

Original article

Quantification of atopy and the probability of rhinitis in preschool children: a population-based birth cohort study

Background: Atopy quantification using IgE levels/skin test diameter (SPT-MWD) may better predict the expression of rhinitis than using atopy as a dichotomous variable.

Objective: To investigate the association between the presence, temporal pattern and severity of rhinitis in preschool children and specific IgE levels/SPT-MWDs.

Methods: Children were followed prospectively to age 5 years in a whole-population birth cohort study. We administered questionnaires ($n = 815$), skin prick tested children ($n = 717$) and measured specific serum IgE ($n = 478$) to inhalant and food allergens. Main outcomes were current rhinitis (CR) and current rhinoconjunctivitis (CRC).

Results: The prevalence of CR and CRC was 26.1% and 12.1%, respectively. The risk of CR and CRC increased significantly with increasing IgE to grass, mite and cat; CRC was also associated with increasing IgE to dog and peanut. Similarly, increasing SPT-MWDs to inhalant allergens were significantly associated with CR and CRC. This association was also shown for grass within the group of atopic children. Perennial and seasonal rhinitis were associated with increasing IgE/SPT-MWD to mite and grass, respectively. Moderate/severe rhinitis was associated with increasing IgE/SPT-MWD to grass. In a multivariate analysis, increasing levels of IgE/SPT-MWD to grass were the strongest independent predictors of both CR (for IgE: OR 1.42, 95% CI 1.23–1.64, $P < 0.001$) and CRC (for IgE: 1.51, 1.30–1.76, $P < 0.001$).

Conclusion: The probability of CR/CRC increases with increasing specific IgE levels or SPT-MWD. With respect to allergic rhinitis, the absolute levels of specific IgE antibody or the size of SPT wheal offer more information than just the presence/absence of sensitization.

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Most studies which investigated the relationship between atopic sensitization and symptoms of allergic disease considered atopy as a simple dichotomous variable, assigning individuals as either 'atopic' or 'nonatopic' based on arbitrary cut-off points for IgE measurement or skin prick testing (1, 2). While such information on the absence of sensitization can be valuable (negative predictive value being as high as 95%), the presence of sensitization is considerably less helpful [for example, only 50% of individuals sensitized to foods have symptoms of food allergy (3, 4)]. Quantification of specific serum IgE antibodies can improve the specificity of these tests. For example, the level of specific IgE may predict the likelihood of patients having symptomatic food allergy (5–9); there is a 95% probability of having a clinical reaction upon exposure to peanut in patients with peanut-specific IgE above 15 kU_A/l (4), and similar prediction models have been established for several other food allergens (4, 8, 9). The size of wheal diameter

following skin testing may be used in a similar fashion (10). We have recently demonstrated a quantitative relationship between specific serum IgE levels to common inhalant allergens and the presence and persistence of childhood wheezing and reduced lung function (11).

The presence of atopic sensitization is a risk factor for the development of upper respiratory symptoms (12–14); outdoor allergens constitute a greater risk for seasonal rhinitis than indoor allergens (15), whereas the latter are associated with perennial rhinitis (1). We hypothesized that similar to food allergy and wheezing, quantification of atopy (by using specific IgE levels and the size of skin test wheal) may better predict the relationship between this trait and upper respiratory symptoms than using atopy as a dichotomous variable. Therefore, in a population-based birth cohort, we evaluated the association between quantified atopy and the presence, temporal pattern and severity of rhinitis symptoms in early childhood.

Methods

Study design

Unselected, population-based birth cohort study – Manchester Asthma and Allergy Study (16, 17). Study was approved by the Local Research Ethics Committee. Written informed consent was obtained from subjects' parents/guardians, and children gave their assent.

Participants

Participants were recruited from the antenatal clinics during the first trimester of pregnancy. Children were followed up prospectively and they attended review clinic at age 5 years (within 4 weeks of birthday).

Outcomes

A validated questionnaire (18) was interviewer-administered to collect information on parentally reported symptoms, physician-diagnosed illnesses and treatments received. We also collected information on environmental tobacco smoke exposure, pet ownership and contact, childcare arrangements and vaccination uptake.

Current rhinitis (CR) was defined as a 'sneezing or a runny or blocked nose when the child DID NOT have a cold or chest infection' during the previous 12-month period. Amongst children with CR, we defined current rhinoconjunctivitis (CRC) as a positive answer to the question 'in the past 12 months, has this nose problem been accompanied by itchy watery eyes?' We assessed the severity of symptoms on the basis of whether they interfered with child's daily activities.

Parents of children with CR were asked to specify the months of the year in which the symptoms occurred. Based on this information, we defined the following categories: seasonal CR [seasonal symptoms in the spring and/or summer (S-CR)]; perennial CR [symptoms throughout the year (P-CR)]; intermittent CR in the winter only and intermittent CR following no pattern.

Skin testing and IgE measurement

We performed skin prick tests (SPT) to *Dermaphagoides pteronyssinus*, cat, dog, mixed grasses, mixed moulds, milk and egg (Bayer, Elkhart, IN, USA). The size of SPT was determined by summing the largest wheal diameter and its perpendicular, and dividing the result by two; this mean wheal diameter (MWD) was quantified in relation to the negative control.

Total and specific serum IgE (*D. pteronyssinus*, cat, dog, grass, milk, egg and peanut) was measured by ImmunoCAP™ (Phadia, Uppsala, Sweden).

Statistical analysis

The primary outcome measures were 'current rhinitis' and 'current rhinoconjunctivitis'. All evaluable cases were used for each part of the analysis. The levels of specific IgE were subject to a log_e-transformation prior to analysis; SPT-MWDs were used as raw data. The relationship between quantitative sensitization and outcome measures was analyzed using logistic regression. Odds ratios (OR) were estimated using the regression models and 95% confidence intervals (95% CI) were generated (Wald), using a *P*-value of 0.05 as significant. Multiple logistic regression analyses were performed, including all the factors identified as significant in the univariate analysis, using a forward stepwise method. Fitted

predicted probability curves according to the concentration of specific IgE/size of SPT-MWD were plotted using the results from the logistic regression. For the quantitative evaluations, the OR are presented for different IgE antibody levels expressing the increased risk associated with increasing antibody levels. As a logarithmic transformation was used, all calculations were made using the logarithmic scale, i.e. the OR was estimated as $\exp(rb)$ and *r*, the distance between a certain IgE antibody level and the level indicating the absence of IgE, was defined as $r = \ln(x_2) - \ln(x_1)$. Therefore, the OR indicates an increase in the risk of CR/CRC per logarithmic unit increase of specific IgE levels or unit increase in SPT-MWD. Statistical analysis was carried out using SAS System V8.01 (SAS Institute, Cary, NC, USA) and SPSS 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Of 1085 children born into the study, we reviewed 1025 at age 5 years; 122 randomized to an environmental intervention (17) and 88 with incomplete data were excluded from this analysis. All of the remaining 815 children (54.7% boys) had questionnaire data; skin tests were performed on 717 (88%) and 478 (58.7%) provided blood sample for IgE measurement; 470 children had both skin tests and IgE data.

As previously reported (19), CR was reported by the parents of 213 children (26.1%) and CRC by 99 (12.1%).

The distribution of the levels of specific IgE and SPT-MWD to the inhalant allergens amongst children with and without CR is shown in Fig. 1A,B.

Specific IgE and current rhinitis and rhinoconjunctivitis

Using specific IgE as a continuous variable, the risk of CR increased significantly with increasing specific IgE to grass pollen (OR 1.38, 95% CI 1.21–1.58, *P* < 0.001) corresponding to OR of 3.58 at 10 kU_A/l and 5.10 at 30 kU_A/l (Fig. 2A). Similarly, the probability of CRC increased 1.49-fold per logarithmic unit increase in specific IgE to grass pollen (95% CI 1.30–1.71, *P* < 0.001), corresponding to an OR of 4.84 at 10 kU_A/l and 7.50 at 30 kU_A/l (Fig. 2B). In addition, similar associations were seen with increasing levels of specific IgE to mite and cat for CR, and to mite, cat, dog and peanut for CRC (Table 1).

When the levels of specific IgE for the individual allergens were summed, the strength of the effect was weakened, both for CR and for CRC (Table 1). In a multivariate model including only the levels of specific IgE to all allergens, increasing level of specific IgE to grass pollen was the only independent predictor of both CR and CRC (*P* < 0.001, data available on request). Whilst children with CR or CRC had significantly higher total IgE compared with those without (*P* = 0.02 and *P* = 0.008, respectively), the association between total IgE level and both CR and CRC appeared weaker than that of the specific IgE levels (Table 1). This was confirmed in a further multivariate analysis, which

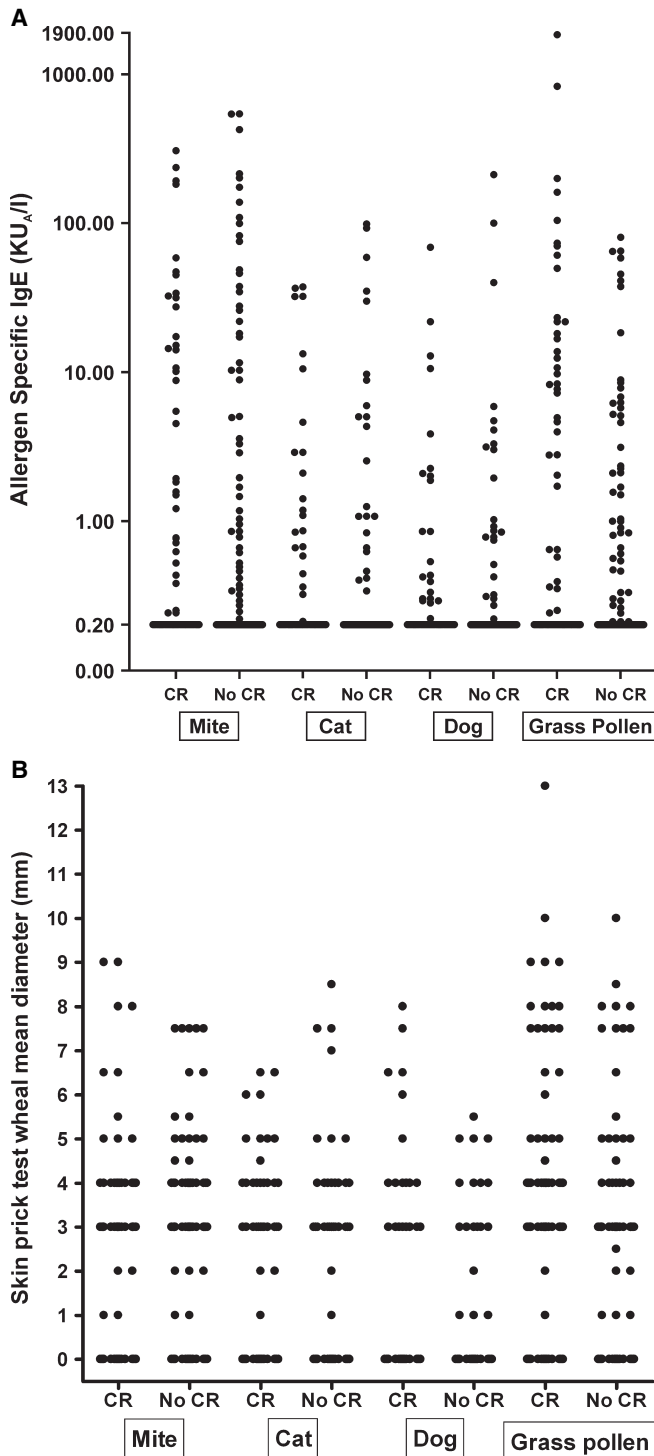


Figure 1. (A, B) Distribution of the levels of specific IgE (A) and SPT-MWD (B) to the inhalant allergens amongst children with and without CR.

included both total and specific IgE data: total IgE was not associated with either of the outcomes, whereas for specific IgE to grass pollen the OR remained unchanged (data available on request).

Skin prick tests and current rhinitis and rhinoconjunctivitis

Analyzing the relationship between CR and CRC and the size of the skin test MWD, we found significant associations with increasing size of individual MWD to grass pollen ($P < 0.001$), mite ($P \leq 0.002$), cat ($P < 0.001$) and dog ($P < 0.001$); there was also a significant association between CR and increasing size of MWD to mould ($P = 0.04$; Table 1).

When SPT-MWD for the individual allergens were summed, the strength of the effect was weakened, both for CR and for CRC (Table 1). A multivariate model including only the SPT-MWD to all allergens suggested that the only independent associate of both CR and CRC was increasing SPT-MWD to grass pollen ($P < 0.001$, data available on request).

Specific IgE antibodies and skin test size: effect on severity and temporal pattern of rhinitis

Amongst children with CR, we compared those with mild symptoms (no interference with daily activities; $n = 121$) with children who had moderate/severe symptoms (which interfered with daily activities; $n = 91$). Using mild rhinitis as a reference, the risk of moderate/severe rhinitis increased with increasing specific IgE level and size of SPT-MWD to grass pollen, but not other inhalant or food allergen (IgE: OR 1.23, 95% CI 1.04–1.46, $P = 0.02$; SPT: 1.16, 1.03–1.29, $P = 0.02$). No such association was observed amongst children with CRC.

The most common temporal pattern of CR was to have seasonal symptoms in the spring and/or summer (S-CR, $n = 139$, 65.3%); 22 (10.3%) had perennial CR (P-CR). A further 29 parents (13.6%) reported intermittent CR in the winter only, 16 (7.5%) intermittent CR which followed no pattern and seven did not specify a month in which the rhinitis symptoms occur; these three groups were not subject to further analysis.

The association between the levels of specific IgE and SPT-MWD with S-CR and P-CR is shown in Table 2 (reference group: no CR). P-CR was significantly associated with increasing IgE levels/size of SPT-MWD to mite ($P \leq 0.006$; Fig. 2C), but not to any other allergen. Increasing level of IgE to grass was the strongest predictor of S-CR ($P < 0.001$; Fig. 2D), which was also associated with increasing IgE to peanut and cat; when analyzing SPT results, S-CR was associated with increasing SPT-MWD to all inhalant allergens.

Specific IgE antibodies, skin test size and risk of rhinitis amongst sensitized children

To investigate further the relationship between quantitative atopy, CR and CRC, we repeated the analysis amongst children who would be considered sensitized

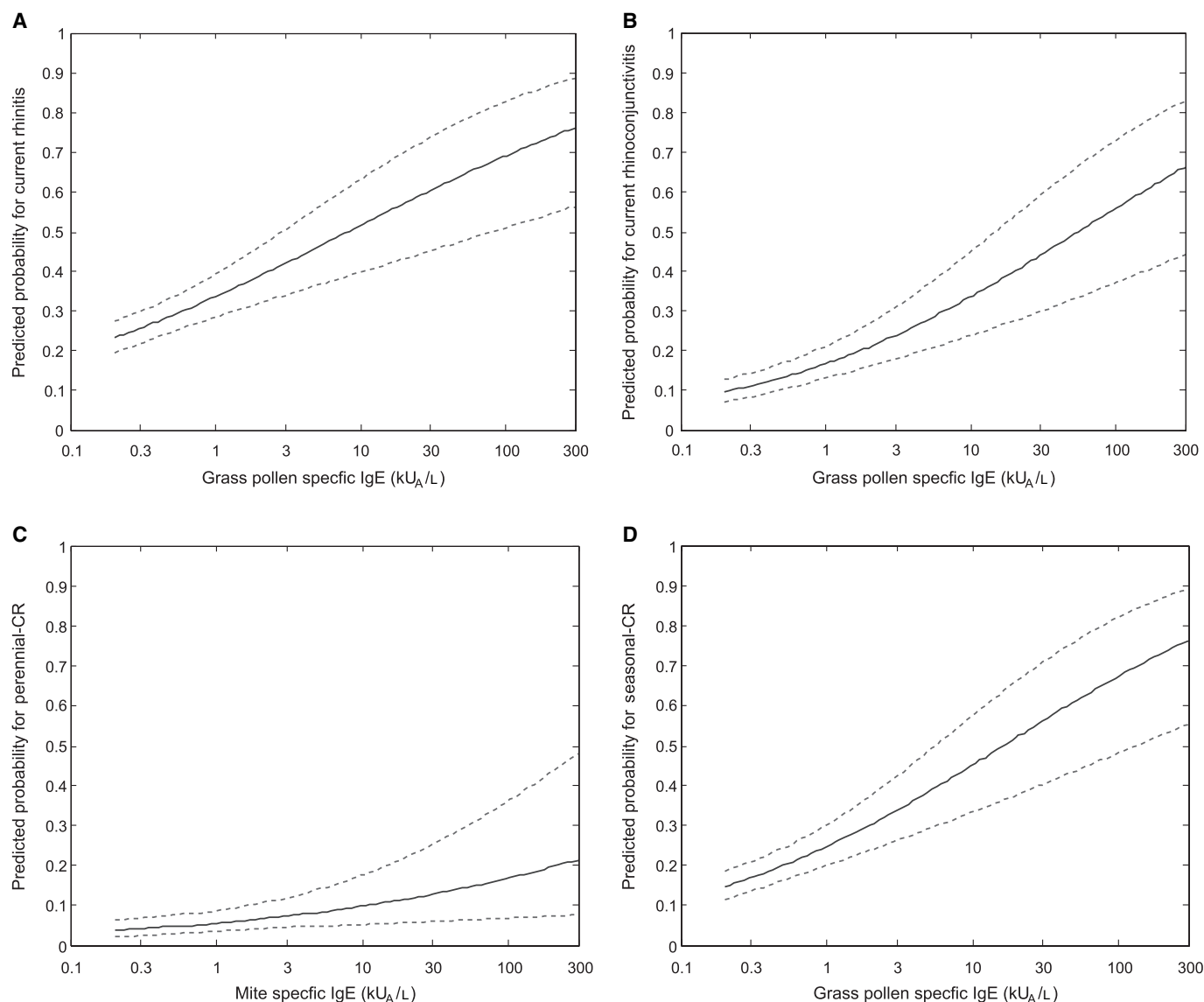


Figure 2. (A–D) Fitted predicted probability curves (and 95% CI) for current rhinitis (A) and for current rhinoconjunctivitis (B) at a given IgE value for grass pollen, derived from the logistic regression analysis. Fitted predicted probability curves (and 95% CI) for perennial CR at a given IgE value for mite (C), and for seasonal CR at a given IgE value for grass pollen (D), derived from the logistic regression analysis.

using standard definitions [specific IgE > 0.2 kU_A/L, MWD 3 mm greater than negative control (11)]. Using these definitions, 167 children were assigned as sensitized based on IgE data, and 192 based on skin testing. Even in this group, increasing level of specific IgE to grass pollen was associated with significantly increased risk of CR (OR 1.29, 95% CI 1.11–1.50, $P = 0.001$) and CRC (1.38, 1.17–1.63, $P < 0.001$), with similar effects seen for grass pollen SPT-MWD (Table 3). In this group, there was no association between CR or CRC and increasing level of specific IgE/SPT-MWD to other inhalant or food allergens, nor with total IgE.

Multivariate analysis

To assess the relative contribution of specific IgE levels and size of SPT-MWD to the risk of CR and CRC, we performed a multivariate logistic regression analysis, controlling for all the factors, which we previously found to be associated with rhinitis in the univariate analyses (19) [CR: male gender, maternal asthma and hay fever, paternal hay fever, wheeze and eczema in the first year of life, position in sibship (first born or not); CRC: as above, with the exception of male gender and position in sibship].

The risk of rhinitis increases with increasing IgE levels/SPT-MWD

Table 1. The association between levels of serum-specific IgE/skin prick test wheal diameters, current rhinitis and current rhinoconjunctivitis at age 5 years (the OR indicate an increase in risk of CR/CRC per logarithmic unit increase of specific IgE levels/unit increase in skin test wheal diameter)

	Current rhinitis						Current rhinoconjunctivitis					
	IgE (n = 478)			SPT (n = 717)			IgE (n = 478)			SPT n = 717		
	OR	95% CI	P	OR	95% CI	P	OR	(95% CI)	P	OR	95% CI	P
Dust mite	1.15	1.03–1.29	0.02	1.19	1.08–1.31	0.001	1.17	1.03–1.34	0.02	1.20	1.07–1.34	0.002
Cat	1.23	1.01–1.50	0.04	1.31	1.15–1.49	<0.001	1.34	1.09–1.67	0.007	1.39	1.21–1.59	<0.001
Dog	1.24	0.98–1.56	0.07	1.40	1.19–1.65	<0.001	1.41	1.10–1.80	0.006	1.37	1.16–1.62	<0.001
Grass pollen	1.38	1.21–1.58	<0.001	1.28	1.18–1.38	<0.001	1.49	1.30–1.71	<0.001	1.35	1.23–1.47	<0.001
Mould	†			1.45	1.01–2.09	0.04	†			1.07	0.65–1.78	0.79
Peanut	1.27	0.96–1.67	0.09	‡			1.52	1.14–2.03	0.005	‡		
Milk	1.22	0.83–1.79	0.31	1.37	0.84–2.22	0.20	1.39	0.90–2.15	0.14	1.07	0.64–1.78	0.81
Egg	1.09	0.65–1.83	0.73	1.17	0.92–1.48	0.22	1.20	0.64–2.24	0.57	1.04	0.75–1.44	0.82
Total IgE	1.16	1.02–1.31	0.02	NA			1.25	1.06–1.47	0.008	NA		
Sum of inhalant allergens*	1.29	1.17–1.41	<0.001	1.12	1.08–1.17	<0.001	1.35	1.22–1.50	<0.001	1.14	1.10–1.19	<0.001
Sum of all allergens§	1.27	1.16–1.39	<0.001	1.11	1.07–1.15	<0.001	1.34	1.21–1.49	<0.001	1.12	1.08–1.17	<0.001

*Sum of mite, cat, dog and grass pollen specific IgE levels/SPT-MWD;

†Specific IgE to mould not measured at age 5 years;

‡Children not skin tested to peanut at age 5 years;

§Sum of mite, cat, dog, grass pollen, peanut, milk and egg specific IgE levels/SPT-MWD; NA, not applicable.

Table 2. Association between levels of serum specific IgE/skin prick test wheal diameters to specific allergens and the pattern of rhinitis symptoms

Allergen	Perennial rhinitis (P-CR) [n = 19 (SPT), 17 (IgE)]			Seasonal rhinitis (S-CR) [n = 126 (SPT), 82 (IgE)]		
	OR	95% CI	P	OR	95% CI	P
Mite						
SPT	1.32	1.09–1.61	0.005	1.18	1.05–1.31	0.004
IgE	1.31	1.08–1.59	0.006	1.11	0.97–1.28	0.12
Cat						
SPT	1.20	0.89–1.62	0.24	1.36	1.19–1.56	<0.001
IgE	1.18	0.77–1.80	0.46	1.25	1.00–1.56	0.05
Dog						
SPT	1.16	0.69–1.96	0.57	1.48	1.24–1.77	<0.001
IgE	1.16	0.71–1.90	0.54	1.26	0.98–1.63	0.07
Grass pollen						
SPT	1.16	0.95–1.43	0.16	1.36	1.25–1.49	<0.001
IgE	1.16	0.82–1.66	0.41	1.49	1.29–1.72	<0.001
Mould						
SPT	1.62	0.80–3.29	0.18	1.59	1.09–2.32	0.02
IgE	†			†		
Peanut						
SPT	‡			‡		
IgE	1.00	0.45–2.25	1.00	1.38	1.03–1.85	0.03
Milk						
SPT	0.38	0–11001.87	0.85	1.50	0.89–2.52	0.13
IgE	1.23	0.51–2.98	0.65	1.31	0.86–1.99	0.21
Egg						
SPT	0.23	0–40 567.5	0.81	1.26	0.98–1.62	0.07
IgE	0.04	0–335.2	0.48	1.21	0.69–2.13	0.51

†Specific IgE to mould not measured at age 5 years;

‡Children not skin tested to peanut at age 5 years.

Reference group: No CR.

Group numbers for the analyses: P-CR SPT n = 556, IgE n = 365; S-CR SPT n = 665, IgE n = 430.

In these models, increasing level of grass pollen specific IgE or increasing size of grass pollen SPT-MWD remained the strongest independent associates of both CR and CRC (Table 4). The significant associates and the size of their effect varied slightly depending on whether SPT or IgE data were used.

We performed a similar multivariate analysis with respect to the temporal pattern of symptoms, controlling for all the factors significantly associated with perennial-CR and seasonal-CR in the univariate analysis (for P-CR: wheeze and eczema in the first year of life, pattern of cat ownership; for S-CR: wheeze and eczema in the first year of life, male gender, maternal asthma, maternal and paternal hay fever and position in sibship; Table 5). Similar to the results in the whole population, increasing levels of specific IgE or increasing SPT-MWD to mite allergen were found to be significantly associated with P-CR, whereas S-CR was strongly associated with increasing IgE levels/SPT-MWD to grass pollen.

Discussion

Principal findings

Our data show that independent predictors of the presence of current rhinitis and rhinoconjunctivitis in 5-year-old children are the absolute level of specific IgE or the size of the skin test MWD to grass pollen. These associations remained after adjusting for potential confounding variables, including gender, parental history of rhinitis and asthma, personal history of wheeze and eczema and the position in sibship. Not surprisingly, we demonstrated quantitative association between the

Table 3. Quantification of IgE antibodies and skin prick tests and current rhinitis and rhinoconjunctivitis at age 5 years amongst sensitized children

	Current rhinitis						Current rhinoconjunctivitis					
	IgE (n = 167)			SPT (n = 192)			IgE (n = 167)			SPT (n = 192)		
	OR	95% CI	P	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P
Dust mite	1.03	0.90–1.17	0.68	0.95	0.84–1.08	0.44	1.02	0.87–1.19	0.83	0.96	0.83–1.11	0.56
Cat	1.08	0.87–1.33	0.50	1.08	0.94–1.25	0.27	1.16	0.92–1.45	0.23	1.16	1.00–1.36	0.05
Dog	1.07	0.84–1.36	0.58	1.18	0.99–1.40	0.06	1.20	0.93–1.54	0.17	1.15	0.96–1.37	0.13
Grass pollen	1.29	1.11–1.50	0.001	1.13	1.02–1.26	0.02	1.38	1.17–1.63	<0.001	1.24	1.10–1.40	<0.001
Mould	†			1.21	0.82–1.79	0.35	†			0.84	0.50–1.41	0.51
Peanut	1.07	0.81–1.43	0.62	‡			1.26	0.93–1.71	0.13	‡		
Milk	0.89	0.58–1.37	0.60	1.17	0.75–1.82	0.48	0.98	0.60–1.59	0.93	0.92	0.53–1.59	0.76
Egg	0.75	0.43–1.33	0.33	1.00	0.78–1.27	0.99	0.77	0.38–1.54	0.45	0.87	0.61–1.25	0.46
Sum of inhalant allergens*	1.28	1.12–1.46	<0.001	1.06	0.99–1.13	0.10	1.33	1.14–1.56	<0.001	1.11	1.03–1.20	0.004
Sum of all allergens§	1.29	1.11–1.49	<0.001	1.05	0.99–1.11	0.12	1.34	1.13–1.59	<0.001	1.07	1.02–1.13	0.02

*Sum of mite, cat, dog and grass specific IgE/skin prick test mean wheal diameter;

†Specific IgE to mould not measured at age 5 years;

‡Children not skin tested to peanut at age 5 years;

§Sum of mite, cat, dog, grass pollen, peanut, milk and egg specific IgE/skin prick test mean wheal diameter; NA, not applicable.

Table 4. Multivariate analysis of the risk factors for current rhinitis and current rhinoconjunctivitis

	Current rhinitis					
	Model 1 – SPT (n = 675)			Model 2 – IgE (n = 451)		
	OR	95% CI	P	OR	95% CI	P
Maternal asthma	1.78	1.15–2.77	0.01	2.23	1.31–3.81	0.003
First born	1.87	1.29–2.71	0.001	2.15	1.37–3.37	0.001
Wheeze in the first year of life	2.16	1.44–3.22	<0.001	2.18	1.34–3.56	0.002
Grass pollen	1.29	1.18–1.42	<0.001	1.42	1.23–1.64	<0.001
Dog	1.22	1.00–1.48	0.049	NS		

	Current rhinoconjunctivitis					
	Model 1 – SPT (n = 689)			Model 2 – IgE (n = 451)		
	OR	95% CI	P	OR	95% CI	P
Maternal asthma	2.27	1.31–3.94	0.004	3.21	1.67–6.16	<0.001
Paternal hay fever	1.93	1.13–3.29	0.02	2.36	1.23–4.54	0.01
Wheeze in the first year of life	1.95	1.13–3.34	0.02	NS		
Grass pollen	1.33	1.20–1.47	<0.001	1.51	1.30–1.76	<0.001
Cat	1.19	1.02–1.39	0.03	NS		

NS, not significant.

Factors included in the analysis for CR: male gender, maternal asthma and hay fever, paternal hay fever, wheeze and eczema in the first year of life, position in sibship (first born or not).

Factors included in the analysis for CRC: maternal asthma and hay fever, paternal hay fever, wheeze and eczema in the first year of life.

specific IgE levels and size of skin test to grass pollen with seasonal rhinitis, whilst increasing specific IgE levels/skin test size to mite were independent associates of perennial

Table 5. Multivariate analysis of the risk factors for perennial and seasonal rhinitis

	Perennial CR					
	Model 1 – SPT (n = 518)			Model 2 – IgE (n = 340)		
	OR	95% CI	P	OR	95% CI	P
Wheeze in the first year of life	4.53	1.67–12.29	0.003	3.86	1.34–11.08	0.01
Mite	1.37	1.11–1.68	0.003	1.31	1.05–1.62	0.02

	Seasonal CR					
	Model 1 – SPT (n = 630)			Model 2 – IgE (n = 407)		
	OR	95% CI	P	OR	95% CI	P
Maternal asthma	1.77	1.07–2.94	0.03	2.63	1.42–4.87	0.002
First born	2.22	1.42–3.45	<0.001	2.51	1.45–4.36	0.001
Wheeze in the first year of life	1.80	1.11–2.93	0.02	1.99	1.10–3.63	0.02
Grass pollen	1.35	1.22–1.48	<0.001	1.54	1.32–1.81	<0.001
Dog	1.26	1.02–1.57	0.03	NS		

NS, not significant.

Factors included in the analysis for perennial CR: wheeze and eczema in the first year of life and pattern of cat ownership.

Factors included in the analysis for seasonal CR: wheeze and eczema in the first year of life, male gender, maternal asthma, maternal and paternal hay fever and position in sibship (first born or not).

rhinitis. Furthermore, our data suggest a quantitative relationship between allergic sensitization and the severity of rhinitis symptoms. In addition, we have extended this observation in demonstrating that the same associations hold for grass pollen within the group of children defined as atopic using standard definitions (11). These findings confirm our hypothesis that IgE-mediated sensitization is

not dichotomous in its relation with the expression, severity and temporal pattern of upper respiratory symptoms.

Limitations

As with all epidemiological studies in preschool children, we relied on accurate parental reporting of child's symptoms and accepted the limitations of this approach. We were not able to obtain skin prick test data or specific IgE measurements for all children studied (88.0% had skin tests and 58.7% IgE). However, it is unlikely that this has influenced our results, as we found no significant differences between the children with and without these data in the socioeconomic status, maternal age, gestational age, birth weight, family history of allergic diseases, parental smoking, breastfeeding, pet ownership, vaccination uptake, childcare arrangements and any of the outcomes studied. Furthermore, the retention in this large, unselected population-based birth cohort was excellent, with approximately 95% follow-up rate by age 5 years. The generalizability is further strengthened by the fact that the prevalence of allergic sensitization among the parents of children is similar to that of young adults in the UK (20), suggesting that our results are applicable to the general population. As fewer children gave blood for the measurement of specific IgE than underwent skin prick testing, fewer children were used in the analysis of the former, which may account for the small differences in the results (however, all of the trends remained the same).

Meaning of the study

Many studies have identified allergic sensitization as a major risk factor for the presence and severity of clinical symptoms (16, 21, 22). However, most such studies have considered sensitization as either present or not, based on arbitrarily defined cut-off values (23–25). Our findings add to the current knowledge by demonstrating a quantitative rather than dichotomous relationship between atopy and the presence and severity of upper respiratory symptoms in preschool children. Furthermore, even when children without allergic sensitization were excluded from the analysis, the same quantitative relationship was observed, emphasizing the potential importance of the quantitative approach.

Increasing levels of specific IgE or increasing skin test size to inhalant allergens, but not food allergens (with the exception of peanut), were shown to be significantly associated with rhinitis. We speculate that the association between peanut specific IgE and rhinitis (observed in the univariate, but not multivariate analysis) may be consequent to the cross-reactivity between peanut and grass pollen (26–28).

In a marked contrast to our findings for lower respiratory symptoms and lung function (11), the associations between quantitative atopy and symptoms were weakened when the IgE levels/sizes of skin tests for individual allergens were summed. Multivariate analyses established grass pollen as the only allergen associated with current rhinitis and rhinoconjunctivitis in our population. Additionally, our data showed perennial rhinitis to be independently associated with increasing IgE levels/skin test size to mite. Clearly, different clinical presentations of allergic airway disease are associated with different patterns of quantitative atopy, with the sum of inhalant allergens being important in wheezing (11), grass pollen in seasonal and dust mite in perennial rhinitis.

Clinical implications

A proportion of sensitized individuals have no symptoms of allergic disease. In some sensitized individuals, exposure to sensitizing allergen has no effect on symptoms and may be a coincidental finding. Our results may have important implications in clinical practice: the quantification of allergic sensitization may offer more information to the clinician than just the presence/absence of atopy, as it may increase the confidence that allergic sensitization has an impact on the expression and severity of symptoms. However, the quantitative information can be used in a reliable way only if we have repeatable and reproducible measures. Whilst newer tests can measure the IgE antibodies with very high precision in quantitative terms (29–31), our findings regarding skin testing are more difficult to generalize to the clinical setting, where such tests are performed by different individuals using a range of tools, with extracts sometimes containing variable quantities of major allergens.

In conclusion, in the diagnosis and treatment decision-making process of the upper airways diseases, we may benefit from abandoning atopic sensitization in favor of 'quantitative atopy'.

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