Total IgE levels and asthma prevalence in the US population: Results from the National Health and Nutrition Examination Survey 2005-2006

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Background: The inability to measure IgE-based sensitivity to all allergens has limited our understanding of what portion of asthma is related to IgE. Total IgE measurement can potentially overcome this limitation.

Objective: We sought to determine the association between total IgE levels and asthma.

Methods: The National Health and Nutrition Examination Survey 2005-2006 examined a representative sample of the US population 6 years of age and older.

Results: The median total IgE level was 40.8 kU/L (interquartile range, 15.5-114 kU/L). Total IgE levels varied with age, sex, race/ethnicity, serum cotinine level, body size, and socioeconomic status. The prevalence of current asthma was 8.8%. The prevalence of atopy was 42.5%, as defined by 15 specific IgEs. The adjusted odds ratio (OR) for asthma with a 10-fold increase in total IgE level was 2.18 (95% CI, 1.66-2.87). Total IgE level predicted asthma only among atopic subjects (OR, 2.41; 95% CI, 1.62-3.60) and not among nonatopic subjects (OR, 1.11; 95% CI, 0.72-1.71; interaction $P = .005$). Among atopic subjects, the association between total IgE level and asthma became stronger as the number of positive specific IgE test results increased. Asthma was present at even the lowest levels of total IgE, regardless of atopic status. Approximately 92% of atopic subjects were identified by 6 specific IgEs, but to increase the identification to more than 99% required 11 specific IgEs.

Conclusion: Total IgE levels are associated with asthma only among persons who have positive results for at least 1 allergen-specific IgE. Asthma independent of IgE is not uncommon in the US population. The complete identification of atopic subjects in a population requires a large panel of allergen-specific IgEs. (J Allergy Clin Immunol 2009;124:447-53.)

Key words: *Asthma, prevalence, IgE, total, specific, atopy, nonatopic*

Allergy has long been known to play an important role in asthma. Sensitization to specific allergens can make asthma more difficult to control. For certain allergens, the combination of sensitization and exposure to high levels of the allergen can decrease asthma control.[1,2] Allergic sensitization also plays a role in the development of asthma. Illi et al[3] reported that the development of sensitization to perennial allergens early in life (<3 years of age) combined with exposure to high allergen levels was predictive of chronic asthma and reduced lung function at age 13 years.

The extent of asthma related to IgE-mediated sensitization is controversial. Rackemann[4] proposed that not all asthma has an allergic basis but that there existed a nonallergic form of asthma that was more prevalent in adults. This intrinsic form of asthma was defined by the lack of sensitization to asthma-specific allergens. The concept of intrinsic asthma was challenged by later studies, which reported that the prevalence of asthma increased with increasing levels of total IgE among subjects with negative allergen skin test responses[5-7] and that asthma did not exist below certain levels of total IgE.[6,8]

The National Health and Nutrition Examination Survey (NHANES) 2005-2006 was the first nationwide assessment of total and allergen-specific IgE antibodies in the US population. The NHANES sample offers a unique opportunity to determine the role of total IgE levels in the prevalence of asthma.

METHODS

Survey

Data were obtained from the NHANES 2005-2006, which was designed to assess the health and nutritional status of the civilian, noninstitutionalized US population. The NHANES 2005-2006 oversampled low-income subjects, adolescents (12–19 years of age), persons 60 years of age and older, African Americans, and Mexican Americans among others. The NHANES classifies participants into 4 main racial/ethnic groups: non-Hispanic whites, non-Hispanic blacks, Mexican Americans, and others. Family income is classified by the poverty income ratio: the ratio of the family's income to the appropriate poverty threshold for a family of that specific size. The NHANES 2005-2006 protocol was approved by the National Center for Health Statistics, Centers for Disease Control and Prevention, Institutional Review Board. Informed consent was obtained from all participants 18 years and older. In addition to written consent from their parents, all participants 12 to 17 years of age signed an assent form. Details of the survey design and

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Abbreviations used
ECRHS: European Community Respiratory Health Survey
LLOD: Lower limit of detection
NHANES: National Health and Nutrition Examination Survey
OR: Odds ratio
ULOD: Upper limit of detection

implementation of NHANES 2005-2006 can be found online at http://www.cdc.gov/nchs/nhanes.htm.

Assessment of asthma

The primary outcome for this analysis was doctor-diagnosed current asthma. A participant had to respond in the affirmative to the following questions to be classified as asthmatic: (1) Has a doctor or other health professional ever told you that you have asthma? (2) Do you still have asthma? A responsible adult provided information for sample persons less than 16 years of age and for subjects who could not self-report.

Total and allergen-specific IgE levels

Participants aged 6 years and older were tested for total IgE and the following 15 allergen-specific IgE antibodies against aeroallergens (*Alternaria alternata*, *Aspergillus fumigatus*, Bermuda grass *[Cynodon dactylon]*, birch *[Betula verrucosa]*, cat dander, cockroach *[Blatella germanica]*, dog dander, dust mite [*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*], mouse urinary proteins, oak *[Quercus alba]*, ragweed *[Ambrosia elatior]*, rat urinary proteins, Russian thistle *[Salsola kali]*, and rye grass *[Lolium perenne]*). The panel of specific IgEs was selected for the United States as a whole and not optimized for any specific region. Total and specific IgE levels were measured with the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, Mich). 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 less than the LLOD, NHANES provided fill values equal to the LLOD divided by the square root of 2. For each allergen-specific IgE assay, the upper limit of detection (ULOD) was 1,000 kU/L, and NHANES provided the fill value of 1,000 kU/L when the ULOD was exceeded. For total IgE testing, no samples exceeded the ULOD of 50,000 kU/L. For this analysis, atopy was defined as at least 1 positive allergen-specific IgE test result, with a positive test result defined as a concentration of 0.35 kU/L or greater.

Sample and response rate

These analyses were limited to participants aged 6 years and older who were examined in the mobile examination center (n = 8,086) because the diagnosis of asthma is difficult to establish in early childhood and examinees less than 6 years of age had a limited panel of allergen-specific IgE tests.

Of the 8,086 participants aged 6 years and older who were eligible for IgE testing, 7,398 (91.5%) had blood drawn for total IgE measurement. Of these 7,398 participants, 97.6% (SE = 0.35) had a detectable level of total IgE (a concentration was imputed for observations less than the LLOD, see above). The prevalence of asthma was not statistically different between participants with and without total IgE results (8.8% vs 8.7%, respectively; $P = .99$). Across the 15 allergen-specific IgE tests, the percentage of eligible participants with reported results ranged from 90.7% to 91.5%.

Statistical analyses

The distribution of total serum IgE in the US population aged 6 years and older was log-normal. Thus total IgE levels were logarithmically transformed (base 10) for statistical analyses. Differences in geometric mean concentrations of total IgE across population characteristics were tested with the F-statistic, and differences in prevalences of asthma across population characteristics were tested with the χ^2 statistic.

The main association of interest was between total IgE concentration (continuous and $\log_{10}$ transformed) and asthma. Unadjusted and adjusted odds ratios (ORs) for that association were estimated with logistic regression. ORs were adjusted for age, sex, race, education, poverty, body mass index, and serum cotinine levels ($\log_{10}$ transformed). Differences in ORs across population characteristics were assessed with 2-way interaction terms.

Results were stratified by 3 different categories of allergen-specific IgE results to assess the contribution of allergen-specific IgE to the association between total IgE levels and asthma: at least 1 positive allergen-specific IgE test result (atopy), the number of positive allergen-specific IgE test results, and summed concentrations of allergen-specific IgE. Differences in ORs across strata were tested with an interaction term. Statistical significance was established *a priori* at .05 for main effects and .10 for interactions.

The sample weight variable WTMEC2YR was used in all analyses to obtain unbiased national estimates. The survey design variables SDMVSTRA and SDMVPSU were used to adjust the SEs for the complex survey design. Analyses were performed with R version 2.9.0[9] survey package (version 3.15)[10] to adjust for the NHANES complex sampling design and confirmed with SAS (Version 9.1.3; SAS, Inc, Cary, NC) survey sampling procedures. Matching analysis and figures were constructed with the R packages Matching[11] and lattice,[12] respectively.

RESULTS

Distribution of total IgE

The median total IgE level was 40.8 kU/L (interquartile range, 15.5-114 kU/L). The median total IgE level peaked at 52.7 kU/L in the 16- to 19-year age group and decreased in older groups, reaching a nadir of 32.6 kU/L in the group 70 years and older. Median values were higher for male than for female subjects; for non-Hispanic Blacks and Mexican-Americans than for non-Hispanic whites; for subjects with less than a 12th grade education, increased poverty, higher serum cotinine levels, and higher body mass indices; and for subjects with at least 1 positive specific IgE result (Fig 1, *A*, and Table I).

Prevalence of asthma and atopy

Current asthma was reported by 8.8% of the population (Table I). The prevalence of asthma differed significantly by age, race/ethnicity, sex, poverty, serum cotinine level, and body size. The prevalence of asthma was higher among atopic than nonatopic subjects (12.9% vs 5.8%, $P < .001$, Table I). The percentage of asthmatic subjects who had 1 or more positive specific IgE results was 62.1% (SE = 1.87). The adjusted OR for the association between atopy and asthma among this population was 2.41 (95% CI, 1.94-2.99). The adjusted OR did not vary significantly ($P > .05$) across the age groups studied: 6 to 19 years (OR, 2.73; 95% CI, 1.97-3.80); 20 to 49 years (OR, 2.79; 95% CI, 1.95-3.98); 50 years or older (OR, 1.94; 95% CI, 1.25-3.01).

Association between total IgE levels and asthma

The geometric mean for total IgE level was significantly higher among asthmatic subjects than nonasthmatic subjects (81.1 vs 40.8 kU/L, $P < .0001$). The distribution density curve for asthmatic subjects compared with nonasthmatic subjects was shifted toward higher total IgE levels; however, there is considerable overlap between the curves (Fig 1, *B*).

The adjusted OR for asthma for a 10-fold increase in total IgE levels (eg, 1-10, 10-100, and 100-1,000) was 2.18 (95% CI,