), respectively, $P = 0.86$].

Lung function and airway reactivity. There was no difference in FEV₁ per cent predicted values or airway reactivity between children with and without CRC (Table 4). Children with CRC had significantly higher sR_{aw} (i.e. reduced lung function) compared to those without CRC (Table 4). However, in the multivariate analysis adjusting for the presence of wheeze, there were no differences in sR_{aw} between children with or without CRC (kPa/s, estimated marginal means and 95% CI: 1.23, 1.18–1.27 vs 1.19, 1.17–1.21, CRC vs no CRC, $F = 2.01$, $P = 0.16$); there was no interaction between current wheeze and CRC ($F = 0.39$, $P = 0.54$).

Discussion

Principal findings

Our data show that symptoms suggestive of allergic rhinitis in an epidemiological setting are very common in early childhood, and frequently occur concurrently with other allergic disorders (wheeze, eczema). Family history of asthma or hay fever and child's allergic sensitization (in particular to grass pollen and cat) were significant and independent predictors of rhinoconjunctivitis. The observation that doctor diagnosis of rhinitis or hay fever was only reported by a minority of the parents of symptomatic children confirms that this condition is under-diagnosed. Most cases of rhinitis were associated with low morbidity, and this may partly account for the low diagnostic rate.

Almost half of the children reporting rhinoconjunctivitis were not sensitized, raising the question of the nature of the phenotype of 'nonallergic rhinoconjunctivitis'. However, there were very few differences in predictors and associates of 'allergic' and 'nonallergic rhinoconjunctivitis'. This suggests that rather than overestimating the prevalence of the disease by not taking sensitization into account, including only sensitized children in the definition of the phenotype may effectively exclude a considerable number of symptomatic children.

We found no effect of rhinoconjunctivitis on either severity or frequency of wheeze; similarly, amongst children with rhinoconjunctivitis, the presence of wheeze did not affect the severity of their rhinitis. There were no differences in lung function and airway reactivity between children with or without rhinoconjunctivitis after adjusting for the presence of wheeze, suggesting that wheeze severity, increased airway reactivity and reduced lung function are not associated with upper respiratory symptoms in this age group.

Limitations

We have used CRC as the most stringent epidemiological definition of allergic rhinitis. However, this differs from

Table 2. Risk factors for atopic compared with nonatopic rhinoconjunctivitis

	Current rhinoconjunctivitis		<i>P</i> -value†
	Atopic, <i>n</i> (%)	Nonatopic, <i>n</i> (%)	
Male gender	32/47 (68.1)	20/41 (48.8)	0.07
One or both parents atopic	42/47 (89.4)	39/41 (95.1)	0.32
Maternal atopy	30/47 (63.8)	27/41 (65.9)	0.84
Paternal atopy	29/47 (61.7)	28/41 (68.3)	0.52
Maternal hay fever	17/47 (36.2)	12/41 (29.3)	0.49
Paternal hay fever	15/47 (31.9)	13/41 (31.7)	0.98
Maternal asthma	10/47 (21.3)	15/41 (36.6)	0.11
Paternal asthma	9/47 (19.1)	5/41 (12.2)	0.37
Maternal eczema	7/47 (14.9)	7/41 (17.1)	0.78
Paternal eczema	5/47 (10.6)	6/41 (14.6)	0.57
First born	25/47 (53.2)	22/41 (53.7)	0.97
Age started at nursery			
Home	8/37 (21.6)	8/36 (22.2)	Reference group
0–6 months	3/37 (8.1)	4/36 (11.1)	0.75*
7–12 months	4/37 (10.8)	2/36 (5.6)	0.49*
After 12 months	22/37 (59.5)	22/36 (61.1)	1.0*
Never breastfed	12/45 (26.7)	9/39 (23.1)	0.71
Cat ownership	15/47 (32.6)	9/41 (22.0)	0.27
Dog ownership	4/47 (8.7)	7/41 (17.1)	0.24
Maternal smoking	5/47 (10.6)	6/41 (14.6)	0.57
Paternal smoking	14/47 (29.8)	10/41 (24.4)	0.57
Asthma ever	12/47 (25.5)	14/41 (34.1)	0.38
Wheeze ever	25/47 (53.2)	24/41 (58.5)	0.62
Phenotypes of wheeze			
Wheeze never	16/40 (40.0)	14/35 (40.0)	Reference group
Transient early wheeze	6/40 (15.0)	10/35 (28.6)	0.31*
Late-onset wheeze	5/40 (12.5)	4/35 (11.4)	0.91*
Persistent wheeze	13/40 (32.5)	7/35 (20.0)	0.41*
Current wheeze	19/47 (40.4)	13/41 (31.7)	0.40
Wheeze in the first year of life	12/44 (27.3)	15/37 (40.5)	0.21
Eczema ever	29/47 (61.7)	18/41 (43.9)	0.10
Current eczema	22/46 (47.8)	11/41 (26.8)	0.04
Eczema in the first year of life	21/44 (47.7)	12/38 (31.6)	0.14
CRC-interference with daily activities	31/47 (66.0)	24/41 (58.5)	0.47
Seasonal pattern of CRC symptoms			
Intermittent	5/47 (10.6)	1/39 (2.6)	Reference group
Perennial	3/47 (6.4)	5/39 (12.8)	0.11*
Spring/summer	36/47 (76.6)	31/39 (79.5)	0.19*
Winter	3/47 (6.4)	2/39 (5.1)	0.40*
Cumulative Der p 1 exposure (µg/g; GM and 95% CI)	29.67 (18.92–46.99)	28.50 (16.95–48.42)	0.90
Cumulative Fel d 1 exposure (µg/g; GM and 95% CI)	33.12 (15.03–72.24)	29.37 (13.87–62.80)	0.84
Cumulative Can f 1 exposure (µg/g; GM and 95% CI)	21.54 (10.91–42.10)	27.11 (14.15–51.42)	0.62
Endotoxin load (U/mg; GM and 95% CI)	16.44 (12.18–22.20)	13.74 (9.58–16.69)	0.43

CRC, current rhinoconjunctivitis; GM, geometric mean; CI, confidence interval.

* *P*-value derived from logistic regression.† *P*-value derived from chi-square test except where marked with *.

clinical practice, in which allergic rhinitis is usually diagnosed in patients with appropriate symptoms and evidence of allergic sensitization.

In large-scale epidemiological studies, ISAAC questionnaire rhinitis core questions are most commonly used to identify a population with symptoms suggestive of rhinitis (12, 18, 19). The validity of these has been demonstrated for older children; when compared with SPTs, the questions on rhinoconjunctivitis were highly

specific (92.8%) but not very sensitive (25.7%; 20). Our population was younger compared with previously mentioned studies, and it is possible (although unlikely) that this has affected the outcomes.

Epidemiological studies in large populations of pre-school children are based on parental reporting. We cannot exclude a possibility of reporting bias from symptomatic parents, but this is unlikely to have affected the results.

Table 3. Frequency and severity of wheeze amongst current wheezers ($n = 155$) in relation to the presence or absence of current rhinoconjunctivitis

	Current rhinoconjunctivitis		<i>P</i> -value
	Yes, <i>n</i> (%)	No, <i>n</i> (%)	
Number of wheezing attacks $\geq 4^*$	14/38 (36.8)	34/117 (29.1)	0.37
Sleep disturbance ≥ 1 night per week*	11/38 (28.9)	27/117 (23.1)	0.47
Speech limitation* $\ddagger$	9/38 (23.7)	23/117 (19.7)	0.59
Nocturnal awakenings with SOB $\dagger$	19/38 (50)	51/117 (43.6)	0.49
Nocturnal awakening with tightness of chest $\dagger$	15/38 (39.5)	43/117 (36.8)	0.76
Use of medication for wheeze/asthma (inhaled or systemic)*	28/38 (73.7)	81/117 (69.2)	0.6
Number of visits for wheezing or asthma*			
Asthma Nurse ≥ 4	1/38 (2.6)	1/115 (0.9)	0.44
Family Doctor ≥ 4	5/38 (13.2)	14/116 (12.1)	1.00
Hospital emergency department ≥ 1	2/38 (5.3)	11/115 (9.6)	0.52
Number of school days missed due to wheezing or asthma $\geq 6^*$	2/38 (5.3)	17/117 (14.5)	0.16
Hospital admissions due to asthma $\geq 1^*$	3/38 (7.9)	8/117 (6.8)	0.73

SOB, shortness of breath.

* Questions refer to the last 12 months.

$\dagger$ Questions refer to the child's lifetime.

$\ddagger$ Wheeze severe enough to limit the child's speech to only one or two words at a time between breaths.

Table 4. Lung function and airway reactivity in children with and without current rhinoconjunctivitis

	Current rhinoconjunctivitis		<i>P</i> -value
	Yes, <i>n</i> (%)	No, <i>n</i> (%)	
sR _{aw} (GM and 95% CI)	1.21 (1.16–1.27)	1.16 (1.14–1.17)	0.03
FEV ₁ per cent predicted (mean and 95% CI)	108.5 (104.5–112.4)	111.1 (109.7–112.5)	0.19
Airway reactivity – positive EVH challenge, <i>n</i> (%)	6/74 (8.1)	30/482 (6.2)	0.54

GM, geometric mean; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; sR_{aw}, specific airway resistance.

Meaning of the study

Our results confirm that the prevalence of current rhinitis and rhinoconjunctivitis in children in the UK is amongst the highest in the world (2–4, 19), and that there is a strong genetic component (as evidenced by the two- to threefold increase in risk associated with parental allergic diseases; 21). Whilst in some studies rhinoconjunctivitis was reported to be more prevalent in boys (21), we did not confirm this finding.

In contrast to several previous studies (22), we found no association between position in sibship and the risk of rhinoconjunctivitis. Daycare attendance (23), endotoxin exposure (24) and immunizations (25) have been suggested as protective factors; we failed to reproduce these findings (we have to note that vaccination uptake in our cohort was almost 100%).

The evidence regarding the effect of breastfeeding on allergic disease is inconclusive, with some studies reporting protection (26), others an increased risk (27) or no effect (21). In our population, duration of breastfeeding did not alter the risk of having rhinoconjunctivitis. We showed no association between ETS exposure and

rhinoconjunctivitis, which is consistent with other studies (21) and with our previous finding on the lack of effect of ETS on atopy (28).

The question of the relationship between allergen exposure and development of allergic disease is under considerable debate (29). In the univariate analysis, we found children with CRC to have significantly lower mite allergen exposure compared to those without, and further analysis confirmed this amongst nonsensitized children only. This finding failed to reach significance in the multivariate model.

The association between pet exposure, sensitization and allergic disease is complex, with some studies showing an increase, decrease or no effect of pet exposure (30). Our findings add to this controversy, by showing no association between CRC and pet exposure.

Despite the fact that we used a stringent epidemiological definition of allergic rhinitis (4), almost half of these children were not sensitized to any inhalant or food allergen. However, apart from the presence/absence of allergic sensitization, very few differences were found when comparing these two groups of clearly symptomatic children. Furthermore, there was no difference in the severity of symptoms, and no difference in seasonal pattern. This raises the question of the nature of these phenotypes and whether in some young children symptoms may precede the evidence of allergic sensitization. We speculate that at least some of these children may initially have only local IgE production in response to a sensitizing allergen, which has been demonstrated in the nasal mucosa of patients with allergic rhinitis (31), and may subsequently progress to a systemic IgE production detectable by means of skin tests or measurement of serum-specific IgE. This may explain the striking similarities found between atopic and nonatopic symptomatic children (as they would share the same disease pathways),

and highlights the need for the development of techniques for the detection of local tissue allergy. There is also the possibility that these children were sensitized to allergens not tested, or that they have a non IgE-mediated type of allergy, although either of the two is unlikely. Continued follow up of these children is warranted to determine whether or not they develop evidence of allergic sensitization. The Isle of Wight study has shown that a significant proportion of children (11.2%) had delayed atopy that only became overt at the age of 10 (32). In addition, these investigators have also identified a small proportion of children with symptoms of allergic diseases amongst the group of those who never had any evidence of allergic sensitization at the age of 10 – 31.4% for rhinitis ever and 0.5% for persistent rhinitis (32). These findings, as well as ours, demonstrate that in some children the presence of allergic diseases is independent from allergic sensitization and highlight the need for further clarification of the role of atopy in the development of symptoms suggestive of allergic disease in childhood.

In contrast to studies amongst older children and adults (1, 33–35), we found no difference in wheeze frequency or severity between children with or without rhinitis; likewise, there were no differences between these

two groups in lung function or airway reactivity after the analysis was adjusted for the presence of wheeze, suggesting that in this age group upper respiratory symptoms are not as yet associated with lower respiratory disease. This raises an important question as to whether the population of young children with rhinoconjunctivitis should be considered as an ideal target for secondary prevention therapeutic intervention to reduce the risk of progressing towards the lower respiratory tract disease, thus reducing the burden of asthma in later childhood and adulthood.

Acknowledgments

The authors would like to thank the MAAS children and their parents for their continued support and enthusiasm. We greatly appreciate the commitment they have given to the project. We would also like to acknowledge the hard work and dedication of the study team (research fellows, nurses, physiologists, technicians and clerical staff). Particular thanks go to Julie Morris for statistical advice.

Declaration of sources of funding: Asthma UK Grant No. 04/014. SM is supported by a grant from Fundação para a Ciência e Tecnologia, Portugal – POCI 2010.

References

1. Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**(Suppl. 5):S147–S334.
2. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998;**351**:1225–1232.
3. Strachan D, Sibbald B, Weiland S, Ait-Khaled N, Anabwani G, Anderson HR et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997;**8**:161–176.
4. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733–743.
5. Newacheck PW, Stoddard JJ. Prevalence and impact of multiple childhood chronic illnesses. *J Pediatr* 1994;**124**:40–48.
6. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004;**24**:758–764.
7. Thompson AK, Juniper E, Meltzer EO. Quality of life in patients with allergic rhinitis. *Ann Allergy Asthma Immunol* 2000;**85**:338–347.
8. Simons FE. Learning impairment and allergic rhinitis. *Allergy Asthma Proc* 1996;**17**:185–189.
9. Meltzer EO. The prevalence and medical and economic impact of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;**99**(6 Pt 2):S805–S828.
10. Simpson BM, Custovic A, Simpson A, Hallam CL, Walsh D, Marolia H et al. NAC Manchester Asthma and Allergy Study (NACMAAS): risk factors for asthma and allergic disorders in adults. *Clin Exp Allergy* 2001;**31**:391–399.
11. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. *Lancet* 2001;**358**:188–193.
12. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;**8**:483–491.
13. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;**332**:133–138.
14. Lowe L, Murray CS, Custovic A, Simpson BM, Kissen PM, Woodcock A. Specific airway resistance in 3-year-old children: a prospective cohort study. *Lancet* 2002;**359**:1904–1908.
15. Nielsen KG, Bisgaard H. Lung function response to cold air challenge in asthmatic and healthy children of 2–5 years of age. *Am J Respir Crit Care Med* 2000;**161**:1805–1809.
16. Simpson A, Simpson B, Custovic A, Craven M, Woodcock A. Stringent environmental control in pregnancy and early life: the long-term effects on mite, cat and dog allergen. *Clin Exp Allergy* 2003;**33**:1183–1189.

17. Tavernier GO, Fletcher GD, Francis HC, Oldham LA, Fletcher AM, Blacklock G et al. Endotoxin exposure in asthmatic children and matched healthy controls: results of IPEADAM study. *Indoor Air* 2005;**15**(Suppl. 10): 25–32.
18. Vanna AT, Yamada E, Arruda LK, Naspitz CK, Sole D. International Study of Asthma and Allergies in Childhood: validation of the rhinitis symptom questionnaire and prevalence of rhinitis in schoolchildren in Sao Paulo, Brazil. *Pediatr Allergy Immunol* 2001;**12**: 95–101.
19. Anderson HR, Ruggles R, Strachan DP, Austin JB, Burr M, Jeffs D et al. Trends in prevalence of symptoms of asthma, hay fever, and eczema in 12–14 year olds in the British Isles, 1995–2002: questionnaire survey. *BMJ* 2004;**328**: 1052–1053.
20. Braun-Fahrlander C, Wuthrich B, Gassner M, Grize L, Sennhauser FH, Varonier HS et al. Validation of a rhinitis symptom questionnaire (ISAAC core questions) in a population of Swiss school children visiting the school health services. SCARPOL-team. Swiss Study on Childhood Allergy and Respiratory Symptom with respect to Air Pollution and Climate. International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol* 1997;**8**:75–82.
21. Peroni DG, Piacentini GL, Alfonsi L, Zerman L, Di Blasi P, Visona' G et al. Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors. *Clin Exp Allergy* 2003;**33**:1349–1354.
22. Rasanen M, Laitinen T, Kaprio J, Koskenvuo M, Laitinen LA. Hay fever, asthma and number of older siblings – a twin study. *Clin Exp Allergy* 1997;**27**: 515–518.
23. Meer G, Janssen NAH, Brunekreef B. Early childhood environment related to microbial exposure and the occurrence of atopic disease at school age. *Allergy* 2005;**60**:619–625.
24. Braun-Fahrlander C. Environmental exposure to endotoxin and other microbial products and the decreased risk of childhood atopy: evaluating developments since April 2002. *Curr Opin Allergy Clin Immunol* 2003;**3**:325–329.
25. Garcia-Marcos L, Suarez-Varela MM, Canflanca IM, Garrido JB, Quiros AB, Lopez-Silvarrey VA et al. BCG immunization at birth and atopic diseases in a homogeneous population of Spanish schoolchildren. *Int Arch Allergy Immunol* 2005;**137**:303–309.
26. Mimouni BA, Mimouni D, Mimouni M, Gdalevich M. Does breastfeeding protect against allergic rhinitis during childhood? A meta-analysis of prospective studies. *Acta Paediatr* 2002;**91**: 275–279.
27. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax* 2001;**56**:192–197.
28. Murray CS, Woodcock A, Smillie FI, Cain G, Kissen P, Custovic A. Tobacco smoke exposure, wheeze, and atopy. *Pediatr Pulmonol* 2004;**37**:492–498.
29. Murray CS, Woodcock A, Custovic A. The role of indoor allergen exposure in the development of sensitization and asthma. *Curr Opin Allergy Clin Immunol* 2001;**1**:407–412.
30. Simpson A, Custovic A. Pets and the development of allergic sensitization. *Curr Allergy Asthma Rep* 2005;**5**: 212–220.
31. Coker HA, Durham SR, Gould HJ. Local somatic hypermutation and class switch recombination in the nasal mucosa of allergic rhinitis patients. *J Immunol* 2003;**171**:5602–5610.
32. Kurukulaaratchy RJ, Matthews S, Arshad SH. Defining childhood atopic phenotypes to investigate the association of atopic sensitization with allergic disease. *Allergy* 2005;**60**:1280–1286.
33. Cibella F, Cuttitta G, La Grutta S, Hopps MR, Passalacqua G, Pajno GB et al. Bronchial hyperresponsiveness in children with atopic rhinitis: a 7-year follow-up. *Allergy* 2004;**59**:1074–1079.
34. Cuttitta G, Cibella F, La Grutta S, Hopps MR, Bucchieri S, Passalacqua G et al. Non-specific bronchial hyperresponsiveness in children with allergic rhinitis: relationship with the atopic status. *Pediatr Allergy Immunol* 2003;**14**: 458–463.
35. Ciprandi G, Cirillo I, Tosca MA, Vizzaccaro A. Bronchial hyperreactivity and spirometric impairment in patients with perennial allergic rhinitis. *Int Arch Allergy Immunol* 2004;**133**:14–18.