

Furry Animal Allergen Component Sensitization and Clinical Outcomes in Adult Asthma and Rhinitis



Bright I. Nwaru, PhD^{a,b}, Shintaro Suzuki, MD, PhD^{a,c}, Linda Ekerljung, PhD^a, Sigrid Sjölander, PhD^d, Roxana Mincheva, MD, PhD^a, Erik P. Rönmark, MD, PhD^a, Madeleine Råding, PhD^a, Eva Rönmark, PhD^e, Magnus P. Borres, MD, PhD^{d,f}, Bo Lundbäck, MD, PhD^a, and Jan Lötval, MD, PhD^a Gothenburg, Uppsala, and Umeå, Sweden; and Tokyo, Japan

What is already known about the topic? Evidence on the role of sensitization to furry animal allergen components in adult asthma is lacking.

What does this article add to our knowledge? Sensitization to specific dog, cat, and horse allergen components and their sensitization patterns were risk factors for asthma, rhinitis, and markers of asthma severity.

How does this study impact current management guidelines? Identifying those with furry animal allergen component sensitization, particularly those with polysensitization, may help to identify patients at heightened risk of severe asthma.

BACKGROUND: Sensitization to allergen components has been linked to asthma in children, but studies in adults are lacking.

OBJECTIVE: To study the relation of sensitization to furry animal allergen components to risk of asthma, rhinitis, and markers of asthma severity in adults.

METHODS: From the West Sweden Asthma Study, a random population-representative sample of adults aged 16 to 75 years, 2006 participants were clinically examined; 1872 were analyzed for serum IgE level to a mix of aeroallergens. Those with an IgE

level of more than 0.35 kU_A/L to cat, dog, or horse allergen components were analyzed for specific cat (*Felis domesticus* [Fel d 1, Fel d 2, and Fel d 4]), dog (*Canis familiaris* [Can f 1, Can f 2, Can f 3, and Can f 5]), and horse (*Equus caballus* [Equ c 1]) allergen components. We defined monosensitization, double sensitization, and polysensitization (>2 components) patterns and applied cluster analysis to derive distinct sensitization clusters.

RESULTS: Sensitization to each allergen component, lipocalins, each sensitization pattern, and each sensitization cluster (nonsensitized, Fel d 1–driven sensitized, and multisensitized clusters) was associated with substantial increased risk of asthma, rhinitis, concomitant asthma and rhinitis, and Asthma Control Test–controlled asthma. Fel d 1, Can f 1, Can f 2, Can f 3, polysensitization, and multisensitized cluster were further associated with increased fractional exhaled nitric oxide and eosinophil levels, but with lower PD₂₀ methacholine (provocative dose of methacholine causing a 20% drop in FEV₁) values. There was no association with asthma exacerbations, FEV₁ predicted values, emergency visits or regular oral steroid use, and neutrophil levels.

CONCLUSIONS: Sensitization to furry animal allergen components is an important predictor of asthma, rhinitis, and markers of asthma severity with increased blood eosinophils, fractional exhaled nitric oxide, and airway hyperreactivity. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1230-8)

Key words: Asthma; Adults; Component-resolved diagnostics; Cat components; Dog components; Horse components; Cluster analysis; Furry animal; Severe asthma; Western Sweden

^aKrefting Research Centre, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

^bWallenberg Centre for Molecular and Translational Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

^cDivision of Allergology and Respiratory Medicine, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

^dImmunoDiagnostics, ThermoFisher Scientific, Uppsala, Sweden

^eDepartment of Public Health and Clinical Medicine, Occupational and Environmental Medicine, The OLIN Unit, Umeå University, Umeå, Sweden

^fDepartment of Women's and Children's Health, Uppsala University, Uppsala, Sweden

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Corresponding author: Bright I. Nwaru, PhD, Krefting Research Centre, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, P.O. Box 424, Gothenburg SE-405 30, Sweden. E-mail: bright.nwaru@gu.se.

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INTRODUCTION

Across all ages, allergic sensitization is an important determinant of asthma and rhinitis.^{1,2} In populations of the northern

Abbreviations used

ACT- Asthma Control Test
Can f- Canis familiaris
Equ c- Equus caballus
Fel d- Felis domesticus
FENO- Fractional exhaled nitric oxide
PD₂₀- Provocative dose of methacholine causing a 20% drop in FEV₁

hemisphere, in addition to pollen, furry animals are 1 of the principal sensitizers and leading contributors to the burden of asthma and allergic rhinitis.³⁻⁶ Recent advancements in molecular-based component-resolved diagnostics have enabled defining individual allergenic molecules and their underlying phenotypes, thus giving the opportunity to detect relevant clinical allergen molecules (allergen components) that can be useful for predicting clinical outcomes.⁷⁻⁹ A number of studies have investigated the associations between sensitization to furry animal allergen components and allergic airway diseases, but most studies have been undertaken in the pediatric population.¹⁰⁻¹² There is a paucity of data in adults, and this is particularly true for unselected adult populations, using epidemiological approaches.

Large epidemiological studies most often describe any specific IgE or skin prick test as the sole indicator of animal dander sensitization. These studies help to describe the prevalence of sensitization, but are hampered by the fact that cross-reactive molecules, such as serum albumin, are present in the extracts used, which can lead to an overestimation of sensitization rates to a particular animal.¹³⁻¹⁷ Lipocalins are the most important allergens for both cat and dog sensitization, and, for example, *Felis domesticus* (Fel d 4) and *Canis familiaris* (Can f 2) show a 25% sequence identity.^{18,19} Madhurantakam et al¹⁹ reported cross-reactivity between Fel d 4 and Can f 2, although the sequential identity observed in their study was less than 22%. Thus, single epitopes of these lipocalins can result in IgE cross-reactivity. Fel d 1, a uteroglobulin, is a major cat allergen, and Can f 5, a prostatic kallikrein, is a major dog allergen.¹⁸ Multiple sensitization toward lipocalins, kallikrein, and uteroglobulin components has been associated with increased bronchial inflammation in children and young adults with severe asthma.²⁰⁻²² We investigated the associations between sensitization to furry animal (cat, dog, and horse) allergen components and asthma, allergic rhinitis, and markers of asthma severity in a representative unselected population from western Sweden. We evaluated the role of specific allergen components, assessed the role of sensitization patterns, and studied the role of data-driven allergen component sensitization clusters.

METHODS

Study population

We analyzed data from the West Sweden Asthma Study, which has been described in detail elsewhere.^{23,24} Briefly, a postal questionnaire was sent to 30,000 randomly selected 16- to 75-year-old adults living in West Sweden in the region of Västra Götaland in 2008. Västra Götaland includes the city of Gothenburg. A total of 18,087 completed questionnaires were received, giving a response rate of 62% when corrected for untraced and diseased subjects.

Among the responders to the questionnaire, 2000 were randomly selected and invited to extensive clinical investigations, of which 1172 participated (among them 130 with doctor-diagnosed asthma). In addition, on the basis of the questionnaire responses, all those who reported doctor-diagnosed asthma or ever had asthma and used asthma medication or reported asthma symptoms during the previous year were invited to the clinical examinations (n = 1524); 834 of them participated. Altogether, 2006 subjects took part in the clinical examinations; in total, 964 of them had asthma (Figure 1). Of the 2006 who participated in the clinical examinations, measurements of IgE level to a mix of aeroallergens were undertaken in 1872 (93%) subjects who gave blood samples (Figure 1). These measurements were not performed on the remaining participants for refusal to give blood samples or inability to find the veins for serum collection.

Assessment of allergen-specific IgE components

Blood samples were collected at the clinical visits and sera stored at -80°C. Analysis of IgE levels against a mix of aeroallergens (Phadiatop) was undertaken and subjects with titers of 0.35 kU_A/L or more then had measurements taken for IgE antibody levels against the following specific allergens included in the mix (cat, dog, horse, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Cladosporium herbarum*, birch, timothy grass, and mugwort). The measurements of IgE levels were performed using the ImmunoCAP system (Phadia AB, Uppsala, Sweden) and IgE values of 0.35 kU_A/L or more for an individual allergen were taken as positive. Subjects who were sensitized to either cat, dog, or horse were then assessed for the following allergen components using ImmunoCAP: Fel d 1, Fel d 2, and Fel d 4 for cat; Can f 1, Can f 2, Can f 3, and Can f 5 for dog; and *Equus caballus* (Equ c 1) for horse.

Sensitization patterns and allergen component clusters

In addition to studying the specific allergen components in relation to the study outcomes, we grouped the lipocalins (Fel d 4, Can f 1, Can f 2, and Equ c 1) and determined the sensitization patterns (monosensitization, double sensitization, and polysensitization). Monosensitization involved IgE positivity to only 1 allergen component, double sensitization involved IgE positivity to only 2 components, and polysensitization involved positivity to more than 2 components.

We further applied cluster analysis to the data, in which all the allergen components (Fel d 1, Fel d 2, Fel d 4, Can f 1, Can f 2, Can f 3, Can f 5, and Equ c 1) were included in the model. Cluster analysis is one of the data-driven approaches used to identify latent group of individuals in a data set who have similar characteristics on the basis of the variables used to define the clusters.²⁵ By implementing cluster analysis to the data, we used the *k*-means clustering and applied the Jaccard similarity coefficient as a measure for forming the clusters when dealing with binary data.

Outcomes

The study outcomes covered current asthma, allergic rhinitis, concomitant asthma and allergic rhinitis, and several markers of asthma severity. *Current asthma* was defined as follows: ever had asthma or ever diagnosed with asthma by a doctor and at least 1 of the following: reported use of asthma medication, or recurrent wheeze, or attacks of shortness of breath during the last 12 months. *Allergic rhinitis* was defined as follows: having had sneezing, runny nose, or nasal blocking apart from colds during the last 12 months and having these nasal symptoms occurring simultaneously with

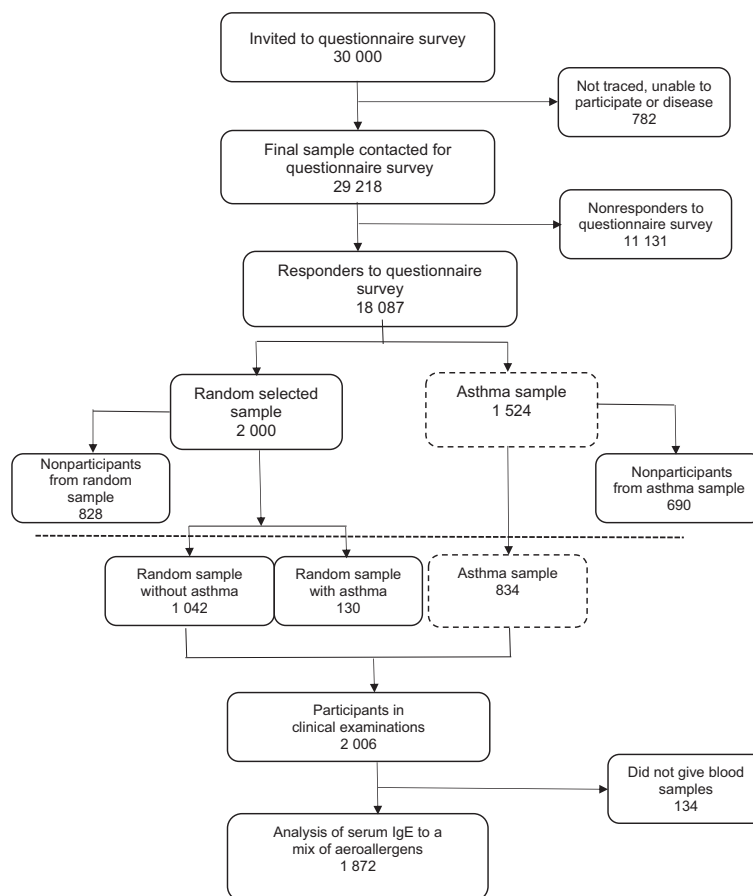


FIGURE 1. Flowchart of the study population. The study was based on a questionnaire survey from which a random sample and an asthma sample were selected.

itching and running eyes. *Concomitant asthma and allergic rhinitis* was defined as concurrently having current asthma and allergic rhinitis. *Markers of asthma* severity included (1) Asthma Control Test (ACT) controlled asthma, corresponding to an ACT score of more than 19; (2) number of asthma exacerbations during the last 12 months; (3) impaired lung function corresponding to an FEV₁ of less than 70% predicted values; (4) lung-related emergency department visits or regular use of oral steroids during the past 12 months; and (5) measures of airway inflammation, including fractional exhaled nitric oxide (FENO), degree of PD₂₀ methacholine reactivity (provocative dose of methacholine causing a 20% drop in FEV₁), and levels of neutrophils and blood eosinophils.

Potential confounding factors

From both the survey questionnaire and the clinical interview, we collected information on several potential confounding factors, including age, smoking, body mass index, degree of urbanization, exposure to dust/fumes at the place of work, whether or not participants were raised on a farm, educational attainment, and family history of allergy and asthma. Given the large panel of potential confounding factors included in the current analysis, we undertook a propensity score analysis²⁶ to derive a confounding propensity score for each participant. One of the usefulness of propensity score analysis in observational epidemiology is to reduce the dimensionality of frequently large panel of potential confounding factors

through estimating a score that integrates the panel of confounders, which can then be subsequently used for adjustment in a multiple regression analysis.²⁶ The propensity score was derived by regressing the panel of confounding variables against sensitization to any allergen component as the outcome, which was expressed in the form of the following equation: $\text{logit}(Y) = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + \dots + b_kX_k$, where Y is sensitization to any allergen component and b_1 to b_k are the regression coefficients of the confounding factors (X_1 to X_k). For each participant, the sum of regression coefficients from the equation was calculated and the calculated scores were then used in the multiple regression analysis relating the allergen components and the study outcomes. Therefore, in adjusting for the impact of confounding, we used the derived propensity scores rather than including each confounding factor in adjusted statistical models.

Statistical analyses

We used the Pearson chi-square test to examine differences between categorical variables. The analysis of report of clinical symptoms of asthma and rhinitis was based on those with Phadiatop measurement, whereas the analysis of the markers of asthma severity was restricted to those with physician-diagnosed asthma. We used logistic regression to investigate the associations between sensitization to the allergen components and the risk of current asthma, current rhinitis, concomitant asthma and rhinitis, ACT-controlled

asthma, FEV₁ less 70% predicted values, and lung-related emergency visits or regular use of oral steroids. We used a zero-inflated regression model to examine the associations between allergen component sensitization and number of asthma exacerbations during the last 12 months. We used linear regression to assess the associations between the allergen components and the standardized values of FENO, neutrophil, eosinophil, and PD₂₀ methacholine measurements. We first analyzed each specific allergen component in relation to the outcomes; we then analyzed the polysensitization patterns (using nonsensitized participants as the reference category) in relation to the outcomes and finally the data-driven allergen component clusters (using cluster 1 [nonsensitized] as the reference category) in relation to the outcomes. Each model was adjusted for the propensity scores described earlier. The effect estimates were accompanied by their respective 95% CIs. All analyses were carried out using Stata statistical package version 15 (StataCorp, College Station, Texas).

RESULTS

Characteristics of participants

The analyzed study population consisted of 1872 subjects, which constituted those who had Phadiatop measurement (Figure 1). Table E1 in this article's Online Repository at www.jaci-inpractice.org presents the distribution of sensitization to the specific allergen components, sensitization patterns, and component clusters by age and sex. Of the specific allergen components, the most common sensitization was to Fel d 1, whereas sensitization to Fel d 2 and Can f 2 was least common. Monosensitization was more common than double sensitization or polysensitization; cat was the most common sensitizer among those with monosensitization. By applying cluster analysis, we derived 3 distinct clusters: cluster 1 (named "nonsensitized") composed of participants who were not sensitized to any furry animal allergen component; cluster 2 ("Fel d 1–driven sensitized") composed of participants who were primarily mono-sensitized to Fel d 1; and cluster 3 ("multicomponent sensitized") composed of participants who were simultaneously sensitized to most animal allergen components. Cluster 2 (Fel d 1–driven sensitized) was the most common group among those sensitized to allergen components, and the most common sensitizer among this cluster was cat. Apart from Fel d 2 and Can f 2, the likelihood of sensitization to the allergen components statistically significantly decreased by age in both males and females. Within each sex, the proportion of sensitization across the age groups was usually higher in males than in females in most cases (see Table E1).

Table E2 in this article's Online Repository at www.jaci-inpractice.org presents the relation between the background characteristics and sensitization patterns. Older adults were less likely to be sensitized than younger adults. Those raised on a farm were less likely to be mono- and polysensitized than those not raised on a farm. Monosensitization and double sensitization increased with increasing level of education. Those with family history of allergy or asthma were more likely to be mono-, double-, and polysensitized than those without (see Table E2). Table E3 in this article's Online Repository at www.jaci-inpractice.org presents the relation of the background characteristics to the allergen component clusters. Determinants of the likelihood of belonging to cluster 1 (nonsensitized) included older age, ex- and current smoking, being raised on a farm, lower

education attained, and no family history of allergy or asthma. Determinants of membership of clusters 2 and 3 were younger age, not being raised on a farm, and family history of allergy and asthma. Nonsmoking and lower education additionally determined the likelihood of membership of cluster 2, whereas lower degree of urbanization additionally determined membership of cluster 3.

Sensitization to allergen components and outcomes

After adjusting for the confounding propensity scores, sensitization to each specific furry animal allergen component (compared with no sensitization), each sensitization pattern (mono-, double, and polysensitization compared with no sensitization), and clusters 2 and 3 (compared with cluster 1) was associated with a substantially increased risk of current asthma, current allergic rhinitis, and concomitant asthma and allergic rhinitis (Figures 2 and 3).

Regarding markers of asthma severity, none of the specific allergen components, sensitization patterns, nor component clusters were statistically significantly associated with asthma exacerbations (Figures 2 and 3), emergency visits or regular use of oral steroids, and neutrophil levels (Table 1). However, Fel d 1, Can f 1, Can f 2, Can f 3, polysensitization, and cluster 3 (multisensitized) were associated with increased FENO and eosinophil levels (Table 1). Fel d 1, Equ c 1, Can f 1, polysensitization, and cluster 3 (multisensitized) were associated with lower PD₂₀ methacoline values. Fel d 1, Fel d 4, Equ c 1, Can f 1, lipocalins, each sensitization pattern, and clusters 2 and 3 were further associated with increased likelihood of having ACT-controlled asthma (Figures 2 and 3). We also analyzed the associations between the crude cat, dog, and horse allergen extracts and the study outcomes, finding comparable results to those seen with allergen components (see Tables E4 and E5 in this article's Online Repository at www.jaci-inpractice.org). However, sensitization to allergen components in general had higher odds ratios compared with whole allergens (Figure 2; see also Table E4); for example, the association between Equ c 1 and current asthma had an odds ratio of 11.8, but that of whole horse extract was 6.8.

DISCUSSION

Both specific cat, dog, and horse components and their sensitization patterns were associated with substantially increased risk of current asthma, allergic rhinitis, and concomitant asthma and rhinitis. Sensitization to allergen components was not associated with asthma exacerbations, FEV₁ predicted values, lung-related emergency visits or regular use of oral steroids, or neutrophil levels. However, Fel d 1, Fel d 4, Equ c 1, Can f 1, lipocalins, the sensitization patterns, and allergen component clusters increased the likelihood of having ACT-controlled asthma. Fel d 1, Can f 1, Can f 2, Can f 3, polysensitization, and cluster 3 (multisensitized) increased FENO and eosinophil levels. Finally, Fel d 1, Equ c 1, Can f 1, polysensitization, and cluster 3 (multisensitized) were associated with lower PD₂₀ methacoline values. These results were comparable when we considered the crude cat, dog, and horse allergen extracts, although the results for the allergen components were generally of larger magnitude of odds ratio than those of the whole allergen extracts.

The West Sweden Asthma Study is a population-representative sample of adults living in western parts of

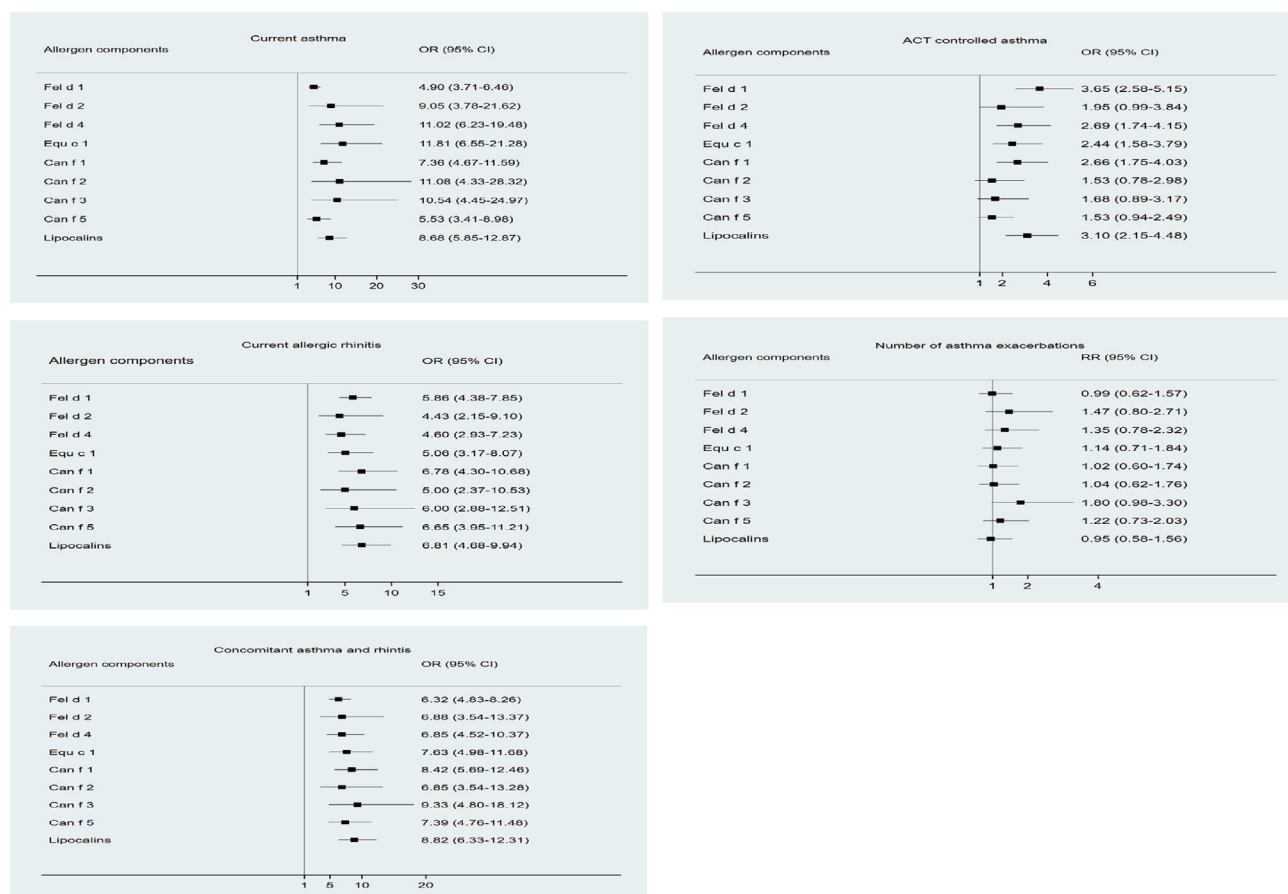


FIGURE 2. Adjusted associations between sensitization to furry animal allergen components and risk of current asthma, current allergic rhinitis, concomitant asthma and allergic rhinitis, ACT-controlled asthma, and number of asthma exacerbations. Lipocalins represent sensitization to any of Fel d 1, Equ c 1, Can f 1, and Can f 2. RR is the risk ratio derived from Poisson regression for number of asthma exacerbations as a count data.

Sweden, but the current clinical sample was enriched with those with asthma. The results of the associations between furry animal allergen components and the study outcomes may be generalizable to the source population of western Sweden and by extension the generality of the Swedish population of the same age.^{23,24} However, the estimates of prevalence of the outcomes may not be generalizable beyond the study population. In populations of this region, in addition to pollen, furry animals are one of the main sensitizers and thus drive the burden of asthma and allergic rhinitis.³⁻⁶ Our study has shown that both extracts and components of furry animals may substantially contribute to the risk of asthma, allergic rhinitis, and some markers of asthma severity, particularly on eosinophilic inflammatory markers. This finding provides the potential for molecular targeting of the indicted allergen components for the assessment of subsequent risk of asthma, allergic rhinitis, and markers of asthma severity. In measuring the allergen components, we used singleplex testing, which has been sparsely used in previous studies. In comparison with the commonly used multiplex testing using microarray technology, the singleplex testing appears to have a better degree of resolution and thus makes IgE-derived antibody assays the preferred approach for routine diagnostic allergy testing.²⁷ Clearly, the approach of determining IgE from whole

allergen extract may provide less precise pathway to appreciate the putative impact of allergic sensitization on clinical outcomes of asthma.^{20,28,29} One of the limitations of our study was that we measured only specific allergen components of cat and dog and 1 component of horse. Consequently, we cannot generalize our findings to the impact of other furry animal allergen components on clinical outcomes of asthma. Some evidence has shown that Fel d 7 and Can f 4 may possess important clinical features, but further studies are needed to fully explore their clinical utility.^{27,30} The cross-sectional design of our study is a further limitation, and so our findings may not reflect temporality of the associations between allergen components and the study outcomes.

Although only a few studies have evaluated the relationship between sensitization to aerosol allergen components and respiratory disease, including asthma, most of the existing studies have been implemented in the pediatric population.^{10-12,20-22} A study in a southwestern Swedish pediatric population showed that children who were sensitized to Can f 2 and Equ c 1 and those sensitized to multiple lipocalin components were at a greater risk of having more severe asthma, defined on the basis of FEV₁ values and eosinophil levels.²² These findings agree with our results, except for FEV₁ predicted values where we found no

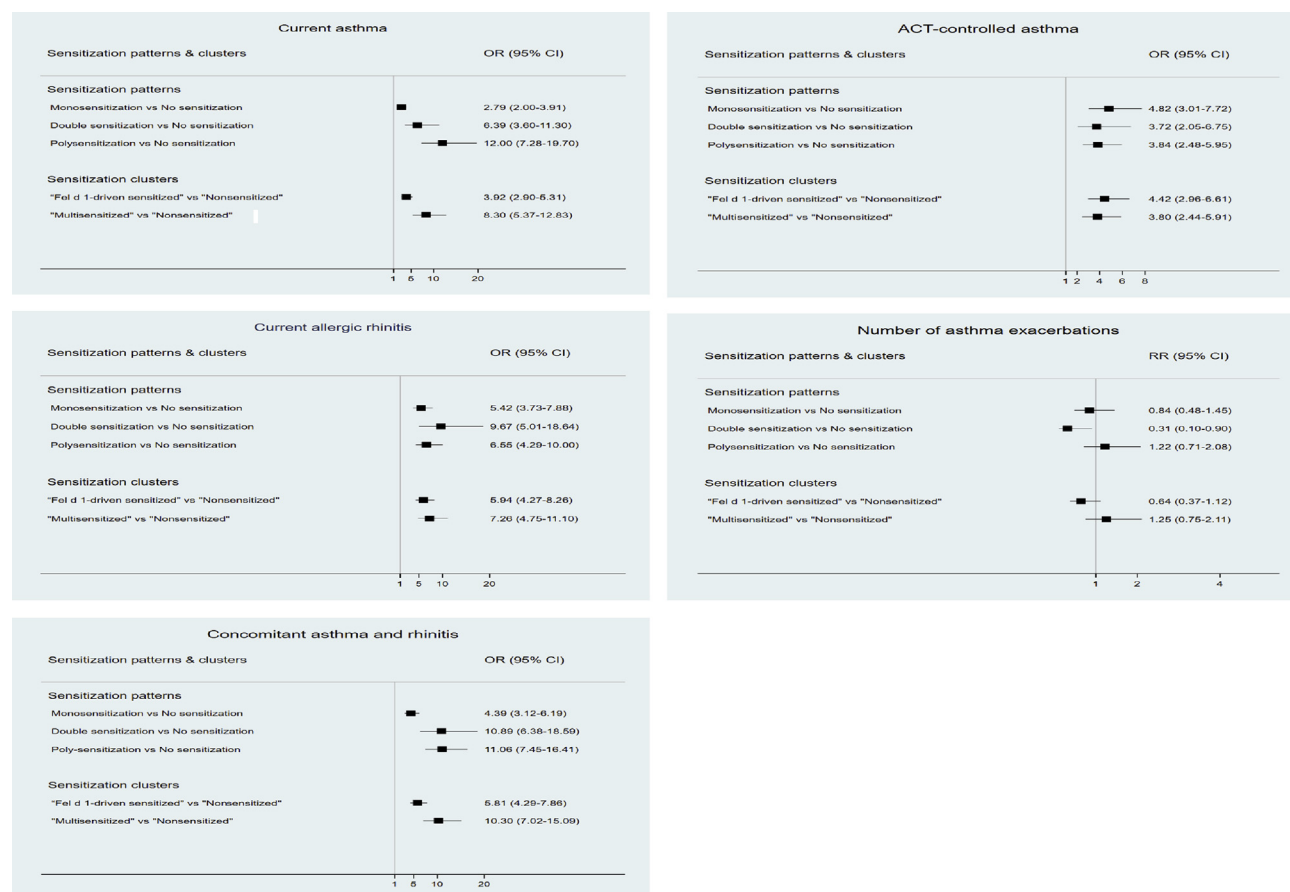


FIGURE 3. Adjusted associations between furry animal allergen component sensitization patterns and clusters and risk of current asthma, current allergic rhinitis, concomitant asthma and allergic rhinitis, ACT-controlled asthma, and number of asthma exacerbations. RR is the risk ratio derived from Poisson regression for number of asthma exacerbations as a count data.

statistically significant association between any of the specific allergen components, polysensitization patterns or component clusters, and predicted values of FEV₁. Another study from southwestern Sweden has also shown that sensitization to Fel d 1 and Can f 1 and polysensitization to cat and dog allergen components predicted cat and dog allergy in children.¹² In the same setting, a recent analysis of children aged 10 to 18 years showed that although Can f 4 and Can f 6 were associated with positive nasal provocation test results (as an indicator of clinical symptoms of dog allergy), Can f 5 was associated with negative provocation results.³¹ Similar to our findings, a study from northern Sweden reported that sensitization to more than 1 cat, dog, or horse allergen component was associated with an increased risk of asthma in children aged 11 to 12 years.¹¹ In children aged 11 years, by using latent variable modeling, Simpson et al¹⁰ derived 3 cluster groups of allergen component sensitization on the basis of a panel of 61 allergen components coming from 51 allergen sources, including cat, dog, and horse extracts. They found that the components, although differentially associated with clinical outcomes, were associated with an increased risk of asthma and allergic rhinitis and lower FEV₁ predicted values, but no association was observed with eczema.¹⁰ In a population combining children and adults (3-60 years of age), Uriarte and Sastre³² reported that sensitization to 2 or more

cat, dog, and horse allergen components was associated with severe respiratory symptoms (severe asthma and rhinitis). A similar study combining children and adults recruited from both primary and specialist care centers in Sweden showed that Fel d 2 and Fel d 4, but not Fel d 1, were associated with increased FENO levels and blood eosinophil counts in patients with asthma who were originally sensitized to cat, dog, or horse extracts.³⁰

In line with the various findings reported in pediatric populations across settings, our results indicate that sensitization to furry animal allergen components is an important predictor of clinical outcomes of asthma and eosinophilic markers of asthma severity. This is the first robust analysis of the role of furry animal allergen components in asthma and its severity in an adult population, in that we have been able to show the role of both specific allergen components, their polysensitization patterns, and data-driven allergen component clusters in clinical outcomes of asthma, including subjectively reported and objectively measured markers of asthma severity. With just monosensitization, the risk of allergic rhinitis was almost double that of asthma; the risk of double sensitization was also greater in allergic rhinitis than in asthma, but that of polysensitization was almost double in asthma than in allergic rhinitis. We did not find any association between allergen component sensitization and number of exacerbations, FEV₁ predicted values, lung-related emergency

TABLE I. Associations between sensitization to furry animal allergen components and indicators of asthma severity

Allergen	FEV ₁ less 70% predicted values* (n = 20), OR (95% CI)	Lung-related emergency visits or regular use of oral steroids during past 12 mo* (n = 47), OR (95% CI)	FENO levels,* coefficient (95% CI)	Degree of PD ₂₀ methacholine reactivity,* coefficient (95% CI)	Neutrophil levels,* coefficient (95% CI)	Eosinophil levels,* coefficient (95% CI)
Fel d 1	1.02 (0.41 to 2.53)	1.05 (0.57 to 1.94)	0.30 (0.10 to 0.51)	−0.35 (−0.68 to −0.02)	−0.14 (−0.33 to 0.04)	0.02 (−0.17 to 0.21)
Fel d 2	2.03 (0.57 to 7.32)	1.03 (0.35 to 3.05)	0.31 (−0.06 to 0.68)	−0.46 (−1.03 to 0.11)	0.20 (−0.14 to 0.54)	0.53 (0.20 to 0.87)
Fel d 4	1.19 (0.42 to 3.38)	0.58 (0.25 to 1.35)	0.21 (−0.03 to 0.46)	−0.34 (−0.70 to 0.01)	0.14 (−0.08 to 0.37)	0.24 (0.02 to 0.46)
Equ c 1	1.22 (0.43 to 3.44)	0.49 (0.20 to 1.20)	0.01 (−0.24 to 0.26)	−0.44 (−0.79 to −0.09)	0.02 (−0.21 to 0.24)	0.15 (−0.07 to 0.38)
Can f 1	2.12 (0.84 to 5.34)	0.80 (0.38 to 1.67)	0.26 (0.03 to 0.49)	−0.41 (−0.78 to −0.04)	−0.10 (−0.31 to 0.12)	0.24 (0.03 to 0.46)
Can f 2	1.19 (0.26 to 5.37)	0.98 (0.33 to 2.86)	0.60 (0.24 to 0.96)	−0.16 (−0.72 to 0.39)	−0.05 (−0.38 to 0.28)	0.47 (0.14 to 0.79)
Can f 3	1.04 (0.23 to 4.66)	1.13 (0.42 to 3.03)	0.45 (0.10 to 0.80)	−0.24 (−0.79 to 0.29)	0.12 (−0.20 to 0.44)	0.39 (0.07 to 0.70)
Can f 5	0.81 (0.23 to 2.83)	1.10 (0.51 to 2.38)	0.11 (−0.16 to 0.37)	−0.32 (−0.72 to 0.08)	0.04 (−0.20 to 0.28)	0.20 (−0.04 to 0.44)
Lipocalins	1.20 (0.48 to 3.00)	0.51 (0.25 to 1.03)	0.21 (−0.01 to 0.42)	−0.34 (−0.67 to −0.01)	0.03 (−0.16 to 0.23)	0.18 (0.01 to 0.38)
Sensitization patterns						
Not sensitized	Reference	Reference	Reference	Reference	Reference	Reference
Monosensitization†	0.19 (0.02 to 1.50)	1.42 (0.68 to 2.98)	0.15 (−0.12 to 0.42)	−0.23 (−0.67 to 0.21)	−0.17 (−0.43 to 0.08)	0.02 (−0.23 to 0.27)
Double sensitization†	1.44 (0.43 to 4.87)	0.67 (0.22 to 2.07)	0.12 (−0.24 to 0.48)	−0.21 (−0.75 to 0.32)	−0.09 (−0.40 to 0.22)	−0.12 (−0.43 to 0.19)
Polysensitization†	0.79 (0.26 to 2.38)	0.69 (0.30 to 1.57)	0.37 (0.11 to 0.62)	−0.59 (−1.00 to −0.18)	−0.01 (−0.24 to 0.23)	0.27 (0.03 to 0.50)
Sensitization clusters						
Cluster 1 (nonsensitized)	Reference	Reference	Reference	Reference	Reference	Reference
Cluster 2 (Fel d 1–driven sensitized)	0.60 (0.20 to 1.83)	0.98 (0.48 to 1.97)	0.20 (−0.04 to 0.44)	−0.03 (−0.73 to 0.05)	−0.16 (−0.38 to 0.05)	−0.03 (−0.25 to 0.18)
Cluster 3 (multisensitized)	0.81 (0.26 to 2.45)	0.87 (0.40 to 1.91)	0.29 (0.03 to 0.54)	−0.48 (−0.91 to −0.05)	0.02 (−0.21 to 0.26)	0.28 (0.05 to 0.52)

OR, Odds ratio.

*Adjusted for propensity score including the following variables: sex, age, smoking status, body mass index, degree of urbanization, dust exposure at workplace, living on the farm during childhood, educational level, and family history of allergy or asthma.

†Monosensitization represents sensitization to only 1 furry animal allergen component; double sensitization represents sensitization to only 2 furry animal allergen components; and polysensitization represents sensitization to more than 2 furry animal allergen components.

visits or regular use of oral steroids, and neutrophil levels. However, we found that specific cat, dog, and horse components and their sensitization patterns were associated with an increased likelihood of achieving ACT-controlled asthma, which may possibly indicate that the allergic asthma phenotypes are better controlled in this population. Furthermore, we have previously reported that the use of inhaled corticosteroids was common in this population: although at the population level 7% to 8% use inhaled corticosteroids, it was used by more than 40% of patients with asthma either as a lone therapy or as a combination treatment.³³ Another important contribution of our study to the literature relates to the findings that allergen component sensitization, particularly polysensitization, was associated with increased FENO and eosinophil levels, and associated with lower PD₂₀ methacholine reactivity values, an indication that sensitization to furry animal allergen components is an important predictor of particularly eosinophilic inflammatory markers of asthma severity. These results were similar to results of the associations between the crude cat, dog, and horse allergen extracts, an indication that, in place of crude allergen extracts, the corresponding specific allergen components of each furry animal are of value for predicting clinical asthma and allergy outcomes. Extended benefits of allergen components are that they enhance characterization of individual allergen molecules, underlying allergen phenotypes, and delineation of potential cross-reactivity, features not possible with whole allergen extracts.⁷⁻⁹

CONCLUSIONS

We have demonstrated that sensitization to specific furry animal allergen components and their sensitization patterns are a good predictor of risk of asthma and rhinitis, and markers of asthma severity, particularly markers typical of eosinophilic allergic asthma in adults. However, they were not associated with common markers of severity. Those sensitized to multiple allergen components are at greater risk of having eosinophilic inflammatory markers of severity. Detection of sensitization to allergen components provides an opportunity to screen subjects at risk for developing asthma, particularly eosinophilic asthma with high FENO levels and increased airway hyperreactivity. Component-resolved diagnostics in asthma is therefore potentially beneficial for identification of individuals who are sensitized to multiple aeroallergens and can thus facilitate the optimization of management of respiratory allergic disease in this subgroup of patients.

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TABLE E1. Frequency of specific allergen component sensitization, polysensitization patterns, and allergen component clusters by age within sex

Allergen	All (n = 850), n (%)	≤30 y (n = 107), n (%)	31-45 y (n = 236), n (%)	46-60 y (n = 228), n (%)	61-75 y (n = 279), n (%)	P value for trend*
Male						
Fel d 1	156 (18.3)	34 (31.8)	54 (22.9)	48 (21.0)	20 (7.2)	<.001
Fel d 2	19 (2.2)	3 (2.8)	7 (3.0)	8 (3.5)	1 (0.4)	.067
Fel d 4	59 (6.9)	14 (13.1)	25 (10.6)	17 (7.5)	3 (1.1)	<.001
Equ c 1	54 (6.3)	14 (13.1)	21 (8.9)	16 (7.0)	3 (1.1)	<.001
Can f 1	65 (7.6)	14 (13.1)	23 (9.7)	21 (9.2)	7 (2.5)	<.001
Can f 2	20 (2.3)	3 (2.8)	5 (2.1)	11 (4.8)	1 (0.4)	.191
Can f 3	21 (2.5)	5 (4.7)	7 (3.0)	8 (3.4)	1 (0.4)	.012
Can f 5	43 (5.1)	12 (11.2)	14 (5.9)	14 (6.1)	3 (1.1)	<.001
Lipocalins†	93 (10.9)	20 (18.7)	37 (15.7)	28 (12.3)	8 (2.9)	<.001
Monosensitization‡	83 (9.8)	23 (21.5)	22 (9.3)	24 (10.5)	14 (5.0)	<.001
Double sensitization‡	33 (3.9)	4 (3.7)	16 (6.8)	9 (3.9)	4 (1.4)	.022
Polysensitization‡	65 (7.6)	14 (13.1)	26 (11.0)	20 (8.8)	5 (1.8)	<.001
Cluster 1 (nonsensitized)	669 (78.7)	66 (61.7)	172 (72.9)	175 (76.7)	256 (91.8)	<.001
Cluster 2 (Fel d 1—driven sensitized)	114 (13.4)	23 (21.5)	41 (17.4)	32 (14.0)	18 (6.4)	<.001
Cluster 3 (multisensitized)	67 (7.9)	18 (16.8)	23 (9.7)	21 (9.2)	5 (1.8)	<.001
Allergen	All (n = 1022), n (%)	≤30 y (n = 165), n (%)	31-45 y (n = 272), n (%)	46-60 y (n = 315), n (%)	61-75 y (n = 270), n (%)	P value for trend*
Female						
Fel d 1	155 (15.2)	38 (23.0)	56 (20.6)	45 (14.3)	16 (5.9)	<.001
Fel d 2	25 (2.4)	6 (3.6)	8 (2.9)	8 (2.5)	3 (1.1)	.082
Fel d 4	58 (5.7)	12 (7.3)	21 (7.7)	21 (6.7)	4 (1.5)	.004
Equ c 1	59 (5.8)	18 (10.9)	20 (7.3)	21 (6.7)	0 (0.0)	<.001
Can f 1	73 (7.1)	17 (10.3)	24 (8.8)	27 (8.6)	5 (1.8)	.001
Can f 2	25 (2.4)	7 (4.2)	4 (1.5)	12 (3.8)	2 (0.7)	.123
Can f 3	30 (2.9)	5 (3.0)	10 (3.7)	12 (3.8)	3 (1.1)	.194
Can f 5	61 (6.0)	17 (10.3)	15 (5.5)	22 (7.0)	7 (2.6)	.005
Lipocalins†	105 (10.3)	24 (14.5)	33 (12.1)	39 (12.4)	9 (3.3)	<.001
Monosensitization‡	81 (7.9)	21 (12.7)	26 (9.6)	22 (7.0)	12 (4.4)	.001
Double sensitization‡	39 (3.8)	10 (6.1)	15 (5.5)	9 (2.9)	5 (1.8)	.006
Polysensitization‡	72 (7.0)	15 (9.1)	22 (8.1)	30 (9.5)	5 (1.8)	.005
Cluster 1 (nonsensitized)	830 (81.2)	119 (72.1)	209 (76.8)	254 (80.6)	248 (91.8)	<.001
Cluster 2 (Fel d 1—driven sensitized)	113 (11.1)	27 (16.4)	42 (15.4)	31 (9.8)	13 (4.8)	<.001
Cluster 3 (multisensitized)	79 (7.7)	19 (11.5)	21 (7.7)	30 (9.5)	9 (9.5)	.006

*P value for trend across age groups.

†Any of the 4 lipocalin allergens Fel d 4, Can f 1, Can f 2, and Equ c 1.

‡Monosensitization represents sensitization to only 1 furry animal allergen component; double sensitization represents sensitization to only 2 furry animal allergen components; and polysensitization represents sensitization to more than 2 furry animal allergen components.

TABLE E2. Background characteristics by monosensitization, double sensitization, and polysensitization to furry animal allergen components

Background characteristic	Frequency (N = 1872), n (%)	Monosensitization* (n = 164 [9%]), n (%)	P value	Double sensitization* (n = 72 [4%]), n (%)	P value	Polysensitization* (n = 137 [7%]), n (%)	P value
Sex			.161		.941		.618
Male	850 (45.4)	83 (9.8)		33 (3.9)		65 (7.6)	
Female	1022 (54.6)	81 (7.9)		39 (3.8)		72 (7.0)	
Age (y)			<.001		<.001		<.001
≤30	272 (14.5)	44 (16.2)		14 (5.1)		29 (10.7)	
31-45	508 (27.1)	48 (9.4)		31 (6.1)		48 (9.4)	
46-60	543 (29.0)	46 (8.5)		18 (3.3)		50 (9.2)	
61-75	549 (29.4)	26 (4.7)		9 (1.6)		10 (1.8)	
Smoking status			.009		.979		.250
Nonsmokers	1,037 (55.4)	108 (10.4)		41 (3.9)		80 (7.7)	
Ex-smokers	512 (27.3)	36 (7.0)		15 (2.9)		40 (7.8)	
Current smokers	314 (16.8)	20 (6.4)		14 (4.5)		17 (5.4)	
Missing information	9 (0.5)						
BMI (kg/m ²)			.326		.460		.799
<25	675 (36.1)	67 (9.9)		24 (3.6)		49 (7.3)	
25-29.9	820 (43.8)	65 (7.9)		31 (3.8)		63 (7.7)	
≥30	376 (20.1)	32 (8.5)		17 (4.5)		25 (6.6)	
Missing information	1 (0.0)						
Exposure to dust/fumes at workplace			.471		.106		.318
No	1,356 (72.4)	122 (9.0)		58 (4.3)		104 (7.7)	
Yes	492 (26.3)	39 (7.9)		13 (2.6)		31 (6.3)	
Missing information	24 (1.3)						
Raised on a farm			.002		.084		.045
No	1,632 (87.2)	155 (9.5)		68 (4.2)		126 (7.7)	
Yes	224 (12.0)	7 (3.1)		4 (1.8)		9 (4.0)	
Missing information	16 (0.8)						
Degree urbanization			.102		.457		.144
>10,000 inhabitants	1,396 (74.6)	131 (9.4)		51 (3.6)		95 (6.8)	
≤10,000 inhabitants	476 (25.4)	33 (6.9)		21 (3.8)		42 (8.8)	
Highest education attained			.004		.019		.338
Less than high school	359 (19.2)	20 (5.6)		6 (1.7)		15 (4.2)	
High school	698 (37.3)	58 (8.3)		28 (4.0)		66 (9.5)	
Tertiary	806 (43.0)	86 (10.7)		38 (4.7)		56 (6.9)	
Missing information	9 (0.5)						
Family history of allergy or asthma			<.001		<.001		<.001
No	1,022 (54.6)	59 (5.8)		21 (2.0)		50 (4.9)	
Yes	850 (45.4)	105 (12.3)		51 (6.0)		87 (10.2)	

BMI, Body mass index.

*Monosensitization represents sensitization to only 1 furry animal allergen component; double sensitization represents sensitization to only 2 furry animal allergen components; and polysensitization represents sensitization to more than 2 furry animal allergen components.

TABLE E3. Background characteristics by furry animal allergen component clusters

Background characteristic	Cluster 1 (nonsensitized) (n = 1499 [80.0%]), n (%)	P value	Cluster 2 (Fel d 1-driven sensitized) (n = 227 [12.1%]), n (%)	P value	Cluster 3 (multisensitized) (n = 146 [7.8%]), n (%)	P value
Sex		.176		.120		.903
Male	669 (78.7)		114 (13.4)		67 (7.9)	
Female	830 (81.2)		113 (11.1)		79 (7.7)	
Age (y)		<.001		<.001		<.001
≤30	185 (68.0)		50 (18.4)		37 (13.6)	
31-45	381 (75.0)		83 (16.3)		44 (8.7)	
46-60	429 (79.0)		63 (11.6)		51 (9.4)	
61-75	504 (91.8)		31 (5.6)		14 (2.5)	
Smoking status		.009		.018		.320
Nonsmokers	808 (77.9)		144 (13.9)		85 (8.2)	
Ex-smokers	421 (82.2)		51 (10.0)		40 (7.8)	
Current smokers	263 (83.8)		31 (9.9)		20 (6.4)	
BMI (kg/m ²)		.614		.300		.610
<25	535 (79.3)		87 (12.9)		53 (7.8)	
25-29.9	661 (80.6)		100 (12.2)		59 (7.2)	
≥30	302 (80.3)		40 (10.6)		34 (9.0)	
Exposure to dust/fumes at workplace		.052		.111		.342
No	1072 (79.1)		175 (12.9)		109 (8.0)	
Yes	409 (83.1)		50 (10.2)		33 (6.7)	
Raised on a farm		<.001		.001		.013
No	1283 (78.6)		214 (13.1)		135 (8.3)	
Yes	204 (91.1)		12 (5.4)		8 (3.6)	
Degree urbanization		.878		.114		.031
>10,000 inhabitants	1119 (80.2)		179 (12.8)		98 (7.0)	
≤10,000 inhabitants	380 (79.8)		48 (10.1)		48 (10.1)	
Highest education attained		<.001		<.001		.254
Less than high school	318 (88.6)		25 (7.0)		16 (4.5)	
High school	546 (78.2)		83 (11.9)		69 (9.9)	
Tertiary	626 (77.7)		119 (14.8)		61 (7.6)	
Family history of allergy or asthma		<.001		<.001		<.001
No	892 (87.3)		73 (7.1)		57 (5.6)	
Yes	607 (71.4)		154 (18.1)		89 (10.5)	

BMI, Body mass index.

TABLE E4. Associations between sensitization to furry animal allergen extracts and risk of current asthma, current allergic rhinitis, concomitant asthma and allergic rhinitis, ACT-controlled asthma, and number of asthma exacerbations

Allergen (prevalence)	Current asthma, *OR (95% CI)	Current allergic rhinitis,* OR (95% CI)	Concomitant asthma and allergic rhinitis,* OR (95% CI)	ACT-controlled asthma,* OR (95% CI)	No. of asthma exacerbations,* RR† (95% CI)
Cat (19.3%)	4.88 (3.77-6.32)	6.07 (4.63-7.97)	6.24 (4.84-8.04)	4.28 (3.04-6.03)	0.97 (0.60-1.56)
Dog (16.8%)	5.96 (4.48-7.93)	6.26 (4.67-8.39)	7.27 (5.55-9.50)	3.49 (2.48-4.90)	1.19 (0.75-1.87)
Horse (10.2%)	6.75 (4.64-9.83)	5.54 (3.84-7.99)	6.54 (4.72-9.06)	2.60 (1.78-3.79)	1.37 (0.87-2.16)

OR, Odds ratio.

*Adjusted for propensity score that included the following variables: sex, age, smoking status, body mass index, degree of urbanization, dust exposure at workplace, living on the farm during childhood, educational level, and family history of allergy or asthma.

†Risk ratio derived from Poisson regression for number of asthma exacerbations as a count data.

TABLE E5. Associations between sensitization to furry animal allergen extracts and indicators of asthma severity

Allergen (prevalence)	FEV ₁ less 70% predicted values,* OR (95% CI)	Lung-related emergency visits or regular use of oral steroids during past 12 mo,* OR (95% CI)	FENO levels,* coefficient (95% CI)	Degree of PD ₂₀ methacholine reactivity,* coefficient (95% CI)	Neutrophil levels,* coefficient (95% CI)	Eosinophil levels,* coefficient (95% CI)
Cat (19.3%)	0.75 (0.30 to 1.84)	0.63 (0.34 to 1.15)	0.28 (0.08 to 0.49)	−0.32 (−0.67 to 0.02)	−0.10 (−0.29 to 0.09)	0.14 (−0.05 to 0.33)
Dog (16.8%)	0.74 (0.42 to 1.43)	0.78 (0.42 to 1.43)	0.30 (0.09 to 0.50)	−0.23 (−0.56 to 0.10)	−0.01 (−0.20 to 0.17)	0.15 (−0.03 to 0.34)
Horse (10.2%)	0.85 (0.32 to 2.28)	0.73 (0.37 to 1.44)	0.19 (−0.03 to 0.40)	−0.52 (−0.84 to −0.20)	−0.07 (−0.27 to 0.13)	0.17 (−0.03 to 0.37)

OR, Odds ratio.

*Adjusted for propensity score that included the following variables: sex, age, smoking status, body mass index, degree of urbanization, dust exposure at workplace, living on the farm during childhood, educational level, and family history of allergy or asthma.