Allergen-specific IgG Antibody Levels Modify The Relationship Between Allergen-Specific IgE And Wheezing In Childhood

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Abstract

Background—Increase in IgE-antibodies to inhalant allergens is associated with an increased likelihood of wheezing. The role of allergen-specific IgG and IgG_4 in relation to wheezing is yet to be determined.

Objective—To investigate whether Fel d 1-specific IgG and IgG_4 antibodies modify the association between cat allergen-specific IgE and childhood wheezing.

Methods—We used data from two population-based birth cohorts (UK, n=473 and Australia, n=1336). Current wheeze was defined as wheezing in the previous 12 months at age 5 (UK) and 14 years (Australia). We determined cat allergen-specific IgE (whole extract), and IgG and IgG_4 antibodies (purified rFel d 1). We used logistic regression to estimate the relationship between wheeze and the quantitative allergen antibody levels.

Results—In the univariate analysis risk of wheezing increased significantly with increasing cat-specific IgE (UK: OR 1.56, 95%CI 1.28–1.90, Australia 1.29, 1.19–1.40). rFel d1-specific IgG or IgG_4 had no significant effect on wheeze in either population. However, a different pattern of the relationship between antibody levels and wheezing emerged in the multivariate analysis. In the UK, cat-specific IgE increased the risk of wheeze (2.01, 1.29–3.12, p=0.002), whilst rFel d 1-specific IgG decreased the risk (0.46, 0.21–0.99, p=0.05). This finding was replicated in Australia

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(IgE: 1.46, 1.28–1.68, p<0.001; IgG: 0.66, 0.44–0.99, p=0.049). There was no significant association between IgG$_4$ antibodies and wheezing in either population.

Conclusions—rFel d 1-specific IgG, but not IgG$_4$ antibodies significantly modify the association between cat specific IgE and childhood wheezing, with the risk of symptoms decreasing with increasing IgG.

BACKGROUND

The presence of allergen-specific IgE antibodies is associated with increased risk of wheezing in children[1] and adults[2], and with increasing severity of asthma and diminished lung function when the individual is exposed to sensitizing allergen[3–5]. We have previously demonstrated that the absolute specific IgE antibody levels offer more information about the relationship between IgE-mediated sensitization and respiratory symptoms than just the presence of specific IgE, and found total IgE to be a poorer predictor of wheeze than the sum of specific IgEs[6, 7]. These data suggested that labeling subjects as sensitized or not based on an arbitrary cut-off is an oversimplification of a trait that is not dichotomous in its relationship with the symptoms of allergic disease[8].

Allergen exposure is associated with increasing risk of IgE-mediated sensitization[9, 10]. However, several studies have shown that at very high levels of exposure (in particular to allergens associated with furry animals) the risk of clinically relevant specific sensitization appears to decrease[11–14]. Explanations for this observation include the possibility that very high exposures may produce an IgG and IgG$_4$ antibody responses without concomitant IgE-mediated sensitization (a modified T-helper-2 cell response[11]), and potential blocking effects of IgG$_4$ (which is co-produced with IgE) on IgE-mediated effector mechanisms[14]. Other studies by contrast have found no evidence of a protective effect of cat ownership or high levels of allergen-specific IgG or IgG$_4$ against IgE sensitization or ensuing respiratory symptoms[15, 16]. However interpretation of these latter studies is limited respectively by relatively low sample size[15] and by the fact that IgG measurements were made against mixtures[16] which results in a dominant contribution from low affinity antibodies to the resulting titres, potentially masking biologically relevant high affinity IgG[17].

We have readdressed these issues of relationships between IgE and IgG responses in the study on cat allergy and risk for wheeze. We focus exclusively on school children in the age range in which the association between sensitization to inhalant allergens and wheezing illness is strongest[18]. We have utilized two large population-based birth cohorts studied independently in two geographical areas (United Kingdom and Australia), amounting to ~1900 subjects in whom high affinity IgG responses to Fel d 1 allergen has been measured in parallel with cat-specific IgE.

METHODS

Study design, setting and participants

Two population samples were studied (Manchester and Perth): the Manchester Asthma and Allergy Study (MAAS)[19, 20] and The Western Australia Pregnancy Cohort (RAINE) Study[18] are unselected population-based birth cohort studies described in detail elsewhere. Both studies were approved by local research ethics committees. Informed consent was obtained from all parents, and children gave their assent if appropriate.

Manchester, UK—Subjects were recruited from the antenatal clinics when all pregnant women were screened for eligibility during the first trimester of pregnancy[19]. Children were followed prospectively and attended review clinic at age five years (± four weeks)[21].

Perth, Western Australia—The Western Australia Pregnancy Cohort Study is a prospective birth cohort established between 1989–1992. Participants were recruited from public antenatal clinics at King Edward Memorial Hospital and nearby private practices. At the time of enrollment the parents completed a questionnaire about their own respiratory illness, smoking behavior and general health. Children were followed prospectively with a clinical assessment and blood collection at age 14 years.

Definitions of variables

Primary outcome measure - Current wheeze—Identical validated questionnaires were administered in both cohorts to collect information on parentally reported symptoms. Current wheeze was defined as a positive response to the question "Has your child had wheezing or whistling in the chest in the last 12 months?" at age 5 years (UK) and age 14 years (Australia).

Antibody measurement—Allergen specific antibody levels were determined using ImmunoCAP™ assay (Phadia AB, Uppsala, Sweden). For the IgE antibody determinations the commercially available reagents of whole allergen extract for cat were used. For the allergen-specific IgG antibody measurements purified recombinant Fel d 1 (rFel d 1) allergen ImmunoCAP was used. Recombinant Fel d1 was produced by Phadia AB and subsequently coupled to the solid phase of flexible, hydrophilic, cellulose sponge polymer matrix activated by CNBr chemistry. The purified components were covalently coupled to the activated solid phase via the amino groups of the proteins according to standard ImmunoCAP methodology as previously described.

In a sub-samples from the UK (n=280) we determined the level of specific IgE antibodies to rFel d 1.

Statistical methods

Logistic regression was used to estimate the relationship between the outcome variables and the quantitative allergen specific antibody level. Odds Ratios (OR) were estimated using the regression model and tests of significance and 95% confidence intervals were according to

Wald, using a p-value of 0.05 as significant. Fitted predicted probabilities were plotted using the results from the logistic regression.

The levels of specific antibodies were subject to a logarithmic transformation prior to analysis; OR are presented for different antibody levels expressing the increased or decreased risk associated with increasing antibody levels. Since a logarithmic transformation was used all calculations were done on the logarithmic scale, i.e. the OR was estimated as $\exp(r*b)$ and r, the distance between a certain antibody level and the level indicating the absence of antibody, was defined as $r=\ln(x_2)-\ln(x_1)$. Computerized statistical analysis was carried out using SAS System V8.01.

RESULTS

Participants

Of 1085 children born into the study in the UK who gave consent to a further follow-up, 128 were prenatally randomized to environmental control[22] and excluded from this analysis; 957 children were followed in the observational cohort. Of the children in the observational cohort, 876 (91.5%) attended the 5 year clinic follow-up of whom 534 (62%) agreed to provide blood sample. Due to availability of the sample, IgE was measures in 534, IgG in 453 and IgG_4 in 461 children; all three specific antibodies were available in 453 children (243 male). Of those, 91(20.1%) reported current wheezing at age 5 years. Children who were excluded did not differ from those included in terms of family history, parental smoking, maternal age, socioeconomic status, gestational age, birth weight, history of wheeze and skin test results.

1336 adolescents in Australia (687 male) had a complete data comprising questionnaires and blood test results. Of those, 179 (13.4%) reported current wheezing at age 14.

Allergen specific IgE, IgG and IgG_4 antibody levels and wheezing

Univariate analysis—Allergen specific IgE, IgG and IgG_4 antibody levels amongst children with current wheezing and those without in the two populations are presented in Figure 1, and in relation to cat ownership in Table 1. In the UK cohort, there was an excellent correlation between the cat extract-specific and rFel d 1-specific IgE antibodies (r=0.88, Figure 2).

As expected, cat-specific IgE antibodies were higher amongst children with current wheeze in both populations. In the UK cohort, 22% of the children with current wheeze had cat-specific IgE antibody levels >0.35kU/L compared to only 5% amongst non-wheezers (p<0.0001). In Australian cohort, cat-specific IgE exceeded 0.35kU/L in 28% of wheezers and 14% of non-wheezers (p<0.001). There were no differences in rFel d 1-specific IgG antibody levels between wheezers and non-wheezers in either population (Figure 1).

In the univariate logistic regression analyses, the predicted risk of current wheeze in both populations increased significantly with increasing cat-specific IgE antibody levels (Table 2); the results indicated 1.56 and 1.29-fold increase in risk per logarithmic unit increase in cat IgE antibody level in the UK and Australia respectively. There was no comparable

significant effect of rFel d 1-specific IgG or IgG_4 antibody levels on current wheeze in either population (Table 2).

Multivariate analysis—A markedly different relationship was observed when rFel d1 specific total IgG antibody levels and cat-specific IgE were employed as covariates in the multivariate logistic regression analyses (Figure 3). In the UK cohort, cat-specific IgE antibodies increased the risk of current wheeze (OR 2.01, 95% CI 1.29–3.12, p=0.002), whilst rFel d 1-specific IgG antibody levels decreased the risk of current wheezing (0.46, 0.21–0.99, p=0.05). This finding was replicated in the Australian cohort (IgE: OR 1.46, 95% CI 1.28–1.68, p<0.001; IgG: OR 0.66, 95% CI 0.44–0.99, p=0.049 Figure 3, panels A and B). These results indicated 2-fold and 1.33-fold increase in the risk of wheezing per logarithmic unit increase in cat IgE antibody level, with 2.17-fold and 1.28-fold decrease in the risk of wheezing per logarithmic unit increase in rFel d 1-specific IgG antibody levels in the UK and Australia respectively. In contrast, we found no significant association between rFel d 1-specific IgG_4 antibodies and current wheezing (UK: 1.08, 0.91–1.28, p=0.37; Australia: 1.04, 0.96–1.14, p=0.35, Figure 3, panels C and D). In addition, we found no statistically significant interaction between IgE and IgG or IgG_4 antibody levels in either population.

DISCUSSION

Principal findings

In two independent unselected birth cohorts from distinct geographic areas (United Kingdom and Australia), we demonstrated that the association between cat-specific IgE antibodies and childhood wheezing is significantly modified by rFel d 1-specific IgG antibodies. The risk of current wheezing increased significantly with increasing cat-specific IgE, with rFel d 1-specific IgG antibody levels significantly decreasing the risk. In contrast, there was no association between rFel d 1-specific IgG_4 and wheezing. We postulate that the IgG-antibody associated effects observed here are due to IgG_1 which is the most abundant IgG subclass accounting for 5–20 % of total IgG antibody in most subjects[17, 23–26], although we cannot rule out contributions from other minor subclasses.

Limitations and strengths

Although retention in both birth cohorts was excellent, in the UK sample we analyzed data from approximately half of the subjects (mostly because the child refused venepuncture). We emphasize that there was no difference between children excluded or included in the analysis in any relevant parameter. Furthermore, the prevalence of allergic sensitization amongst the parents of the children is similar to that of young adults in the UK[21], suggesting the subjects are representative of the general population.

We made every effort to minimize false positive results due to multiple testing. The analysis was hypothesis-driven, and limited to one carefully defined phenotype which was ascertained based on the answer to the identical question in both populations.

The assay technique we used has been shown to accurately quantify IgE antibodies to a variety of allergens including cat in a superior manner compared with other IgE antibody

methods[27, 28]. The IgE antibody determinations using ImmunoCAP have also been shown to be better correlated with clinical disease than for other IgE antibody assays[29]. For IgG and IgG$_4$ antibodies this type of information is much more scarce, and no literature on comparison of different commercially available methods is available. However, Aalberse *et al* have concluded that for IgG$_1$, IgG$_2$ and IgG$_3$ purified allergen components like the Fel d 1 should be used[17]. This is necessary because while allergen extracts contained several components that bind to specific IgE and IgG$_4$ antibodies, extracts from domestic animals and mite also contain antigens similar to and sometimes cross-reactive with bacterial structures. Both allergic and non-allergic individuals produce IgG antibodies as part of their defense against such microbes, and this makes it difficult to evaluate results using a full extract containing both allergens and such antigens[17]. Accordingly, in this study recombinant Fel d 1 was used to determine the IgG antibody responses and to distinguish those from a general antibody response to antigens from microbes.

We acknowledge that most study participants who were sensitized to cat were also sensitized and exposed to multiple other allergens (e.g. dust mite). However, if anything this would dilute rather than strengthen the associations we report.

Interpretation

IgG$_4$ antibodies comprise <5% of IgG, and the putative role of IgG$_4$ has been reviewed in detail recently[17]. The spectrum of functions ascribed to this antibody are diverse and include both reaginic activity[30, 31] and interference with IgE-mediated effector mechanisms. For example, IgG$_4$ has been postulated to block IgE-dependent resistance to schistosomiasis[32] and filariasis[33, 34] and very high levels of specific IgG$_4$ antibody are common in both diseases. A protective effect of both IgG and IgG$_4$ antibodies has been suggested in modification of allergic reactions. For example, the blocking of the Prausnitz–Küstner reaction by naturally occurring factors in serum was described as early as 1935[35]. It was subsequently demonstrated that naturally occurring IgG antibodies to Fel d 1 blocked skin test reactions[36]. More recently, in specific allergen immunotherapy the increase in IgG$_4$ antibodies has been shown to correlate significantly with clinical improvement[23, 24, 37]. However, it is as yet unclear whether allergen-specific IgG$_4$ has a causal relationship or is just a marker of the protective effect.

It is noteworthy that the immunological scenarios in which negative associations between serum levels of allergen-specific IgG$_4$ and the expression of IgE-associated immunoinflammatory responses appears most consistent (notably parasitism[32–34], specific immunotherapy[23, 24, 37] and occupational exposures to aeroallergen[14]) share as a common feature ultra-intense chronic immune stimulation. The very high levels of specific IgG$_4$ attained in these situations suggest that this Th2-dependent IgG subclass is selectively expanded under these circumstances (it may even then represent up to 80% of total IgG antibodies[17]), which is not surprising given that initial (and sometimes persistent) boosting of specific IgE commonly occurs in parallel.

In contrast the immune response to cat allergen which is driven by normal domestic exposure involves much lower levels of immune stimulation, and in these circumstances IgG$_4$ is a less prominent feature of the overall specific immune response. Our finding that

IgG (putative IgG_1) and not IgG_4 is associated in cat-exposed children with blocking of the clinical effects of cat-specific IgE may reflect this differing balance.

Our findings have potential implications in relation to design of therapeutic strategies in established atopic asthma amongst cat allergic subjects. The currently favoured targets for design of more effective SIT are T-regulatory cells and specific IgG_4 antibody, but the successful design of effective therapies to achieve these aims has not yet been achieved. However, if our conclusions from this study prove to be correct, i.e. if a major component of the Fel d 1 specific IgG which we demonstrated here to interfere with the expression of IgE-associated symptoms is indeed IgG_1, then selective boosting of this antibody via administration of allergen/Th1-adjuvant could be considered as an alternative therapeutic strategy. An attraction of this alternative approach is the ready availability of clinically proven Th1 adjuvants for human use, which may facilitate more rapid development of new therapeutic vaccines for clinical testing.

The degree to which this rationale may be applicable to other types of allergens needs to be determined in further studies.

Conclusions

In two independent population-based birth cohorts from distinct geographic areas, we have demonstrated that rFel d 1-specific IgG, but not IgG_4 antibodies significantly modify the association between cat-specific IgE and childhood wheezing. The risk of symptoms increases significantly with increasing cat-specific IgE, while rFel d 1-specific IgG antibody levels significantly decreased the risk. Our data suggest that Fel d 1-specific IgG interferes with the expression of IgE-associated respiratory symptoms. Thus, measurement of allergen-specific IgG antibodies may improve the diagnostic accuracy of specific IgE antibodies in childhood wheezing illness.

Acknowledgments

Abbreviations

IgE	Immunoglobulin E
IgG	Immunoglobulin G
Fel d 1	*Felis Domesticus* allergen 1
rFel d 1	recombinant *Felis Domesticus* allergen 1
MAAS	Manchester Asthma and Allergy Study

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Clinical Implications

Fel d 1-specific IgG interferes with the expression of IgE-associated respiratory symptoms. Therefore, measurement of allergen-specific IgG antibodies may improve the diagnostic accuracy of specific IgE antibody measurement in childhood wheezing illness.
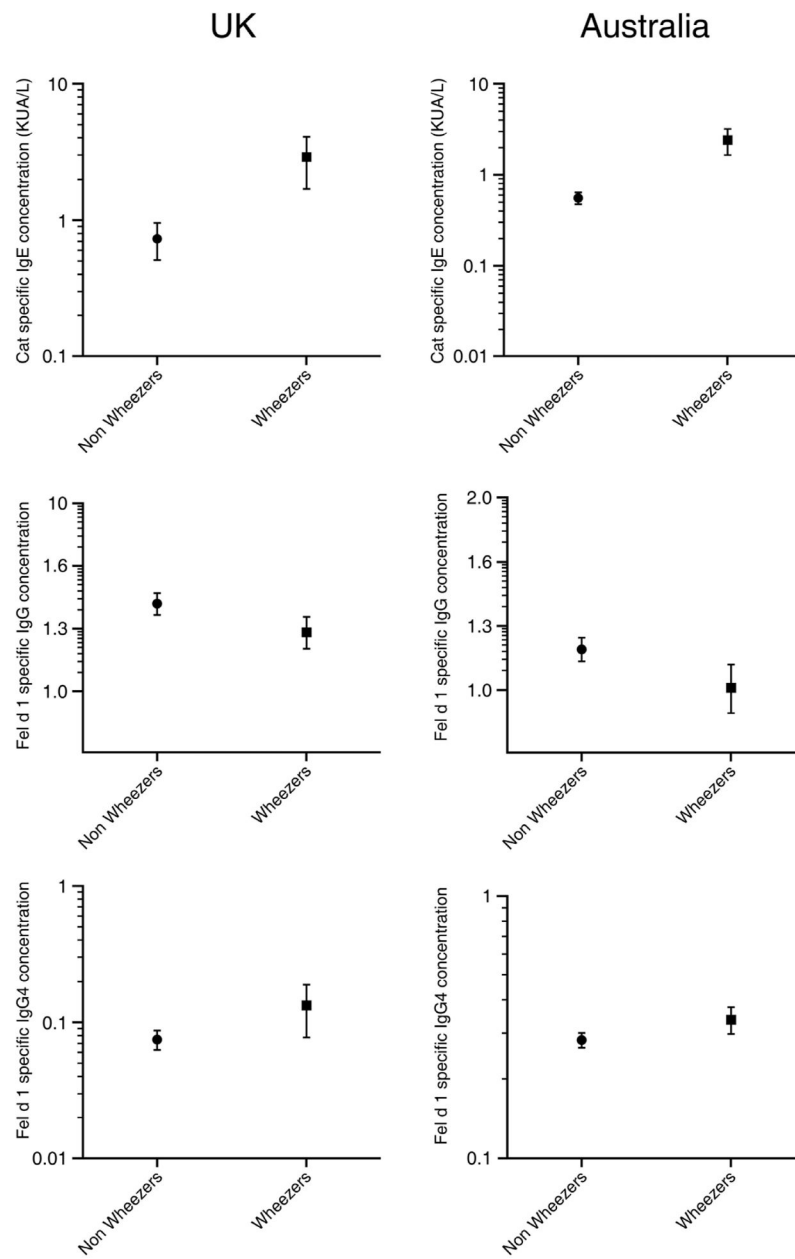
Figure 1.
Cat allergen specific IgE, and rFel d 1-specific IgG and IgG$_4$ antibody levels amongst children with current wheezing and those without in the UK and Australian cohort
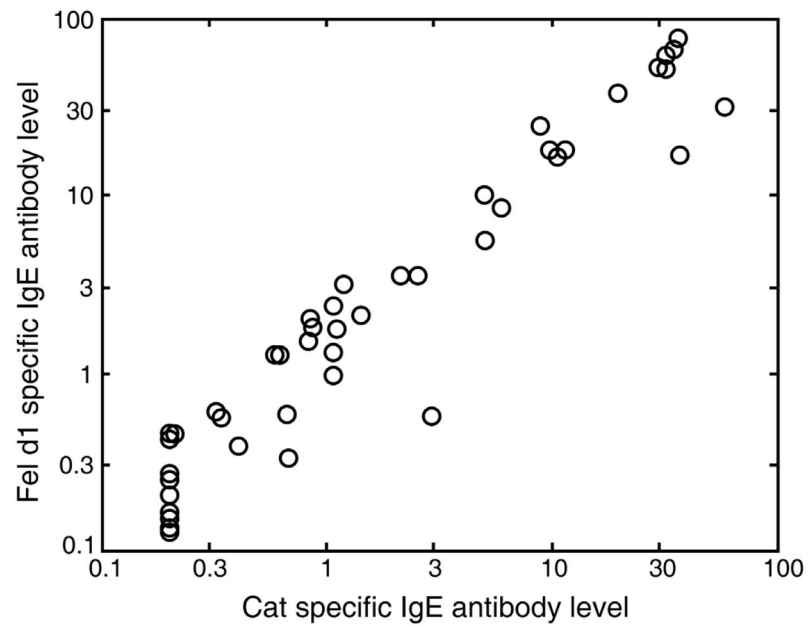
Figure 2.
Excellent correlation between IgE antibodies of whole allergen extract for cat and IgE antibodies to rFel d1
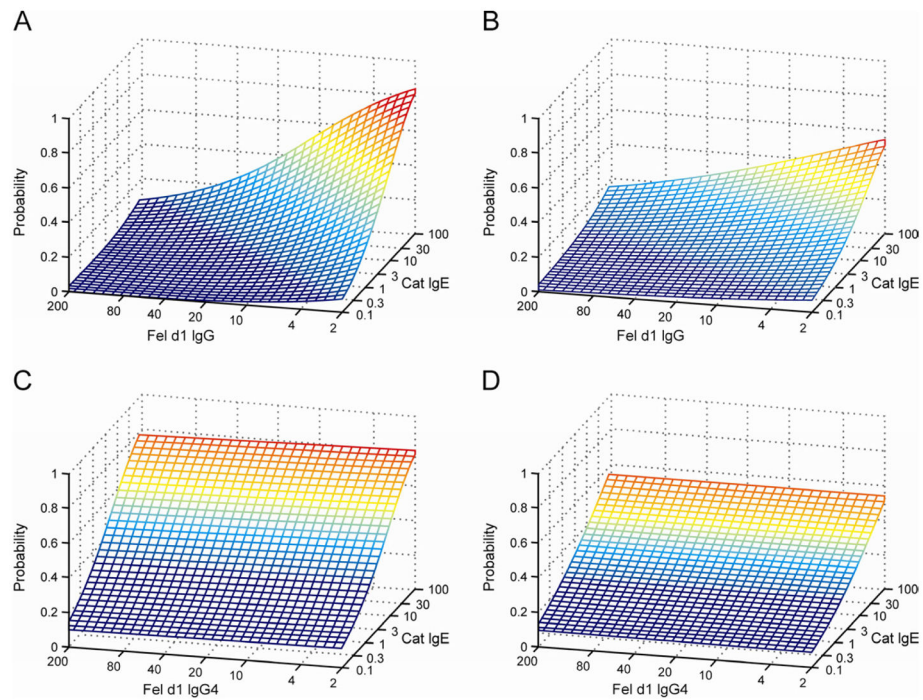
Figure 3.

Panels A and B: Fitted predicted probability for current wheeze at a given cat-specific IgE value and rFel d 1-specific IgG value derived from the multivariate logistic regression analysis, for children in the UK (A) and Australia (B).

Panels C and D: Fitted predicted probability for current wheeze at a given cat-specific IgE value and rFel d 1-specific IgG_4 value derived from the multivariate logistic regression analysis, for children in the UK (C) and Australia (D).

Table 1

Cat allergen specific IgE, and rFel d 1-specific IgG and IgG_4 antibody levels amongst children currently living in homes with without cat(s) in the UK and Australian cohort

		Whole population		Cat owner		Not cat owner		p-value (cat owners vs. Non-cat owners)
		Mean	95%CI	Mean	95% CI	Mean	95% CI	
UK	**Cat-specific IgE**	0.26	0.24–0.28	0.31	0.25–0.38	0.24	0.22–0.26	0.01
	rFel d 1-specific IgG	1.19	1.15–1.24	1.46	1.30–1.64	1.13	1.09–1.17	<0.0001
	rFel d 1-specific IgG_4	0.12	0.11–0.13	0.13	0.11–0.15	0.12	0.11–0.13	0.30
Australia	**Cat-specific IgE**	0.30	0.28–0.31	0.30	0.27–0.33	0.29	0.27–0·31	0.33
	rFel d 1-specific IgG	1.19	1.16–1.23	1.28	1.22–1.35	1.13	1.10–1.16	<0.0001
	rFel d 1-specific IgG_4	0.11	0.10–0.13	0.15	0.12–0.18	0.09	0.08–0.10	<0.0001

Table 2

Univariate analysis: Relationship between current wheezing and allergen-specific antibodies in two populations

	UK		Australia	
	OR	**95%CI**	**OR**	**95%CI**
Cat-specific IgE	1.56	1.28–1.90	1.29	1.19–1.40
rFel d 1-specific IgG	1.05	0.68–1.64	0.92	0.77–1.10
rFel d 1-specific IgG$_4$	1.13	0.98–1.29	1.08	0.97–1.19