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Analysis of allergen specific IgE cutpoints to cat and dog in the suburban Detroit Childhood Allergy Study

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INTRODUCTION

Patients often consult an allergist to determine whether symptoms are being triggered by common airborne allergens. After obtaining a detailed medical history, allergy testing is typically performed to confirm specific allergen sensitivity consistent with their clinical history. For example, when patients report nasal symptoms upon pet exposure, confirmatory tests to assess sensitization to cat or dog are often performed. Testing modalities often include skin testing, but *in vitro* evaluation of allergen-specific IgE (sIgE) levels is preferred when patients are unable to discontinue antihistamines, when widespread skin conditions are present or if preferred by the patient or clinician.[1]

Historically, *in vitro* allergen tests have been dichotomously interpreted as positive or negative, at a threshold of 0.35 kU/L sIgE; a level based primarily on the technical limitations of a first generation of sIgE assays. However, recently the precision and reliability of *in vitro* IgE detection systems have improved markedly.2 For example, the Pharmacia CAP system can reliably identify sIgE antibody levels as low as 0.1kU/L.[3] In this report, we determined the extent to which cat and dog sIgE levels lower than the traditional threshold of 0.35 kU/L, correlated with self-reported symptoms associated with exposure to these pets. The data for this analysis was systematically collected as part of an ongoing general risk birth cohort study in suburban Detroit, the Childhood Allergy Study (CAS).

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1. Conception and design of the study
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3. Analysis and interpretation of the data
4. Preparation or critical revision of the manuscript

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METHODS

Population

CAS was conducted among HMO members in metropolitan Detroit and is a general-risk birth cohort study of the natural history and environmental determinants of pediatric allergy.. All pregnant HMO members ≥18 years of age, living in a predefined geographic area, with an estimated date of confinement between April 15, 1987 and August 31, 1989, were invited to participate. Only full term infants (at least 36 weeks gestation) were included. Therefore, recruitment was based on common characteristics including HMO membership, delivery date, and geographic location.

Of the 1194 eligible subjects, 953 women provided written consent to participate. Infants from 106 women were not further enrolled because their cord blood was not obtained. Of the remaining 847 infants, six had cord blood considered contaminated by maternal blood and six more were ineligible at subsequent review of entry criteria. Mothers of the remaining 835 children were asked to complete interviews annually through age 6–7 years when children were invited to complete a clinic visit. In May 2005, the oldest children reached 18 years of age. After their 18th birthday, children and their parents were contacted to obtain information on allergy symptoms, asthma, and other health and exposure histories through telephone interviews. Teens and parents were then invited to provide blood samples for measurement of total and specific IgE, including IgE to cat and dog allergen. There were no exclusions for blood collection, such as concurrent medication use or viral illness, and samples were collected throughout the year at the convenience of participants. Teens and parents did not have their blood drawn on the same day as the interview. All aspects of this research were approved by the institutional human subjects boards of review of all participating institutions.

Symptoms

Participating CAS teens and their parents were asked at the teen's 18 year visit whether they ever developed any of the following symptoms upon exposure to cats or dogs: 1. cough, 2. wheeze, 3. chest tightness, 4. shortness of breath, 5. runny/stuffy nose or sneezing, 6. itchy or watery eyes, or 7. hives/itchy red bumps on the skin.

Based on the seven symptoms above, subjects were initially classified, *a priori*, into four categories (as symptoms ever being present or absent in relation to cat or dog exposure):

- **a.** Any pet-related (cat or dog) symptom report ("yes" to any of the seven symptoms)
- **b.** Pet-related rhinoconjunctivitis symptoms ("yes" to #5 and/or #6)
- **c.** Pet related lower respiratory or asthma symptoms ("yes" to at least one of: #1, 2, 3, 4)
- **d.** Pet related skin symptom ("yes" to #7)

sIgE Assessment

Venous blood was collected for assessment of sIgE, and stored at −80°C until assayed. Measurements of sIgE were performed following the standard manufacturer's protocols using the Phadia UniCAP system (Phadia AB U.S., Portage, MI). Allergen-specific IgE was analyzed for dog and cat as well as a battery of other allergens. One percent of all assays were repeated in a different assay run on a different day to provide estimates of interassay reliability. The geometric mean coefficient of inter-assay variation was 5.9% for all 6 allergens.

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Analysis

We created ROC curves[4] to evaluate the predictive ability of cat-, and separately, dog-sIgE levels in relationship to the gold standard of patient report of symptoms when around cat(s)/ dog(s).

The curve was constructed by using each unique value of the predictor variable, in our case, pet-sIgE as a possible cutpoint, calculating the corresponding sensitivity and specificity based on that cutpoint, and then plotting sensitivity versus 1 – specificity. Using the ROC analysis, we selected the optimal cutpoint by using the value that maximized the sum of sensitivity plus specificity. This is equivalent to using the Youden's J index.[5] We compared the sensitivity and specificity for the selected cutpoint to the traditional threshold value of 0.35 using McNemar's test.

We present the positive (PPV) and negative predictive value (NPV) for descriptive purposes. These should be interpreted with care as they depend directly on the prevalence of the disease (symptoms in our case). Individuals were categorized as "misclassified" if either they had a sIgE greater than or equal to the corresponding cutpoint and had no symptoms or conversely, if they had symptoms but their specific IgE was less than the selected IgE cutpoint.

Three separate, but not independent, samples for analysis: teen (N=564), mother (N=470) and father (N=364) are included. We decided *a priori* to use these samples as separate analysis datasets and selected the teen data as the sample in which to determine the optimal cutpoints (sometimes called the training sample). The teen sample was selected for two reasons: 1) the teens were the primary focus of the research and, 2) they provided the largest sample size. After the analyses were completed for each symptom group among the teens, the mother and father datasets were used for validation.

RESULTS

Five hundred and sixty four teenagers were interviewed about symptoms that occurred concomitantly with pet exposure. Of these, 29.6% (95% Confidence Interval = CI, 25.9–33.6) reported having any symptoms around cats, while 11.3% (95% CI, 8.9–14.3) reported asthma symptoms around cats, and 4.3% (95% CI, 2.7–6.3) reported skin symptoms around cats (Table 1). Only one teen reported rhinoconjunctivitis symptoms that had not already been classified as being in the "any" symptom category around cat, therefore, the rhinoconjunctivitis symptom classification was not meaningfully different from the any symptom category and we thus excluded that classification group from further analysis. (Tables illustrating data specific for respiratory versus cutaneous symptoms can be viewed on the online supplement).

Of the 564 teenagers surveyed, 14.5% (95% CI, 11.7–17.7) reported any symptoms around dogs, while 5.7% (95% CI, 3.9–7.9) reported asthma symptoms around dogs, and 3.4% (95% CI, 2.0 – 5.2) reported skin symptoms around dogs (Table 1). Similarly, only 9 teens reported rhinoconjunctivitis symptoms that had not already been classified as having any symptom around dogs, so again, that classification group was excluded from dog analyses. Table 1 also shows prevalence data for the mothers (n = 470) and fathers (n = 346).

Table 2 summarizes results of the ROC analysis using cat sIgE level as a predictor of any of the 7 previously mentioned symptom categories when exposed to cat. The optimal cutpoint, as selected by the Youden's J index (the sum of the sensitivity and specificity) in the teen data was 0.12 kU/L. As expected, there was greater sensitivity for the 0.12kU/L cutpoint of 63.5 (95% CI, 55.7–70.8), which was statistically higher than the sensitivity for the

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traditional 0.35kU/L cutpoint of 49.1 (95% CI, 41.3–56.9, P<0.01). The "trade-off" for this higher sensitivity was the requisite lower specificity for the 0.12kU/L cutpoint of 85.9 (95%CI, 82.1–89.2) compared to 91.9% (88.8–91.4, P<0.01) for the 0.35kU/L cutpoint. The misclassification rates were identical, again reflecting the inherent inverse relationship between sensitivity and specificity.

Table 3 shows similar results when dog-sIgE was analyzed among the teen population. In this case, an optimal cutpoint of 0.20kU/L was selected using Youden's J index. Notably, the sensitivity of sIgE was lower for dogs in comparison to cats across each sIgE cutoff level.

In general, the parental validation population analyses for both cat and dog mirrored that of the teens with the sensitivity of any sIgE level being lower in the maternal analysis when compared to teens or fathers (Tables 2 and 3). For example, regarding cat-related symptoms, the sensitivity at the 0.12kU/L cutpoint [55% (45.7–64.1%)] compared favorably to the 0.35kU/L level [38.3% (9.6–47.6%)], as did the sum of sensitivity and specificity among the maternal validation population. A similar pattern was also seen among fathers providing evidence of replication of the lower cutpoints in the two validation populations (Table 2).

The parental validation results for the 0.2 kU/L sIgE cutpoint for dog-related symptoms among teens showed a similar overall pattern of relative performance. However, in fathers, a slightly higher Youden's J index was observed at the traditional 0.35 kU/L compared to the 0.2 kU/L level, although the difference was minimal (Table 3).

DISCUSSION

To our knowledge this is the first paper to report the performance characteristics of allergen specific IgE levels between 0.1 and 0.35 kU/L in a general risk population. Our data suggest that dog and cat allergen sIgE levels, when applied below the traditional cutoff value of 0.35 kU/L are related to self-reported symptoms consistent with clinical allergy and yield performance characteristics similar to or slightly better than the traditionally accepted threshold. Accepting somewhat lower, yet reliably detected IgE levels than traditionally relied upon as evidence of allergen sensitization has direct practical implications regarding patient management. Clinicians often evaluate patients who relate convincing histories consistent with allergy when exposed to easily identifiable allergens, such as pets. However, on occasion, confirmatory testing for sensitization, such as skin prick tests (SPT) or *in vitro* testing (using the traditional threshold of 0.35 kU/L) are negative and the clinician may incorrectly conclude that allergen-specific management strategies such as avoidance or allergen desensitization are irrelevant and not discuss these potentially beneficial intervention options. For instance, patients with a strong clinical history of cat allergy yet negative skin testing may have detectable specific IgE lower than the traditional threshold. Our data imply that it is likely that some of these patients have symptoms that are truly triggered by cat exposure and may benefit from removal of cats from the environment or desensitization either with cat extract alone or as a component of multiallergen immunotherapy.

Our data should not be interpreted as promoting the concept that low-levels of IgE should be used indiscriminately or in isolation to diagnose "allergy." We view our results as primarily an opportunity to discuss how it may be possible to refine and potentially improve individual patient management based on a suggestive clinical history taken in the context of a situation where confirmatory allergen testing has known limitations. Experts that have closely analyzed the performance characteristics of allergen-specific IgE tests, even at relatively high levels, continue to caution that "the most prudent use of a positive specific

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IgE antibody result is as a risk factor for allergic disease and not as a definitive indicator of the presence of allergic disease."[2] In fact, it is clear that higher levels of allergen specific IgE are more likely to be associated with clinical manifestations of allergy.[6, 7] However, this does not mean that the presence of low-level IgE should be ignored as evidence of sensitization, especially in the context of a strong clinical history. We believe these data support the contention that any level of reliably detected allergen-specific IgE, in the context of a suggestive history, may indicate "true" sensitization. The degree to which these low levels of IgE are likely to be linked to allergen-triggered symptoms in an individual patient can best be determined by clinicians who can link the test result with the strength of the patient's history before a decision is made whether avoidance measures or possible desensitization should be recommended or considered. The definitive answer as to "when" or "whether" one can unquestionably link symptoms to allergen exposure is rarely available to the clinician since neither clinical history alone nor sensitization alone are sufficient to unequivocally diagnose allergic disorders and even when both are present, a reliable diagnosis may remain elusive.[8] Admittedly, self-reported symptom histories are subjective and as utilized in this report, may be suboptimal for defining true clinical sensitivity and specificity of *in vivo* or *in vitro* testing.[9–12] Practically, one should be willing to accept somewhat lower levels of allergen specific IgE as "confirmatory" when the clinical history is strongly suggestive. Direct allergen challenge tests would be a more suitable method for validating tests but even these tests have limitations and are not practical in many settings.[13, 14]

The 2008 ACAAI/AAAAI Diagnostic Testing Practice Parameters suggest that *in vitro* immunoassays have sensitivities averaging 70% to 75% for most allergens when compared with symptoms induced after natural or controlled organ challenge tests.[1] Studies also cite specificity ranging from 30–95%.[1,15] In the current analysis, the sensitivity at the 0.35 kU/L level is lower than this estimate with similar specificity when comparing *in vitro* sIgE testing with reported clinical symptoms. Symptom reports are clearly not equivalent to allergen challenge and the observed lower sensitivity is likely due to a number of subjects reporting symptoms that mimic allergy but would prove to be irreproducible upon allergen challenge. Similarly, the populations analyzed in allergen challenge studies are likely to differ from our population where symptom reports may relate to clinical conditions that would not be of sufficient impact to prompt evaluation or consideration for allergen challenge. However, the interview data we collected regarding symptoms of pet allergy is similar to the information that would be collected by clinicians in daily practice. However, in practice the timing and recency of symptoms with pet exposure and sIgE measurement would likely be closely correlated.

In vitro tests must discriminate low allergen sIgE levels from nonspecific background binding. Standardization of IgE antibody assays should take into account the quality and performance of the reagents, reproducibility of the test results, and the clinical sensitivity and specificity documented on routine samples.2,[16] Technology has improved remarkably over the years from the initial RAST, to the current state-of-the-art quantitative third generation assays (Turbo RAST, Immulite, and ImmunoCAP).[17–19]

However, even among these advanced technologies, there is variability in their ability to detect IgE at the 0.35 kU/L level.[20] In the present analysis we used ImmunoCAP, which has a reported limit of detection of <0.1 kU/L for 95% of included allergens.[3] Our data suggest that consideration be given to accepting a lower detectable level of sIgE as evidence of sensitization when the relationship is clearly suggested by history.

To some extent, consideration of low sIgE levels is analogous to the use of intradermal skin testing (IDST) when a clinical history of airborne allergen sensitization is suggestive but the

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results of epicutaneous skin prick tests (SPT) are negative or equivocal. It is accepted that the IDST is more sensitive than the SPT.[1,14, 21, 22] In a recent editorial, Oppenheimer addresses the question of differentiating a true-positive from a false-positive IDST and emphasizes the importance of interpreting this test in the context of clinical history while recognizing the difficulty allergists face in interpreting the meaning of a positive IDST paired with a negative SPT.[14] In fact, IDST, with inherently lower specificity compared to prick testing, is recommended when the overall intent of the evaluation is to maximize sensitivity, such as in anaphylaxis to medications or stinging insects.[23,24] Similar to IDST, perhaps the higher level of sensitivity afforded by using lower-than-traditional specific IgE levels could also be helpful in the context of supporting recommendations for a diagnostic or therapeutic trial away from suspected high-level workplace allergen exposure.

There are several limitations to our study. Self-reported symptoms in response to an interviewer's directed questions regarding pet-related symptoms may lead to different rates of reporting in comparison to an evaluation in a clinician's office where a patient has sought evaluation. Population-based samples likely elicit a less biased distribution of a history of symptoms since it is not based on a patient-prompted office visit. However, the last date of a symptom-pet exposure episode was not collected; thus a gap in time between such an episode and sIgE measurement is not known. Provocative challenge to cat or dog would have been preferable for confirming clinical hypersensitivity and as the standard to evaluate IgE test performance. Also, skin prick or intradermal testing would have been useful to evaluate in conjunction with the clinical histories and *in vitro* testing. In addition, the study population was not diverse with regards to geographic location, age group or ethnicity, which may impact whether these results are reflective of the general population. Finally, we chose to analyze clinical and laboratory data related to only two allergens, dog and cat. Typically, patients are aware of times when they are exposed to these pets and therefore, they can more accurately link allergen exposure to symptom onset. It is likely that different allergens would yield different test performance characteristics in terms of best-performing threshold values and their strength of association with clinical symptoms.

In conclusion, we may need to reevaluate a dichotomous view of sIgE cutpoints. In our opinion, it may be appropriate to accept that any reliably detected level of allergen specific IgE, even those somewhat below those traditionally used in clinical practice, may indicate sensitization. Therefore, when the clinical history is strongly suggestive of clinical allergy to a specific allergen, these lower levels of allergen specific IgE may be appropriate to use as a criterion to guide individual patient management decisions that rely on allergen identification including specific allergen avoidance strategies or consideration of allergen immunotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Prevalence of symptoms when exposed to pets

	Teen (n =564)	Mother (n=470)	Father (n=346)
	% of patients (95% CI) Number of patients	% of patients (95% CI) Number of patients	% of patients (95% CI) Number of patients
Subjects reporting symptoms related to cat exposure			
Any symptoms	29.6 (25.9-33.6) N = 167	25.5 (21.6 – 29.7) N = 120	19.4 (15.3 – 23.9) N = 67
Asthma symptoms (cats)	11.3 (8.9-14.3) N=64	15.5 (12.4 – 19.1) N = 73	10.7 (7.6 – 14.4) N = 37
Skin symptoms	4.3 (2.7-6.3) N=24	6.0 (4.0 – 8.5) N= 28	2.3 (1.0 – 4.5) N = 8
Subjects reporting symptoms related to dog exposure			
Any symptoms	14.5 (11.7-17.7) N=82	12.3 (9.5 – 15.7) N = 58	8.1 (5.4 – 11.5) N = 28
Asthma symptoms	5.7 (3.9-7.9) N=32	8.5 (6.1 – 11.4) N = 40	4.6 (2.7 – 7.4) N = 16
Skin symptoms	3.4 (2.0-5.2) N=19	3.4 (2.0 – 5.5) N = 16	1.7 (0.6 – 3.7) N = 6

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Table 2

Cat specific IgE levels and prediction of any symptom when exposed to cats

IgE Cutoff (kU/L)	Sensitivity Rate (95% CI)	Specificity Rate (95% CI)	Sum of Sensitivity + Specificity	PPV	NPV	Percent Misclassified
Teen Sample (N=564)						
0.12	63.5 (55.7-70.8)	85.9 (82.1-89.2)	149.4	65.4 (57.6-72.7)	84.8 (80.9-88.2)	20.7 (17.5-24.3)
0.35	49.1 (41.3-56.9)	91.9 (88.8-94.4)	141	71.9 (62.7-79.9)	81.1 (77.2-84.6)	20.7 (17.5-24.3)
	**	**				
Mothers (N=470)						
0.12	55.0 (45.7-64.1)	87.4 (83.5-90.7)	142.4	60.0 (50.2-69.2)	85.0 (80.9-88.5)	20.9 (17.3-24.8)
0.35	38.3 (29.6-47.6)	92.9 (89.6-95.3)	131.2	64.8 (52.5-75.8)	81.5 (77.3-85.1)	21.1 (17.5-25.0)
	**	**				
Fathers (N=346)						
0.12	68.7 (56.2-79.4)	87.1 (82.6-90.8)	155.8	56.1 (44.7-67.0)	92.0 (88.1-95.0)	16.5 (12.7-20.8)
0.35	52.2 (39.7-64.6)	93.2 (89.6-95.9)	145.4	64.8 (50.6-77.3)	89.0 (84.9-92.4)	14.7 (11.2-18.9)
	**	**				

** $p<0.01$ comparing 0.12kU/L to 0.35kU/L sIgE levels

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Table 3

Dog specific IgE levels and prediction of any symptom when exposed to dogs

IgE Cutoff (kU/L)	Sensitivity Rate (95% CI)	Specificity Rate (95% CI)	Sum of Sensitivity + Specificity	PPV	NPV	Percent Misclassified
Teen Sample (N=564)						
0.20	56.1 (44.7-67.0)	79.5 (75.6-83.0)	135.6	31.7 (24.3-40.0)	91.4 (88.3-93.9)	23.9 (20.5-27.7)
0.35	41.5 (30.7-52.9)	86.1 (82.7-89.1)	127.6	33.7 (24.6-43.8)	89.6 (86.5-92.3)	20.4 (17.1-24.0)
	**	**				
Mothers (N=470)						
0.20	46.6 (33.3-60.1)	87.6 (84.0-90.6)	134.2	34.6 (24.2-46.2)	92.1 (89.0-94.6)	17.4 (14.1-21.2)
0.35	39.7 (27.0-53.4)	93.0 (90.0-95.2)	132.7	44.2 (30.5-58.7)	91.6 (88.5-94.1)	13.6 (10.6-17.1)
	*	**				
Fathers (N=346)						
0.20	53.6 (33.9-72.5)	84.3 (79.8-88.1)	137.9	23.1 (13.5-35.2)	95.4 (92.2-97.5)	18.2 (14.3-22.7)
0.35	50.0 (30.6-69.4)	89.0 (85.0-92.2)	139	28.6 (16.6-43.3)	95.3 (92.2-97.4)	14.2 (10.7-18.3)
	p = 0.32	**				

* p<0.05 in comparing 0.20vkU/L to 0.35kU/L sIgE levels

** p<0.01 comparing 0.20 kU/L to 0.35kU/L sIgE levels