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**Age, sex, and the association between skin test responses and IgE titres
with asthma**

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ABSTRACT

Background: Skin prick tests (SPTs) and allergen-specific serum IgE (sIgE) measurements are the main diagnostic tools for confirming atopic sensitization. Results are usually reported as "positive" or "negative", using the same arbitrary cut-offs (SPT>3mm, sIgE>0.35 kU_A/L) across different ages and sexes. We investigated the influence of age and sex on the interpretation of allergy test in the context of childhood asthma.

Methods: In a population-based birth cohort (n=1051), we ascertained the information on asthma/wheeze (validated questionnaires), and performed SPTs and sIgE measurement to inhalant allergens (dust mite, cat, dog) at follow-ups between ages three and 11 years. We investigated the association between quantitative sensitisation (sum of SPT mean wheal diameters [MWD] and sIgE titres to the three allergens) and current wheeze and asthma across ages and sexes.

Results: We observed a significant association between the SPT MWD and sIgE titres and wheeze/asthma at most ages and for both sexes. However, the strength of this association was age and sex-dependent. For SPTs, the strength of the association between MWD and asthma increased with increasing age; we observed the opposite pattern for sIgE titre. For any given SPT MWD/sIgE titre,

boys were significantly more likely to express clinical symptoms, particularly in early life; this difference between males and females diminished with age, and was no longer significant by age 11 years.

Conclusions: Age and sex should be taken into account when interpreting the results of skin tests and sIgE measurement, and age- and sex-specific normative data are needed for these allergy tests.

Key words: childhood asthma, wheeze, age, sex, quantitative atopy, sIgE, skin tests

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INTRODUCTION

Atopic sensitization has been identified as a risk factor for asthma in a series of epidemiological studies (1-4). Skin prick tests (SPTs) and measurements of serum allergen-specific IgE antibodies (sIgE) are the most commonly used diagnostic tools for confirming sensitization. Both of these allergy tests are usually reported as either positive or negative (1-4), with SPT mean wheal diameter (MWD) at least 3mm greater than the negative control and sIgE titre >0.35 kU_A/L generally considered as indices of sensitization (5). However, these cut-offs are arbitrary, and different decision points are sometimes utilized.

In relation to the presence or absence of allergic disease, using the results of SPTs and sIgE measurement as dichotomous outcomes has high negative predictive values, but relatively poorer positive predictive values (5, 6), and individuals classified as “sensitised” often do not express any symptoms of allergic disease (7). There is compelling evidence in food allergy that quantification of sensitization to food allergens (either as the size of skin test MWD or sIgE titre) predicts allergic reactions with much greater certainty than dichotomous cut-offs (8, 9). Similarly, we have previously shown in the context of respiratory allergy that the increasing titre of sIgEs to common inhalant allergens (mite, cat and dog) is strongly associated with childhood wheezing and diminished lung

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function (10), with a similar association between sIgE titre to grass pollen and symptoms of rhinitis (11). Furthermore, the sum of sIgE titres to mite, cat and dog amongst wheezy children aged three years strongly predicted the risk of wheeze persistence into later childhood (10). Quantification of atopic sensitisation may also have a role in ascertaining asthma control, with emerging evidence that asthma severity and the risk of future exacerbations increase with increasing size of skin tests and sIgE titres (12).

Total and specific IgE levels have been shown to change with age, sex, location/exposure and ethnicity (13-15). Total IgE tends to increase in childhood until the age of 9-10 years, after which the levels generally plateau (16). There is also evidence that males have higher total IgE compared to females (17). Similarly, the size of skin test reaction to both allergens and histamine changes with age (18, 19). Despite this evidence, current interpretation of these commonly used allergy tests in the context of respiratory allergy does not generally take into account either age or sex of the patient (20).

We hypothesized that the relationship between atopic sensitization and asthma differs between boys and girls, and at different ages. To address our hypothesis, we investigated the effects of age and sex on the association between sensitisation as a quantitative trait (size of skin test wheal diameter and titre of sIgE) and childhood wheezing and asthma.

METHODS

Study population

The Manchester Asthma and Allergy Study is a population-based birth cohort (21, 22). Subjects were recruited prenatally and followed prospectively. Local Research Ethics Committee approved the study; parents gave written informed consent.

Data sources

Children attended review clinics at ages three, five, eight and 11 years. Validated questionnaires were interviewer-administered to collect information on parentally-reported symptoms and treatments received. We assessed sensitization to *Dermatophagoides pteronyssinus*, cat and dog using skin prick

tests at all ages (Bayer, Elkhart, Ind, USA); we measured sIgE to these inhalant allergens at ages three, five and eight years (ImmunoCAP™, Phadia, Uppsala, Sweden).

Definition of variables

Quantitative atopic sensitisation: SPT MWD for each individual allergen was determined by summing the largest wheal diameter and its perpendicular axis, then dividing by two. We used the sum of SPT MWDs to dust mite, cat and dog, and the sum of sIgE titres to these three allergens as markers of quantitative sensitisation. The choice of allergens was based on our previous data that such definition of quantitative sensitisation rendered the strongest association between aeroallergen sensitization with wheeze presence and persistence in our study population (10, 11).

To take into account the increase in histamine reactivity that occurs through life (19), we also expressed SPT results as a ratio of MWD to allergens/MWD to histamine control (10 mg/ml) at each age.

Current wheeze: Defined as a positive response to the question “Has your child had wheezing or whistling in the chest in the last 12 months?”

Current asthma: Defined as the presence of any two of the following three features: 1) Current wheeze; 2) Current use of asthma medication; and 3) Physician-diagnosed asthma ever (23).

Statistical analysis

Logistic regression was used to investigate whether quantitative atopy (separate models using SPT MWD and sIgE as covariates) is associated with wheeze/asthma at each age. Estimates of the magnitude of the effect were quantified as odds ratios (ORs) with 95% confidence intervals (95% CI). We then investigated whether the association between quantitative atopic sensitisation and current wheeze/asthma was modified by sex by including a covariate for sex-by-sensitisation interaction for each age group. Predicted probability curves were constructed using results obtained from logistic regression.

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Analysis was then extended to a discrete-time longitudinal model to investigate whether the magnitude of quantitative sensitisation is significantly associated with current wheeze/asthma. We investigated: (i) a main effects model where we assumed that the effect of quantitative sensitisation on current wheeze/asthma was independent of age; and (ii) whether the effect of quantitative sensitisation on current wheeze/asthma was significantly modified by age by including an interaction term for quantitative sensitisation and age in model (i).

As asthma, eczema and rhinitis may coexist in the same individual children more commonly than expected by chance (24, 25), we carried out additional analyses to assess the above associations with asthma presenting with coexisting eczema and rhinitis.

RESULTS

Participant flow and demographics

Participant flow is shown in Figure E1. Of the 1184 recruited participants, 133 were randomized to a primary prevention study and were excluded from this analysis. Of the 1051 eligible subjects (586 males), 864 underwent SPTs at age three years (of those, 23.5% had current wheeze, 14.7% had asthma, 9% were sensitized), 858 at age five (23.1% wheeze, 22.8% asthma, 12.9% sensitized), 836 at age eight (18.3% wheeze, 17.9% asthma, 15% sensitized) and 715 at age 11 years (20.8% wheeze, 20.7% asthma, 11.2% sensitized). Blood sample for sIgE measurements was provided by 178 children at age three years (21.9% wheeze, 9.6% asthma, 21.9% sensitized), 534 at age five (22.7% wheeze, 20.5% asthma, 22.5% sensitized) and 511 at age eight (18.4% wheeze, 16.0% asthma, 30.3% sensitized). There were no significant differences in the outcomes and demographic characteristics between children included and excluded from the analyses (data available on request).

The cross-sectional association between skin test MWDs and sIgE titres to each individual allergen (mite, cat and dog) at different ages and the probability of contemporaneous current wheeze in the whole population is shown in Table E1; the results amongst males and females separately are presented in Table E2.

Quantitative sensitisation and the risk of wheeze and asthma: The impact of age

Current wheeze: Statistically significant differences in the relation between SPT MWD and current wheeze were found at different ages (Figure 1A), with the strength of the association increasing with increasing age. The relative odds ratios from discrete longitudinal analysis comparing the association between SPT MWD and sIgE titre and wheeze between different ages are shown in Table 1. There were significant differences in the strength of the association of SPT MWD and wheeze between ages three and eight and 11 years, and ages five and eight years, but not between ages three and five, and eight and 11 years (Figure 1A, Table 1). However, no significant differences were observed between age groups for the association between sIgE titre and current wheeze (Figure 1B).

Current asthma: Similar to the findings for current wheeze, the strength of the association between SPT MWD and asthma increased with increasing age, with significant differences in the slope between different ages (Figure 2A, Table 2). Statistically significant differences in the strength of the association were also observed between sIgE titres and asthma at different age groups, but in contrast to the association for SPT MWDs, the strength of the association between sIgE and asthma decreased with increasing age (Table 2, Figure 2B).

Quantitative sensitisation and the risk of wheeze and asthma: The impact of sex

There was a significant association ($p < 0.01$) between wheeze and asthma and the sum of SPT MWDs in both sexes and for all age groups (Table E3). The relation was also significant between the sIgE titres and both outcomes, except at age three years among girls ($p = 0.14$). Figure 3 shows predicted probability curves illustrating the relation between quantitative atopic sensitisation and current asthma amongst males and females (the associations for wheeze were almost identical; Table E3). For a given SPT MWD, males were significantly more likely to have wheeze/asthma than females at ages three and five years (Figure 3A-B). This sex difference diminished with age, and was no longer significant by age 8 years (Figure 3C). Similarly, for a given sIgE titre, males were more likely to have clinical symptoms (Figure 3). However, this was statistically significant only at age five for wheeze ($p = 0.03$).

An interactive logistic regression test revealed no significant interaction between sex and SPT MWD

in relation to current wheeze/asthma in all age groups, except at the age 11 years ($p=0.04$), and no significant interaction between sex and sIgE titre.

Analysis of the effect of age and sex on the association between quantitative sensitisation and asthma with coexisting eczema and rhinitis rendered similar results (Tables E4-5). Expressing SPT results as a ratio of MWD to allergens/MWD to histamine did not materially alter the results for any of the outcomes (Table E6-7).

DISCUSSION

Key findings

In a population-based birth cohort, we observed a significant association between the SPT MWD and sIgE titres to common inhalant allergens and wheeze/asthma at different ages, and for both sexes.

However, the strength of this association was both age and sex-dependent. For SPTs, the strength of the association between MWD and asthma increased with increasing age; we observed opposite pattern for sIgE titre. For any given SPT MWD or sIgE titre, boys were significantly more likely to express clinical symptoms, particularly in early life; this difference between males and females appeared to diminish with age.

Limitations

As is the case with most epidemiological studies, we relied on parental reporting of symptoms to define current wheezing and asthma, and we acknowledge that this may lead to overestimation of their true prevalence. Although the definition of current asthma which we used is more stringent than a simple report of wheezing or a physician-diagnosed asthma only, it is reliant on parental reporting.

Although the follow up rate of participant in the cohort was high, we were unable to obtain data on all outcomes (including answers to all questions, skin tests and sIgE) for all children. This was particularly relevant for the assessment of sIgE at age three years, which was measured in a relatively small proportion of children whose parents agreed to venepuncture. It is likely that as a consequence of having lower number of study participants who provided blood sample for sIgE measurement at

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this age, we observed a significant association between sIgE titres and wheezing at all ages, with the exception of three-year old girls. However, it is of note that in the analyses which we carried out, there was no difference between children included or excluded in demographic characteristics and primary outcome measures, suggesting that it is unlikely that this has influenced the main results.

We have not measured sIgE at age 11 years; however, we present the sIgE data at three different ages (three, five and eight years), which allowed us to carry out longitudinal analyses.

Our definition of quantitative sensitisation included SPT and sIgE responses to mite, cat and dog, which were then related to lower respiratory tract symptoms. We wish to emphasise that different allergens may be relevant in other geographical regions, and for different clinical outcomes.

One strength of the study is a relatively large sample of children from the population-based birth cohort, suggesting that our results are broadly applicable to the general population.

We acknowledge that recent developments in molecular or component-resolved diagnostics may facilitate better assessment of allergic diseases compared to skin prick or sIgE tests to extracts made from whole allergen sources (26-28). However, it is likely that standard SPTs and sIgE measurements are going to be widely used in large parts of the world for years to come.

Meaning of the study

There was a striking difference in the age-related association between SPT MWDs and sIgE titres with wheezing and asthma. For SPT MWDs, we found that the strength of the association with clinical symptoms increased as the age increased. However, the opposite pattern was observed for sIgE titres, with the strength of the association with disease decreasing with increasing age. This may be due to differences between the two tests, with SPTs assessing the sIgE bound to mast cells in skin, and serum sIgE detecting free sIgE. One possible reason for the decrease in the strength of the association between sIgE and clinical symptoms in the older age groups could be due to the changes in the total IgE. The ratio of sIgE to total IgE may be a better biomarker in relation to the symptoms of allergic disease compared to sIgE titre *per se*. If the total IgE titres increase at a faster rate than sIgE, this could decrease the ratio of total IgE/sIgE and hence reduce the probability of symptoms at a

given sIgE level. It has recently been reported that among sensitised children, allergen-specific IgG antibodies and sIgG/sIgE ratios may be associated with the size of skin test responses and the probability of clinical symptoms (29). Little is known about temporal changes in inhalant allergen-specific IgG antibodies, or IgG/IgE ratios during childhood. One important message offered by our results is that sIgE and SPT should not be used interchangeably to determine atopic sensitisation, and that these two tests provide complementary, rather than identical information.

Our results suggest that for a given value of SPT MWD and sIgE titre, boys are more likely than girls to exhibit wheezing and asthma at all ages (although the magnitude of this differences appeared to diminish with age). It is well known that sex influences asthma development in a time-dependent fashion, with higher prevalence and more severe symptoms in boys than girls. However, this pattern reverses during adolescence, with females having a greater incidence and severity of symptoms as they reach adulthood (30). Most published reports speculate that this is due to a numerous changes occurring during puberty, although no precise mechanistic explanation for this time-dependent switch has been established.

In summary, our results suggest that in clinical practice both age and sex need to be taken into account when interpreting the results of allergy tests (skin tests and specific IgE measurement). We suggest that age- and sex-specific normative data for both skin tests and sIgE are needed to fully capitalize on the potential value of these tests in the context of lower respiratory symptoms during childhood.

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LEGEND FOR FIGURES

Figure 1. Fitted probability curves from longitudinal analysis of the effect of age on the relation between quantitative atopy and current wheeze.

A) SPT MWD

B) sIgE titre

Figure 2. Fitted probability curves from longitudinal analysis of the effect of age on the relation between quantitative atopy and current asthma.

A) SPT MWD

B) sIgE titre

Figure 3. Predicted probability curves illustrating the relation between quantitative atopy and current asthma amongst males and females.

A-C) SPT MWD

D-F) sIgE titre

TABLES

Table 1. The relative odds ratios from discrete longitudinal analysis comparing the association between SPT MWD and sIgEs and current wheeze.

Bold: significant changes in association

Age group comparisons	Relative odds ratios	Lower confidence interval (LCL)	Upper confidence interval (UCL)	P – value
SPT MWD (mite+cat+dog)				
3 and 5	1.03	0.96	1.11	0.43
3 and 8	1.22	1.12	1.33	<0.001
3 and 11	1.14	1.05	1.24	0.002
5 and 8	1.21	1.12	1.30	<0.001
8 and 11	1.05	0.98	1.13	0.14
sIgE titre (mite+cat+dog)				
3 and 5	0.96	0.92	1.00	0.056
3 and 8	0.97	0.93	1.01	0.18
5 and 8	0.99	0.97	1.01	0.23

Table 2. The relative odds ratios from discrete longitudinal analysis for the association between quantitative sensitisation and asthma at different ages.

Bold: Significant changes in association.

Age group comparisons	Relative odds ratios	Lower confidence interval (LCL)	Upper confidence interval (UCL)	P – value
SPT MWD (mite+cat+dog)				
3 and 5	1.04	0.96	1.12	0.34
3 and 8	1.20	1.10	1.30	<0.001
3 and 11	1.14	1.05	1.24	0.002
5 and 8	1.17	1.09	1.26	<0.001
8 and 11	1.06	0.99	1.13	0.10
sIgE titre (mite+cat+dog)				
3 and 5	0.97	0.94	0.99	0.029
3 and 8	0.97	0.94	0.99	0.029
5 and 8	0.98	0.97	0.99	0.04









