

## Gender Differences in Total and Allergen-specific Immunoglobulin E (IgE) Concentrations in a Population-based Cohort from Birth to Age Four Years

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While serum immunoglobulin E (IgE) concentration has been shown to be related to allergic disease, there have been few studies of the natural history of IgE development in young children. This study compared total and allergen-specific serum IgE concentrations, by gender, from birth through 4 years of age using a population-based cohort of normal children followed from 1987 to 1993. Subjects were enrolled from a geographically defined area through membership in a large health maintenance organization, and they resided in the northern suburbs of Detroit, Michigan. Total IgE concentrations were measured at birth and at 2 and 4 years of age. Specific IgE concentrations to selected common inhalant allergens (dust mite (*Dematophagoides farinae*), cat, ragweed (*Ambrosia artemisiifolia*), and timothy grass (*Pheleum pratense*)) were measured at 2 and 4 years of age. Total IgE increased with age from birth to 4 years for boys and girls, and was higher in boys at 2 and 4 years of age. Girls demonstrated significant increases in IgE to mite and cat and decreases in IgE to ragweed and timothy from 2 to 4 years of age, whereas there was little change for boys except an increase in IgE to ragweed. Differences in IgE development between young boys and girls may partially account for the higher prevalence of asthma in boys than in girls. *Am J Epidemiol* 1998;147:1145–52.

gender; IgE; pediatrics

Although serum immunoglobulin E (IgE) concentration has been shown to be related to allergic disease in children and adults (1), there have been few descriptive studies of IgE development in young children. Many studies have presented cross-sectional or hospital-based descriptive data on IgE in newborns, infants, and children (1–18), but few studies have presented data on children followed longitudinally. Of the studies that have presented longitudinal data (19–24), many focused on selected populations of children, such as children at higher risk of developing allergic disease (19, 20, 22), or did not include data by gender (23). Only two longitudinal studies presented data on gender differences in IgE, but children under the age of 6 years were not included in one study (21) and the second only had IgE data at two points in time, birth and age 18 months (24). The purpose of this study was to evaluate the pattern of total and allergen-specific IgE, by age and gender, in a large, prospectively

evaluated, population-based cohort of children from birth to 4 years of age. We assessed whether total IgE increases similarly in boys and girls and whether boys and girls are equally likely to develop and to continue production of IgE antibodies specific for common inhalant allergens.

### MATERIALS AND METHODS

The data used in this analysis were collected as part of an ongoing study to evaluate the environmental determinants of allergic diseases in a population of children followed from birth. Selection of the study cohort has been previously described in detail (25). Briefly, all women aged 18 years and older, with a prenatal appointment at one of seven clinics serving northern middle class suburbs of Detroit, Michigan, were approached for study recruitment. To be eligible, a woman had to be a member of the Health Alliance Plan health maintenance organization and have an estimated date of confinement between April 15, 1987 and August 31, 1989, with delivery planned for one of the three hospitals serving the health maintenance organization patients. Additionally, women had to reside within an area surrounding the clinics as defined by contiguous zip codes. Research nurses recruited women during midterm prenatal visits. In the case of multiple pregnancies or births during the study period,

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Abbreviations: ELISA, enzyme-linked immunosorbent assay; IgA, immunoglobulin A; IgE, immunoglobulin E; IU, international units.

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only one child per family was eligible for study. All aspects of the study were approved by the Henry Ford Hospital Human Rights Committee and written informed consent was obtained at all appropriate times.

At delivery, a cord blood sample was obtained. The serum was separated and stored at  $-20^{\circ}\text{C}$  until assay. Cord blood IgE levels were quantitated with an enzyme-linked immunoassay (ELISA) (25). The antibody used in both the capture and detection steps was affinity-purified anti-human IgE (Kirkegaard & Perry Laboratories, Gaithersburg, Maryland).

Standard curves were constructed from appropriate dilutions of a patient serum that had been standardized against the US reference standard. The average net optical densities produced by unknown samples were converted to units of IgE (international units or IU) by calculation from the computer-fitted standard curve. Six internal standards were included with each assay run. The routine sensitivity of the assay was 0.02 IU/ml of IgE, and the average interassay coefficient of variation was 17.6 percent, which we believe to be an acceptable magnitude given that we were measuring extremely low IgE levels. Similarly, the concentration of immunoglobulin A (IgA) was measured by ELISA to evaluate possible contamination of the cord sera with maternal blood. Sera with IgA values of  $>39\text{ }\mu\text{g/ml}$  were considered potentially contaminated with maternal blood and excluded from analyses (25).

A study nurse made home visits and obtained blood specimens at 2 and 4 years of age for IgE measurement. For these samples obtained when the infants were 2 and 4 years old, the total IgE assay was modified to reflect the higher IgE concentrations expected in the samples. The standard curve extended from 0.29 to 5.75 IU/ml and the interassay coefficient of variation was 12.8 percent.

Allergen-specific IgE concentrations were measured using a modification of a biotin-avidin amplified ELISA (26, 27). Each allergen extract was diluted to previously determined optimum concentrations in 60 mmol/L carbonate/bicarbonate, pH 7 buffer and adsorbed overnight to plastic micro wells (Microstrips, Labsystems, Needham Heights, Massachusetts). The four allergen extracts used were dust mite (*Dermatophagoides farinae*), cat, ragweed (*Ambrosia artemisiifolia*), and timothy grass (*Pheleum pratense*) (mite, ragweed, and timothy extracts, Bayer Corporation, Spokane, Washington; and cat extract, ALK Laboratories, Wallingford, Connecticut). Because serum samples were very limited and based on the assumption that the four allergens were not cross-reactive, a transfer technique was utilized to obtain maximal data. Before being added to a micro well coated with mite, each serum was diluted with an equal volume of saline

and 50  $\mu\text{liter}$  were added to each well. After an overnight incubation, the dilute serum was removed from the mite extract coated well and transferred to a well coated with cat extract. After another overnight incubation, the dilute serum was transferred to a ragweed coated well, and then after another incubation to a grass coated well. After the serum had been removed, each well was processed by adding, with interspersed washes, biotin-antihuman IgE, strep avidin-alkaline phosphatase (Kirkegaard & Perry Laboratories, Gaithersburg, Maryland), and Sigma 104 phosphate substrate (Sigma Chemical, St Louis, Missouri). The resulting density was measured in a micro densitometer. The results of each serum with each allergen were expressed as ratios, calculated by dividing the density of the test serum by the density of a pool of sera from non-allergic individuals processed in the same manner. Values of  $\geq 2.5$  were considered positive. This value is equal to the mean of the negative serum pool plus three standard deviations of the mean (27). In preliminary studies, the results of diluting serum 1:2 were compared with undiluted serum and minimal changes in the resulting ratios were found, in part because the level of background binding was reduced. Similarly, the results of transferring serum were compared to the results obtained when fresh aliquots of serum were added to each allergen and minimal changes in values were found.

### Statistical methods

As expected, IgE values were positively skewed, indicating non-normality. To better fit the assumptions of the various statistical tests used, the IgE values were transformed using the natural logarithm transformation. Statistics were generated on the log-transformed values and were retransformed back to the original units by exponentiation. The retransformed mean is the geometric mean. A graph of the distribution of total IgE values by age was smoothed using a cubic spline method with continuous second derivatives (28) and generated using SAS/GRAPH software with the spline interpolation option (29).

Descriptive statistics include the reference range which represents where approximately 95 percent of the observations should fall. The range was calculated as the mean plus or minus 1.96 standard deviations of the log-transformed values. The range reported was retransformed to the original units by exponentiation.

Due to sporadic difficulties in obtaining blood (resistant children or unavailability at designated time interval), complete information on IgE level was not available for all children at all time points. Therefore, we examined each pairwise comparison of interest using children with results for each pair of time points

(e.g., birth and 2 years) in order to maximize the number of individuals available for each analysis. All comparisons examined were considered of primary importance a priori and the rejection level of 0.05 was used throughout. Student's *t* test was used to test for differences by child's gender in total IgE. We also used this test to examine the change in IgE from 2 years to 4 years and to test the difference between genders.

The percent positive for allergen-specific IgE was estimated as the number positive over the number evaluated. The specific IgE values were considered positive if their value equaled or exceeded 2.5. The category "any allergen" was defined as positive if any of the four specific IgE tests were positive (child was atopic). In contrast, if all four allergen-specific IgE tests were negative, the child was classified as non-atopic. To examine the specific IgE values for differences between genders, we used a chi-square test for differences between proportions. For changes in the percent positive to a specific allergen from 2 to 4 years, we used McNemar's test (30). We also estimated the difference in percent positive between 2 and 4 years of age and its 95 percent confidence interval using McNemar's procedure (31). To see if the change in allergen positivity from 2 to 4 years was different between boys and girls, a *z*-test was constructed using the estimates and their standard errors from McNemar's procedure.

## RESULTS

Of 1,184 eligible pregnant women, 940 women (79.4 percent) were contacted and consented to participate in the study. Cord bloods were not obtained from 99 participants due to fetal loss, birth complications, change in hospital of delivery, or loss of specimen.

Those not enrolled in the study and those with missing cord blood did not differ in terms of mothers' age, fathers' age, mothers' education, and fathers' education from the 841 participants from whom cord blood was obtained (data not shown). Six additional subjects were excluded due to elevated IgA levels. For these analyses, we considered only those individuals of the remaining 835 for whom either a 2-year or a 4-year IgE level was available ( $n = 561$  or 67 percent). Table 1 displays characteristics of the study population by availability of the follow-up IgE measurements. There were no differences in maternal age and parental education among the groups defined by varying levels of follow-up. Paternal age, while statistically different among the four groups, had a range of only 1.3 years.

Only white children were included in the analyses due to the small percentage of other ethnic groups in the study, reducing the sample size to 538 newborns. The mothers of children in the analysis had an average age of 28.9 years  $\pm$  4 years and the fathers 31.3 years  $\pm$  5 years. More than 95 percent of the parents had high school degrees, with 31.6 percent of the mothers and 44.9 percent of the fathers having a college degree.

Table 2 presents the average total IgE measurements at birth, and at ages 2 years and 4 years, by gender and atopic status. Total IgE increases significantly with age from a geometric mean of 0.20 IU/ml at birth to 15.36 at 2 years and 30.17 at 4 years ( $p < 0.001$ ). Figure 1 illustrates the shifts in the distributions of total IgE levels by age. While boys and girls have similar IgE levels at birth ( $p < 0.170$ ) and both increase with age, IgE rose more rapidly in boys and is significantly higher in boys than in girls at both age 2 years ( $p < 0.002$ ) and 4 years ( $p < 0.007$ ) (table 2). For boys, the total IgE level at 2 years and particularly

**TABLE 1. Comparison of subjects by immunoglobulin E (IgE) sampling, parental age, and parental education, for children born from 1987 to 1993 to women who belonged to a health maintenance organization and resided in the northern suburbs of Detroit, Michigan**

| Characteristic                  | Timing of blood samples            |                                           |                                           |                                                    | <i>p</i> value |
|---------------------------------|------------------------------------|-------------------------------------------|-------------------------------------------|----------------------------------------------------|----------------|
|                                 | Cord IgE only<br>( <i>n</i> = 274) | Cord IgE and 2 years<br>( <i>n</i> = 123) | Cord IgE and 4 years<br>( <i>n</i> = 125) | Cord IgE, 2 years and 4 years<br>( <i>n</i> = 313) |                |
| Mean maternal age (years) (SD)* | 28.2 (4.8)                         | 29.0 (4.1)                                | 28.5 (4.7)                                | 29.0 (4.2)                                         | 0.132          |
| Mean paternal age (years) (SD)† | 30.3 (5.3)                         | 31.6 (4.9)                                | 30.9 (5.2)                                | 31.4 (5.0)                                         | 0.039          |
| Mother's highest degree         |                                    |                                           |                                           |                                                    |                |
| High school, no. (%)            | 174 (64)                           | 83 (67)                                   | 79 (63)                                   | 197 (63)                                           | 0.426          |
| College, no. (%)                | 82 (30)                            | 37 (30)                                   | 40 (32)                                   | 108 (35)                                           |                |
| Father's highest degree         |                                    |                                           |                                           |                                                    |                |
| High school, no. (%)            | 145 (54)                           | 62 (50)                                   | 63 (50)                                   | 155 (50)                                           | 0.638          |
| College, no. (%)                | 110 (41)                           | 55 (45)                                   | 53 (42)                                   | 148 (47)                                           |                |

\* SD, standard deviation.

† Two infants with cord IgE only, one infant with cord IgE and 2 years, and five infants with all three measurements had unknown father's age.

**TABLE 2. Distribution of total immunoglobulin E (IgE) measurements by age, gender,\* and atopic status† for children born from 1987 to 1993 to women who belonged to a health maintenance organization and resided in the northern suburbs of Detroit, Michigan**

| Gender, age, and atopic status | No. | Geometric mean | Mean (SD)‡   | 95% reference range§ |
|--------------------------------|-----|----------------|--------------|----------------------|
| <b>Both sexes</b>              |     |                |              |                      |
| Birth                          | 538 | 0.20           | -1.61 (1.17) | 0.02-2.00            |
| 2 years                        | 418 | 15.36          | 2.73 (1.21)  | 1.44-164.3           |
| 4 years                        | 417 | 30.17          | 3.41 (1.30)  | 2.36-385.7           |
| <b>Boys</b>                    |     |                |              |                      |
| Birth                          | 265 | 0.22           | -1.54 (1.11) | 0.02-1.90            |
| 2 years                        | 202 | 18.58          | 2.92 (1.22)  | 1.75-197.5           |
| 4 years                        | 216 | 35.59          | 3.57 (1.36)  | 2.46-515.7           |
| <b>Non-atopic</b>              |     |                |              |                      |
| 2 years                        | 143 | 18.36          | 2.91 (1.26)  | 1.57-214.8           |
| 4 years                        | 130 | 27.44          | 3.31 (1.21)  | 2.55-295.7           |
| <b>Atopic</b>                  |     |                |              |                      |
| 2 years                        | 56  | 18.67          | 2.93 (1.10)  | 2.15-161.9           |
| 4 years                        | 79  | 52.72          | 3.96 (1.53)  | 2.64-1,051.4         |
| <b>Girls</b>                   |     |                |              |                      |
| Birth                          | 273 | 0.19           | -1.68 (1.23) | 0.02-2.08            |
| 2 years                        | 216 | 12.86          | 2.55 (1.18)  | 1.28-129.4           |
| 4 years                        | 201 | 25.25          | 3.23 (1.21)  | 2.38-268.0           |
| <b>Non-atopic</b>              |     |                |              |                      |
| 2 years                        | 141 | 14.51          | 2.67 (1.22)  | 1.33-158.6           |
| 4 years                        | 119 | 24.36          | 3.19 (1.21)  | 2.27-261.0           |
| <b>Atopic</b>                  |     |                |              |                      |
| 2 years                        | 65  | 9.92           | 2.29 (1.13)  | 1.09-90.4            |
| 4 years                        | 74  | 28.76          | 3.36 (1.17)  | 2.93-282.1           |

\* Comparison of the difference in IgE level between boys and girls yielded *p* values of 0.170 at birth, 0.002 at 2 years, and 0.007 at 4 years.

† Children classified as atopic had a positive IgE concentration ( $\geq 2.5$ ) to one or more of four specific allergens.

‡ Mean and standard deviation (SD) of natural log-transformed total IgE values.

§ The reference range is expected to include 95 percent of all observations.

at 4 years of age was lower in the non-atopic group when compared with the group of boys with at least one positive test for allergen-specific IgE. However, for girls, the total IgE among the non-atopic group was higher at age 2 years and only slightly lower at age 4 years. As with total IgE for the combined group, the reference ranges were extremely wide and the ranges for the atopic and non-atopic children substantially overlapped.

Comparing IgE levels in a longitudinal fashion among the subgroup of children with measurements at two points in time (birth and 2 years, birth and 4 years, and 2 and 4 years), and by gender, IgE was again found to significantly increase with age ( $p < 0.001$  for each paired comparison). Table 3 presents the mean difference over the three time periods by gender in this group of children. Total IgE increased more rapidly in

boys than girls between birth and 2 years of age and between birth and 4 years of age, with differences that were of borderline statistical significance.

Table 4 displays the percent of children with positive IgE levels for the perennial allergens mite and cat, the seasonal allergens ragweed and timothy grass, and for a combined group of children demonstrating a positive result to any allergen. For mite, cat, ragweed, and the combination of any allergen group, the percent positive for the total cohort increased from 2 to 4 years of age. For timothy grass, the percent positive decreased from 2 to 4 years. The percent positive for boys at 4 years compared with 2 years increased for all allergen categories. The pattern was different for girls, with increases for mite (+4.0) and cat (+9.5), but decreases for ragweed (-2.1) and timothy (-4.3).

There was little difference between boys and girls at 2 years of age between the allergen categories (table 4). At 4 years of age, girls have a higher percent positivity to cat allergen ( $p < 0.006$ ) and a lower positivity to ragweed ( $p < 0.031$ ) and timothy ( $p < 0.286$ ).

Table 5 compares the paired difference over time in allergen-specific positivity for children with measurements at both 2 and 4 years, and the results are similar to those of the entire group shown in table 4. There was a statistically significant increase in percent positive to cat allergen ( $p < 0.004$ ), and an increase in positivity to mite ( $p < 0.088$ ), with a small increase for ragweed ( $p < 0.273$ ). The percent positive to timothy decreased somewhat ( $p < 0.267$ ). The percent positive for any allergen increased ( $p < 0.021$ ).

Separate comparisons for boys and girls were also generally consistent with the cross-sectional analyses including all study children. The boys showed increases between 2 and 4 years of age for all but timothy, with a more dramatic increase for ragweed ( $p < 0.003$ ). The girls demonstrated marked differences in positivity for each antigen, with increases for mite ( $p < 0.052$ ) and cat ( $p < 0.009$ ), and decreases for ragweed ( $p < 0.035$ ) and timothy ( $p < 0.102$ ). Comparing the pattern of change over time between boys and girls, there was a significant difference only for ragweed.

## DISCUSSION

The major strength of this study is the prospective evaluation of IgE in a relatively large and population-based sample of young children. This study design reduces the potential for the biases which may be present in some previous studies which relied on cross-sectional data or were limited to small numbers of children from at-risk populations. Our study population is representative of middle-class Caucasian chil-

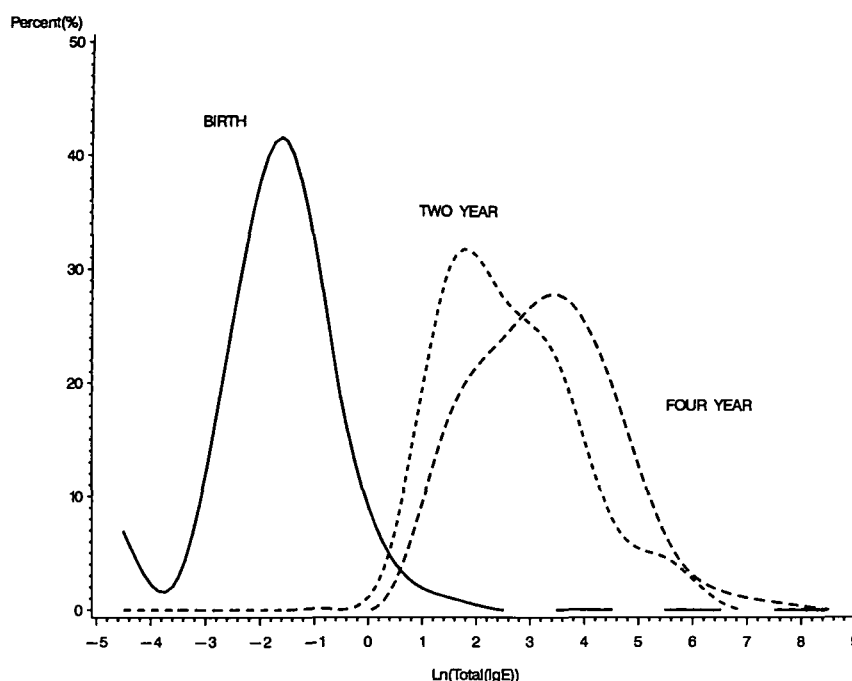


**FIGURE 1.** Distribution of log total immunoglobulin E (IgE) concentration (spline smoothed) at birth and at 2 and 4 years of age among children born from 1987 to 1993 to women who belonged to a health maintenance organization and resided in the northern suburbs of Detroit, Michigan.

**TABLE 3.** Comparison of change in log total immunoglobulin E (IgE) concentrations for boys and girls born from 1987 to 1993 to women who belonged to a health maintenance organization and resided in the northern suburbs of Detroit, Michigan

| Comparison          | Boys |                  |      | Girls |                  |      | p value |
|---------------------|------|------------------|------|-------|------------------|------|---------|
|                     | No.* | Mean difference† | SD‡  | No.*  | Mean difference† | SD   |         |
| Birth and 2 years   | 202  | 4.52             | 1.39 | 216   | 4.27             | 1.43 | 0.063   |
| Birth and 4 years   | 216  | 5.08             | 1.65 | 201   | 4.80             | 1.36 | 0.056   |
| 2 years and 4 years | 153  | 0.67             | 1.02 | 144   | 0.63             | 0.98 | 0.780   |

\* Number of children in comparison varies depending on whether a child had studies at both times.

† Mean difference is defined as higher age minus lower age where the value of total IgE is in log units.

‡ SD, standard deviation.

dren residing in the midwestern United States. While we did experience substantial loss to follow-up due primarily to families moving from the area, our remaining participants did not appear to differ materially in terms of parents' age and education. It is possible that children born into families with allergic parents or siblings, and therefore a potential inherited tendency towards higher IgE levels, may have differentially relocated to avoid local allergen exposure.

As expected, we found that total serum IgE increased with age. However, there were significant differences in the development of IgE between boys and girls. We were surprised to find that the difference in total serum IgE concentrations between boys and girls was clearly present by 2 years of age. These differences were consistent whether the entire popula-

tion or only those children with samples at each pair of time points were analyzed. Serum IgE by age irrespective of gender was comparable to other unselected populations reported from Spain (14), Finland (16), and the southern United States, but was significantly higher in boys than girls at both 2 and 4 years of age, even though the cord blood concentrations of these children had not differed by gender. In Sweden, Hattevig et al. (23), who studied girls only, reported a mean cord IgE concentration (0.2 IU/ml) similar to the girls in this study (0.19 IU/ml), although the Swedish levels found at 2 and 4 years were relatively lower (6.1 and 8.8, respectively). In a longitudinal study of persons aged 6 years and older in Tucson, Arizona, Sherrill et al. (32) reported that IgE was similar in males and females within their reference group of

**TABLE 4. Comparison of positive\* specific immunoglobulin E (IgE) tests at 2 and 4 years of age between boys and girls born from 1987 to 1993 to women who belonged to a health maintenance organization and resided in the northern suburbs of Detroit, Michigan**

| Age and specific IgE | Total |            | Boys |            | Girls |            | <i>P</i> value, boys vs girls |
|----------------------|-------|------------|------|------------|-------|------------|-------------------------------|
|                      | No.   | % positive | No.  | % positive | No.   | % positive |                               |
| 2 years              |       |            |      |            |       |            |                               |
| Mite                 | 416   | 2.2        | 205  | 2.4        | 211   | 1.9        | 0.748                         |
| Cat                  | 418   | 13.2       | 205  | 11.2       | 213   | 15.0       | 0.311                         |
| Ragweed              | 417   | 8.4        | 205  | 6.8        | 212   | 9.9        | 0.292                         |
| Timothy              | 414   | 17.6       | 203  | 17.2       | 211   | 18.0       | 0.898                         |
| Any allergen         | 414   | 30.2       | 203  | 28.6       | 211   | 31.8       | 0.521                         |
| 4 years              |       |            |      |            |       |            |                               |
| Mite                 | 421   | 5.2        | 216  | 4.6        | 205   | 5.9        | 0.663                         |
| Cat                  | 420   | 19.1       | 216  | 13.9       | 204   | 24.5       | 0.006                         |
| Ragweed              | 421   | 11.4       | 216  | 14.8       | 205   | 7.8        | 0.031                         |
| Timothy              | 421   | 15.7       | 216  | 17.6       | 205   | 13.7       | 0.286                         |
| Any allergen         | 420   | 37.6       | 216  | 37.0       | 204   | 38.2       | 0.841                         |

\* "Positive" is defined as a value  $\geq 2.5$ .**TABLE 5. Comparison of change in degree of positive specific immunoglobulin E (IgE) from 2 years to 4 years of age, by gender,\* for children born from 1987 to 1993 to women who belonged to a health maintenance organization and resided in the northern suburbs of Detroit, Michigan**

| Gender and specific IgE | No. | % positive |         | Difference† | 95% CI‡      | <i>P</i> value |
|-------------------------|-----|------------|---------|-------------|--------------|----------------|
|                         |     | 2 years    | 4 years |             |              |                |
| <i>Both sexes</i>       |     |            |         |             |              |                |
| Mite                    | 307 | 2.9        | 5.5     | 2.6         | -0.4 to 5.6  | 0.088          |
| Cat                     | 308 | 14.3       | 21.4    | 7.1         | 2.4 to 11.9  | 0.004          |
| Ragweed                 | 308 | 9.1        | 11.0    | 1.9         | -1.5 to 5.4  | 0.273          |
| Timothy                 | 305 | 17.1       | 14.4    | -2.6        | -7.2 to 2.0  | 0.267          |
| Any allergen            | 304 | 31.3       | 38.8    | 7.6         | 1.2 to 13.9  | 0.021          |
| <i>Boys</i>             |     |            |         |             |              |                |
| Mite                    | 158 | 3.2        | 3.8     | 0.6         | -3.1 to 4.4  | 0.739          |
| Cat                     | 158 | 11.4       | 15.8    | 4.4         | -1.7 to 10.6 | 0.162          |
| Ragweed                 | 158 | 7.0        | 15.2    | 8.2         | 3.0 to 13.5  | 0.003          |
| Timothy                 | 156 | 18.0       | 18.0    | 0.0         | -6.6 to 6.6  | 0.999          |
| Any allergen            | 156 | 29.5       | 38.5    | 9.0         | 0.4 to 17.6  | 0.043          |
| <i>Girls</i>            |     |            |         |             |              |                |
| Mite                    | 149 | 2.7        | 7.4     | 4.7         | 0.0 to 9.4   | 0.052          |
| Cat                     | 150 | 17.3       | 27.3    | 10.0        | 2.7 to 17.3  | 0.009          |
| Ragweed                 | 150 | 11.3       | 6.7     | -4.7        | -8.9 to -0.4 | 0.035          |
| Timothy                 | 149 | 16.1       | 10.7    | -5.4        | -11.8 to 1.0 | 0.102          |
| Any allergen            | 148 | 33.1       | 39.2    | 6.1         | -3.3 to 15.5 | 0.208          |

\* Comparison of the difference between boys and girls in change from 2 to 4 years yielded *p* values of 0.180 for mite, 0.246 for cat, 0.001 for ragweed, 0.254 for timothy, and 0.653 for any allergen.

† Difference in percent positive between 2 and 4 years of age.

‡ CI, confidence interval.

non-atopic nonsmokers, except in age group 6–20 years, where IgE levels in boys were slightly higher than those in girls. Other studies (10, 14, 15, 24) have suggested that young boys have higher total IgE levels than girls by late childhood.

To our knowledge, no data have been reported regarding specific IgE concentrations by gender in young children. As with total serum IgE, the pattern of

specific IgE responses also varied by gender in our study population. Between 2 and 4 years of age, there was little change in boys except for an increase in ragweed-specific IgE, whereas in girls there was considerable change with the indoor allergen IgEs increasing and the seasonal allergen IgEs decreasing. As isolated findings, these differences in allergen-specific IgE would be of questionable significance; however,

they are consistent with the findings of others showing more allergic disease in boys than girls prior to puberty (33). We also considered the possibility that these changes in specific IgE levels were caused by technical problems related to the low total IgE concentrations typical of pediatric samples or the transfer technique we employed for the measurements. If technical problems had influenced results, they should have affected samples from boys and girls equally since the samples were not segregated by gender during analysis. Controls run within all assays showed no evidence that the sensitivity of the assays changed over the course of the study (data not shown).

The decline with age in the prevalence of positive tests for some of the specific IgEs was unexpected. Several previous studies (22, 23, 34) have also shown decreasing prevalence of food-specific and aeroallergen-specific IgE during early childhood. These studies have been interpreted by some as evidence of gradual maturation of the immune system resulting in a dampening of IgE responses.

The wide overlap we found in total IgE concentrations between non-atopic and atopic children is similar to that previously reported for older children and adults (7). While this overlap reduces the diagnostic value of total serum measurements for allergic disease, it is interesting that studies in both children and adults have shown stronger correlations between total serum IgE and asthma than between allergen-specific IgE and asthma. This closer association of total IgE with asthma challenges some assumptions about the relationship between allergic disease and asthma. The association between total IgE and asthma, and our observation that total IgE increases more rapidly in boys than girls during early childhood is consistent with the many previous reports of a higher prevalence of asthma among boys than girls prior to puberty (35).

Our data indicate that gender differences in the production of IgE are present by 2 years of age. The early appearance of these differences suggests that there are gender-related genetic differences in IgE control. These gender differences in IgE development may be related to the differences in risk factors associated with asthma and differences in the prevalence of asthma between boys and girls. Further analyses of environmental factors that might play a role in IgE development in this cohort are ongoing.

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