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Sensitization to cat and dog allergen molecules in childhood and prediction of symptoms of cat and dog allergy in adolescence: A BAMSE/MeDALL study

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Abstract

Background—Sensitization to individual cat and dog allergen molecules can contribute differently to development of allergy to these animals.

Objective—We sought to investigate the association between sensitization patterns to cat and dog allergen molecules during childhood and symptoms to these furry animals up to age 16 years.

Methods—Data from 779 randomly collected children from the Barn/Children Allergy/Asthma Milieu Stockholm Epidemiologic birth cohort at 4, 8, and 16 years were used. IgE levels to cat and dog were determined by using ImmunoCAP, and levels to allergen molecules were determined by using an allergen chip based on ISAC technology (Mechanisms for the Development of Allergy chip). Allergy was defined as reported rhinitis, conjunctivitis, or asthma at exposure to cat or dog.

Results—Cross-sectionally, IgE to Fel d 1 and cat extract had similar positive predictive values for cat allergy. IgE to Can f 1 showed a higher positive predictive value for dog allergy than dog extract IgE. Sensitizations to Fel d 1 and Can f 1 in childhood were significantly associated with symptoms to cat or dog at age 16 years. Polysensitization to 3 or more allergen molecules from cat or dog was a better longitudinal predictor of cat or dog symptoms than results of IgE tests with cat or dog allergen extract, respectively. Cross-sectionally, cat/dog-polysensitized children had higher IgE levels and more frequent symptoms to cat and dog than monosensitized children.

Conclusions—Sensitization to Fel d 1 and Can f 1 in childhood and polysensitization to either cat or dog allergen molecules predict cat and dog allergy cross-sectionally and longitudinally significantly better than IgE to cat or dog extract.

Keywords

Allergy; allergen; Barn/Children Allergy/Asthma Milieu Stockholm Epidemiologic; birth cohort; cat; children; dog; IgE; ISAC technology; microarray; pet; sensitization; Can f 1; Can f 5; Fel d 1; prediction

Allergy to cat and dog is common in the Western world,^{1,2} and the prevalence of sensitization to furry animals has increased both in Europe^{1,3} and the United States.⁴ It is well known that increased IgE levels to furry animal allergens are associated with allergy-related symptoms.^{5–7} Using ImmunoCAP, we recently reported an increase in sensitization to cat (from 6.4% to 19.0%) and dog (from 4.8% to 22.6%) in children followed from 4 to 16 years of age in the population-based Barn/Children Allergy/Asthma Milieu Stockholm Epidemiologic (BAMSE) birth cohort.⁸

A number of allergen molecules have been described in cats (*Felis domesticus*) and dogs (*Canis familiaris*). The major cat allergen is the uteroglobulin Fel d 1,⁹ which accounts for 60% to 90% of all IgE reactivity to cat dander.^{10,11} Among the minor cat allergens are the serum albumin Fel d 2, the lipocalins Fel d 4 and Fel d 7, and the latherin-like Fel d 8.^{12,13}

The major dog (*Canis familiaris*) allergen Can f 1, together with Can f 2, Can f 4, and Can f 6, belongs to the lipocalin family. Can f 3, a serum albumin, and Can f 4 have been reported to be allergens of less importance.^{14,15} Can f 5, a prostatic kallikrein in male dog urine, has recently been reported to be recognized by up to 70% of dog-sensitized patients.^{14,16}

More knowledge is needed in the area of pet allergy, where the clinical history often is inconclusive and many patients are polysensitized to several furry animals, such as cat, dog, and horse. Furthermore, some allergen molecules might be poorly represented in crude allergen extracts,¹⁷ leading to uncertain results. However, molecular allergy diagnostics allow for an increased accuracy in allergy diagnosis and prognosis and are able to reveal the specific pet allergen molecules responsible for sensitization and symptoms.¹⁸

The aims of the present study, which is part of the European Union–funded project Mechanisms for the Development of Allergy (MeDALL; <http://medall-fp7.eu/>)¹⁹ program, were (1) to investigate IgE reactivity to individual cat and dog allergen molecules in childhood through adolescence for the first time by using the BAMSE birth cohort, (2) compare the results with cat and dog extract IgE levels, (3) identify risk markers in preschool- and school-aged children for allergic symptoms to cat and dog up to the age of 16 years, and (4) assess the phenotypes of monosensitized and polysensitized subjects to cat and dog allergens.

Methods

Study cohort

The BAMSE study is an unselected population-based birth cohort study of 4089 children.^{20,21} For this study, data from baseline and the 4-, 8-, and 16-year follow-ups, the time points when blood was drawn, were used in conjunction with serologic allergy testing. At the respective follow-ups, sera were available for 64%, 60%, and 62% of the population. Background data were retrieved from the baseline questionnaire. Reported respiratory symptoms at pet exposure were obtained from the questionnaires at 4, 8, and 16 years of age. Symptoms to cat and dog were defined as reported symptoms from the upper airways, lower airways, or both at exposure to cat/dog (for definitions of symptoms, see the Methods section in this article's Online Repository at www.jacionline.org).

For 1699 (42%) children, blood samples were obtained from the same children at each of the 3 time points of clinical follow-up (4, 8, and 16 years). A subset of 798 children was randomly picked by using the Stata software randomization function (StataCorp, College Station, Tex), providing 2394 (3 × 798) serum samples for analysis. Complete data on reported airway symptoms to cat and dog were available in 779 of these children, which constitute our study population. Permission for the study was obtained from the Regional Ethical Review board at Karolinska Institutet at each follow-up, and parents of participating children/children themselves (when applicable) provided informed consent.

Allergen-specific IgE measurement

Serum samples were initially tested with ImmunoCAP (Thermo Fisher AB, Uppsala, Sweden) for allergen-specific IgE antibodies to cat (e1) and dog (e5) extract. The results

were expressed in kilounits of allergen per liter, and a positive test result was defined as 0.35 kU_A/L or greater. An IgE antibody level of greater than 100 kU_A/L was given the value of 101 kU_A/L in statistical evaluations.

IgE reactivity to the cat allergen molecules Fel d 1, 2, and 4, as well as the dog allergen molecules Can f 1, 2, 3, 5, and 6, were analyzed with an allergen chip based on ISAC technology (Thermo Fisher) developed in the MeDALL FP7-funded research program.²² In brief, serum aliquots of 35 µL were incubated on the microarray for 120 minutes at room temperature, and slides were washed and incubated with fluorescence-labeled anti-IgE antibodies (Thermo Fisher) for 30 minutes. Chips were then washed, dried, and analyzed with a Laser Scan Confocal microarray reader (LuxScan 10K/A; Capital-Bio, Beijing, China). The results were evaluated with Phadia Microarray Image Analysis software and are reported in ISAC standardized units. The cutoff was set at 0.3 ISAC standardized units for IgE detection (ISU-E).

Statistical analysis

Results are expressed as numbers and proportions (percentages). Group IgE levels are expressed as medians and ranges. Median ISU-E values were calculated on values of greater than the cutoff. Two-tailed *t* tests were used for 2-sample tests of proportions, as well as on the logarithmic scale for group comparisons of IgE levels. Positive predictive values (PPVs), which were defined as the number of true-positive results (ie, cat/dog-symptomatic and specific allergen-sensitized subjects) divided by the number of true-positive results plus the number of false-positive results (ie, all subjects sensitized to the specific allergen), respectively, and binomial exact 95% CIs for the PPVs, were calculated. Negative predictive values (NPVs), which were defined as the number of true-negative results (ie, cat/dog-asymptomatic subjects without sensitization to the specific allergen) divided by the number of true-negative results plus the number of false-negative results (ie, all subjects not sensitized to the specific allergen), respectively, and binomial exact 95% CIs for the PPVs, were calculated. Odds ratios (ORs) for symptoms to cat or dog, respectively, in relation to sensitization were estimated by using logistic regression models and 95% CIs. Fitted predicted probability estimates were plotted according to the number of IgE-reactive (> 0.3 ISU-E) cat or dog allergen molecules, respectively, per subject by using the results from the logistic regression. Logistic regression with clustered SEs was also used to investigate cat/dog symptoms in relation to sensitization to different allergen molecules using both crude ORs and ORs adjusted for concomitant sensitization to the other allergen molecules. *P* values of less than .05 and 95% CIs not including 1 were considered significant. All statistical analyses were performed with Stata statistical software (release 14.0, StataCorp).

Results

Demographic characteristics of the study population, including reported symptoms and sensitization to cat and dog extracts

Baseline characteristics were similar between the children included in the study and children in the original cohort (see Table E1 in this article's Online Repository at www.jacionline.org). No significant differences were seen between the 2 groups except for a

higher prevalence of allergic heredity in the study group. However, this difference in prevalence did not affect the results (data not shown). The prevalences of IgE reactivities to cat and dog extract (ImmunoCAP) at the 3 different time points were 6.8%, 13.9%, and 19.8% for cat and 5.1%, 11.6%, and 22.9% for dog, respectively. At 4, 8, and 16 years, reported upper and/or lower respiratory symptoms were 4.8%, 7.1%, and 11.2% to cat and 3.1%, 3.1%, and 5.5% to dog (see Table E2 in this article's Online Repository at www.jacionline.org). Conjunctival challenges with cat or dog extract were performed in 34 cat- or dog-sensitized children without reported cat or dog symptoms, respectively (see the Methods section and Table E3 in this article's Online Repository at www.jacionline.org).

IgE reactivity to microarrayed pet allergen molecules

IgE reactivity to any of the 3 cat allergen molecules tested increased from 9.2% at 4 years to 14.5% at 8 and 21.8% at 16 years. Fel d 1 was the dominant sensitizing cat allergen during the entire childhood (8.7% to 20.3%; Fig 1, *A*) and in line with the rates of sensitization to cat extract. Fel d 1 also induced the highest IgE levels at all 3 time points (Fig 2). Only 4.4% to 7.1% of the subjects sensitized to any cat allergen molecule had IgE to Fel d 2, Fel d 4, or both but not to Fel d 1.

The proportion of children with IgE reactivity to any of the 5 dog allergen molecules increased from 3.6% through 8.2% to 14.8% at the corresponding time points, which was lower in comparison with dog extract ImmunoCAP results (5.1%, 11.6%, and 22.9% at ages 4, 8, and 16 years, respectively). The most frequently recognized dog allergen was Can f 5 (1.9% to 12.6%; Fig 1, *B*), but the highest IgE levels were directed toward Can f 1 (Fig 2).

Cross-sectional IgE reactivity to pet allergen molecules in relation to symptoms

IgE levels to Fel d 1 were significantly higher at each of the analyzed ages among children with symptoms to cat compared with nonsymptomatic children (Fig 2, *A*). No such associations could be seen for the dog allergen molecules in relation to dog symptoms. However, there were too few observations of IgE reactivity to the minor dog allergens Can f 2 and Can f 3 to allow for any statistical calculations. Even though a large proportion of children sensitized to a single dog allergen molecule at 16 years of age were sensitized to Can f 5 (81%), only about one tenth of them reported symptoms to dog (data not shown).

Cross-sectional PPVs were calculated for symptoms among subjects with IgE reactivity to cat or dog allergens extract or to the different pet allergen molecules (Table I). PPVs were significantly higher for IgE reactivity to Can f 1 compared with dog extract at 8 (53.8% vs 20.0%) and 16 (44.2% vs 18.5%) years of age. No significant differences in PPVs were seen for IgE to Can f 5 or Fel d 1 compared with dog or cat allergen extracts with ImmunoCAP, respectively. NPVs were quite similar for the different tested allergens and varied between 91.0% (Fel d 4 at 16 years) and 99.3% (dog extract at 8 years, data not shown). For corresponding sensitivity and specificity values, see Table E4 in this article's Online Repository at www.jacionline.org.

The proportion of children cosensitized to cat and dog allergen molecules increased from 4 to 16 years (Fig 3). Having IgE reactivity to both cat and dog allergen molecules increased the median IgE levels to Fel d 1 and Can f 1 and increased the prevalence rates of allergic

symptoms to cats and dogs compared with being sensitized to 1 furry animal only (Fig 3). Of the 197 (25.3%) children with IgE reactivity to at least 1 cat or dog allergen at 16 years of age, 80 (40.6%) reported symptoms to cat, dog, or both at the same age. In the sensitized but asymptomatic group of 177 children, 26.5% were sensitized to cat or dog allergens at all ages (4, 8, and 16 years), and 47.9% were sensitized only at age 16 years (data not shown).

Longitudinal IgE reactivity to pet allergen molecules in relation to symptoms

We also assessed our data longitudinally by investigating the ORs of reported symptoms to cat or dog at 16 years of age in relation to IgE reactivity to the cat and dog allergen molecules and whole extracts at 4 and 8 years of age. At ages 4 and 8 years, IgE reactivity to each of the cat or dog allergen molecules or to cat or dog extract was significantly associated with reported symptoms to cat or dog at age 16 years, respectively (Fig 4, upper part). However, when adjusting for sensitization to the other cat allergen molecules, only IgE reactivity to Fel d 1 remained significantly associated with symptoms (OR, 13.7; 95% CI, 8.3-22.7; Fig 4, lower part). Similarly, only IgE levels to Can f 1 were significantly associated with symptoms to dog at age 16 years after adjusting for sensitization to the other dog allergen molecules at 4 and 8 years of age (OR, 8.0; 95% CI, 2.3-27.7; Fig 4, lower part, and see Table E5 in this article's Online Repository at www.jacionline.org).

Sensitization to more than 1 cat allergen molecule at age 4 or 8 years significantly increased the likelihood of reporting cat allergy at 16 years of age (Fig 5, A and B). A 95% probability of cat symptoms at 16 years of age was present for 4-year-old children with IgE reactivity to all 3 cat allergen molecules. However, sensitization to cat extract at 4 and 8 years of age predicted only a 50% probability of cat symptoms at age 16 years. Similarly, sensitization to an increasing number of dog allergen molecules at age 4 or 8 years gave rise to a higher probability of symptoms to dog at 16 years of age (Fig 5, B and C). Sensitization to at least 3 dog allergens at 4 years of age led to an 81% likelihood for dog symptoms at 16 years of age. For comparison, the likelihood of dog symptoms at 16 years of age only reached 20% and 30% when sensitization to dog extract with ImmunoCAP at 4 or 8 years of age was used, respectively.

Discussion

For the first time, we present a cross-sectional and longitudinal population-based study showing the effect of sensitization to cat and dog allergen molecules during early childhood in relation to future clinical respiratory symptoms at cat or dog exposure. The novel findings are that polysensitization (ie, sensitization to 3 cat or dog allergen molecules, respectively) at 4 or 8 years of age is superior in predicting future cat or dog symptoms than sensitization to cat or dog extract, respectively. Furthermore, sensitization to both cat and dog allergen molecules is associated with more prevalent cat- and dog-related symptoms and higher IgE levels to these molecules. With respect to dog, our results indicate that sensitization to Can f 1 is the most important prognostic marker of dog allergy and superior to measurement of IgE levels to dog allergen extract (ImmunoCAP), whereas measurement of IgE levels to Can f 5 shows a weaker association to dog allergy. Moreover, we show that sensitization to Fel d 1 is a predictor of cat allergy at 16 years of age. Finally, monosensitized and polysensitized

subjects appear to belong to 2 different allergy phenotypes. Thus molecular allergy diagnostics offer important advantages for the diagnosis of cat and dog allergy in early childhood and help to predict the course of disease to adolescence.

The strengths of the study are the large sample size of children from a population-based birth cohort and the high follow-up rate; nearly 80% from baseline answered the questionnaire at the 16-year follow-up, and there are blood samples from 42% at all 3 clinical follow-ups.

One limitation of the small sample sizes in some subgroups is illustrated by large CIs in the corresponding analyses. Therefore the associated results need to be confirmed by other studies.

Another limitation could be the geographic relevance of the findings given the fact that the study is based on a Swedish cohort. However, we do not believe that exposure to furry animals or reactions on exposure to cat or dog allergens differ substantially among children in our cohort compared with those in children in the Western world as a whole. Breeds of cats and dogs are usually the same in major parts of the Western world.

Yet another limitation might be that symptom data are based on questionnaires and that avoidance of animals might be difficult to assess. What might introduce a misclassification is limited contact with animals and not precisely knowing about current allergy to cats or dogs. To eliminate this bias, we performed conjunctival challenges with cat or dog extracts that actually confirmed the questionnaire data (see the Methods section and Table E3 in the online repository).²³

We found that sensitization to Fel d 1 and Can f 1 at 4 and 8 years of age are risk markers of cat and dog allergy at 16 years of age, as is cosensitization to several cat or dog allergen molecules. The dominant role of IgE to Fel d 1 compared with Fel d 2 and Fel d 4 in cat-sensitized patients was observed in each of the tested age groups. We also noted that the prevalence of IgE to Fel d 1 almost tripled from 4 to 16 years of age and reached 20% in the oldest age group. Fel d 1 was the only cat allergen molecule independently predictive for cat symptoms and also induced the highest IgE levels among the analyzed cat allergen molecules, which reflects that Fel d 1 accounts for the major allergenic activity in cat dander.⁷ Compared with other mammalian allergens, Fel d 1 stands out because of its very dominant role in cat allergy.⁹ Thus testing with cat allergen molecules provides additional strength in predicting current or future cat allergy.

Regarding sensitization to dog allergen molecules, we found that the prevalence more than tripled from childhood to adolescence, but the prevalence rates were lower compared with those to cat allergen. Interestingly, Can f 5, a kallikrein protein that is suggested to be found only in male dogs,¹⁴ was the most prevalent dog allergen molecules recognized by IgE in all age groups. A large proportion of children who were sensitized to a single dog allergen molecule had IgE to Can f 5, but only about one of 10 of them reported symptoms to dog. This allergen has been reported as a major allergen among European subjects with dog allergy; among these subjects, 26 (70%) of 37 were sensitized, 14 of whom lacked IgE reactivity to Can f 1, Can f 2, or Can f 3.¹⁴ Sensitization to Can f 5 was also recently

highlighted among children with severe asthma who, compared with children with controlled asthma, had an IgE response to more than 3 animal-derived allergen molecules, of which Can f 5 was one.^{24,25} However, adjustment for cosensitization to other allergen molecules was not performed. Furthermore, these studies were all investigating small samples of allergic patients. In our large population-based study Can f 1 was more related to dog symptoms than Can f 5, and Can f 1 also induced the highest IgE levels. Furthermore, IgE reactivity to Can f 1 was the only parameter that independently could predict future symptoms to dog. Thus having IgE to Can f 1 seems to be the strongest marker related to development of dog allergy, which is of importance when allergen-specific immunotherapy treatment is to be considered. In contrast, according to current literature, having IgE to Can f 5 appears, at least according to our data, to be more prominent for allergic airway disease in general than for dog allergy in particular. One of the novelties of our study is that the associations described are observed in a population-based longitudinal study and are not due to selection bias or lack of adjustment. Thus the findings are of public health relevance.

For the diagnosis of cat allergy in our population, we also noted that IgE testing with just 1 cat allergen molecule, Fel d 1, is as good as testing for IgE to cat allergen extract (ImmunoCAP), which is line with previous observations.⁷ Importantly, for diagnosis of dog allergy, measuring IgE levels to Can f 1 seems to have advantages over measuring IgE levels to dog allergen extract (ImmunoCAP). In fact, IgE reactivity to Can f 1 in childhood predicted the development of dog allergy in adolescence significantly better than IgE reactivity to dog allergen extract. Actually, dog allergen extracts have shown considerable heterogeneity in their allergen composition, which will have a negative influence on the accuracy of diagnosis of dog allergy.¹⁷

Interestingly, we also observed that cosensitization to cat and dog allergen molecules became more common with increasing age. Being cosensitized to both cat and dog allergen molecules was associated with higher IgE levels to cat and dog allergen molecules and a higher proportion of subjects having symptoms compared with being monosensitized to either cat or dog allergen molecules. Notably, few children with IgE to only 1 dog allergen molecule reported symptoms at 16 years of age. This can be explained by IgE to Can f 5, which was the dominant sensitizing molecule in this group of children.

At age 4 or 8 years, the possibility to predict symptoms at age 16 years increased with the number of IgE-reactive cat or dog allergens. A high number of IgE-reactive allergens (3 cat molecules and 3 dog molecules) at a young age (4 years) was associated with a very high probability (95% and 81%, respectively) of having symptoms to cat or dog at exposure in adolescence. The results are in line with previous findings in which multiple sensitizations were shown to be a risk marker for asthma in children.^{24,26,27} However, other studies were either based on a small sample of allergic patients or did not focus specifically on sensitization to cat or dog allergen molecules in relation to cat or dog symptoms. If the present study is confirmed, immunotherapy in young children with polysensitization to cat and dog allergen molecules might be a treatment of choice because of the risk of persistence of symptoms. In such children molecular-based allergy diagnostics with individual allergen molecules will be of considerable importance.

The common IgE tests with crude allergen extract might be sufficient for cat allergy but less likely for dog allergy. In addition, young children with high IgE levels to Fel d 1 or Can f 1 or children who are polysensitized to cat or dog allergen molecules, as well as children sensitized to both cat and dog allergen components, are more likely to have present and future allergy and might be more important to treat (eg, with more frequent doctor's office visits or early immunotherapy to cat or dog).

In conclusion, this is the first study to elucidate the benefit of using cat and dog allergen molecules longitudinally and in a population-based sample as predictors of cat and dog allergy development from childhood to adolescence. Molecular-based allergy diagnostics offer new opportunities for improving the diagnosis of furry animal allergy and in particular dog allergy. Our data suggest that different allergy phenotypes exist and that both clinical management and research should be considered differently in patients with monosensitization versus polysensitization to cat, dog, or both.

Methods

Definition of symptoms and background characteristics (questionnaire answers)

Cat allergy—*Asthma at age 4 years:* Has your child had trouble with wheezy breathing or cough after contact with the following after the age of 2 years? (*Yes* and *cat* indicated)

Rhinitis/conjunctivitis at age 4 years: Has your child after the age of 2 years ever had trouble with sneezing, runny nose, stuffy nose, or red itchy eyes after contact with the following? (*Yes* and *cat* indicated)

Asthma at age 8 years: Has your child had wheezing, raspy breathing, or disruptive cough in conjunction with any of the following since age 4 years? (*Yes* and *cat* indicated)

Rhinitis/conjunctivitis at age 8 years: Has your child been afflicted with sneezing, runny nose, stuffy nose, or red irritated eyes in conjunction with any of the following since age 4 years? (*Yes* and *cat* indicated)

Asthma at age 16 years: Has your child had respiratory symptoms or a troublesome cough after contact with any of the following in the past 12 months? (*Yes* and *cat* indicated)

Rhinitis/conjunctivitis at age 16 years: Has your child had nose or eye symptoms without simultaneously having a cold after contact with any of the following in the past 12 months? (*Yes* and *cat* indicated)

Dog allergy—*Asthma at age 4 years:* Has your child had trouble with wheezy breathing or cough after contact with the following after the age of 2 years? (*Yes* and *dog* indicated)

Rhinitis/conjunctivitis at age 4 years: Has your child after the age of 2 years ever had trouble with sneezing, runny nose, stuffy nose, or red itchy eyes after contact with the following? (*Yes* and *dog* indicated)

Asthma at age 8 years: Has your child had wheezing, raspy breathing, or disruptive cough in conjunction with any of the following since age 4 years? (*Yes* and *dog* indicated)

Rhinitis/conjunctivitis at age 8 years: Has your child been afflicted with sneezing, runny nose, stuffy nose, or red irritated eyes in conjunction with any of the following since age 4 years? (*Yes* and *dog* indicated)

Asthma at age 16 years: Has your child had respiratory symptoms or a troublesome cough after contact with any of the following in the past 12 months? (*Yes* and *dog* indicated)

Rhinitis/conjunctivitis at age 16 years: Has your child had nose or eye symptoms without simultaneously having a cold after contact with any of the following in the past 12 months? (*Yes* and *dog* indicated)

Background characteristics—Heredity allergy: Mother, father, or both with a doctor’s diagnosis of asthma and asthma medication and/or a doctor’s diagnosis of hay fever in combination with furred pets and/or pollen allergy at the time of the baseline questionnaire.

Breast-fed 4 months: Exclusively breast-fed for 4 months or more.

Parental smoking: Either of the parents smoked at least 1 cigarette per day at the time of the first questionnaire.

Young mother at birth (25 years): Mother’s age less than 25 years at birth of the child.

White collar parent: Socioeconomic status for the household according to dominance order: “Socioeconomic division (SEI); Reports on Statistical Coordination 1982:4.”

Cat ownership: Having a cat at home at the time of baseline and 1-year questionnaires.

Dog ownership: Having a dog at home at the time of baseline and 1-year questionnaires.

Conjunctival challenge

A random subset of 34 children (median age, 19.3 years; age range, 17.9-20.1 years) who had never reported symptoms to cat or dog at exposure at any of the 3 time points but were sensitized to cat or dog underwent conjunctival challenges with cat or dog allergen extract to elucidate whether they were still asymptomatic. The challenge was performed with a single drop (about 0.03 mL) of 100,000 SQ-E of undiluted Aquagen of cat or dog allergen extract (ALK-Abelló Nordic) in the lower conjunctival sac in one eye and normal saline (NaCl 0.9%) solution in the other eye. The substance was unknown to the patients. The left eye was chosen for provocation. The patients were informed not to rub the eyes after instillation. The same investigator (A.A.) performed all challenges. Conjunctival signs of redness and chemosis were graded 10 minutes after the provocation^{E1} and assessed by using a 4-grade score, as follows: 0, no signs at all; 1, mild; 2, moderate; and 3, severe signs.

Extended Data

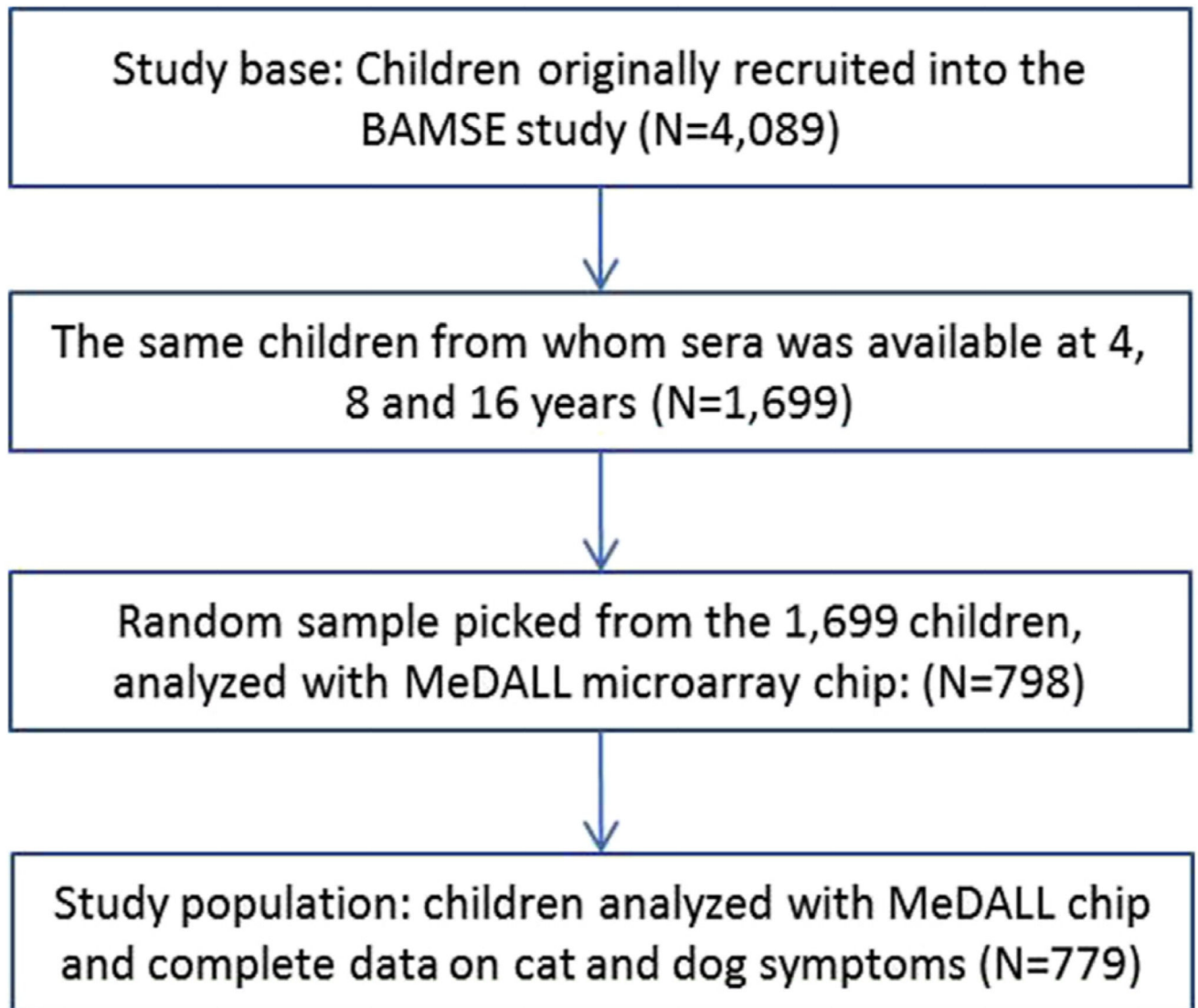


Fig E1.
Flow chart of children in the BAMSE cohort study base (n = 4089) and study population (n = 779).

Table E1
Baseline (median age, 2 months) and age 1-year characteristics of the study group (n = 779) compared with children in the original cohort (n = 4089)

Variables	Study base cohort* (n = 4089)			Study population* (n = 779)			P value
	No.	Percent	95% CI	No.	Percent	95% CI	
Female sex	2024	49.5	48.0-51.0	393	50.4	46.9-54.0	.63

Variables	Study base cohort* (n = 4089)			Study population* (n = 779)			P value
	No.	Percent	95% CI	No.	Percent	95% CI	
Heredity allergy	1200	29.7	28.3-31.1	258	33.2	29.9-36.7	.05
Breast-fed 4 mo	3116	79.5	78.2-80.8	609	79.2	76.2-82.0	.84
Parental smoking	855	21.0	19.8-22.3	159	20.5	17.7-23.5	.75
Young mother at birth (< 25 y)	319	7.8	7.0-8.7	58	7.4	5.7-9.5	.73
White collar parent	695	17.3	16.1-18.5	112	14.5	12.1-17.2	.06
Older siblings	1980	48.4	46.9-50.0	389	49.9	46.4-53.5	.44
Cat ownership [†]	405	11.1	10.1-12.1	85	11.8	9.6-14.3	.39
Dog ownership [†]	221	6.4	5.7-7.2	38	5.6	4.1-7.4	.54

* Missing values between 0 and 170 observations in the study base cohort and between 0 and 7 observations in the study population.

[†] At baseline, age 1 year, or both.

Table E2
Symptoms at exposure to cat and dog, respectively, at 4, 8, and 16 years of age (n = 779)

Age	Any symptom (asthma and/or rhinitis), no. (%)	Asthma, no. (%)	Rhinitis, no. (%)	Asthma and rhinitis, no. (%)
Cat symptoms				
4 y	37 (4.7)	25 (3.2)	27 (3.5)	15 (1.9)
8 y	55 (7.1)	19 (2.4)	52 (6.7)	16 (2.0)
16 y	87 (11.2)	36 (4.6)	83 (10.7)	32 (4.1)
Dog symptoms				
4 y	24 (3.1)	15 (1.9)	18 (2.3)	9 (1.2)
8 y	24 (3.1)	10 (1.3)	22 (2.8)	8 (1.0)
16 y	43 (5.5)	23 (3.0)	39 (5.0)	19 (2.4)

Table E3
Conjunctival challenge with cat/dog extract* in a subset of adolescents (median age, 19.2 years; age range, 17.9-20.1 years) without reported symptoms to cat/dog at exposure at 16 years of age but with IgE reactivity (0.3 ISU) to at least 1 cat/dog allergen component at 16 years of age, respectively (n [cat] = 18, n [dog] = 16)

<u>IgE reactivity to cat allergen molecules (0.3 ISU-E)</u>		<u>IgE reactivity to dog allergen molecules (0.3 ISU-E)</u>	
Cat allergen	Challenged (n = 18)	Dog allergen	Challenged (n = 16)
Fel d 1, no. (%)	14 (77.8)	Can f 1, no. (%)	1 (6.3)
IgE level (ISU-E), median (range)	0.49 (0.32-20.12)	IgE level (ISU-E)	16.5
Fel d 2, no. (%)	3 (16.7)	Can f 2, no. (%)	1 (6.3)
IgE level (ISU-E)	0.3, 0.55, 0.62	IgE level (ISU-E)	1.17
Fel d 4, no. (%)	3 (16.7)	Can f 3, no. (%)	3 (18.8)
IgE level (ISU-E)	1.9, 3.22, 6.16	IgE level (ISU-E)	0.36, 0.53, 21.91
		Can f 5, no. (%)	15 (93.8)
		IgE level (ISU-E), median (range)	1.56 (0.38-34.93)
		Can f 6, no. (%)	3 (18.8)
		IgE level (ISU-E)	0.41, 0.41, 0.47
Reaction at provocation, no. (%)	3 (16.7)	Reaction at provocation, no. (%)	1 (6.3)
Highest IgE reactivity if reaction, cat allergen, (degree of reaction)	Fel d 1 = 20.12 (2) Fel d 1 = 9.12 (1) Fel d 1 = 0.49 (1)	Highest IgE reactivity if reaction, dog allergen, (degree of reaction)	Can f 1 = 16.5 (1)

Degree of reaction: 1, mild; 2, moderate; and 3, severe.

* Four subjects were challenged with both cat and dog extracts (but with an at least 1-week interval).

Table E4
Diagnostic sensitivity (true-positive rate) and specificity (true-negative rate) for cat or dog symptoms, respectively, and presence or absence of IgE reactivity to cat/dog extract or allergen molecules at 4, 8, and 16 years of age (n = 779)

	Sensitivity	Specificity
4 y		
Cat extract	43.2% (27.1% to 60.5%)	95.0% (93.2% to 96.5%)
Any cat component	45.9% (29.5% to 63.1%)	92.6% (90.5% to 94.4%)

	Sensitivity	Specificity
Fel d 1	45.9% (29.5% to 63.1%)	93.1% (91.1% to 94.8%)
Fel d 2	21.6% (9.83% to 38.2%)	99.3% (98.4% to 99.8%)
Fel d 4	8.1% (1.7% to 21.9%)	99.1% (98.1% to 99.6%)
Dog extract	45.8% (25.6% to 67.2%)	96.2% (94.5% to 97.4%)
Any dog component	33.3% (15.6% to 55.3%)	97.4% (95.9% to 98.4%)
Can f 1	25.0% (9.8% to 46.7%)	98.8% (97.7% to 99.5%)
Can f 2	20.8% (7.1% to 42.2%)	99.7% (99.0% to 100%)
Can f 3	4.2% (0.1% to 21.1%)	99.6% (98.8% to 99.9%)
Can f 5	16.7% (4.7% to 37.4%)	98.5% (97.4% to 99.3%)
Can f 6	8.3% (1.0% to 27.0%)	99.5% (98.6% to 99.9%)
8 y		
Cat extract	83.3% (70.7% to 92.1%)	91.2% (89.0% to 93.2%)
Any cat component	83.6% (71.2% to 92.2%)	90.7% (88.4% to 92.8%)
Fel d 1	83.6% (71.2% to 92.2%)	91.4% (89.2% to 93.4%)
Fel d 2	38.2% (25.4% to 52.3%)	97.5% (96.1% to 98.5%)
Fel d 4	16.4% (7.8% to 28.8%)	99.2% (98.2% to 99.7%)
Dog extract	78.3% (56.3% to 92.5%)	90.4% (88.1% to 92.4%)
Any dog component	75.0% (53.3% to 90.2%)	93.9% (92.0% to 95.5%)
Can f 1	58.3% (36.6% to 77.9%)	98.4% (97.2% to 99.2%)
Can f 2	16.7% (4.7% to 37.4%)	99.5% (98.6% to 99.9%)
Can f 3	25.0% (9.8% to 46.7%)	99.6% (98.8% to 99.9%)
Can f 5	50.0% (29.1% to 70.9%)	95.2% (93.5% to 96.6%)
Can f 6	29.2% (12.6% to 51.1%)	99.2% (98.3% to 99.7%)
16 y		
Cat extract	80.5% (70.6% to 88.2%)	87.9% (85.2% to 90.2%)
Any cat component	79.3% (69.3% to 87.3%)	85.4% (82.6% to 88.0%)
Fel d 1	75.9% (65.5% to 84.4%)	86.7% (83.9% to 89.1%)
Fel d 2	29.9% (20.5% to 40.6%)	95.8% (94.0% to 97.2%)
Fel d 4	23.0% (14.6% to 33.2%)	97.4% (95.9% to 98.5%)
Dog extract	76.7% (61.4% to 88.2%)	80.3% (77.2% to 83.1%)
Any dog component	65.1% (49.1% to 79.0%)	88.2% (85.6% to 90.4%)
Can f 1	44.2% (29.1% to 60.1%)	96.7% (95.2% to 97.9%)
Can f 2	9.3% (2.6% to 22.1%)	99.2% (98.2% to 99.7%)
Can f 3	9.3% (2.6% to 22.1%)	99.0% (98.1% to 99.6%)
Can f 5	53.5% (37.7% to 68.8%)	89.8% (87.4% to 91.9%)
Can f 6	25.6% (13.5% to 41.2%)	97.0% (95.5% to 98.1%)

Value are shown as proportions (95% CIs).

Table E5
Sensitization matrix: allergen molecules at 4, 8, and 16
years of age

Cat							
No., 4 y	No., 8 y	No., 16 y	Fel d 1	Fel d 2	Fel d 3	Fel d 4	Fel d 6
707	666	609	-	-	-	-	-
4	3	5	-	-	-	-	X
0	1	6	-	X	-	-	-
0	1	1	-	X	-	-	X
52	70	95	X	-	-	-	-
3	1	15	X	-	-	-	X
10	27	31	X	X	-	-	-
3	10	17	X	X	-	-	X
Dog							
No., 4 y	No., 8 y	No., 16 y	Can f 1	Can f 2	Can f 3	Can f 5	Can f 6
751	715	664	-	-	-	-	-
1	3	3	-	-	-	-	X
8	32	55	-	-	-	X	-
0	1	8	-	-	-	X	X
2	0	1	-	-	X	-	-
0	0	1	-	-	X	X	-
0	0	2	-	-	X	X	X
0	0	1	-	X	-	X	-
0	0	1	-	X	-	X	X
2	2	0	-	X	-	-	-
4	8	9	X	-	-	-	-
1	2	2	X	-	-	-	X
4	5	10	X	-	-	X	-
0	1	10	X	-	-	X	X
0	1	1	X	-	X	-	-
0	1	2	X	-	X	X	-
1	2	1	X	-	X	X	X
1	0	1	X	X	-	-	-
2	0	0	X	X	-	-	X
1	1	1	X	X	-	X	-
0	0	3	X	X	-	X	X
0	1	0	X	X	X	X	-
1	4	3	X	X	X	X	X

X, Sensitized (≥ 0.3 ISU-E); -, not sensitized (<0.3 ISU-E).

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Abbreviations used

BAMSE	Barn/Children Allergy/Asthma Milieu Stockholm Epidemiologic
ISU-E	ISAC standardized units for IgE detection
MeDALL	Mechanisms for the Development of Allergy
NPV	Negative predictive value
OR	Odds ratio
PPV	Positive predictive value

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Clinical implications

IgE to Fel d 1, Can f 1, and polysensitization to cat or dog allergen molecules in preschool- or school-aged childhood are predictive risk markers for the development of allergy to cat and dog at age 16 years.

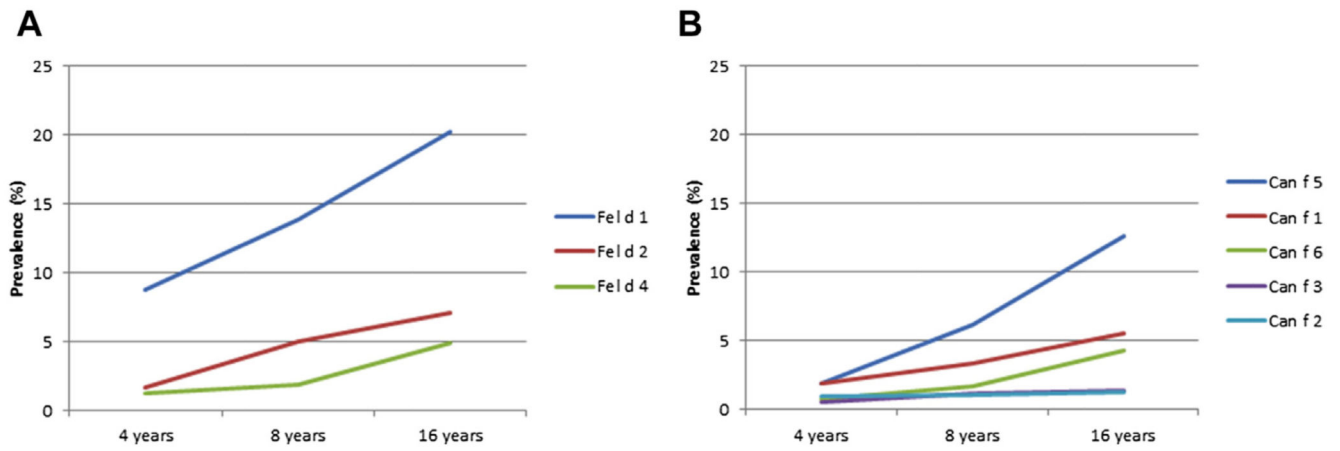
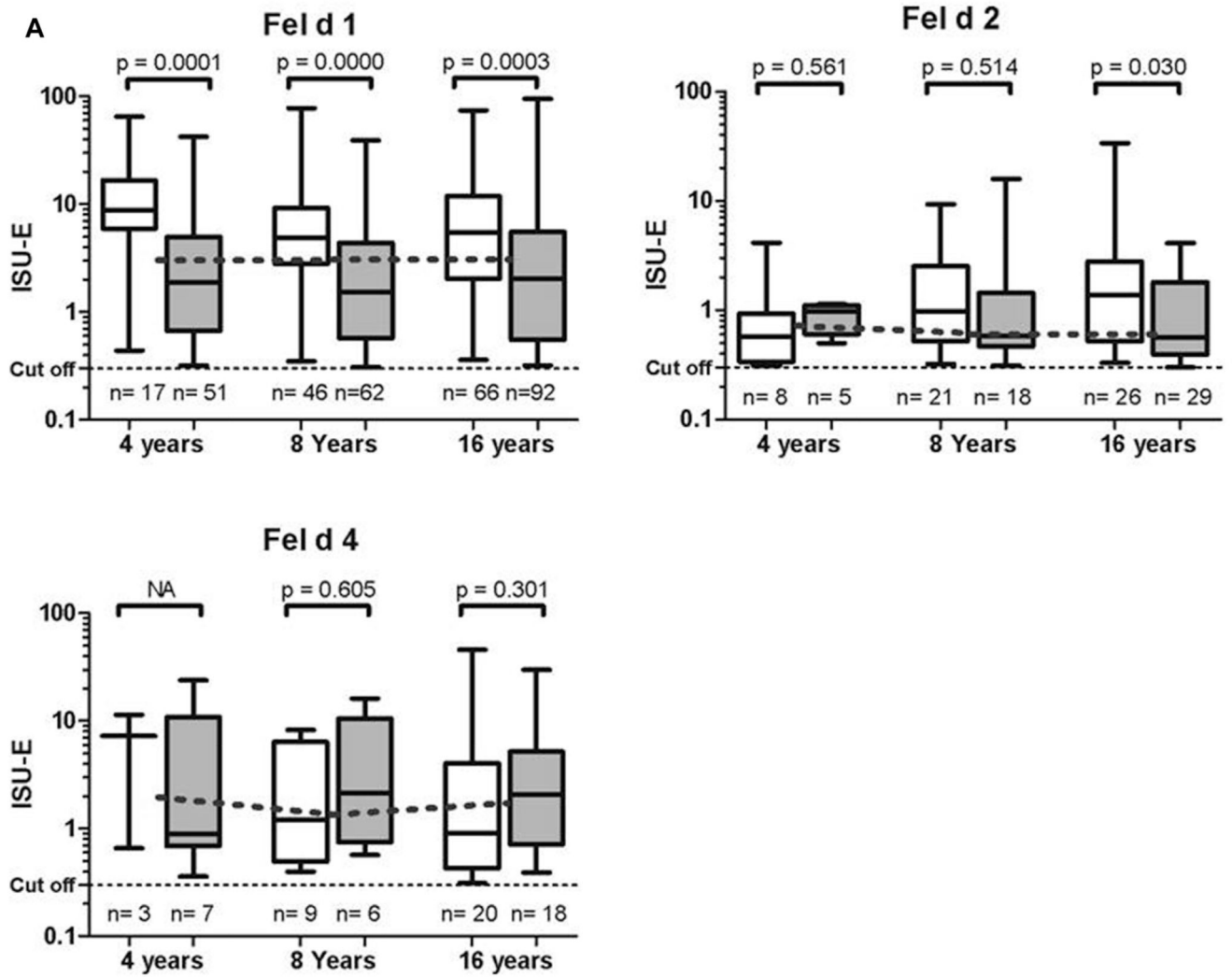


Fig 1. Prevalence (percentage) of IgE reactivity (≥ 0.3 ISU-E) to cat (**A**) and dog (**B**) allergen components at 4, 8, and 16 years of age (n = 779).



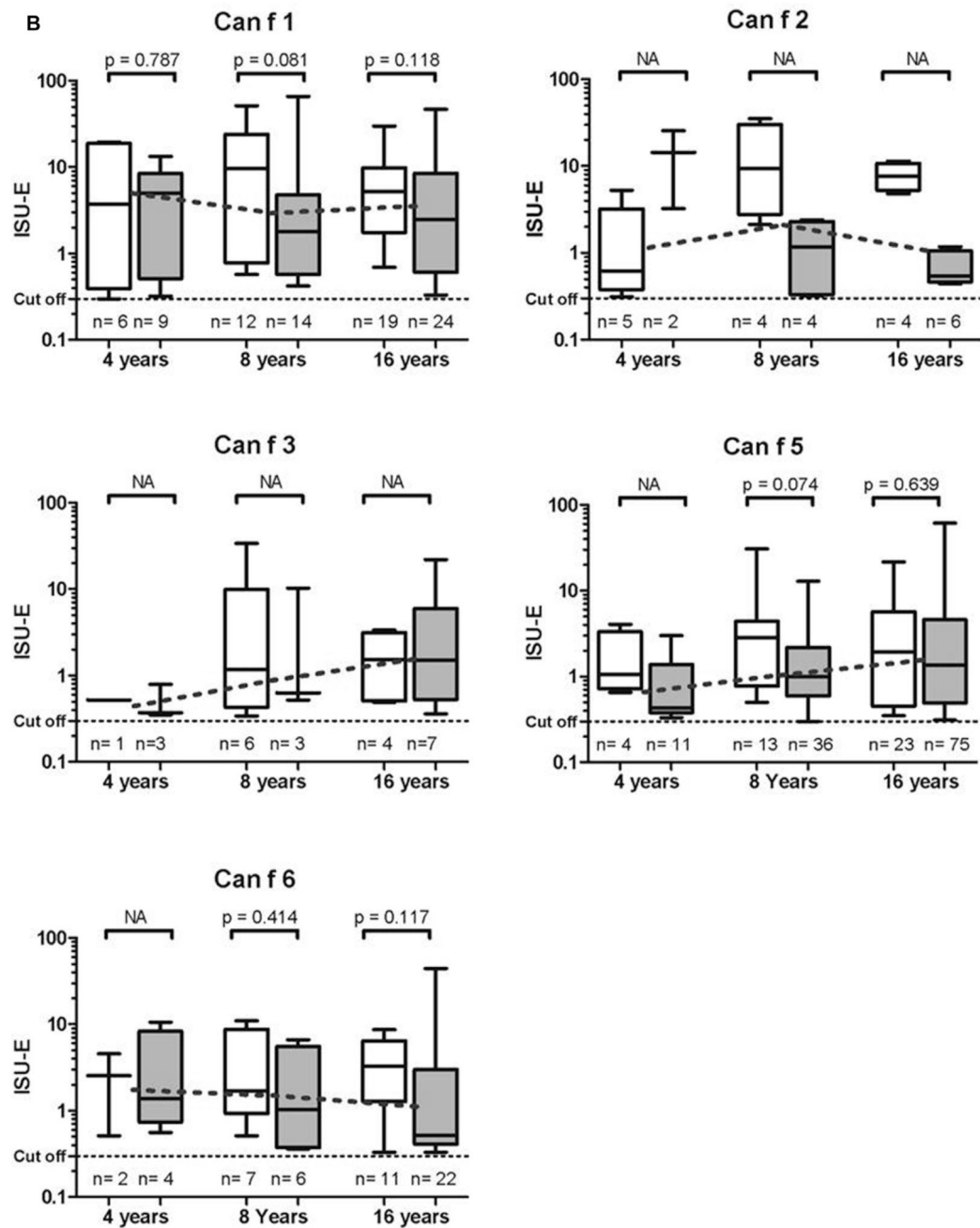


Fig 2. Allergen-specific IgE levels (> 0.3 ISU-E) to cat (A) and dog (B) allergens in children with (white box plots) or without (gray box plots) symptoms to cat, dog, or both at 4, 8, and 16 years of age. Median IgE levels per age group (connected dotted lines) and P values are indicated. n, Number of children with positive results (N = 779); NA, not applicable (subgroup number < 5 observations).

Overlap in IgE reactivity

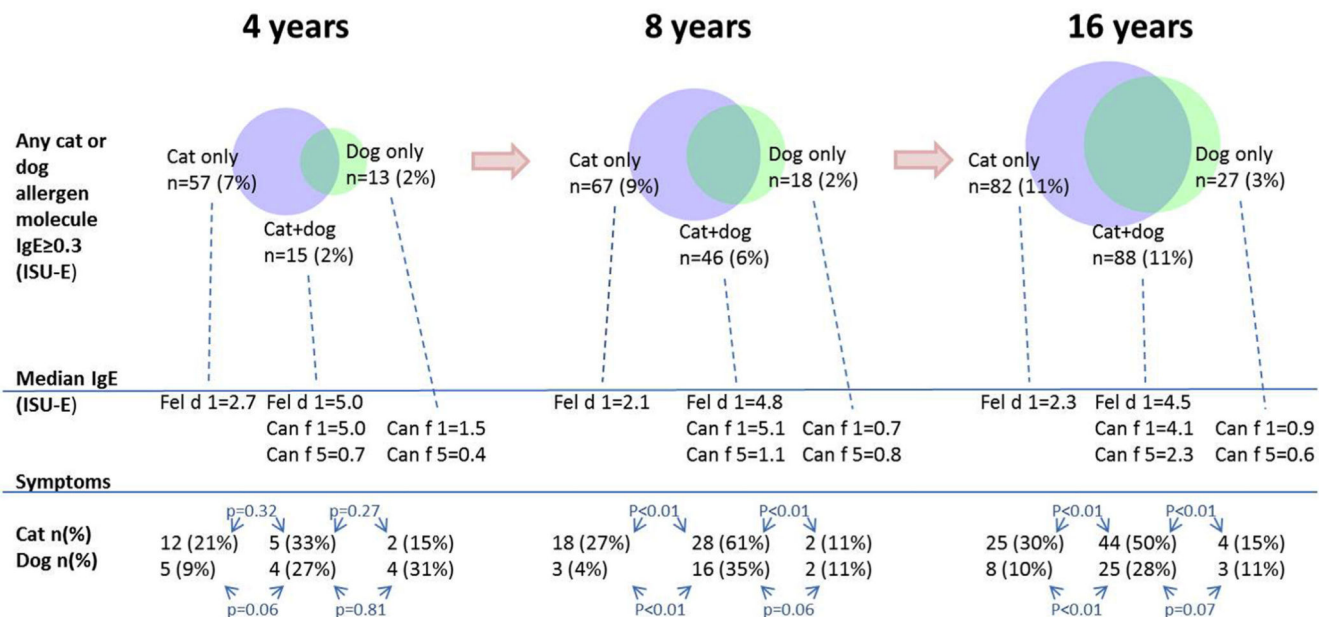


Fig 3. Overlapping IgE reactivity (≥ 0.3 ISU-E) to cat and dog allergen components and median IgE levels to Fel d 1 (cat), Can f 1 (dog), and Can f 5 (dog) at 4, 8, and 16 years of age. Cat/dog symptom prevalence in the subgroups is shown (n = 779). *Blue circles*, IgE reactivity (≥ 0.3 ISU-E) to any cat allergen component: Fel d 1, Fel d 2, or Fel d 4. *Green circles*, IgE reactivity (≥ 0.3 ISU-E) to any dog allergen component: Can f 1, Can f 2, Can f 3, Can f 5, or Can f 6.

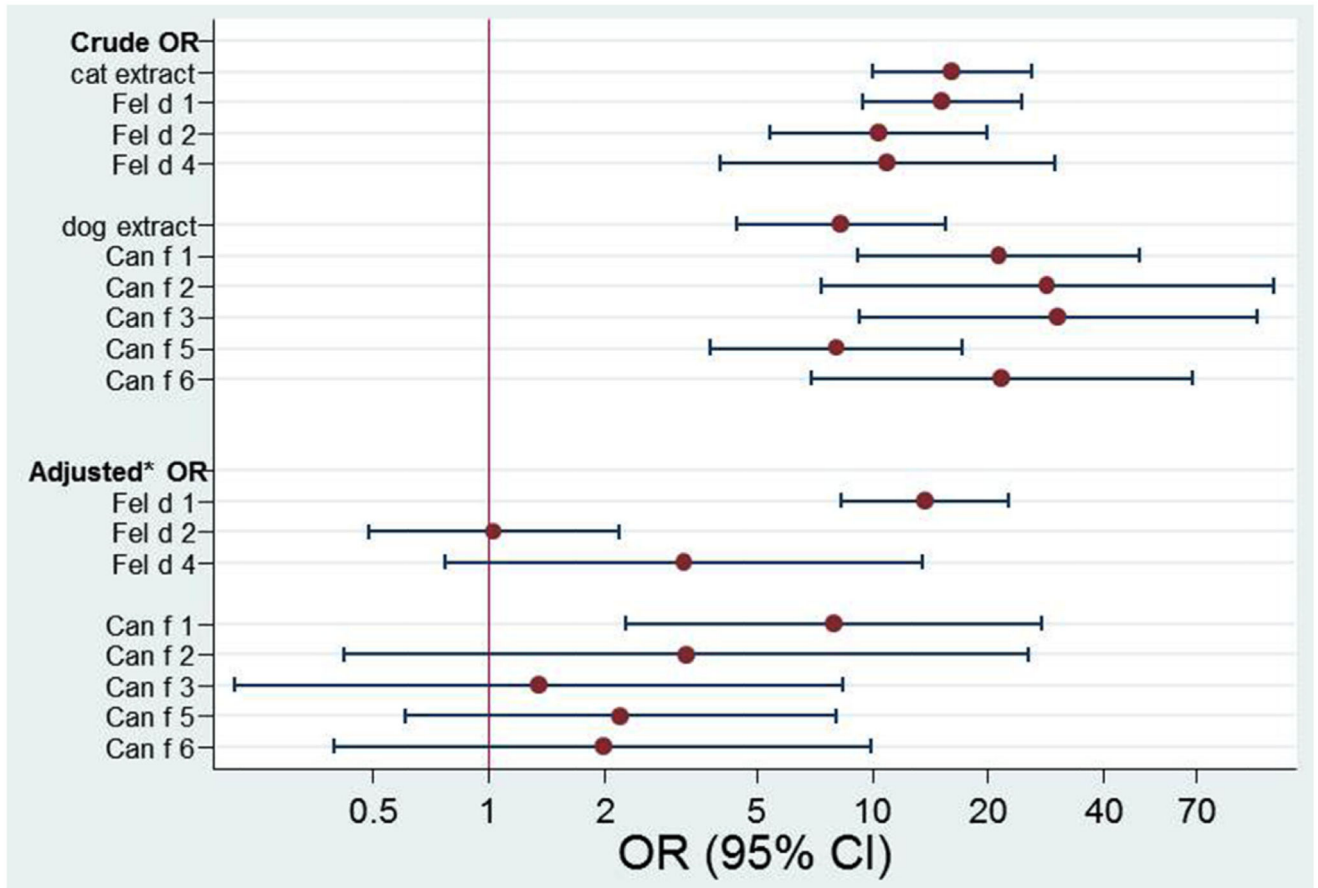


Fig 4.

Longitudinal logistic regression. Crude and adjusted ORs for IgE sensitizations to cat and dog allergen (ISU-E 0.3) at 4 and 8 years of age in relation to reported cat/dog allergy at 16 years of age (n = 779). *Adjusted for concomitant sensitization to the other cat or dog components, respectively. For sensitization matrix, see Table E5.

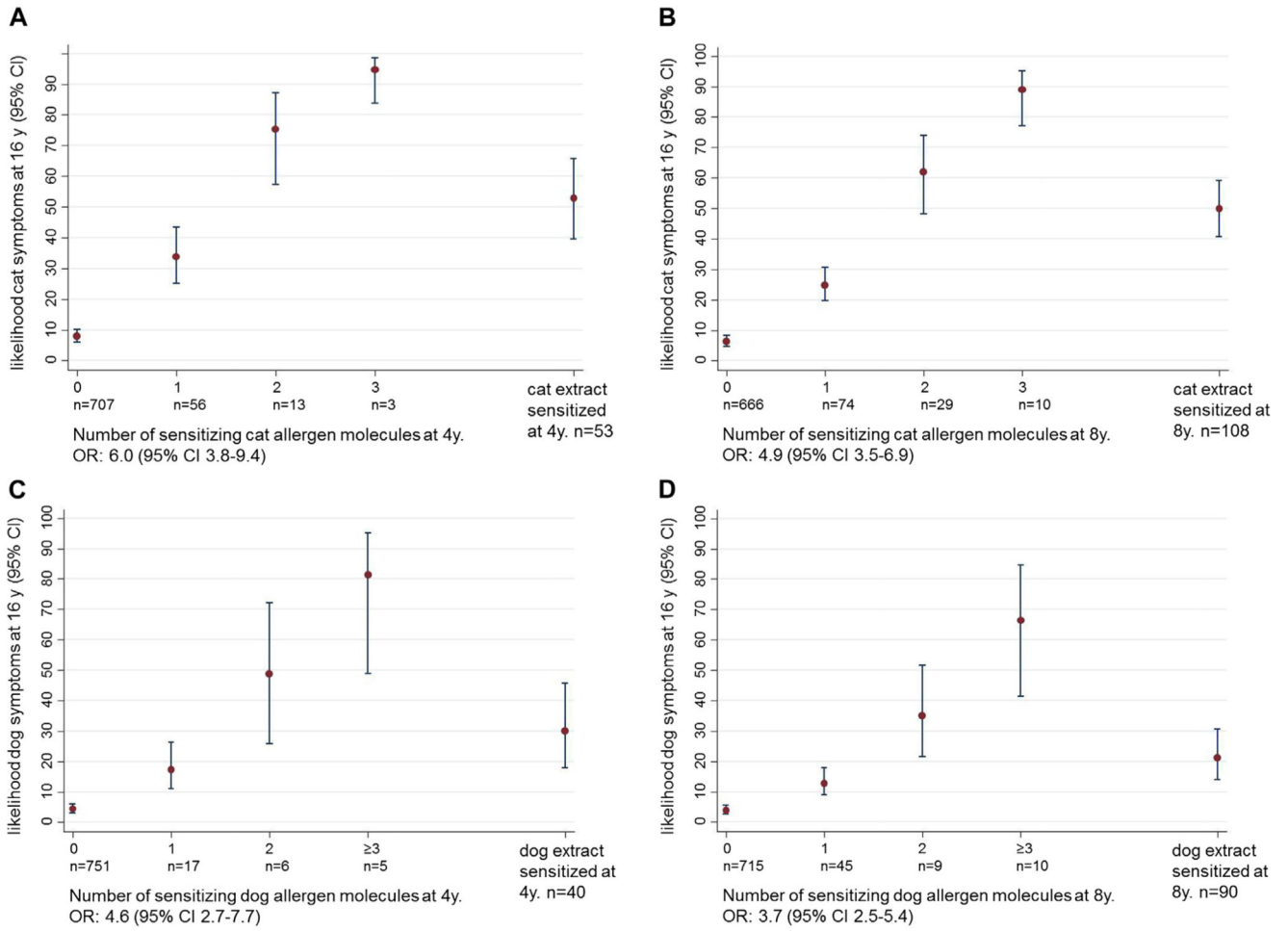


Fig 5. **A and B,** Likelihood (*y-axis*, percentage) of reporting symptoms to cat at 16 years of age depending of the number of IgE-reactive cat allergens (Fel d 1, Fel d 2, and Fel d 4) and ImmunoCAP cat extract sensitization (*x-axes*) at 4 (Fig 5, *A*) and 8 (Fig 5, *B*) years of age. **C and D,** Likelihood (*y-axis*, percentage) of reporting symptoms to dog at 16 years of age depending of the number of IgE-reactive dog allergens (Can f 1, Can f 2, Can f 3, Can f 5, and Can f 6) and ImmunoCAP dog extract sensitization (*x-axes*) at 4 (Fig 5, *C*) and 8 (Fig 5, *D*) years of age. Numbers, ORs, and 95% CIs are shown (n = 779).

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Table I
Cross-sectional PPVs: proportion of cat/dog-symptomatic children among subjects with IgE reactivity to cat/dog extract (ImmunoCAP) versus cat/dog allergen molecules (microarray; binomial exact 95% CIs; n = 779)

Cat						
Age	Cat extract	Fel d 1	Fel d 2	Fel d 4		
4 y	30.2% (18.3% to 44.3%)	25.0% (15.3% to 37.0%)	61.5% (31.6% to 86.1%)	30.0% (6.7% to 65.2%)		
8 y	41.7% (32.2% to 51.5%)	42.6% (33.1% to 52.5%)	53.8% (37.2% to 69.9%)	60.0% (32.3% to 83.7%)		
16 y	45.5% (37.4% to 53.7%)	41.8% (34.0% to 49.9%)	47.3% (33.7% to 61.2%)	52.6% (35.8% to 69.0%)		
Dog						
Age	Dog extract	Can f 1	Can f 2	Can f 3	Can f 5	Can f 6
4 y	27.5% (14.6% to 43.9%)	40.0% (16.3% to 67.7%)	71.4% (29.0% to 96.3%)	25% (0.6% to 80.6%)	26.7% (7.8% to 55.1%)	33.3% (4.3% to 77.8%)
8 y	20.0% (12.3% to 29.8%)	53.8% (33.4% to 73.4%)	50% (15.7% to 84.3%)	66.7% (29.9% to 92.5%)	25.0% (13.6% to 39.6%)	53.8% (25.1% to 80.8%)
16 y	18.5% (13.1% to 25.0%)	44.2% (29.1% to 60.1%)	40.0% (12.2% to 73.8%)	36.4% (10.9% to 69.2%)	23.5% (15.5% to 33.1%)	33.3% (18.0% to 51.8%)

Boldface values indicate significant differences (95% CIs not overlapping) compared with IgE to dog/cat extract (ImmunoCAP), respectively. NPVs varied between 91.0% (Fel d 4 at age 16 years) and 99.3% (dog extract at age 8 years).