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Allergy-related outcomes in relation to serum IgE: Results from the National Health and Nutrition Examination Survey 2005–2006

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Abstract

Background—The National Health and Nutrition Examination Survey (NHANES) 2005–2006 was the first population-based study to investigate levels of serum total and allergen-specific immunoglobulin E (IgE) in the general US population.

Objective—We estimated prevalence of allergy-related outcomes and examined relationships between serum IgE levels and these outcomes in a representative sample of the US population.

Methods—Data for this cross-sectional analysis were obtained from the NHANES 2005–2006. Study subjects aged 6 years and older (N=8086) had blood taken for measurement of total IgE and 19 specific IgEs against common aeroallergens, including *Alternaria alternata*, *Aspergillus fumigatus*, Bermuda grass, birch, oak, ragweed, Russian thistle, rye grass, cat dander, cockroach, dog dander, dust mite (*Dermatophagoides farinae* and *D. pteronyssinus*), mouse and rat urine proteins; and selected foods (egg white, cow's milk, peanut, and shrimp). Serum samples were analyzed for total and allergen-specific IgEs using the Pharmacia CAP System. Information on allergy-related outcomes and demographics was collected by questionnaire.

Results—In the NHANES 2005–2006, 6.6% reported current hay fever and 23.5% suffered from current allergies. Allergy-related outcomes increased with increasing total IgE (adjusted ORs for a 10-fold increase in total IgE =1.86, 95% CI:1.44–2.41 for hay fever and 1.64, 95% CI: 1.41–1.91 for allergies). Elevated levels of plant-, pet-, and mold-specific IgEs contributed independently to allergy-related symptoms. The greatest increase in odds was observed for hay fever and plant-specific IgEs (adjusted OR=4.75, 95% CI:3.83–5.88).

Conclusion—In the US population, self-reported allergy symptoms are most consistently associated with elevated levels of plant-, pet-, and mold-specific IgEs.

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Clinical implications: Allergy-related outcomes are most strongly associated with elevated levels of plant-, pet-, and mold-specific IgEs. Although increases in total IgE may contribute independently to allergy-related outcomes, the magnitude of the effect is small.

Keywords

allergen; allergy; allergic sensitization; serum IgE

INTRODUCTION

Allergic sensitization and disease are common among the US population. Over half of the population is estimated to be atopic, and millions of Americans suffer from allergic disease; more than 50 million people are affected by asthma and hay fever alone.^{1–5}

While the public health significance of asthma is well recognized,⁶ economic and social burden of allergic diseases is not limited to asthma. Many allergic conditions carry considerable direct and indirect cost implications and substantially affect quality of life.^{7, 8} In the United States, for example, health care and treatment expenditures for allergic rhinitis have almost doubled from the year 2000 (\$6.1 billion) to the year 2005 (\$11.2 billion).⁹ It has been estimated that allergic rhinitis results in 3.5 million lost work days and 2 million lost school days annually.⁷ Despite the increasing morbidity of allergic conditions, allergy-related outcomes other than asthma have been less well characterized in population-based studies.

The National Health and Nutrition Examination Survey (NHANES), which is a major survey program of National Center for Health Statistics, included a new allergy-focused component in the 2005–2006 survey cycle. As part of the new Allergy Component, total immunoglobulin E (IgE) and specific IgEs to a panel of 19 allergens were measured in the survey participants. The NHANES 2005–2006 was the first population-based study to assess serum IgE levels specific to a wide variety of indoor, outdoor and food allergens in the general US population. Although skin test results from previous NHANES surveys have been published, none of the previous surveys have examined this many allergens across a broad age range. In fact, the NHANES 2005–2006 is the first study that enables both qualitative and a quantitative examination of population-level associations between allergic conditions and sensitization. Using the NHANES 2005–2006 data, we estimated the prevalence of allergy-related outcomes (other than asthma), and examined associations between these outcomes and levels of total and allergen-specific IgEs in a nationally representative sample of the US population. The objective of this report is to provide insight on the importance of sensitization patterns in common allergic conditions; this is the first population-based study to use quantitative data analysis and to account for clustering of allergen-specific IgEs.

METHODS

Study population

Data for this cross-sectional analysis were obtained from the NHANES 2005–2006, a national survey designed to assess the health and nutritional status of adults and children in the US. The NHANES used a complex, multistage design to sample the civilian, non-institutionalized US population. To ensure adequate sample sizes of certain subgroups of the population, the NHANES 2005–2006 oversampled persons of low-income, adolescents (12–19 years), elderly individuals (≥ 60 years of age), African Americans, and Mexican Americans among others. All study subjects who completed the household interview were also invited to participate in the Health Examination Component that was conducted in the Mobile Examination Center. Because examinees less than 6 years of age did not have a complete panel of allergen-specific IgE tests, we limited the study population to participants aged 6 years and older who were examined in the Mobile Examination Center (N=8086). Of

these 8086 participants who were eligible for IgE testing, 7398 (91.5%) had serum total IgE measurements available and 7268 (89.9%) had data available for all 19 allergen-specific IgEs. The NHANES 2005–2006 was approved by the NCHS Research Ethics Review Board,¹⁰ and all participants provided written informed consent. Detailed description of the survey design and implementation of NHANES 2005–2006 can be found online at <http://www.cdc.gov/nchs/nhanes.htm>.¹¹

Assessment of allergy-related outcomes

The allergy questionnaire, a part of the new Allergy Component added to the NHANES 2005–2006, obtained information on allergy-related outcomes, including diagnosis of allergic diseases, recent symptoms, and co-morbidities (e.g., asthma, sinus infections). We chose 2 primary outcomes for the analysis: current allergies and current hay fever. Current allergies were ascertained with positive responses to the following two questions: 1) *Has a doctor or other health professional ever told you that you have allergies?* and 2) *During the past 12 months, have you had any allergy symptoms or allergy attack?* Correspondingly, participants who had current hay fever responded in the affirmative to the following two questions: 1) *Has a doctor or other health professional ever told you that you have hay fever?* and 2) *During the past 12 months, have you had an episode of hay fever?* To reduce potential selection bias, we included an outcome that was not based on physician's diagnosis (i.e., current rhinitis) for additional analysis. Questions on sneezing and nasal symptoms (e.g., *During the past 12 months, have you had a problem with sneezing, or a runny, or blocked nose when you did not have a cold or the flu?*) were used to obtain information on current rhinitis symptoms. All outcomes were based on self-report; an adult family member provided information for study participants younger than 16 years of age.

Measurement of serum total and allergen-specific IgE antibodies

Participants aged 6 years and older were tested for total IgE and 19 allergen-specific IgE antibodies by using the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, Michigan). Specific IgE levels were measured against 15 aeroallergens [*Alternaria alternata*, *Aspergillus fumigatus*, Bermuda grass (*Cynodon dactylon*), birch (*Betula verrucosa*), cat dander, cockroach (*Blattella germanica*), dog dander, dust mite (*Dermatophagoides farinae* and *D. pteronyssinus*), mouse urine proteins, oak (*Quercus alba*), ragweed (*Ambrosia elatior*), rat urine proteins, Russian thistle (*Salsola kali*), rye grass (*Lolium perenne*)] and 4 food allergens [egg white, cow's milk, peanut (*Arachis hypogaea*), shrimp (*Pandalus borealis*)]. The lower limit of detection (LLOD) was 2.00 kU/L for total IgE and 0.35 kU/L for each of the allergen-specific IgEs. For samples below the detection limit, NHANES reported fill values equal to the LLOD divided by the square root of 2. The upper limit of detection (ULOD) for the allergen-specific IgE assays was 1000 kU/L. Samples that exceeded the ULOD, were assigned a value of 1000 kU/L. None of the samples exceeded the upper limit of detection of the total IgE (50 000 kU/L). Details of the laboratory methods and quality control procedures can be found elsewhere.¹²

Other study measures

In the analysis, we considered age, sex, race/ethnicity, socioeconomic status (education at household level, poverty index), serum cotinine level, and body mass index as potential confounders. The socio-demographic data were based on self-report.

Statistical analysis

All analyses were performed with R version 2.11.1, and figures were constructed using the R lattice package. The R survey package (version 3.22-3) was used to account the complex sample design of NHANES, the sampling weights (WTMEC2YR) and design variables

(SDMVSTRA; SDMVPSU) were applied to all analyses. The total and allergen-specific serum IgEs were logarithmically transformed for the statistical analysis because of skewed distributions. We used F-statistics to test differences in geometric mean concentrations of total serum IgE across population characteristics, and χ^2 -statistics to test differences in prevalences of allergy-related outcomes across the population characteristic categories.

For descriptive purposes, we estimated the prevalence of allergen-specific sensitization in the study population. To evaluate associations between allergy-related outcomes and IgE (total and allergen-specific IgEs), we used logistic regression to calculate odds ratios with 95% confidence intervals. For total IgE, we examined whether the association was modified by age, gender, or race/ethnicity. When assessing racial/ethnic interactions, we excluded the group 'others' from the analysis because of racial/ethnic heterogeneity in this group. For main effects, statistical significance was established at .05, and a *P* value of less than .10 was considered evidence of interaction. All odds ratios presented here were adjusted for socio-demographic factors. We did not adjust for allergen-specific IgEs individually, because our earlier work demonstrated that the allergen-specific IgEs group into clusters that share similarities in biological and statistical properties.¹³ Using different statistical methodologies, including hierarchical clustering, factor analysis, and multidimensional scaling, we identified 7 IgE clusters. To avoid problems of collinearity, we calculated odds ratios and 95% confidence intervals for each of the identified IgE clusters: 1) plants (grass-, tree-, weed-, and peanut-specific IgEs); 2) dust mites (*D. farinae* and *D. pteronyssinus*); 3) pets (dog and cat); 4) cockroach and shrimp; 5) rodents (mouse and rat); 6) molds (*Alternaria* and *Aspergillus*); and 7) foods (egg white, cow's milk), mutually adjusting for the presence of the other clusters. Finally, we investigated the independent effects of total IgE and specific IgEs by modeling them together.

RESULTS

In the NHANES 2005–2006, prevalence of diagnosed hay fever was 11.3%, and 6.6% reported current hay fever. One-third of the participants (33.9%) had diagnosed allergies, and 23.5% suffered from current allergies. The weighted characteristics of the study population are presented in Table I. The prevalence of the primary outcomes (current hay fever, current allergies) varied significantly by socio-demographic variables (Table I). The prevalence increased with age until it peaked in the fourth decade of life, and thereafter declined. Both current hay fever and current allergies were more commonly reported by women than by men, by non-Hispanic whites than by other racial/ethnic groups, and by highly educated and wealthier individuals than by less educated and less affluent study participants. The prevalence of the primary outcomes was inversely associated with levels of serum cotinine, and increased with increasing body mass index.

Current rhinitis symptoms, including sneezing and/or nasal symptoms in the absence of a cold or the flu, were reported by approximately one-third of the population; 24.2% reported seasonal symptoms in the past 12 months, whereas 10.0% had symptoms year round (perennial symptoms). As expected, the prevalence of sneezing and nasal symptoms was significantly higher among those who reported current hay fever or who had current allergies than among those who did not report these outcomes (84.6% vs. 30.5%; 76.8% vs. 20.9%, respectively; *P* < .01 for difference). Almost two-thirds (61.2%) of those who reported current rhinitis symptoms had diagnosed allergies. Among hay fever sufferers, rhinitis symptoms were mainly seasonal in nature (i.e., occurring 1–3 seasons); 60.6% of those who had current hay fever reported seasonal symptoms of rhinitis.

Almost half of the total population (43.7%) had detectable levels of specific IgE to at least one of the tested allergens (Table I). The prevalence of allergic sensitization was

significantly higher for those who reported current hay fever or current allergies (74.4% for current hay fever, 57.9% for current allergies). Correspondingly, at least half (52.7%) of the individuals who reported current rhinitis symptoms had detectable levels of specific IgEs to at least one allergen. The majority of the individuals who had detectable levels of specific IgEs were poly-sensitized; less than one-fourth of the sensitized subjects (21.6%) were mono-sensitized (Table I).

Figures 1 and 2 illustrate the prevalence of sensitization in the US population among those with and without current hay fever and current allergies. Hay fever and allergy sufferers were most often sensitized to grass and other plant-related allergens. For example, almost half (44.2%) of those who had current hay fever were sensitized to rye grass (Figure 1), and 60.1% had detectable levels of allergen-specific IgEs at least for one of the plant allergens (Figure 2). Sensitization to rodent allergens was least common; 3.1% of those who reported allergy-related outcomes were sensitized to rodent allergens. While the prevalence of sensitization tended to be higher in children, especially for pet- and mold-specific IgEs, the sensitization patterns between the age groups did not differ appreciably (Figure E1 in Online Repository).

To further characterize the associations between the primary outcomes and specific IgEs, we modeled specific IgE concentrations as continuous variables. Figures 3 and 4 show unadjusted and adjusted odds ratios for the associations between the allergy-related outcomes and allergen-specific IgEs and IgE clusters. The adjusted odds ratios for the outcomes correspond to a 10-fold increase in specific IgE concentrations. After adjusting for potential confounders (socio-demographic variables and other IgE clusters), increases in plant-, pet-, and mold-specific IgEs were most consistently associated with allergy-related outcomes (Figure 4). We did not find strong evidence for effect modification by age. The patterns of the associations were similar among children and adults, except for food-specific IgEs (data not shown). Detailed information on patterns of food allergy is published elsewhere.¹⁴ Current hay fever, as expected, was most strongly associated with increased levels of plant-specific IgEs (adjusted OR = 4.75 95% CI: 3.83–5.88).

Sensitization patterns for current rhinitis symptoms (Figure E2) were comparable to those with current hay fever and current allergies. The odds of having perennial symptoms of rhinitis increased most with elevated levels of pet-specific IgEs (adjusted OR = 2.56, 95% CI: 1.73–3.79). Seasonal symptoms were associated with elevated levels of plant-, pet- and mold-specific IgEs, most strongly with plant-specific IgEs (adjusted OR = 2.35, 95% CI: 1.71–3.22).

Regardless whether allergen-specific IgE was modeled as a continuous or as a dichotomous (data not shown) variable, the results did not change appreciably; presence of plant-, pet-, mold-specific IgEs remained most consistently associated with the studied outcomes.

Total IgE levels varied significantly across socio-demographic variables (Table I). A detailed description of the distribution of total IgE in the NHANES 2005–2006 can be found elsewhere.¹⁵ Table II shows unadjusted and adjusted effect estimates for the associations between the log-transformed total IgE levels and the primary outcomes, current hay fever and current allergies. Increased levels of total IgE were consistently associated with both primary outcomes. Irrespective of whether total IgE was modeled as a continuous or a dichotomized variable (cut offs: median and 100kU/L), the modeling results remained statistically significant (Table II, Table E1 in the Online Repository). The strongest associations were seen for current hay fever (adjusted OR for a ten-fold increase in total IgE = 1.86, 95% CI: 1.44–2.41). In Table II, we also present stratum-specific odds ratios for different age, gender, and race/ethnicity groups. The association between total IgE and

current allergies was stronger among children than among adults, suggesting effect modification by age for current allergies. This may reflect differences in the prevalence of co-morbid conditions between age groups. Prevalence of asthma, for example, was significantly higher among children than adults.¹⁵

We clarified the role of specific IgEs in relation to total IgE by modeling them together (Online Repository Figures E3 and E4). Although the patterns of association between the specific IgEs and IgE clusters and the primary allergic outcomes remained similar after adjusting for total IgE levels, the odds ratios were apt to attenuate (compare Figure 3 to Figure E3, Figure 4 to Figure E4). Increases in total IgE had a small but independent effect on the primary allergic outcomes after adjusting for most of the specific IgEs and IgE clusters. However, the associations between current hay fever and total IgE did not remain statistically significant when adjusting for plant-specific IgEs, especially for rye grass-specific IgE (Figures E3 and E4).

Because comorbid conditions (e.g., asthma, sinus infections) are common among allergic individuals, we also examined the prevalences of these conditions and levels of total and specific IgEs among individuals with and without these co-morbidities (Results presented in the Online Repository). Of note, the highest levels of serum markers of atopy, both total and specific IgEs, were found in asthmatic individuals (Figure E5).

DISCUSSION

The NHANES 2005–2006 provided a unique opportunity to evaluate how levels of total IgE and allergen-specific IgEs relate to allergic conditions and symptoms in the US population. None of the previous NHANES studies have examined both qualitative and quantitative patterns of atopy in relation to allergy-related outcomes. Moreover, this many allergens have been examined in only a few large-scale European studies.^{16–18} Although several studies have investigated allergic outcomes in relation to clinical markers of atopy, limited information on quantitative relationships and sensitization patterns is available. In the NHANES 2005–2006, elevated levels of plant-, pet-, and mold-specific IgEs were most consistently associated with allergy-related outcomes. Dust mites were one of the most common sensitizers in this population, but mite-specific IgEs did not remain strongly associated with the reported symptoms. Consistent with published data,¹⁹ the majority of the allergen-specific IgEs were more prevalent among those who reported allergy-related outcomes than among asymptomatic individuals.

Allergies affect a substantial proportion of the US population; more than one-third of the NHANES 2005–2006 participants reported diagnosed allergies. Of those who reported diagnosis of any type of allergic condition, over 50% had symptoms in the past 12 months. Although the prevalence of allergic conditions appears to be similar to that reported in other national surveys,^{2–5} the prevalence rates may not be directly comparable. Case definitions of allergy-related outcomes tend to vary from one study to another, a fact which complicates comparisons of estimated prevalence rates.^{20, 21} Nonetheless, prevalence patterns across socio-demographic factors were largely similar to those reported in the literature.⁸

In the NHANES 2005–2006, prevalence of self-reported nasal symptoms was comparable to that reported in other national studies of rhinitis (30.2–31.5%).^{20, 22} Although the majority of the NHANES participants who reported current rhinitis symptoms also reported diagnosed allergies, a substantial proportion of the subjects, at least one-third, lacked any diagnosis of allergy. Several studies have shown that a large number of people who have rhinitis-related symptoms remain undiagnosed.^{20, 23, 24} On the other hand, it is well known that rhinitis symptoms can also be non-allergic in nature.²¹

Although allergic rhinitis is considered one of the most common chronic diseases in the US, the prevalence estimates have been highly variable, ranging from 9% to 42%.^{21, 25, 26} In the NHANES 2005–2006, more than half of the subjects with symptoms of rhinitis had detectable levels of specific IgE to at least one allergen, suggesting that approximately 18% of the US population may manifest symptoms of allergic rhinitis. Nathan and coworkers have reported similar rates (14.2%–22.0%) for allergic rhinitis, demonstrating increasing trends in the prevalence over the past decades.^{20, 22} A review focusing on diagnosis of allergy has recently suggested that about 50% respiratory symptoms may be allergic in origin.²⁷

Consistent with previous NHANES findings, sensitization to grass, dust mite, and ragweed allergens was most common in the US population.^{1, 28} Among those who reported any allergy-related symptoms in the past 12 months, sensitization rates were variable, ranging from 24.4% to 44.2% for grass-specific allergens; from 22.3% to 24.9% for dust mite allergens; and from 23.0% to 32.8% for ragweed allergen. It was not unexpected that a larger number of specific IgEs were associated with current allergies than with current hay fever; reported allergy symptoms may relate to a variety of allergic conditions.

Hay fever symptoms were predominantly associated with the presence of plant-specific IgEs, in agreement with published data.^{28, 29} Although hay fever is commonly referred to as seasonal allergic rhinitis, it can also be triggered by perennial allergens. In the NHANES 2005–2006, sensitization to pets was consistently associated with current hay fever and perennial symptoms of rhinitis. This is not an unforeseen finding because dog and cat allergens are not only found in virtually all US homes, but are also most often found in elevated levels.^{30, 31} Pet allergens tend to accumulate on many interior materials within the home, including carpeting, upholstery, and bedding, which can serve as continuous reservoirs for those allergens. Because of the aerodynamic characteristics of cat and dog allergen carrying particles, both allergens become aerosolized easily and remain airborne for long periods of time.^{32, 33}

While sensitization to molds has been associated with many atopic outcomes, studies suggest that sensitization is less frequent to molds than to pollen, animal or dust mite allergens.³⁴ Nonetheless, sensitization to molds is an important risk factor for manifestations of atopy. In NHANES 2005–2006, the magnitude of the effect of sensitization on reported symptoms was comparable between molds and pets.

In contrast to previous findings,²⁸ sensitization to dust mites did not remain significantly associated with any of the allergic outcomes in completely adjusted models. This may reflect differences in age distributions and/or analysis methods. The previous NHANES data covers a narrower age range than the NHANES 2005–2006, and because of smaller number of tested allergens, clustering effects of positive test responses have not been accounted for in the previous surveys. Moreover, the allergenic composition of the house dust extract that was used for skin prick testing in NHANES II is unknown, which complicates interpretation of the results. It is also likely that patients with allergy diagnosis, particularly those who see an allergist, have greater awareness and compliance with environmental control measures for dust mites than those who have not consulted a specialist.³⁵

The level of total IgE is influenced by genetic and environmental factors.²⁷ Because levels of total IgE may overlap between non-atopic and atopic individuals, as well as between different allergic diseases, the level of total IgE is generally considered less clinically relevant than specific IgE data.^{27, 36} In the NHANES 2005–2006, increase in total IgE appeared to have a small, but independent effect on allergy-related outcomes. After controlling for total IgE, the precision of the effect estimates in the models improved,

though the patterns of the associations remained similar. In studies where accounting for clustering of sIgEs is not feasible (e.g., studies with limited number of allergens in the test panel), adjusting for total IgE may help to control confounding by other sIgEs. In fact, the effect of total IgE was less pronounced for grass- and ragweed-specific IgEs among individuals with current hay fever. Rye grass and ragweed were the most common sensitizers among mono-sensitized hay fever sufferers (data not shown), which may partially explain this finding. Furthermore, total IgE levels were significantly lower among individuals who did not report asthma than among asthmatic individuals (Figure E5), in agreement with published data.^{15, 37} Among those participants who reported allergy-related outcomes and who had asthma, a wide spectrum of allergen-specific IgEs were significantly elevated.

Previous studies have shown that not only asthma, but also other co-morbid conditions are associated with hay fever and other forms of allergic rhinitis.^{7, 8, 26, 38, 39} In the NHANES 2005–2006, both asthma and sinus infections were significantly more prevalent among those who reported current hay fever or current allergies than among individuals without allergy-related outcomes.

Because sensitization is a dynamic process and affected by age,⁴⁰ we examined total and specific IgEs in relation to allergy-related outcomes across different age groups. The association between total IgE and current allergies was stronger among children than among adults, perhaps reflecting a higher asthma prevalence in children. Although the specific IgE results did not suggest strong evidence for effect modification by age, the odds ratios for some of the specific IgE clusters tended to be higher among children than among adults. In particular, sensitization to pets and molds seemed to increase the odds of having allergy-related outcomes in children. Sensitization to food allergens was also more common in children than in adults, as previously shown.¹⁴

The cross-sectional nature of the NHANES 2005–2006 is an important limitation of the study. Because temporal relationships are often difficult to determine in cross-sectional studies, we primarily focused on outcomes that required the presence of symptoms in the past 12 months. We recognize that misclassification of outcomes or exposures can introduce bias. In the NHANES, outcome measures were based on questionnaire responses alone, a practice which is common in most large-scale surveys. Allergic symptoms can be difficult to distinguish from symptoms which are non-allergic in origin, because many allergic and non-allergic conditions have similar symptoms.²⁷ Some conditions can even have both non-allergic and allergic etiologies. For example, a large proportion of rhinitis sufferers may have mixed rhinitis, a combination of allergic and non-allergic rhinitis.^{8, 41} A considerable number of individuals with allergies may also remain undiagnosed, because many people tend to use over-the-counter products, instead of seeking medical attention.²⁰ However, we included an allergy-related outcome that was not based on physician's diagnosis (i.e., symptoms of current rhinitis) in our analysis. Although serological measurements provide objective evidence of atopy, the diagnosis of clinically relevant allergy also depends on symptom history. It is well known that the presence of allergen-specific antibodies does not necessarily mean that a person has clinically relevant symptoms when exposed to an allergen.^{19, 36} Because patterns of sensitization tend to vary with climatic and geographic factors, it is possible that the test panel may not have covered all relevant allergens. For example, a recently published list of the major clinically important outdoor aeroallergens in North America includes a number of allergens that were not included in the test panel.²³ On the other hand, in national population-based studies, the test panel cannot be optimized for any specific region. Despite the limitations of the study, we believe that serious differential misclassification is unlikely; both outcomes and serum IgE levels were assessed independently, without prior knowledge of the atopic status.

One of the major strengths of the study is that the sample for the survey was selected to represent the entire US population. Indeed, the NHANES 2005–2006 provides the largest nationally representative dataset of serum IgE levels that has ever been collected on the US population. Although skin testing is often used to determine IgE-mediated sensitivity,⁸ serum-specific IgE immunoassays enabled the expansion of our test panel to include a larger number of allergens. Similar sensitivities have been reported when serum-specific IgEs and skin-prick tests have been compared with respect to the presence of symptoms, although the performance characteristics of these two immunoassays are known to vary.^{8, 42} None of the previous population-based studies in the US have examined both qualitative and quantitative relationships between sensitization and allergy-related symptoms. The NHANES 2005–2006 was also the first study to account for clustering of specific IgEs. Studies have shown that many allergens share structural similarities and can be cross-reactive.^{43, 44} Because IgE-mediated allergy tends to occur to clusters of allergens,^{45, 46} problems of collinearity may arise during the statistical analysis. To discover patterns and relationships in the allergen-specific data, we used cluster analysis, a widely-used method to analyze correlated data. As we have previously reported in abstract form,¹³ the NHANES 2005–2006 specific IgE data group into seven clusters, which not only have optimal statistical properties, but also are biologically relevant.

In summary, the NHANES 2005–2006 demonstrated that a large proportion of the US population suffers from allergies. Almost half of the population is sensitized to at least one allergen and more than half of the individuals diagnosed with allergies reported active symptoms. Our findings highlight the importance of different allergens in common allergic conditions. The reported symptoms, with or without diagnosis of allergy, were most consistently associated with plant-, pet-, and mold-specific IgEs. On the contrary, sensitization to dust mites, which is highly prevalent in the population, was not strongly associated with these outcomes. Although levels of total IgE per se are diagnostically less informative than allergen-specific IgEs, measuring data on both markers of atopy can be beneficial, especially if potential clustering of sIgEs cannot be accounted for in the study. The NHANES data provides valuable information on sensitization patterns, but further studies, preferably of longitudinal design, are needed to understand the complex relationships between allergen exposures and development of allergic sensitization and disease.

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Abbreviations

IgE	immunoglobulin E
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey

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Figure 1. Prevalence of the 19 allergen-specific IgEs in the U.S. population. Prevalence is shown among those who reported current allergy and current hay fever (■) and among those without these primary outcomes (○). Closed symbols represent statistically significant differences, whereas prevalences that are not statistically different are marked with open symbols.

Figure 2.

Prevalence of individual allergen clusters. Prevalence is shown among those who reported current allergy and current hay fever (■) and among those without these primary outcomes (○). Closed symbols represent statistically significant differences, whereas prevalences that are not statistically different are marked with open circles.

Figure 3.

Unadjusted and adjusted odds ratios (95% confidence intervals) for the associations between allergy-related outcomes and allergen-specific IgEs. The models are adjusted for age, sex, race/ethnicity, education, poverty, body mass index, and serum cotinine level. To avoid problems of collinearity, the models are not adjusted for the presence of other allergen-specific IgEs.

Figure 4. Unadjusted and adjusted odds ratios (95% confidence intervals) for the associations between allergy-related outcomes and IgE clusters. The partially adjusted models are adjusted for age, sex, race/ethnicity, education, poverty, body mass index, and serum cotinine level. The completely adjusted models are also adjusted for IgE clusters (i.e., each IgE cluster is mutually adjusted for the presence of other clusters).

TABLE 1
Demographic and allergic characteristics of the NHANES 2005–2006 population among subjects aged 6 years and older*

Characteristic	Unweighted Total N	Weighted % (SE) [†]	Total serum IgE in kU/L / GM (SE) [†]	Current hay fever % (SE) [‡]	Current allergies % (SE) [‡]
Overall	7398		43.3 (1.59)	6.6 (0.61)	23.5 (0.95)
Age					
6–11	924	8.1 (0.05)	51.8 (2.83) [‡]	3.1 (1.48) [‡]	19.2 (2.47) [‡]
12–15	960	6.0 (0.03)	54.4 (3.06)	4.5 (0.79)	18.0 (2.44)
16–19	1022	5.9 (0.04)	55.7 (6.08)	2.3 (0.92)	21.0 (2.56)
20–29	932	14.4 (0.08)	47.0 (3.32)	4.2 (0.95)	21.2 (1.93)
30–39	767	15.3 (0.09)	40.0 (3.28)	8.4 (1.33)	25.0 (1.67)
40–49	782	17.4 (0.09)	42.7 (2.79)	10.1 (1.63)	31.3 (2.41)
50–59	598	14.4 (0.08)	39.3 (2.88)	7.8 (1.95)	28.3 (2.80)
60–69	630	8.9 (0.06)	43.4 (3.61)	8.0 (0.61)	20.8 (1.95)
70+	783	9.6 (0.10)	32.6 (2.34)	5.0 (0.73)	14.8 (1.64)
Sex					
Male	3597	48.6 (0.05)	55.9 (1.80) [‡]	5.5 (0.66) [‡]	19.2 (1.41) [‡]
Female	3801	51.4 (0.05)	34.0 (1.68)	7.6 (0.85)	27.6 (0.87)
Race/ethnicity					
Non-Hispanic White	3026	70.3 (0.28)	35.3 (1.21) [‡]	8.0 (0.89) [‡]	25.9 (1.22) [‡]
Non-Hispanic Black	1927	11.7 (0.20)	78.3 (4.71)	3.9 (0.52)	18.5 (0.93)
Mexican American	1891	9.0 (0.10)	64.7 (3.78)	2.2 (0.50)	12.5 (1.36)
Other	554	9.1 (0.11)	65.6 (5.92)	3.8 (0.70)	22.5 (2.28)
Education (family)					
<12th grade	2065	17.6 (0.14)	53.1 (3.11) [‡]	2.5 (0.29) [‡]	11.9 (1.37) [‡]
12th grade	1736	24.6 (0.12)	43.6 (1.69)	5.1 (0.67)	21.9 (1.38)
>12th grade	3357	55.3 (0.19)	40.6 (2.09)	8.5 (0.76)	27.9 (1.17)
Missing	240	2.4 (0.03)	39.9 (5.82)	8.8 (2.35)	25.7 (4.60)
Poverty Index Quartiles					
1 st [0.00, 1.60)	2783	24.2 (0.16)	55.6 (2.44) [‡]	4.8 (0.81) [‡]	19.4 (1.08) [‡]
2 nd [1.60, 3.06)	1784	24.1 (0.10)	43.2 (2.27)	4.7 (0.67)	20.2 (1.56)

Characteristic	Unweighted Total N	Weighted % (SE) [‡]	Total serum IgE in kU/L / GM (SE) [‡]	Current hay fever % (SE) [‡]	Current allergies % (SE) [‡]
3 rd [3.06, 4.97]	1359	24.2 (0.09)	38.4 (2.18)	6.5 (1.13)	23.9 (2.50)
4 th [4.97, 5.00]	1155	24.2 (0.18)	37.4 (2.03)	10.1 (1.23)	31.2 (1.70)
Missing	317	3.3 (0.04)	49.3 (5.01)	8.3 (3.27)	19.2 (2.65)
Serum cotinine					
1 st [0.011, 0.020]	1807	24.0 (0.16)	36.3 (2.38) [‡]	10.0 (1.21) [‡]	24.8 (1.48) [‡]
2 nd [0.020, 0.067]	1885	25.7 (0.14)	41.9 (1.98)	6.3 (0.80)	25.8 (1.25)
3 rd [0.067, 5.170]	2183	24.9 (0.11)	46.9 (2.32)	4.9 (0.80)	21.8 (1.80)
4 th [5.170, 1156]	1474	24.9 (0.11)	48.9 (2.68)	5.5 (0.85)	21.7 (1.28)
Missing	49	0.4 (0.011)	48.4 (14.79)	0.0 (0.00)	27.3 (7.96)
Body mass index					
Underweight [0.0, 18.5]	888	8.5 (0.051)	42.8 (2.58) [‡]	4.9 (1.68)	20.2 (2.45) [‡]
Normal [18.5, 25.0]	2535	33.0 (0.10)	39.6 (2.04)	6.7 (1.00)	22.1 (0.93)
Overweight [25.0, 30.0]	1959	28.4 (0.08)	45.4 (2.20)	6.5 (0.85)	23.4 (2.08)
Obese [30.0, 130]	1932	29.0 (0.13)	45.7 (2.47)	7.2 (0.90)	26.6 (1.08)
Missing	84	1.1 (0.02)	46.7 (10.98)	2.2 (1.37)	15.7 (4.77)
Degree of sensitization					
Non-sensitized	3755	54.2 (0.12)	20.5 (0.64) [‡]	3.1 (0.44) [‡]	18.0 (1.00) [‡]
Sensitized	3511	43.7 (0.12)	109.0 (5.10)	11.1 (1.15)	30.7 (1.33)
Mono-sensitized	760	10.1 (0.06)	51.8 (3.63)	8.8 (1.66)	22.6 (2.30)
Poly-sensitized	2751	33.6 (0.12)	136.3 (6.28)	11.8 (1.18)	33.2 (1.69)
Missing	132	2.0 (0.07)	44.2 (6.05)	5.9 (2.27)	17.0 (3.23)

* Subjects with available data on total serum IgE included

[‡] Weighted for the multi-stage sampling design of the NHANES

[‡] P-value < 0.05 for the test of differences between subject characteristics categories (missings/unknowns not tested) across total IgE and allergy-related outcomes

Unadjusted and adjusted odds ratios (OR) for the association between total IgE and current hay fever and current allergies stratified by age, sex, and race/ethnicity*

TABLE II

Stratum	Unadjusted OR (95% CI) for current hay fever	Interaction P-value [†]	Adjusted OR (95% CI) for current hay fever [‡]	Interaction P-value [†]	Unadjusted OR (95% CI) for current allergies	Interaction P-value [†]	Adjusted OR (95% CI) for current allergies [‡]	Interaction P-value [†]
All subjects	1.44 (1.20,1.71)	—	1.86 (1.44,2.41)	—	1.34 (1.20,1.51)	—	1.64 (1.41,1.91)	—
Age group		0.51		0.72		<0.01		0.05
Children (6–17 yrs)	1.85 (0.98,3.47)		2.20 (1.09,4.44)		1.95 (1.58,2.41)		2.17 (1.68,2.80)	
Adults (18+ yrs)	1.44 (1.17,1.77)		1.88 (1.39,2.55)		1.28 (1.13,1.46)		1.59 (1.34,1.88)	
Sex		0.25		0.13		0.15		0.11
Male	1.67 (1.28,2.17)		2.13 (1.60,2.82)		1.57 (1.34,1.85)		1.82 (1.50,2.20)	
Female	1.42 (1.12,1.81)		1.67 (1.22,2.29)		1.36 (1.15,1.61)		1.53 (1.28,1.84)	
Race/ethnicity		0.46		0.62		0.42		0.61
Non-Hispanic White	1.73 (1.31,2.29)		1.94 (1.42,2.65)		1.55 (1.36,1.76)		1.76 (1.49,2.07)	
Non-Hispanic Black	1.91 (1.21,3.02)		2.30 (1.36,3.89)		1.51 (1.25,1.83)		1.72(1.47,2.03)	
Mexican American	1.13 (0.55,2.33)		1.53 (0.68,3.44)		1.30 (0.98,1.72)		1.46 (1.02,2.08)	

* Total IgE log10 transformed, continuous variable

[†] P-value for the test that the association between allergy-related outcomes and total IgE differs across strata

[‡] Models are adjusted for age, sex, race/ethnicity, education, poverty, serum cotinine level, and body mass index