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Quantification of atopy, lung function and airway hypersensitivity in adults

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Abstract

Background: Studies in children have shown that concentration of specific serum IgE (sIgE) and size of skin tests to inhalant allergens better predict wheezing and reduced lung function than the information on presence or absence of atopy. However, very few studies in adults have investigated the relationship of quantitative atopy with lung function and airway hyperresponsiveness (AHR).

Objective: To determine the association between lung function and AHR and quantitative atopy in a large sample of adults from the UK.

Methods: FEV₁ and FVC (% predicted) were measured using spirometry and airway responsiveness by methacholine challenge (5-breath dosimeter protocol) in 983 subjects (random sample of 800 parents of children enrolled in a population-based birth cohort enriched with 183 patients with physician-diagnosed asthma). Atopic status was assessed by skin prick tests (SPT) and measurement of sIgE (common inhalant allergens). We also measured indoor allergen exposure in subjects' homes.

Results: Spirometry was completed by 792 subjects and 626 underwent methacholine challenge, with 100 (16.0%) having AHR (dose-response slope > 25). Using sIgE as a continuous variable in a multiple linear regression analysis, we found that increasing levels of sIgE to mite, cat and dog were significantly associated with lower FEV₁ (mite $p = 0.001$, cat $p = 0.0001$, dog $p = 2.95 \times 10^{-8}$). Similar findings were observed when using the size of wheal on skin testing as a continuous variable, with significantly poorer lung function with increasing skin test size (mite $p = 8.23 \times 10^{-8}$, cat $p = 3.93 \times 10^{-10}$, dog $p = 3.03 \times 10^{-15}$, grass $p = 2.95 \times 10^{-9}$). The association between quantitative atopy with lung function and AHR remained unchanged when we repeated the analyses amongst subjects defined as sensitised using standard definitions (sIgE > 0.35 kUa/l, SPT-3 mm > negative control).

Conclusions: In the studied population, lung function decreased and AHR increased with increasing sIgE levels or SPT wheal diameter to inhalant allergens, suggesting that atopy may not be a dichotomous outcome influencing lung function and AHR.

Keywords: IgE, atopy, quantitative assay, lung function, airway hyperresponsiveness

Background

The association between reduced lung function and allergen sensitisation (mainly to inhalant allergens) has been clearly documented, both among children [1-7] and adults [8], often in the context of high allergen exposure [1,8]. A similar association has also been demonstrated for increased airway hyperresponsiveness amongst atopic individuals compared to those not sensitised [7-13].

Most of the studies investigating the relationship between allergen sensitisation and lung function or airway hyperresponsiveness (AHR) considered atopy as a simple dichotomous variable, assigning individuals as atopic or non-atopic based on arbitrary and differing cut-off points, either for IgE measurement or skin prick testing. [1-5,8-11]. Similar is the case for the studies reporting on the association between atopy and wheeze or other symptoms of allergic disease [14,15]. Analysing sensitisation quantitatively has been shown to improve the specificity of these tests. For example, the level of specific IgE may predict the likelihood of patients having

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symptomatic food allergy[16] and the size of the skin prick test wheal can be used in a similar way[17]. We have previously demonstrated similar quantitative relationship between specific serum IgE levels to common inhalant allergens and the presence and persistence of childhood wheezing and reduced lung function[6]. We have also shown a similar association between increasing levels of sIgE or size of skin test wheal to inhalant allergens and the presence of childhood allergic rhinitis[18]. However, very few studies in adults have investigated a quantitative relationship between atopy and lung function. A study in the US has demonstrated that AHR increased significantly amongst adult asthmatics with increasing size of skin test wheals to inhalant allergens [11]. A significant association was also reported amongst non-asthmatic individuals with increasing level of mite specific IgE[12].

We aimed to investigate the associations between the quantification of atopy (using specific IgE levels and the size of skin test wheal to a range of common inhalant allergens) and lung function parameters (FEV₁, FVC) and AHR in a population of adults with and without asthma, evaluating this in the context of smoking habits and indoor allergen exposure.

Methods

Study Population

Detailed phenotyping which included information on symptoms and assessment of lung function, airway reactivity and atopy was carried out amongst parents of children enrolled in a population-based birth cohort study (Manchester Asthma and Allergy Study) [19,20]). We enriched the study population with carefully phenotyped asthmatics fulfilling the following criteria: (1) physician-diagnosed asthma; (2) asthma symptoms (wheeze, cough, chest tightness, or breathlessness) in the previous 12 months; (3) currently using asthma treatment; and (4) no asthma exacerbation or respiratory infection within 4 weeks before the study.[8]. Only subjects of mixed European origin were included in this analysis. The study was approved by the Local Research Ethics Committee. Written informed consent was obtained from all subjects.

Data sources

Symptoms

A validated questionnaire[21] was interviewer-administered to collect information on symptoms, physician-diagnosed illnesses, treatments received, pet ownership and smoking habits.

Lung function

FEV₁ and FVC were assessed using spirometry according to ATS/ERS guidelines[22,23], and expressed as % predicted.

Airway responsiveness

assessed by methacholine challenge using the 5-breath dosimeter protocol, as per ATS guidelines[24].

Atopy

We performed skin prick tests (SPT) to *D. pteronyssinus*, cat, dog, grass pollen mix, tree pollen mix (Staller-gènes, France), and mould mix (Dome-Hollister-Stier, USA). We measured specific serum IgE (sIgE) to *D. pteronyssinus*, cat, dog and grass pollen mix by ImmunoCAP[®] (Phadia, Uppsala, Sweden).

Indoor allergen exposure

We visited homes and collected dust samples from the subjects' bed and the lounge floor by vacuuming 1 m² areas for two minutes in a standardised fashion. Mite (Der p 1), cat (Fel d 1) and dog (Can f 1) allergens were assayed using enzyme-linked immunoassays[25].

Definition of outcomes and exposures

Current asthma

Physician-diagnosed asthma with asthma symptoms and/or use of asthma medication in the last 12 months [26].

Airway hyperresponsiveness (AHR)

expressed as methacholine dose-response slope (MDRS) [27,28]. Participants were considered to have AHR if MDRS was >25.

Allergic sensitisation as a dichotomous variable

SPT wheal mean diameter (WMD)≥3 mm compared to negative control and/or specific IgE (sIgE)>0.35 kU_A/l to any allergen.

Tobacco smoking

Questionnaire information on smoking habits was used to derive continuous measures of smoke exposure for all subjects as smoke-pack-years (SPY): non-smokers = 0; calculated for both current and ex-smokers (SPY=number of cigarettes smoked per day/20 × number of years of smoking).

Allergen exposure

Individual exposure to house dust mite (Der p 1), cat (Fel d 1) and dog (Can f 1) allergens were expressed as allergen concentration per gram of fine dust (µg/g)[29].

Statistical analysis

The primary outcome measures were lung function parameters and AHR. All dynamic lung volumes (FEV₁ and FVC % predicted and FEV₁/FVC) followed a normal distribution and results are expressed as mean and standard deviation (SD). Methacholine dose-response slope (MDRS) distribution was normalised using the transformation 100/(MDRS+10) = tMDRS[27,30]. The levels of specific IgE were subject to a log_e-transformation prior to analysis; skin prick tests WMD were used as raw data. Tobacco smoking and allergen exposure data followed a log_e-distribution.

The correlation between SPT-WMD and sIgE levels for each allergen was assessed using Spearman's rho test. The relationship between quantitative sensitisation and outcome measures was analyzed using linear regression and General Linear Model Univariate ANOVA, with a p-value of 0.05 considered as significant. Regression slope, R^2 (as measure of effect direction and size, respectively) and 95% confidence intervals (95% CI) were estimated using linear regression models. General Linear Model multivariate ANCOVA analyses were performed, including all the factors identified as significant in the univariate analysis. Fitted predicted value curves according to the level of specific IgE/size of SPT-WMD were plotted using the results from the regression analysis. Statistical analysis was carried out using SPSS 15.0 (SPSS Inc., Chicago, IN, USA).

Results

Participants

We contacted 1446 parents of the children recruited in the Manchester Asthma and Allergy Study (population-based birth cohort representative of the general population). Of these, 178 declined the invitation and 99 did not respond. Of the 1169 subjects who expressed an interest, 831 (71.1%) signed informed consent, of whom 800 were included in the analysis (12 with insufficient data and 19 non-Caucasians were excluded). We then enriched the study population with 183 asthmatic patients, with the analysed sample including 983 Caucasian subjects (416 [42.3%] male; mean age 48.3 years, range 19.8-72.9). Demographic characteristics of the study population are presented in Table 1. Skin tests were performed on 730 subjects (74.3%) and 748 (76.1%) provided blood sample for IgE measurement; 680 subjects had both skin tests and IgE data. We found no significant differences between the subjects with and without skin tests and IgE data in any of the outcomes studied. Spirometry was done by 792 subjects (80.6%) and 626 (63.7%) underwent a methacholine challenge, with 100 (16.0%) having AHR (MDRS>25). Of the 748 subjects with IgE data, 473 (63.2%) were atopic with raised specific IgE to one or more allergens. Table 2 presents details of atopic status considering both dichotomous and quantitative definitions. Table 3 presents the correlation between SPT-WMD and sIgE levels for each allergen.

Specific IgE, Skin Prick tests and Lung Function

Table 4 present the associates of the lung function parameters studied. When using IgE measurement to define subjects as atopic or not (*i.e.*, dichotomous definition), there was a strong association between atopy and poorer lung function (FEV₁ and FVC % predicted, FEV₁/FVC) and the same was seen when using SPT to define atopy (Table 4). This was also true when looking at specific

sensitisation to a range of inhalant allergens on either IgE or SPT, with particularly strong associations with sensitisation to cat (e.g., for FEV₁ % predicted on specific IgE $p = 0.0007$, on SPT $p = 5.02 \times 10^{-7}$) and dog (for FEV₁ % predicted on SPT $p = 4.16 \times 10^{-12}$, for sIgE $p = 8.57 \times 10^{-8}$).

Using sIgE as a continuous variable in a linear regression analysis, we found that increasing levels of sIgE to mite, cat and dog were significantly associated with poorer level of FEV₁ % predicted (for mite $p = 0.001$, cat $p = 0.0001$, dog $p = 2.95 \times 10^{-8}$, Table 4 and Figure 1); the same was also observed for FEV₁/FVC, though only increasing levels of sIgE to dog were associated with poorer FVC % predicted (Table 4). Similar findings were observed when using SPT as continuous variable, with significantly poorer lung function with increasing size of SPT-WMD for inhalant allergens (Table 4). This is illustrated for FEV₁ % predicted in Figure 2: mite $p = 8.23 \times 10^{-8}$, cat $p = 3.93 \times 10^{-10}$, dog $p = 3.03 \times 10^{-15}$, grass $p = 2.95 \times 10^{-9}$, mould $p = 0.02$.

When the levels of specific IgE for the individual allergens (mite, cat, dog, grass) were summed, the strength of this effect was slightly weakened or lost for FEV₁ and FVC % predicted and FEV₁/FVC ($p = 0.01$, $p = 0.17$ and $p = 0.002$, respectively). However, this was not the case when adding the sizes of SPT-WMD for the same allergens (FEV₁ % predicted $p = 1.89 \times 10^{-15}$, FVC % predicted $p = 3.20 \times 10^{-6}$, FEV₁/FVC $p = 1.99 \times 10^{-16}$).

Specific IgE, Skin prick tests and Airway Hyperresponsiveness

Associates of airway hyperresponsiveness (MDRS) from univariate regression analysis are shown in Table 5. Increased MDRS was strongly associated with atopy (on either SPT or sIgE, $p \leq 3.14 \times 10^{-14}$) and with sensitisation to all inhalant allergens tested when using dichotomous definitions (Table 5). When analysing this using sensitisation as quantitative measure, we found that increasing levels of sIgE/increasing size of SPT-WMD were strongly associated with increasing MDRS (Table 5 and Figure 3, illustrative of these associations for sIgE level). When the levels of sIgE or SPT-WMD sizes to each individual allergen were summed, this association remained strongly significant ($p = 1.63 \times 10^{-24}$ for sum of sIgE or SPT-WMD).

Specific IgE antibodies, Skin Test Size and Lung Function and Airway Hyperresponsiveness amongst sensitised subjects

To further Investigate the relationship between quantitative atopy, lung function and AHR, we repeated the analysis amongst subjects who would be considered sensitised using standard definitions (e.g., sIgE>0.35 kUa/l, SPT-WMD 3 mm>negative control). Using these definitions, 473 subjects were assigned as sensitised

Table 1 Characteristics of the 983 subjects included in the study

Variable			Total (n)*	% of Total Subjects
Age (y)	Mean	(Range)		
	48.3	(19.8-72.9)	983	100.0
Gender - male	n	(%)		
	416	(42.3)	983	100.0
BMI (%)	Mean	(SD)		
	27.2	5.1	769	78.2
Asthma	n	(%)		
Current Asthma	312	(31.74)	983	100.0
Airway Hyperresponsiveness (AHR)	n	(%)		
AHR-MDRS>25	100	(15.97)	626	63.7
MDRS	GM	(Range)		
	8.229	(0.0-17592.5)	626	63.7
Current Asthma with AHR	n	(%)		
Current Asthma + AHR-MDRS>25	64	(10.22)	626	63.7
Lung Function	Mean	(SD)		
FVC % predicted	111.86	(16.01)	790	80.4
FEV ₁ % predicted	101.20	(18.41)	792	80.6
FEV ₁ /FVC	75.84	(8.71)	790	80.4
Atopy	n	(%)		
SPT	402	55.07	730	74.3
sIgE	473	63.24	748	76.1
Smoking	n	(%)		
Ever smokers	396	(40.28)	983	100.0
Current smokers	114	(11.60)	983	100.0
Smoke-pack-years	GM	(Range)		
	0.0006	(0.0 -104.59)	981	99.8
Pet ownership	n	(%)		
Cat owner (current)	171	21.22	806	81.99
Dog owner (current)	142	17.62	806	81.99
Cat or dog owner (current)	277	34.37	806	81.99
Indoor allergen exposure (µg/g)	GM	(Range)		
Mite (Der p 1)	2.59	(0.20-188.67)	953	96.95
Cat (Fel d 1)	1.42	(0.04-5377.61)	951	96.75
Dog (Can f 1)	0.96	(0.20-3361.02)	948	96.44

*Total number of patients with available data; BMI - Body mass index; AHR - Airway Hyperresponsiveness; MDRS - methacholine dose-response slope; SPT - skin prick tests; sIgE - serum specific Immunoglobulin E; GM - Geometric mean.

Notes: Current Asthma - Physician-diagnosed asthma with asthma symptoms and/or use of asthma medication in the last 12 months[26]; for MDRS, GM calculated from $tMDRS = 100/(MDRS+10)$ [27,30]; for smoke-pack-years and indoor allergen exposure, GM calculated from \log_e transformation.

based on sIgE and 402 based on SPT (Table 1). Even within the group of atopic individuals, increasing level of sIgE or SPT-WMD size to individual allergens was associated with significantly poorer lung function or increasing AHR (data shown for FEV₁ % predicted and MDRS in Table 6).

Multivariate analysis

To assess the relative contribution of sIgE levels and size of SPT-WMD to lung function (FEV₁ % predicted) and AHR (MDRS), we performed a multivariate ANCOVA, controlling for all the factors that we found

associated with these outcomes in the univariate analyses, including current asthma, smoking habits and indoor allergen exposure. In these models (Table 7), increasing level of sIgE to dog remained a strong and highly significant independent associate of FEV₁ and FVC % predicted and FEV₁/FVC; the same was true for increasing level of sIgE/size of SPT-WMD to mite, which remained an independent associates of MDRS. Increasing level of sIgE to mite was an independent associate of FEV₁/FVC. The significant independent associates and the size of their effect varied slightly depending on whether SPT or sIgE data were used.

Table 2 Allergen sensitisation: Dichotomous definitions on SPT and sIgE, SPT wheal mean diameters (WMD, mm) and sIgE level (kU_A/l)

SPT	Dichotomous		Quantitative		Total (n)	% of Total Subjects
	n	(%)	Median*	(Range)		
Mite	256	(35.07)	4.5	(0-19.5)	730	74.26
Cat	175	(23.97)	4.5	(0-20.0)	730	74.26
Dog	112	(15.34)	4.0	(0-16.5)	730	74.26
Tree pollen mix	84	(14.43)	5.0	(0-11.0)	582	59.21
Grass pollen mix	213	(29.18)	5.0	(0-23.0)	730	74.26
Mould mix	32	(4.40)	4.0	(0-12.0)	727	73.96
Specific IgE	n	(%)	GM	(Range)		
Mite	343	(45.86)	0.48	(0.05-160.77)	748	76.09
Cat	211	(28.21)	0.16	(0.05-146.94)	748	76.09
Dog	170	(22.73)	0.14	(0.05-100.48)	748	76.09
Grass pollen mix	336	(44.92)	2.18	(0.05-407.48)	748	76.09

*Median SPT-WMD among subjects with positive SPTs only (median in whole population = 0 for all allergens due to non-sensitised subjects); GM - Geometric mean; SPT - skin prick tests.

Note: for specific IgE, GM was calculated based on log_e transformation.

Discussion

Principal Findings

Our results confirm that sensitisation to inhalant allergens is an associate of lung function and airway hyperresponsiveness in adults. Furthermore, our data suggest that amongst adults there is a quantitative relationship between the level of allergen-specific IgE or the size of skin prick test reaction and the level of lung function and airway hyperresponsiveness, with decreasing lung function and increasing AHR with increasing level of specific IgE or skin test wheal size. We have demonstrated that the absolute level of specific IgE or the size of the skin test wheal diameter to mite and dog remain independent associates of lung function and airway hyperresponsiveness in our sample of adults in the UK after adjusting for potential confounding variables, including current asthma, smoking habits and indoor allergen exposure. In addition, we have extended this observation in demonstrating that the same associations remain within the group of subjects defined as atopic using standard definitions[6].

Limitations and strengths

We were not able to obtain skin prick test data or specific IgE measurements for all subjects studied (74.3% had skin tests and 76.1% IgE). However, it is unlikely that this has

influenced our results, since we found no significant differences between the subjects with and without these data in any of the outcomes studied. Moreover, the prevalence of allergic sensitisation among our subjects is similar to that of young adults in the UK[31], suggesting that our results are applicable to the general population.

As fewer subjects had skin prick testing data than measurements of specific IgE, fewer subjects 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). Similarly, some subjects in our study did not do lung function tests or had a methacholine challenge; however, there was no difference in atopy between the groups with and without these tests.

This was a cross-sectional study, and we cannot comment on the role of quantitative measures of allergen-specific serum IgE or skin prick tests on the change in lung function or AHR over time. This is an important question which needs to be addressed in cohort studies, which are unfortunately lacking in adults.

We acknowledge that the observed associations may differ between different ethnic groups. We decided to carry out our analysis amongst Caucasian participants, as the number of participants of other ethnic origins was too small to make any meaningful conclusions. We therefore wish to emphasise that our finding cannot be extrapolated to other ethnic groups, and further work is essential to address this important question.

We acknowledge that atopy is strongly associated with asthma, which could therefore be a confounder. However, by adjusting for asthma in the multiple regression models, we were able to take this into account and tease out independent associations between quantitative atopy, lung function and AHR. It is also possible that the association of quantitative atopy with lung function

Table 3 Correlation between SPT-WMD (mm) and sIgE levels (kU_A/l) for each allergen

Allergen	Spearman's rho	p value
Mite	0.734	3.63×10^{-116}
Cat	0.696	1.36×10^{-99}
Dog	0.548	1.85×10^{-54}
Grass pollen	0.644	5.51×10^{-81}

Table 4 Associates of FEV₁ and FVC % predicted and FEV₁/FVC (univariate analysis)

Associate	FEV ₁ % predicted			FVC % predicted			FEV ₁ /FVC		
	P	Slope	R ²	P	Slope	R ²	P	Slope	R ²
Atopy on SPT*	0.00001	-5.93	0.03	0.03	-2.61	0.007	5.39×10 ⁻⁸	-9.81	0.03
Mite									
Positive SPT	0.00001	-6.27	0.03	0.01	-3.25	0.009	6.17×10 ⁻⁷	-9.76	0.03
SPT-WMD	8.23×10 ⁻⁸	-1.40	0.04	0.002	-0.75	0.01	4.12×10 ⁻⁹	-2.11	0.05
Cat									
Positive SPT	5.02×10 ⁻⁷	-7.69	0.03	0.02	-2.96	0.007	1.08×10 ⁻⁷	-13.61	0.05
SPT-WMD	3.93×10 ⁻¹⁰	-1.63	0.05	0.0007	-0.81	0.02	2.80×10 ⁻¹⁰	-2.55	0.06
Dog									
Positive SPT	4.16×10 ⁻¹²	-12.22	0.06	0.0001	-6.06	0.02	1.38×10 ⁻¹³	-18.21	0.07
SPT-WMD	3.03×10 ⁻¹⁵	-2.49	0.08	1.70×10 ⁻⁶	-1.41	0.03	8.53×10 ⁻¹⁶	-3.68	0.09
Tree									
Positive SPT	0.73	0.52	0.0002	0.51	0.97	0.0008	0.85	-1.36	0.0005
SPT-WMD	0.93	-0.07	0.00001	0.70	0.02	0.0003	0.37	-0.51	0.002
Grass									
Positive SPT	2.06×10 ⁻⁶	-6.78	0.03	0.004	-3.64	0.01	2.79×10 ⁻⁷	-9.40	0.03
SPT-WMD	2.95×10 ⁻⁹	-1.04	0.05	0.0002	-0.59	0.02	9.62×10 ⁻¹⁰	-1.50	0.05
Mould									
Positive SPT	0.22	-3.22	0.002	0.61	-1.10	0.0004	0.17	-8.17	0.005
SPT-WMD	0.02	-1.53	0.007	0.24	-0.77	0.002	0.006	-2.60	0.01
Atopy on sIgE[#]	0.0007	-4.83	0.02	0.10	-2.03	0.004	0.0001	-7.22	0.02
Mite									
Positive sIgE	0.03	-2.97	0.006	0.45	-0.89	0.0008	0.008	-5.31	0.01
sIgE level	0.001	-0.88	0.01	0.21	-0.30	0.002	0.0004	-1.49	0.02
Cat									
Positive sIgE	0.0007	-5.16	0.02	0.57	-0.75	0.0004	0.00006	-11.76	0.04
sIgE level	0.0001	-1.37	0.02	0.28	-0.33	0.002	0.00003	-2.78	0.04
Dog									
Positive sIgE	8.57×10 ⁻⁸	-8.70	0.04	0.02	-3.39	0.008	7.30×10 ⁻⁸	-16.05	0.06
sIgE level	2.95×10 ⁻⁸	-2.29	0.04	0.004	-1.04	0.01	1.96×10 ⁻⁷	-3.87	0.06
Grass									
Positive sIgE	0.04	-2.82	0.006	0.72	-0.42	0.0002	0.002	-5.83	0.01
sIgE level	0.15	-0.38	0.003	0.82	-0.05	0.00007	0.05	-0.84	0.006
Gender - Female	0.09	2.27	0.004	1.00×10 ⁻⁶	5.66	0.03	0.0009	0.02	0.01
Age (years)	1.22×10 ⁻¹³	-0.62	0.07	3.29×10 ⁻⁶	-0.30	0.03	1.31×10 ⁻³¹	-0.005	0.16
BMI (%)	0.0008	-0.42	0.01	4.80×10 ⁻⁹	-0.64	0.04	0.36	0.001	0.001
Current Asthma	1.18×10 ⁻⁴¹	-17.46	0.21	3.05×10 ⁻¹³	-8.53	0.07	3.68×10 ⁻⁴³	-0.08	0.21
Cat ownership (current)	0.32	-1.65	0.001	0.96	-0.12	2.54×10 ⁻⁶	0.10	-0.01	0.003
Dog ownership (current)	0.25	-1.99	0.002	0.68	-0.60	0.0002	0.14	-0.01	0.003
Ln Der p 1 Exposure (µg/g)	0.62	0.17	0.0003	0.33	0.29	0.001	0.68	-0.001	0.0002
Ln Fel d 1 Exposure (µg/g)	0.39	-0.22	0.0010	0.77	0.08	0.0001	0.01	-0.003	0.008
Ln Can f 1 Exposure (µg/g)	0.0001	-1.22	0.02	0.002	-0.87	0.01	0.003	-0.005	0.01
Smoking (Ever)	0.0008	-4.46	0.01	0.07	-2.08	0.004	0.0001	-0.02	0.02
Ln Smoke-Pack-Years	0.0002	-0.31	0.02	0.03	-0.16	0.006	0.0001	-0.002	0.02

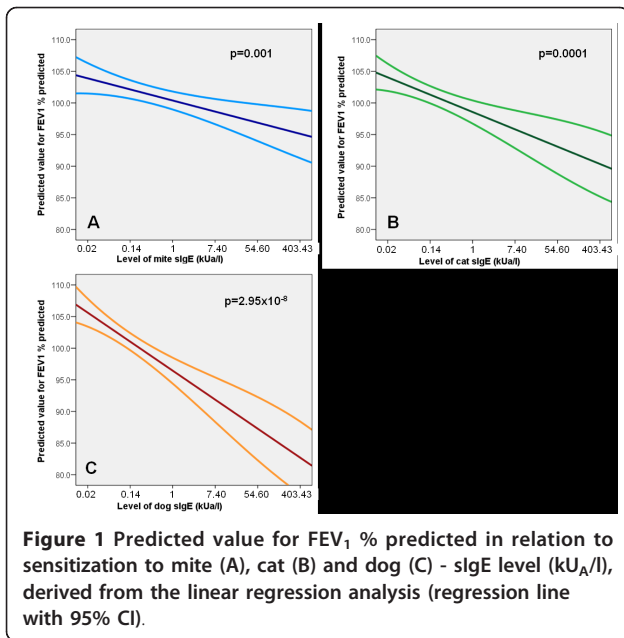
*At least one positive skin prick test result; #At least one positive sIgE result; SPT-WMD - Skin prick test wheal mean diameter (mm); sIgE level (kU_A/l). BMI - Body mass index; AHR - Airway Hyperresponsiveness; MDRS - methacholine dose-response slope; SPT - skin prick tests; sIgE - serum specific IgE; GM - Geometric mean. Current Asthma - Physician-diagnosed asthma with asthma symptoms and/or use of asthma medication in the last 12 months[26].

and AHR differs between asthmatics and healthy individuals. Our study population comprised a sample which is likely to be representative of the general population (800 parents of children enrolled in a population-based birth cohort), enriched by carefully phenotyped asthmatic subjects, giving us a total of 312 patients with current asthma. We enriched the study population with asthma cases to increase the range of lung function values and the number of subjects with AHR, and thus increase the power to detect associations. In addition, by enriching the study population with well-defined group of asthmatics, this design has increased our confidence that we could detect any difference between asthmatics and non asthmatics. In this population, we did not

observe a significant difference between asthmatics and non-asthmatics with respect to the findings on the association between quantitative atopy and our outcomes of interest (i.e. lung function and AHR). However, this finding needs to be interpreted with great caution, as our study might not have sufficient power to detect such differences. This question needs to be addressed in a much larger study, using for example a matched case-control design.

Interpretation

Many studies have identified allergic sensitisation (in particular to inhalant allergens) as a strong associate of lung function[1-8] and airway hyperresponsiveness



investigated the associates of AHR in children, looking at the sizes of skin test wheals when analysing atopy, and demonstrated that the sizes of the reactions to mite, cat, dog and *Aspergillus fumigatus* were independently correlated with airway hyperresponsiveness, particularly when summed. Another study by Nogalo et al.[12] looked specifically at the associations between airway hyperresponsiveness and level of specific mite specific IgE amongst mite-sensitised non-asthmatic children, and found that these were independently associated.

Our findings add to the above by demonstrating a quantitative rather than dichotomous relationship between atopy and the level of lung function and airway hyperresponsiveness in adults, when using both the size of skin prick tests and the level of specific IgE to inhalant allergens. In multivariate analyses adjusted for other relevant associates (such as asthma and smoking), we demonstrated significant independent associations for quantitative dog skin test and IgE levels and lung function, with quantitative mite IgE and skin test responses being associated with airway hyperresponsiveness. It is important to emphasise that the same quantitative relationships were demonstrated even when adults without allergic sensitisation were excluded from the analysis, confirming the importance of the quantitative approach.

[7-13], both in children and in adults, with reduced lung function and increased airway hyperresponsiveness in sensitised compared to non-sensitised individuals. However, as outlined previously, most such studies have considered sensitisation as either present or not[1-5,8-11]. A previous study by Burrows and colleagues[13]

Similar to our previous findings for lower respiratory symptoms and lung function in children[6], but in

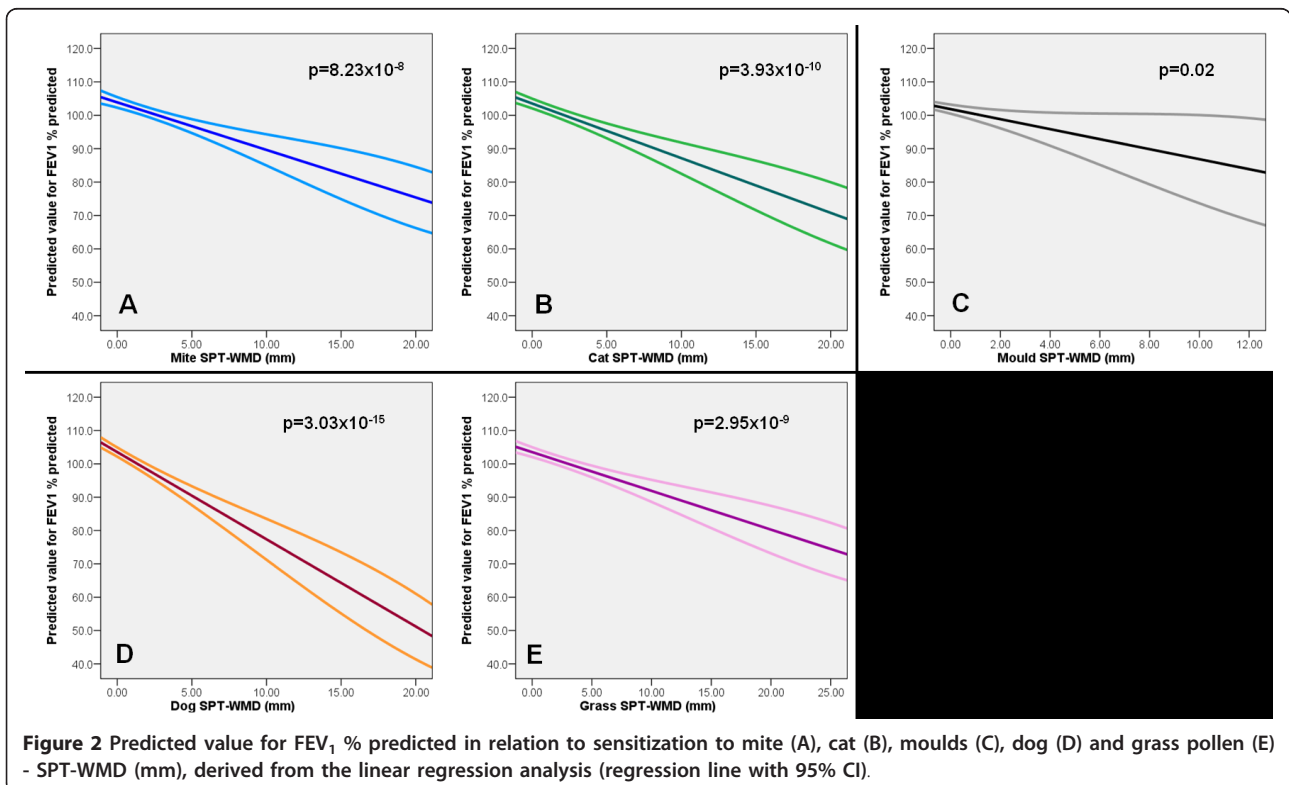


Table 5 Associates of MDRS (univariate analysis)

Associate	tMDRS		
	p	Slope	R ²
Atopy on SPT*			
Mite	4.27×10 ⁻¹¹	-1.43	0.07
Positive SPT	1.05×10 ⁻⁹	-1.43	0.06
SPT-WMD	1.28×10 ⁻¹²	0.033	0.08
Cat	4.31×10 ⁻⁹	-1.55	0.06
Positive SPT	3.09×10 ⁻¹¹	-0.38	0.07
SPT-WMD	3.09×10 ⁻¹¹	-0.38	0.07
Dog	4.30×10 ⁻¹²	-2.32	0.08
Positive SPT	3.95×10 ⁻¹²	-0.51	0.08
SPT-WMD	3.95×10 ⁻¹²	-0.51	0.08
Tree	0.0001	-1.19	0.03
Positive SPT	0.0001	-0.23	0.03
SPT-WMD	0.0001	-0.23	0.03
Grass	1.27×10 ⁻⁷	-1.31	0.05
Positive SPT	5.80×10 ⁻⁸	-0.27	0.05
SPT-WMD	5.80×10 ⁻⁸	-0.27	0.05
Mould	0.003	-1.92	0.02
Positive SPT	0.002	-0.48	0.02
SPT-WMD	0.002	-0.48	0.02
Atopy on sIgE#			
Mite	3.14×10 ⁻¹⁴	-1.72	0.10
Positive sIgE	1.04×10 ⁻¹¹	-1.54	0.08
sIgE level	3.08×10 ⁻¹⁷	-0.39	0.12
Cat	4.83×10 ⁻¹⁶	-2.08	0.11
Positive sIgE	4.83×10 ⁻¹⁶	-0.57	0.14
sIgE level	4.83×10 ⁻¹⁶	-0.57	0.14
Dog	2.55×10 ⁻²¹	-2.59	0.15
Positive sIgE	2.42×10 ⁻²³	-0.72	0.16
sIgE level	2.42×10 ⁻²³	-0.72	0.16
Grass	7.73×10 ⁻¹³	-1.61	0.09
Positive sIgE	1.44×10 ⁻¹³	-0.33	0.09
sIgE level	1.44×10 ⁻¹³	-0.33	0.09
Gender - Female	1.07×10 ⁻⁷	-1.17	0.04
Age (years)	0.39	-0.04	0.001
BMI (%)	0.14	-0.03	0.004
FEV ₁ % predicted	2.55×10 ⁻²⁸	0.08	0.18
FVC % predicted	0.001	0.03	0.02
FEV ₁ /FVC	1.18×10 ⁻²⁷	15.79	0.18
Current Asthma	3.30×10 ⁻³²	-2.89	0.20
Cat ownership (current)	0.42	0.24	0.001
Dog ownership (current)	0.04	-0.61	0.007
Ln Der p 1 Exposure (µg/g)	0.77	0.02	0.0001
Ln Fel d 1 Exposure (µg/g)	0.26	0.06	0.002
Ln Can f 1 Exposure (µg/g)	0.02	-0.13	0.009
Smoking (Ever)	0.08	-0.40	0.005
Ln Smoke-Pack-Years	0.08	-0.03	0.005

*At least one positive skin prick test result; #At least one positive sIgE result; SPT-WMD - Skin prick test wheal mean diameter (mm); sIgE level (kU_A/l)

BMI - Body mass index; MDRS - methacholine dose-response slope; SPT - skin prick tests; sIgE - serum specific IgE. Current Asthma - Physician-diagnosed asthma with asthma symptoms and/or use of asthma medication in the last 12 months[26].

Note: tMDRS = 100/(MDRS+10), thus negative slope means increasing MDRS

contrast to our findings for rhinitis and rhinoconjunctivitis[18], the associations between quantitative atopy and lung function and airway hyperresponsiveness remained strongly significant when the IgE levels/sizes of skin tests for individual allergens (mite, cat, dog and grass) were summed (with the single exception of the sum of sIgE levels and lung function parameters). Clearly, different clinical presentations of allergic

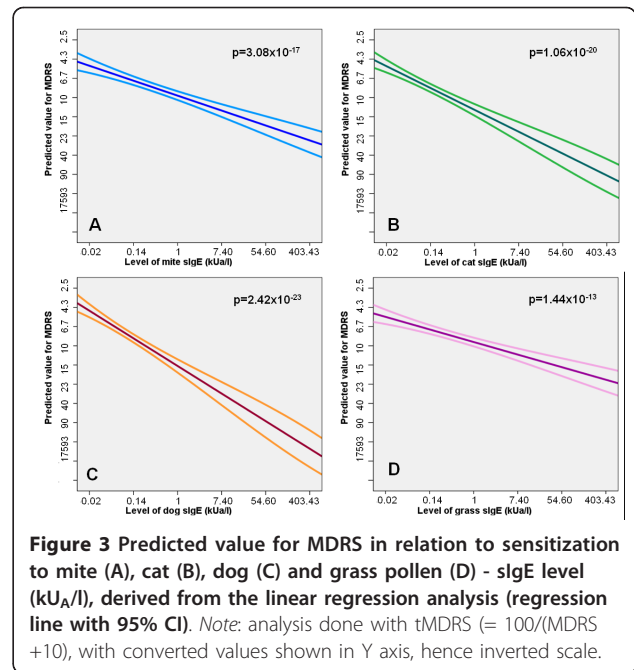


Figure 3 Predicted value for MDRS in relation to sensitization to mite (A), cat (B), dog (C) and grass pollen (D) - sIgE level (kU_A/l), derived from the linear regression analysis (regression line with 95% CI). Note: analysis done with tMDRS (= 100/(MDRS +10), with converted values shown in Y axis, hence inverted scale.

airway disease are associated with different patterns of quantitative atopy, with the sum of inhalant allergens being important in childhood wheezing[6], grass pollen in seasonal and dust mite in perennial rhinitis[18], specific responses to dog in lung function and specific responses to dust mite in airway hyperresponsiveness. Dog allergen is readily inhaled into the lower airways, and may have an immediate impact on lung function. Dust mite allergens are carried on much larger

Table 6 Quantification of IgE and SPT and FEV₁ % predicted and tMDRS amongst sensitised subjects (univariate analysis)

	FEV ₁ % predicted			tMDRS		
	p	Slope	R ²	p	Slope	R ²
SPT-WMD						
Mite	0.001	-1.33	0.04	0.001	-0.19	0.03
Cat	2.26×10 ⁻⁶	-1.41	0.05	1.57×10 ⁻⁵	-0.27	0.06
Dog	3.69×10 ⁻¹¹	-2.43	0.1	2.64×10 ⁻⁶	-0.37	0.07
Tree	0.84	0.07	0.0001	0.08	-0.12	0.01
Grass	3.77×10 ⁻⁶	-1.04	0.05	0.03	-0.11	0.01
Mould	0.17	-0.99	0.005	0.09	-0.29	0.009
sIgE						
Mite	0.09	-0.50	0.004	6.08×10 ⁻⁶	-0.28	0.06
Cat	0.01	-1.05	0.01	1.14×10 ⁻¹⁰	-0.46	0.12
Dog	9.33×10 ⁻⁶	-2.08	0.04	2.90×10 ⁻¹²	-0.59	0.13
Grass	0.35	0.34	0.002	0.02	-0.19	0.03

SPT-WMD - Skin prick test wheal mean diameter (mm); sIgE level (kU_A/l)

SPT - skin prick tests; sIgE - serum specific IgE

Note: tMDRS = 100/(MDRS+10), thus negative slope means increasing MDRS

Table 7 Independent associates of lung function and AHR (multivariate analysis)

Associate	FEV ₁ % predicted			
	Model 1 (SPT-WMD)		Model 2 (slgE level)	
	Adj p	Adj R ²	Adj p	Adj R ²
Age	5.82×10 ⁻⁷	0.04	5.91×10 ⁻⁸	0.04
BMI	0.09		0.48	
Current Asthma	1.64×10 ⁻¹⁴	0.08	3.34×10 ⁻²⁴	0.14
Ln Smoke-Pack-Years	0.02	0.008	0.02	0.008
Ln Can f 1 exposure	0.06		0.07	
Mite	0.16		0.69	
Cat	0.91		0.46	
Dog	0.003	0.01	0.10	
Grass	1.00		NI	
Mould	0.11		NA	

Associate	FVC % predicted			
	Model 1 (SPT-WMD)		Model 2 (slgE level)	
	Adj p	Adj R ²	Adj p	Adj R ²
Age	0.01	0.009	0.01	0.009
BMI	3.65×10 ⁻⁵	0.03	6.23×10 ⁻⁵	0.02
Gender - female	0.0003	0.02	0.001	0.02
Current Asthma	0.0002	0.02	2.91×10 ⁻⁸	0.04
Ln Smoke-Pack-Years	0.44		0.45	
Ln Can f 1 exposure	0.18		0.13	
Mite	0.49		NI	
Cat	0.91		NI	
Dog	0.047	0.006	0.56	
Grass	0.94		NI	

Associate	FEV ₁ /FVC			
	Model 1 (SPT-WMD)		Model 2 (slgE level)	
	Adj p	Adj R ²	Adj p	Adj R ²
Age	9.99×10 ⁻²⁰	0.12	2.51×10 ⁻²³	0.13
Gender - female	0.02	0.008	0.01	0.009
Current Asthma	8.08×10 ⁻¹⁵	0.09	8.52×10 ⁻²¹	0.12
Ln Smoke-Pack-Years	0.004	0.01	0.004	0.01
Ln Can f 1 exposure	0.20		0.33	
Ln Fel d 1 exposure	0.27		0.24	
Mite	0.02	0.008	0.21	
Cat	0.84		0.72	
Dog	0.003	0.01	0.47	
Grass	0.96		NI	
Mould	0.23		NA	

Associate	tMDRS			
	Model 1 (SPT-WMD)		Model 2 (slgE level)	
	Adj p	Adj R ²	Adj p	Adj R ²
Gender - female	3.59×10 ⁻¹³	0.09	3.97×10 ⁻¹³	0.09
Current Asthma	3.82×10 ⁻⁷	0.05	0.0003	0.02
FEV ₁ % predicted	60.3×10 ⁻⁹	0.06	1.04×10 ⁻⁸	0.06
FEV ₁ /FVC	0.001	0.02	2.05×10 ⁻⁵	0.03
Ln Can f 1 exposure	0.25		0.32	
Mite	0.0001	0.03	0.0004	0.02
Cat	0.36		0.45	

Table 7 Independent associates of lung function and AHR (multivariate analysis) (Continued)

Dog	0.56	0.44	
Grass	0.20	0.007	0.01
Mould	0.30	NA	

Models using quantitative measures of sensitisation to inhalant allergens: either SPT-WMD in mm for Model 1 or level of slgE in kU_A/l for Model 2. BMI - body mass index; tMDRS - transformed methacholine dose-response slope (tMDRS = 100/(MDRS+10)); SPT - skin prick tests; slgE - serum specific IgE. Current Asthma - Physician-diagnosed asthma with asthma symptoms and/or use of asthma medication in the last 12 months[26]. NA - not available; NI - not included in model (no association in univariate analysis)

particles and may contribute to the chronic inflammatory process best represented by airway hyperresponsiveness. The importance of dog and mite allergens in this study may also reflect the high concentrations of these allergens in UK homes. Our findings for lung function and airway hyperresponsiveness are consistent with recent studies demonstrating that quantification of IgE may be useful not only to diagnose allergic diseases in young children but to serve as a marker of persistence of wheeze[6] and severity of asthma[32,33].

Conclusions

In our study population, we observed a quantitative relationship between IgE-mediated sensitisation and lung function or airway hyperresponsiveness in adults. Our results have important implications in clinical practice: the quantification of allergic sensitisation may offer more information to the clinician compared to the simple presence or absence of atopy.

Abbreviations

AHR: Airway hyperresponsiveness; **BMI:** Body mass index; **FEV₁:** Forced expiratory volume in one second; **FVC:** Forced vital capacity; **MDRS:** Methacholine dose-response slope; **slgE:** specific serum immunoglobulin E; **SPT:** Skin prick tests; **SPT-WMD:** Skin prick test wheal mean diameter; **SPY:** Smoke pack years.

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Authors' contributions

SM participated in the design of the study, recruited and phenotyped the subjects, analysed and interpreted the data and drafted the manuscript. PM and JS phenotyped a subgroup of subjects. AS and AC conceived the study and its design, participated in its co-ordination and critically revised the manuscript. All authors read and approved the manuscript.

Competing interests

The authors declare that they have no competing interests.

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