

Total serum IgE and its association with asthma symptoms and allergic sensitization among children

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Background: Asthma and wheezing during childhood are associated with elevated total serum IgE and with allergic sensitization to local aeroallergens. However, little is known about the longitudinal relationship between total serum IgE and the development of wheezing and allergic sensitization during childhood.

Objective: The purpose of our investigation was to determine the relationship between total serum IgE and the development of wheezing and allergic sensitization in childhood.

Methods: Our study subjects were participants in the Tucson Children's Respiratory Study who underwent an IgE measurement in at least 1 of 3 surveys (at years 1, 6, and 11) and complete allergy skin tests during the latter 2 surveys. The children's phenotypes were categorized on the basis of skin test response (never, early, and late) and wheezing status (never, early, late, and persistent). Repeated-measures analyses were used, allowing subjects to be included who had unequal numbers of IgE observations (a total of 263 boys and 277 girls).

Results: We found that total serum IgE levels track with age: subjects with high serum IgE levels less than 1 year old continued to have high IgE levels at ages 6 and 11 years. Both persistent wheezing and early sensitization were associated with high serum IgE levels at all ages. Boys who had late or persistent wheezing or who were sensitized early or late had high serum IgE levels as early as age 9 months, whereas only girls with persistent wheezing and early sensitization had elevated IgE levels at that age. Children who wheezed only in the first years of life and not after (ie, those with early wheezing) had serum IgE levels that were not different from those of nonwheezing children.

Conclusion: On the basis of these findings we conclude that although total serum IgE tracks with age, children who are predisposed to persistent wheezing and early sensitization to local aeroallergens already have high levels of IgE at age 9 months. This suggests that the predisposition to respond to environmental stimuli through high levels of IgE precede early allergic sensitization, indicating that there may be a common

defect in the development of the immune system involving IgE production and early allergic sensitization. (*J Allergy Clin Immunol* 1999;104:28-36.)

Key words: Skin test, wheeze phenotypes, epidemiology, longitudinal, IgE, allergy

Although numerous epidemiologic studies have shown strong associations between total serum IgE levels, skin test reactivity to aeroallergens, and asthma prevalence,¹⁻⁹ the nature of these associations is still not well understood. It has been proposed, for example, that noncognate production of IgE (ie, production of IgE that is not driven by one or a few specific allergens) is a significant inherited risk factor for the development of asthma.⁵ Burrows et al¹ have recently shown that subjects with a diagnosis of asthma have total serum IgE levels that are markedly higher than those expected based on the level of IgE observed in their parents. Accordingly, the high levels of total serum IgE observed in asthmatic subjects could be largely explained by the tendency of asthmatic subjects to produce more IgE as a consequence of the inflammatory process in the asthmatic airway. Our own data from the Tucson Children's Respiratory Study have shown that children who later have persistent wheezing during childhood have increased IgE levels even before the development of symptoms. This is in contrast to children who wheezed only in the first few years of life and did not have increased IgE levels.¹⁰

Recent studies by Peat et al⁶ have further illustrated the complex relations between skin test reactivity to allergens and incidence of asthma. These authors found that early (before age 8 years), but not late, allergic sensitization to common aeroallergens was associated with increased risk for the development of bronchial hyperresponsiveness and asthma. Preliminary analyses of data from the Tucson Epidemiological Study of Obstructive Airway Disease (Sherrill, unpublished results) confirm these findings and suggest that late allergic sensitization is associated with lower levels of IgE than early allergic sensitization. These results indicate that longitudinal approaches may be needed to determine the complex relationship between timing of allergic sensitization, longitudinal increases in total serum IgE levels in early life, and the different wheeze phenotypes during childhood.

Because it is well documented that IgE levels are strongly related to allergic sensitization and childhood

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Supported by the US National Heart, Lung, and Blood Institute SCOR Grant HL14136 and NHLBI ROI HL56177.

Received for publication July 18, 1997; revised Mar 17, 1999; accepted for publication Mar 17, 1999.

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0091-6749/99 \$8.00 + 0 1/1/98668

Abbreviation used

REM: Random-effects model

asthma,¹⁻⁴ the current longitudinal analyses examine how total serum IgE (as the dependent variable) changes over time in relation to allergic sensitization at ages 6 and 11 years and to different wheeze phenotypes expressed during childhood.

METHODS

Subjects

Children who were eligible for this study were enrolled in the Tucson Children's Respiratory Study between May 1980 and October 1984.¹¹ Their parents were members of Group Health Associates, a large health maintenance organization in Tucson, Arizona, and were contacted shortly after their children were born regarding participation in the Tucson Children's Respiratory Study. Informed consent was obtained from the parents of 1246 newborns. Children selected for these analyses were required to have at least 1 IgE measurement in 1 of 3 surveys (at years 1, 6, and 11), to have complete allergy skin tests during the latter 2 surveys, and to have complete responses to specific questionnaires concerning respiratory health.

Total serum IgE analysis

Total serum IgE levels were measured from blood obtained during the year-1, year-6, and year-11 surveys. Sera were frozen at -80°C until assayed, and IgE levels were assayed by the paper radioimmunosorbent test by using commercially available kits (Pharmacia Diagnostics, Piscataway, NJ). As previously described,¹² the assay threshold was regarded as 0.1 IU/mL. Each sample was assayed in duplicate, and the mean of the 2 IgE values was used in the analyses. Because the distributions of the raw IgE values tend to be heavily skewed,¹³ they were log-transformed for analyses. Tables listing results from IgE analyses were converted back to original units (IU).

Allergy skin tests

During the year-6 and year-11 surveys, children underwent allergy skin prick tests to 7 aeroallergens common in the Tucson area (house dust mix, olive, Bermuda grass, mulberry, mesquite, careless weed, and *Alternaria* spp).¹⁴ Histamine and a control consisting of 50% glycerine were also applied. Wheal size was recorded as the sum of the 2 diameters at right angles to each other in millimeters.

Skin prick test responses were considered to be positive at any survey if the wheal size of any allergen was greater than 2 mm after subtraction of the control value. Children who had positive skin test responses at the year-6 survey were classified as being "early sensitized," whereas those who had negative skin test responses at the year-6 survey but positive skin test responses at the year-11 survey were classified as being "late sensitized." Subjects who had negative skin test responses during both surveys were considered "non-sensitized." Children who were not skin tested at age 11 but had negative skin test responses at age 6 were excluded from analysis.

Respiratory symptoms

Questionnaires regarding respiratory health of the children were completed during the year-3, year-6, and year-11 surveys. Among other questions, parents were asked whether the child's "chest had ever sounded wheezy or whistling apart from colds" and how frequently the child wheezed. Children were considered to be currently wheezing during any survey in which the parents reported 1 or more wheezing episodes during the past year. In the current analy-

ses 4 phenotypes of wheezing were established. Children who were wheezing during the year-3 survey and not wheezing thereafter were classified as "early wheezers"; children who were "non-wheezers" at the year-3 survey but started wheezing at either the year-6 or year-11 surveys were considered "late wheezers"; and children who were nonwheezers or current wheezers at all 3 surveys were classified as "never" and "persistent" wheezers, respectively. Children who did not have responses to the wheeze question in all 3 surveys were excluded from analysis.

Statistical methods

The longitudinal IgE data were analyzed by using repeated-measures analysis. Because of missing observations, we used a random-effects model (REM).¹⁵ Jones et al^{16,17} have recently demonstrated how the REM procedure, which is generally used for unequally spaced continuous longitudinal data, can also be used for equally spaced data by implementing a "saturated" model. The saturated model fits polynomials, which have order one less than the number of time points to each subgroup. For our data, this meant fitting a quadratic or second-order polynomial because there were 3 time points. A saturated model allows every time point for each subgroup to have a different mean value. The likelihood ratio test, which was calculated as the change in $-2\ln(\text{likelihood})$ between nested models, was used to test for significant differences between groups and group-by-time interactions. For example, to test whether the mean IgE values of persistent wheezers had a different temporal pattern than that of the reference group, a model fitting both groups with quadratic polynomials would be compared with a reduced model, in which the reference group was fitted with a quadratic polynomial and the persistent wheezers were fit with a model containing only an intercept term. Here, a significant increase in $-2\ln(\text{likelihood})$ between these 2 models would indicate that persistent wheezers have a significantly different group-by-time interaction or temporal pattern than the reference group. If the change in $-2\ln(\text{likelihood})$ was not significant but the intercept coefficient estimated for persistent wheezers was, this would imply that the 2 groups had similar temporal patterns in their mean IgE values but that the persistent wheezers differed by a constant amount at each time point. The intercept coefficient would thus be an estimate of this difference, which we call a significant group difference. If this latter intercept coefficient was not significantly different from zero, this indicates no significant differences between the mean IgE values of persistent wheezing and the reference group at any time points.

Three separate repeated-measures analyses were performed on the IgE data. The first (model 1) included only the variables of skin test sensitization, the second (model 2) included only the wheeze phenotypes, and the third (model 3) combined sensitization and the wheeze phenotypes and their appropriate 2-way interaction terms. Because sensitization and wheezing were not assessed during the same surveys as IgE, they were included in the REM analyses as fixed covariables. In other words they could only be included as time-dependent covariables if they were assessed during the same surveys as IgE. However, because there were only 3 time points, the sensitization and wheezing categories were exhaustive (ie, they covered all possible combinations). Three different forms of within-subject covariance structures were considered for each REM analyses, first-order autoregressive, uncorrelated or independent, and the toplitz. The best fitting structure was determined by using Akaike Information Criteria, with the model fully saturated. For all analyses, the uncorrelated covariance structure yielded the best overall fit.

Because it is known that both wheezing prevalence and serum IgE levels differ by sex,⁸ we initially analyzed the data stratified by sex. However, if the stratified results were similar for both sexes, we then combined the 2 groups and included a sex-indicator variable to obtain

TABLE I. Descriptive statistics for subjects who had at least 1 IgE assessment and whose wheezing status could be determined in all 3 surveys

	Boys	Girls
N	263	277
Age (y)*		
Survey year 1	0.84 ± 0.21	0.88 ± 0.24
Survey year 6	6.10 ± 0.58	5.98 ± 0.66
Survey year 11	10.68 ± 0.46	10.74 ± 0.46
Total follow-up (y)*	5.75 ± 4.39	5.45 ± 4.48
Mean no. of observations*	1.95 ± 0.77	1.90 ± 0.78
Sensitization†, no. positive (%)		
Early‡	103 (39.2)	73 (26.4)
Late	36 (13.7)	34 (12.3)
Wheeze†, no. in category (%)		
Never‡	115 (43.7)	171 (61.7)
Early	29 (11.0)	25 (9.0)
Late‡	73 (27.8)	56 (20.2)
Persistent‡	46 (17.5)	25 (9.0)
Interactions, no. in category (%)		
Late sensitization		
Late wheezing	9 (3.4)	8 (2.9)
Persistent wheezing	3 (1.1)	5 (1.8)
Early sensitization		
Late wheezing	24 (9.1)	34 (12.3)
Persistent wheezing	13 (4.9)	30 (10.8)
Distribution of IgE samples		
One sample	32%	35%
Two samples	40%	38%
Three samples	28%	27%

*Means ± SD.

†Count (%).

‡Chi-Square, $P < .05$.

maximum statistical power. Results from the REM analyses are presented as means and SEMs instead of as actual coefficients, which are not always directly interpretable. Statistical hypotheses tests were 2-tailed comparisons, with significance at an α value of .05.

RESULTS

There were 263 boys and 277 girls who met the inclusion criteria. Table I shows descriptive statistics for these subjects. The average ages were similar for boys and girls, with mean estimates around 1, 6, and 11 years of age for those surveys in which IgE measures were taken. Boys and girls had similar lengths of follow-up and numbers of observations. There were significantly more boys than girls who were sensitized early ($P < .002$) and more boys than girls with late and persistent wheezing symptoms ($P < .05$). The number of subjects who were sensitized late and reported either late or persistent wheezing was quite small (range, 3 to 9). Approximately 30% of study participants had either 1 or 3 IgE assessments, and there were no significant differences between boys and girls in their distribution of number of samples.

Association between IgE and skin test sensitization

The results of fitting model 1 to the IgE data are listed in Table II and illustrated in Fig 1. For all sensitization

groups, (nonsensitized, late, and early), mean IgE values increased with age. Boys who were sensitized either early or late had significantly higher IgE levels compared with nonsensitized boys at all ages and also had significantly higher IgE levels than sensitized girls at all ages ($P < .02$; Fig 1). Interestingly, IgE levels at age 1 year in boys were significantly higher ($P \leq .01$) in both sensitized subgroups compared with the nonsensitized subgroup. At both ages 6 and 11 years, boys sensitized early had significantly higher IgE levels than those sensitized late. Among girls (Fig 1), there were no differences in mean IgE related to sensitization at age 1 year, and only the early-sensitized subjects had significantly ($P \leq .05$) elevated IgE levels at age 6 years compared with the nonsensitized subjects. By age 11 years, both early- and late-sensitized girls had significantly ($P \leq .01$) elevated IgE values compared with nonsensitized girls. As in boys, early-sensitized girls also had significantly higher mean values than late-sensitized girls.

Association between IgE and wheeze phenotype

The stratified REM results for the wheeze phenotypes (model 2; Table III) showed similar temporal patterns for both sexes, and thus data for both boys and girls were combined for subsequent analyses with inclusion of a sex-indicator variable. The results show that boys and girls classified as having late or persistent wheezing symptoms had significantly higher mean IgE values than those with no wheezing symptoms. For boys and girls there were no significant differences in mean IgE values between the early wheezing and the nonwheezing category, even in the combined analysis, where maximal power was achieved. Examination of the mean plots (Fig 2) indicates that there were no differences in mean IgE related to wheezing at age 1 year. At ages 6 and 11 years, both boys and girls with persistent and late wheezing had significantly higher IgE levels than did nonwheezing children. Children reporting persistent wheezing had significantly ($P \leq .05$) higher IgE values than late-wheezing children at age 6 years, but not at age 11 years, again for both sexes. Temporal patterns of IgE with age were similar for boys and girls. However, boys had significantly higher IgE levels than girls in all wheezing categories.

Association between IgE levels, wheezing, and skin test sensitization

The results of fitting model 3 are listed in Tables IV and V. This model was used to determine whether the effects found separately in models 1 and 2 were indeed independent or whether they behaved in a synergistic manner. For boys (Table IV), the main effects of wheezing and sensitization, which were statistically significant in independent analysis, remained significant in the combined analysis. However, the expected mean IgE values, as a main effect related to wheezing, were substantially less after adjusting for sensitization, whereas in contrast, the mean IgE values related to sensitization were essentially unchanged. For example, model 2 yields mean esti-

TABLE II. Mean IgE (IU) and 95% confidence intervals for skin test sensitization*

	Survey year 1	Survey year 6	Survey year 11
Girls' sensitization			
Nonsensitized	3.42 (2.76, 4.24)	16.12 (12.01, 21.63)	20.91 (15.58, 28.05)
Late [†]	3.56 (2.18, 5.81)	26.31 (14.90, 46.45)	74.44 (43.00, 128.87)
Early [†]	3.90 (2.79, 5.44)	57.40 (38.03, 86.63)	177.68 (122.44, 257.86)
Boys' sensitization			
Nonsensitized	3.49 (2.65, 4.59)	11.59 (8.14, 16.49)	18.36 (12.65, 26.64)
Late [†]	6.30 (3.93, 10.08)	36.97 (21.35, 63.99)	90.02 (50.99, 158.92)
Early [†]	6.49 (4.84, 8.71)	151.41 (108.51, 211.28)	242.26 (177.04, 331.49)

*Statistical comparisons made by using saturated random-effects model 1 (see Statistical methods section for more details).

[†]Statistically significant group and group-by-time differences compared with nonsensitized subjects.

TABLE III. Mean IgE (IU) and 95% confidence intervals for wheeze phenotypes*

	Survey year 1	Survey year 6	Survey year 11
Girls' wheezing			
Nonwheezers	3.19 (2.57, 3.96)	19.30 (14.96, 24.90)	34.47 (27.24, 43.61)
Early	2.34 (1.58, 3.46)	14.44 (9.57, 21.79)	25.79 (17.09, 38.92)
Late [†]	3.94 (2.88, 5.38)	42.52 (26.05, 69.41)	101.49 (71.32, 144.43)
Persistent [†]	4.81 (3.18, 7.25)	79.04 (48.42, 129.02)	130.32 (79.84, 212.72)
Boys' wheezing			
Nonwheezers	4.39 (3.54, 5.45)	26.58 (20.60, 34.29)	47.47 (36.79, 61.24)
Early	3.29 (2.22, 4.86)	20.09 (13.31, 30.31)	35.87 (24.24, 53.09)
Late [†]	5.42 (4.04, 7.27)	58.56 (41.15, 83.33)	139.77 (98.22, 198.90)
Persistent [†]	6.62 (4.47, 9.80)	107.77 (67.33, 172.50)	179.47 (112.12, 287.26)

*Statistical comparisons made by using saturated random-effects model 2 (see Statistical methods section for more details).

[†]Statistically significant group and group-by-time interactions compared with nonwheezers.

TABLE IV. Mean IgE (IU) and 95% confidence intervals including wheezing and skin test sensitization as main effects and wheezing-by-sensitization interactions for boys*

	Survey year 1	Survey year 6	Survey year 11
Main effects			
Wheezing			
Nonwheezers	2.97 (2.17, 4.07)	9.78 (6.61, 14.47)	12.81 (8.65, 18.95)
Early	2.36 (1.42, 3.93)	7.92 (4.58, 13.72)	10.38 (6.00, 17.97)
Late [†]	4.48 (2.86, 7.03)	19.11 (9.43, 38.69)	54.60 (27.49, 108.42)
Persistent [‡]	5.70 (2.93, 11.09)	18.54 (8.98, 38.29)	24.53 (12.11, 49.68)
Sensitization			
Early [†]	7.39 (4.53, 12.06)	116.75 (67.44, 202.11)	217.02 (132.95, 354.25)
Late [†]	5.42 (3.13, 9.38)	28.50 (14.35, 56.60)	60.34 (30.99, 117.50)
Interactions			
Early sensitization			
Late wheezing [†]	5.37 (3.16, 9.11)	167.34 (98.57, 284.06)	259.82 (153.06, 441.07)
Persistent wheezing [†]	7.24 (4.27, 12.30)	204.38 (111.32, 375.25)	284.29 (157.91, 511.83)
Late sensitization			
Late wheezing	8.67 (3.52, 21.36)	57.40 (22.85, 144.20)	265.07 (97.55, 720.25)
Persistent wheezing	9.39 (3.26, 27.07)	48.91 (16.97, 140.95)	103.54 (34.55, 310.32)

*Statistical comparisons made by using saturated random-effects model 3 (see Statistical methods section for more details).

[†]Statistically significant ($P < .05$) group and group-by-time interactions compared with nonwheezers.

[‡]Statistically significant ($P < .05$) group differences compared with nonwheezers.

mates of “unadjusted” effect of persistent wheezing among boys of 6.62, 107.77, and 179.47, respectively, for ages 1, 6, and 11 years (Table III). By using model 3 to “adjust” for sensitization, means of 5.70, 18.54, and 24.53 for persistent wheezers at the same ages were obtained (Table IV). This suggests that the association between IgE and wheezing is explained in part by sensitization. Among boys (Table IV), late sensitization with

late or persistent wheeze interactions were not significant, but the interactions between early sensitization and late and persistent wheezing were significant. These significant interaction terms suggest that boys with late or persistent wheezing who were sensitized early had expected mean IgE levels that were different than one would predict based solely on the main effects of sensitization and wheezing alone (models 1 and 2). It is impor-

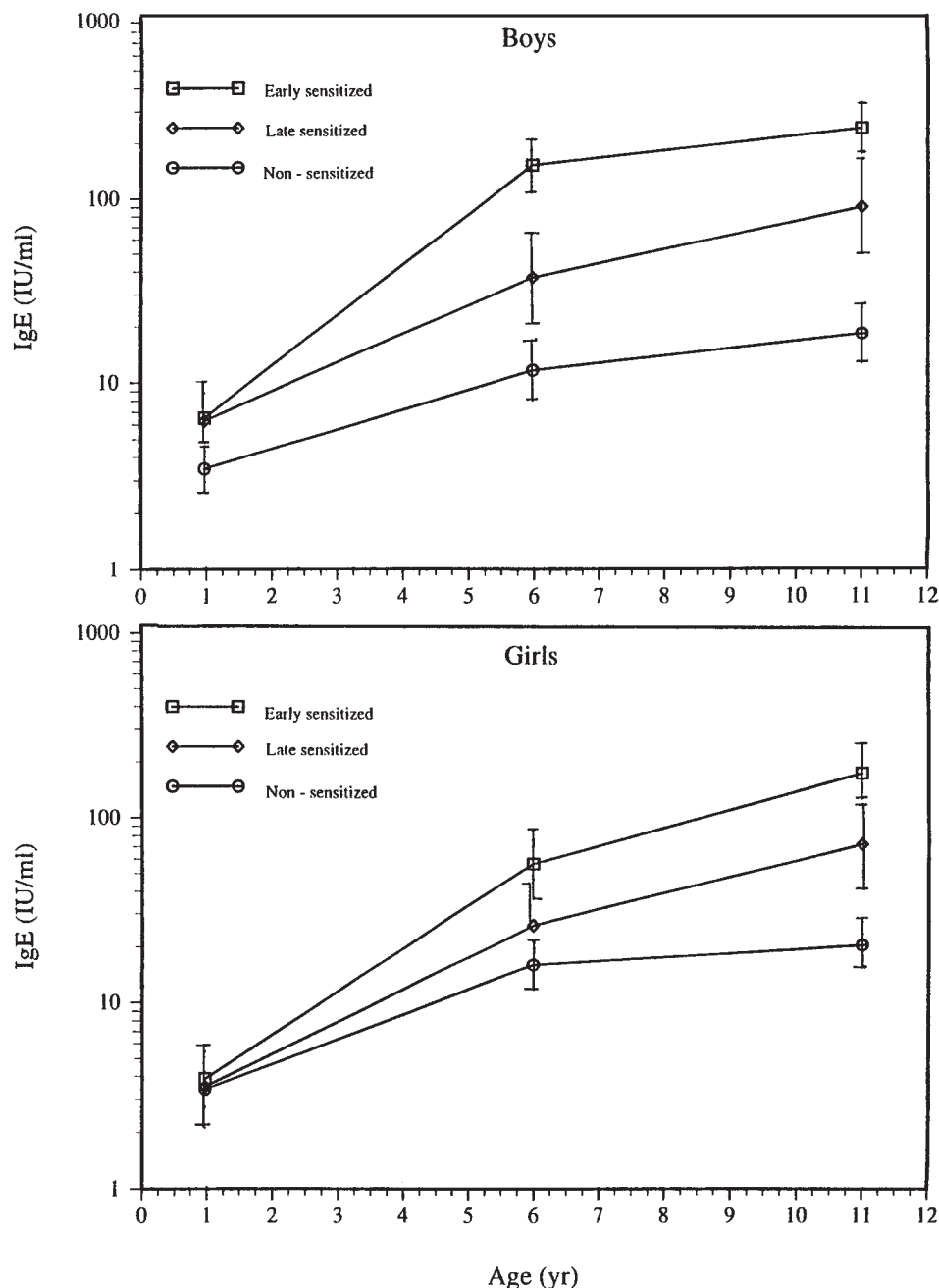


FIG 1. Mean IgE and 95% confidence intervals for model 1 with repeated-measures analyses (see text for details) for boys and girls. Children were considered early sensitized when they had at least 1 positive skin prick test response at age 6 years and late sensitized when they had at least 1 negative skin prick test response followed by a positive skin prick test response at age 11 years. Nonsensitized children had negative skin prick test responses at both ages (reference population).

tant to note that boys who were sensitized early had, independently, IgE levels almost as high as persistent wheezers who were also sensitized early (Fig 3). Mean IgE for boys who were both sensitized early and classified as persistent wheezers did not differ significantly from persistent wheezers at age 1 year but increased dramatically by age 6 years and changed very little thereafter.

The results of fitting model 3 to the girls (Table V)

showed that after adjusting for sensitization, the main effects of wheezing were no longer statistically significant, and the interaction of early sensitization and persistent wheezing was of borderline significance ($P = .06$). The plot of these results (Fig 3) illustrates that the changes in IgE between ages 1 and 6 years for early-sensitized persistently wheezing girls were not as dramatic as those observed among boys, but by age 11 years, mean

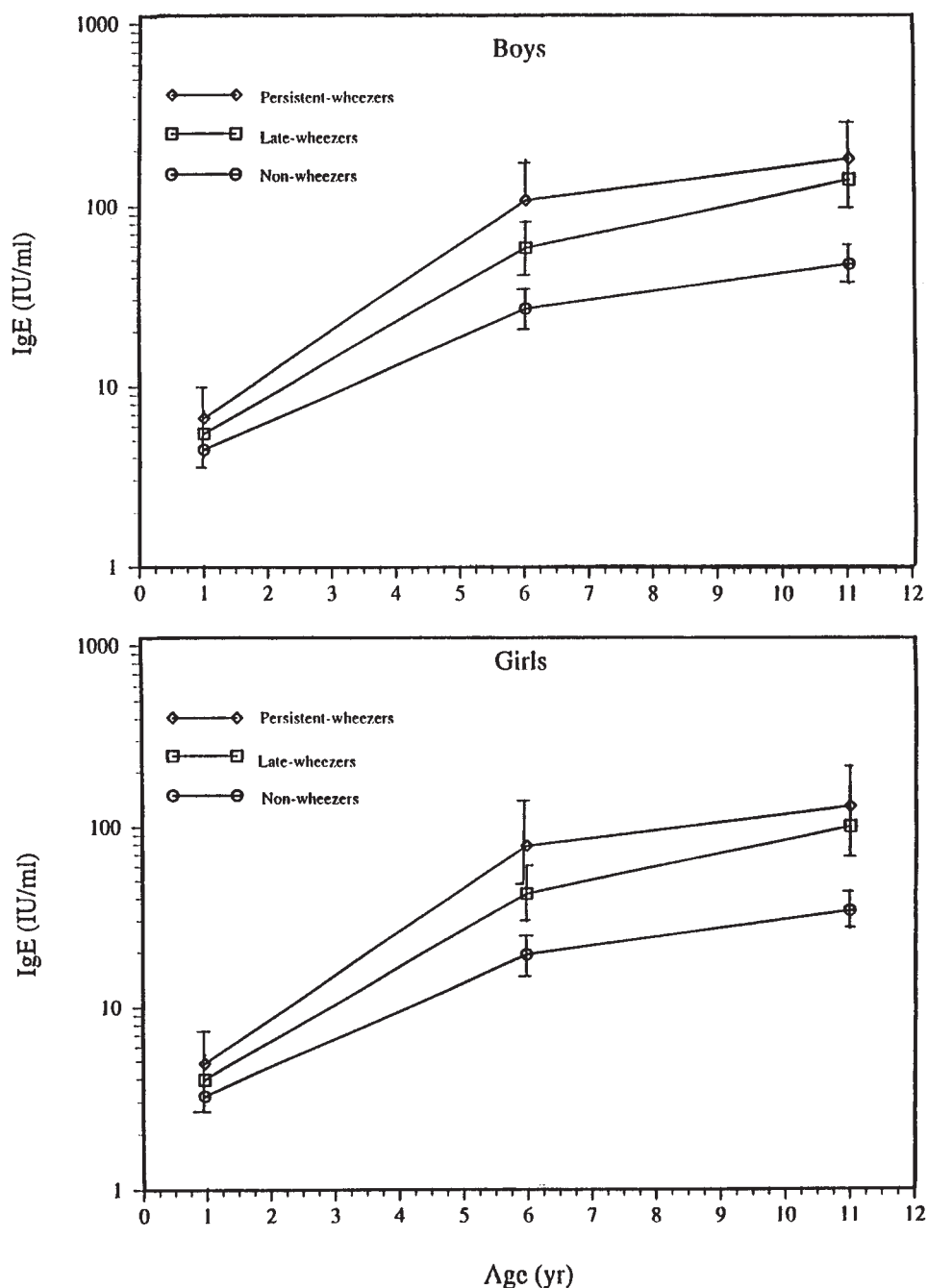


FIG 2. Mean IgE and 95% confidence intervals for model 2 with repeated-measures analyses (see text for details) for boys and girls. Children were considered persistent wheezers if they wheezed at all surveys (ie, years 1, 6, and 11) and late wheezers if they started wheezing at survey years 6 or 11 but not before. Children not wheezing in any survey were the reference population. Subjects who wheezed only in the year-1 survey and not after (ie, early wheezers) did not differ statistically from the reference population and were thus not plotted.

IgE levels for early-sensitized persistently wheezing boys and girls were comparable. Persistently wheezing early-sensitized girls had higher IgE levels than all other subgroups at all ages. This was statistically significant at age 1 year ($P < .02$) based on a single time point comparison. In this respect the mean IgE values of this subgroup behave similarly to those of their male counter-

parts. No other interaction terms were statistically significant for girls. As found with boys, the mean IgE values estimated for sensitization were essentially unchanged by the inclusion of wheezing phenotypes in the analysis, whereas those for wheezing were reduced.

Because other analyses in this study population have suggested ethnic differences in the asthma prevalence

TABLE V. Mean IgE (IU) and 95% confidence intervals including wheezing and skin test sensitization as main effects and wheezing-by-sensitization interactions for girls

	Survey year 1	Survey year 6	Survey year 11
Main effects			
Wheezing			
Nonwheezers	3.42 (2.76, 4.24)	16.12 (12.01, 21.63)	20.91 (15.89, 27.51)
Early	2.59 (1.55, 4.30)	11.94 (6.90, 20.67)	15.80 (9.31, 26.82)
Late	4.85 (2.92, 8.08)	22.42 (13.21, 38.06)	29.67 (17.48, 50.36)
Persistent	3.00 (1.35, 6.71)	13.87 (5.97, 32.23)	18.36 (7.90, 42.64)
Sensitization			
Early [†]	3.90 (2.79, 5.44)	57.40 (38.03, 86.63)	177.68 (122.44, 257.86)
Late [†]	3.56 (2.18, 5.81)	26.31 (14.90, 46.45)	74.44 (43.00, 128.87)
Interactions			
Early sensitization			
Late wheezing	3.78 (2.27, 6.29)	54.05 (30.62, 95.43)	172.43 (99.60, 298.51)
Persistent wheezing [‡]	6.75 (3.40, 13.41)	97.51 (48.15, 197.47)	311.06 (153.61, 629.92)
Late sensitization			
Late wheezing	2.92 (1.31, 6.51)	21.54 (9.27, 50.04)	59.74 (25.72, 138.77)
Persistent wheezing	7.39 (1.77, 30.90)	55.15 (12.68, 239.85)	151.41 (36.21, 633.21)

*Statistical comparisons made by using saturated random-effects model 3 (see Statistical methods section for more details).

[†]Statistically significant group and group-by-time interactions compared with nonwheezers.

[‡]Borderline ($P = .06$) statistically significant group differences compared with nonwheezers.

rates and possibly in IgE levels, we added ethnicity indicator variables for Hispanic parents to the best fitting model 3, which showed no statistically significant differences related to ethnicity.

DISCUSSION

Several prior studies have shown that asthma and recurrent wheezing during childhood are strongly associated with elevated serum IgE and with allergic sensitization to local aeroallergens.^{2,4,9} Recent studies have also shown that total serum IgE is elevated as early as 9 months of age in subjects with persistent wheezing.¹⁰ However, no previous studies have assessed the relationship of increased total serum IgE during childhood to the patterns of development of wheezing symptoms and allergic sensitization. In this longitudinal analysis we examined the association of timing of skin test sensitization and development of wheezing symptoms to the increase of total serum IgE levels during childhood.

We found that total serum IgE levels during childhood track markedly with age. Subjects who had high levels of serum IgE at age 9 months had higher levels of serum IgE than their peers at ages 6 and 11 years. This was true in spite of the fact that, as has been shown by others,¹⁸ children do not usually have detectable levels of specific IgE against local aeroallergens before the age of 3 years, although they may be sensitized to other allergens such as food. This finding suggests that genetic factors may control total serum IgE levels¹⁹ and that a pattern of increased IgE production in response to environmental antigens is established very early in life and persists through childhood. In support of this, subjects who had persistent wheezing (ie, boys and girls who were wheezing at the age of 9 months and would continue wheezing at ages 6 and 11 years) and who would become sensitized early in

life (defined in this study as having positive skin test responses to at least 1 aeroallergen at age 6 years) showed the highest levels of serum IgE throughout childhood.

Our results also emphasize the importance of timing of allergic sensitization. Children who became sensitized to common aeroallergens in our area by the age of 6 years already had high levels of IgE at age 9 months. Among boys this was true irrespective of wheezing status, although this was not the case among girls. Our study therefore suggests that the predisposition to respond to environmental stimuli with high levels of IgE precedes allergic sensitization and therefore that both high IgE production and early allergic sensitization may be the result of a common defect in the development of the immune system. Interestingly, Peat et al⁶ found that children with early-onset positive skin test reactivity (by age 8 to 10 years) were at higher risk of having bronchial hyperresponsiveness, a diagnosis of asthma, and persistence of wheezing by age 12 years compared with children who became sensitized at a later age. Thus it appears that both early allergic sensitization⁶ and high production of IgE in early life¹⁰ may be important risk factors for the development of asthma. Again, this implicates the pattern of development of the immune system in early years as an important determinant of a predisposition to asthma in childhood.

Our data also suggest that boys have a greater predisposition than girls toward development of increased serum IgE levels early in life. Boys who were early sensitizers and were either late or persistent wheezers had the highest serum IgE levels of all subgroups at ages 6 and 11 years (Fig 3). Interestingly, as early as age 9 months, all of the wheezing and sensitization subgroups showed serum IgE levels above those of nonwheezers and early wheezers (reference group). In contrast, only girls who were persistent wheezers and showed early

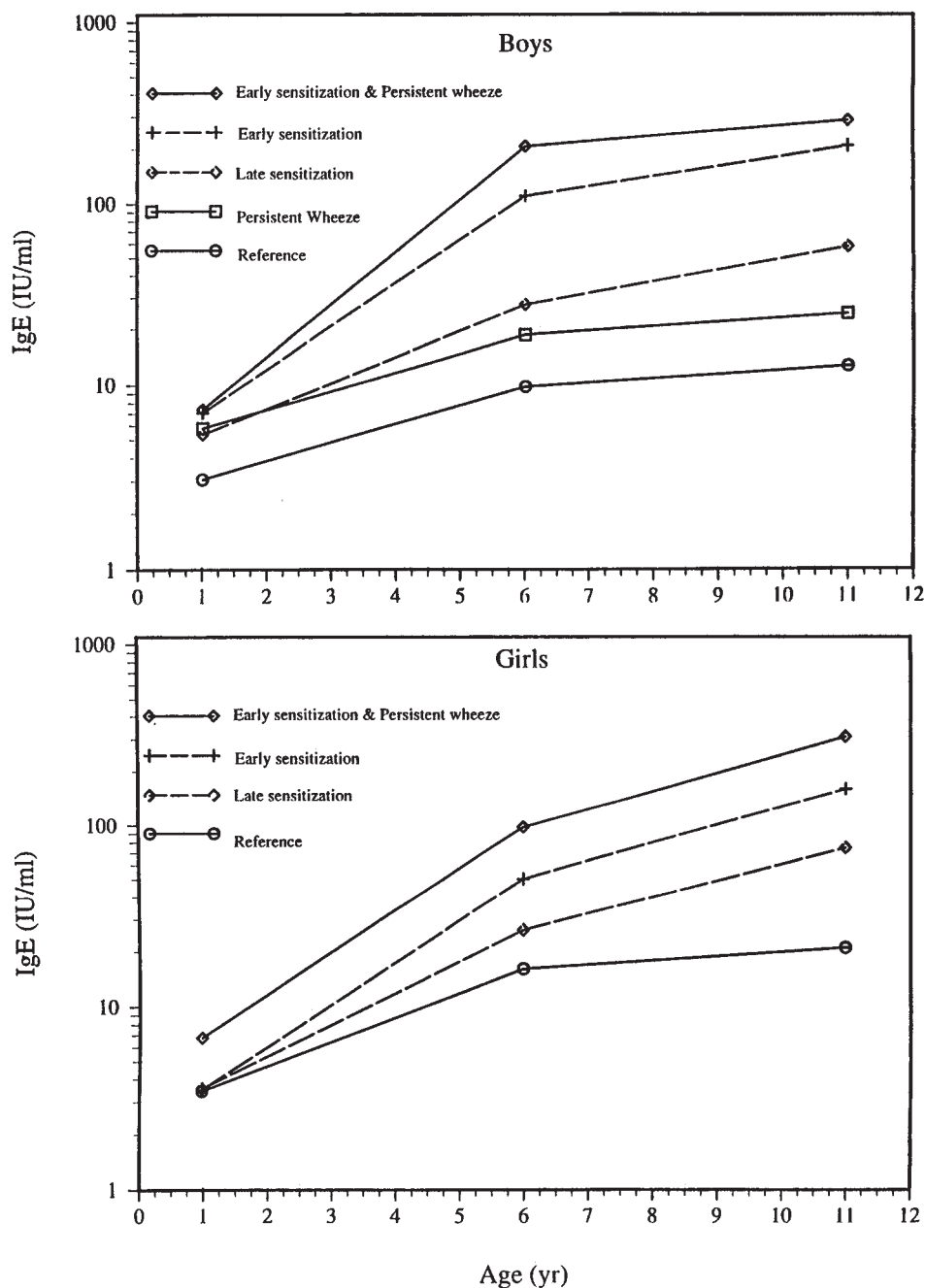


FIG 3. Mean IgE and 95% confidence intervals for model 3 with repeated-measures analyses (see text for details) for boys and girls. Plots are of significant main effects and interactions resulting from the longitudinal analyses, which included both skin test and wheeze categories (see Tables IV and V). Late wheezing was significant in the model for boys but was not plotted for clarity; their IgE curves overlapped with those of persistent wheezers.

sensitization had increased serum IgE levels in their first year. Our data do not offer any explanation of why serum IgE levels differ between boys and girls, but this difference may offer a partial explanation of the higher prevalence of asthma in boys than in girls in the first decade of life.^{20,21}

We were unable to detect any significant elevation of IgE levels among children who wheezed at the year-3

survey but not at later surveys (early wheezers). Wheezing at this early age, at least for the majority of children, appears to be a nonallergic condition. In a study of wheeze-induced lower respiratory tract illnesses during the first years of life in this same population,²² we also concluded that early wheezing did not appear to be an allergic condition. There is also a possibility that we did not have enough subjects in this subgroup and therefore

may not have had the necessary statistical power to demonstrate an association.

It is important to note that wheezing in early life is most often caused by viral lower respiratory tract infections, and the nature of the association between viral infections in early life and subsequent sensitization has not been clearly elucidated.²³⁻²⁵ The idea that viral infections in early life can prime the immune system (in susceptible subjects) is not new. Welliver et al²⁶ showed that children who had bronchiolitis in the first 6 months of life and persistent wheezing up to age 4 years had higher levels of respiratory syncytial virus-specific IgE at the time of the infection. This suggests that there is a selected group of infants with lower respiratory illnesses who are more prone to developing virus-specific IgE and having persistent wheezing. Our data also suggest that early wheezing is indeed associated with higher IgE levels, especially in conjunction with early sensitization. Whether the latter is the cause of early and/or persistent wheezing or whether infections associated with wheezing cause more sensitization and higher IgE remains to be clarified.

Although the elevated IgE levels observed among children who were both sensitized early and persistent wheezers were statistically significant at age 9 months, the large amount of variability seen clinically among individual patients would not make a high IgE level, by itself, a good measure for selecting subjects either at high risk for having wheezing symptoms or for having early sensitization.

One of the assumptions of the REM analyses is that missing observations are "missing completely at random." To test this assumption, we used a procedure recently published by Park and Lee²⁷ that defines indicator variables for each missing data pattern and then fits an extended model that includes these indicator variables and covariables of interest. Because none of these missing data indicator variables were significantly different from zero, we can assume the data are in fact "missing completely at random."

In summary, we have demonstrated that both time of sensitization and wheezing phenotypes are significant predictors of elevated IgE levels among children. When analyzed longitudinally, there is significant tracking of IgE with age, and children who are predisposed to persistent wheezing and early sensitization to local aeroallergens already have high levels of IgE at age 9 months.

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