

A longitudinal study of serum IgE in a community cohort: Correlations with age, sex, smoking, and atopic status

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A number of factors, including age, sex, smoking habits, and atopic status have been reported in cross-sectional studies to influence levels of serum IgE. We have examined the effects of these variables on serum IgE in a community population cohort of 1109 subjects during a longitudinal study in which two serum samples were obtained 8 years apart from each subject. For the entire cohort, mean serum IgE level changed little during the follow-up period (28.9 versus 26.0 IU/ml). Most of the decreases were observed in children and young adults. Subjects more than the age of 35 years demonstrated no systematic change in serum IgE levels. By the end of follow-up (when there were few subjects still less than 16 years of age), significant relationships of IgE to age could no longer be demonstrated in nonatopic subjects. Also, in the nonatopic subjects of this cohort, there were no significant differences in IgE levels between the sexes. Among atopic subjects, there was a clear tendency for IgE to decrease with age, with atopic women more than 35 years of age demonstrating greater declines in IgE levels during follow-up than men of comparable age. The IgE levels in atopic male subjects were significantly higher than in atopic female subjects after the age of 35 years. Smoking was associated with an elevation in serum IgE. In this cohort, the smoking effect appeared to be limited to male subjects. Among allergen skin test negative subjects at the start of the study, IgE levels >1 SD above the group mean were predictive of the subsequent development of allergic skin test reactivity. Although these findings confirm many findings from cross-sectional studies, they provide additional information concerning the epidemiology of IgE in the general population. (J ALLERGY CLIN IMMUNOL 1987;79:919-27.)

Since IgE was identified by Ishizaka and Ishizaka¹ and Johansson et al.² in the late 1960s, a large number of variables have been demonstrated to have strong relationships with serum IgE, making it difficult to define normal population values. The earliest of these was allergen skin test reactivity and/or allergic disease.³⁻⁴ This relationship, with as little as one 2 mm skin test reaction, has been confirmed in many studies.⁵⁻¹⁰ An even greater relationship with extremely high values was described in parasitic disease by Merrett et al.¹¹ More recently, the emphasis in a number of population studies has been on the effects of age,

sex, and smoking. Some years ago, Delespesse et al.¹² found lower levels of IgE in older (more than 70 years of age) compared to younger (less than 40 years of age) adults. More recently, Barbee et al.⁶ and Grundbacher and Massie,⁹ among others, have reported that peak values occur toward the end of the first decade, with a rapid decline during teenage years. After this early decline, most adult studies have demonstrated a continuing decrease in IgE with age,^{6, 8, 10, 13} usually more pronounced in female than male adults. However, Holford-Strevens et al.⁵ found no age-related decline in nonatopic adults aged 20 to 65 years.

If there has been general agreement concerning the effects of atopy and age on IgE levels, the influences of sex and cigarette smoking have not been universally appreciated. After the observation of Gerrard et al.¹⁴ that smokers had higher IgE levels than nonsmokers, Burrows et al.¹⁵ confirmed the finding and found that the effect increased with age and was independent of allergy skin test reactivity. Several subsequent studies confirmed a smoking-IgE relationship.¹⁶⁻²⁰ Freidhoff et al.,¹⁰ however, found IgE levels of male subjects

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Supported by National Heart, Lung, and Blood Institute Specialized Center of Research Grant HL 14136.

Received for publication May 9, 1986.

Accepted for publication Nov. 24, 1986.

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to be higher than levels of female subjects without a significant smoking relationship. In a retrospective follow-up study, Rawle et al.¹³ also found no smoking effect. All the studies noted above have been cross-sectional. Thus, the several variables that may impact on IgE levels have been observed at a single point in time. Longitudinal studies have been limited to infants and children. In these studies, the emphasis has been on genetic factors and the predictive nature of excess IgE levels early in life.²¹⁻²⁴

In 1981 we described the age, sex, and atopic relationships of IgE in a community population sample.⁶ Subsequently, the effects of smoking on IgE were reported in this same population.¹⁵ In this article, we have examined the relationship of these factors and the changes in IgE that have occurred during an 8-year follow-up period in a cohort of 1109 subjects from this community sample. The predictive value of IgE levels in subjects who were initially allergen skin test negative is also described.

METHODS

Study population

The initial study population consisted of a random stratified cluster sample of more than 1600 white, non-Mexican-American households in Tucson, Ariz. Details of the selection process and the study methods have been reported.²⁵ Follow-up data have been obtained on this population in five additional surveys during 8 years as part of a longitudinal study of the development of airway obstructive disease in this community population. During the first survey of the population, all subjects aged 3 years and older were asked to undergo skin testing with five commercially available allergens. Those aged 6 years and older had venous blood collected for total serum IgE determinations. The prevalence of allergen skin test reactivity in 3102 subjects has been reported.²⁶ Similar data concerning the distribution of IgE have also been described in 2743 subjects.⁶ During the sixth survey, 8 years later, allergen skin testing and venous blood sampling were again carried out. The cohort in this study consisted of 1109 subjects who were aged 6 years or older during the initial survey and had both allergen skin testing and serum IgE data recorded during both the first and sixth surveys. In no significant way does the cohort differ from cohorts for whom data were only available for survey 1. Mean ages for the followed and nonfollowed groups (in survey 1) were 44.9 and 43.4 years, respectively. Female subjects accounted for 56% of the cohort versus 53% in the nonfollowed group. Geometric mean IgE values for the followed and nonfollowed groups were 28.9 and 33.9 IU/ml, respectively. Subjects who never smoked made up 49.8% of the cohort compared to 47.4% of survey 1 only subjects. The mean period between testing for this cohort was 8.1 years (± 0.7), with a maximum of 10 years and 9 months and a minimum of 6 years and 4 months. For the analyses of relationships between IgE and smoking, subjects were categorized as follows: smokers had

the habit at the time of the initial survey and continued to smoke in survey 6. Exsmokers had stopped before survey 1 and continued to deny smoking subsequently. Nonsmokers denied ever having used cigarettes. Subjects who were nonsmokers or exsmokers in survey 1 and who subsequently started smoking and smokers who quit smoking between the first and sixth survey were excluded from analyses of smoking effects.

In order to compare the same subjects in survey 1 and survey 6, all ages in figures and the table are indexed to survey 1. Thus, for comparative purposes, subjects are demonstrated to be the same age on both surveys even though their sixth survey ages are an average of 8.1 years older.

Serum IgE determinations

On both surveys, venous blood samples were drawn from subjects aged 6 years and older, and serum was frozen at -70°C until it was analyzed. All determinations were carried out in the same laboratory by the PRIST (Pharmacia Diagnostics, Piscataway, N.J.) technique. Samples were run in duplicate, as was an aliquot of a reference serum in each batch. The survey 1 reference mean value was 68.1 IU/ml, with a 5.1% within-assay coefficient of variation and a between-assay coefficient of variation of 18.1%. Comparable data for survey 6 samples were 70.0 IU/ml for the reference serum mean with coefficients of variation of 4.8% and 19.2%, respectively. All IgE values are reported as the mean of duplicates.

Allergen skin testing

During both the first and sixth surveys, allergen prick tests were performed by trained nurses according to the method of Pepys.²⁷ Details of the skin test procedure and the derivation of a skin test index have been reported previously.²⁶ In brief, the skin test index is determined by grading the size of the reaction to each individual antigen on a scale of 0 to 4 where 0 is no reaction greater than a glycerol control reaction. Grades 1 to 4 were determined by the prevalence of reaction sizes in all subjects free of respiratory disorders or food or drug allergy in our originally enrolled community population. (For example, grade 4 was a reaction that occurred in not $>2\%$ of these subjects.) The sum of the grades for the five individual skin test reactions is the skin test index that can range from 0 to 20.

The same five antigen mixtures (Hollister-Stier Laboratories, Spokane, Wash.) were applied in the same concentrations in both surveys: house dust (1:10), Dematiaceae mold mix (1:100), Bermuda grass (1:20), tree mix (1:20), and weed mix (1:20). A control solution of 50% glycerol was also included. Although the antigen mixtures used in the two surveys were from different commercial lots, we were unable to detect any systematic difference in reactivity in the study population. For the purposes of this study, any reaction greater than control reaction was considered positive. Four categories of skin reactivity are described: consistently positive, consistently negative, conversion from initial negative to positive, and reversion from initial positive to negative.

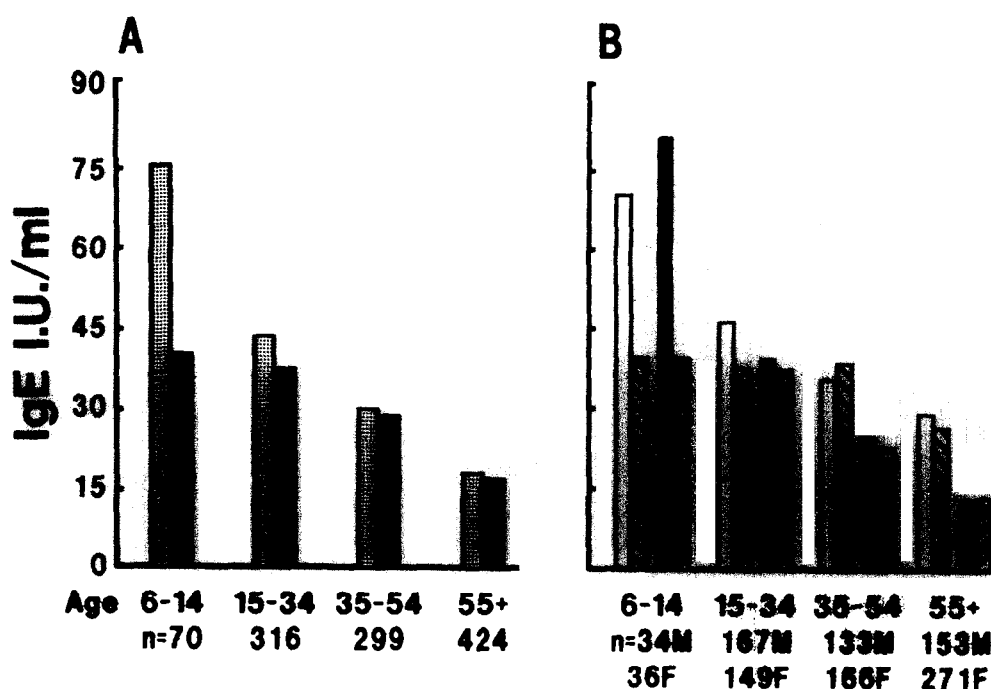


FIG. 1. The relationship of serum IgE with age and sex in surveys 1 and 6. A. Geometric mean IgE levels for survey 1 (stippled) and survey 6 (horizontal stripe) decrease significantly with age in both surveys ($p < 0.001$). A significant longitudinal change is present (between surveys 1 and 6) in the 6 to 14 years age group ($p < 0.001$) and in the 15 to 34 years age group ($p = 0.017$). Age groups for both surveys refer to ages at the time of survey 1. B. Data are separated by sex: male subjects ($\square$) in survey 1, male subjects ($\boxtimes$) in survey 6, female subjects ($\blacksquare$) in survey 1, and female subjects ($\boxtimes$) in survey 6. The longitudinal changes observed in A in the 6 to 14 years age group are also observed in sex-specific groups. Significant male versus female differences in IgE level are present for the 55 years plus age group in survey 1 and for both older age groups in survey 6.

Statistical methods

Data were analyzed on the University of Arizona DEC 10/CDC CYBER 175 computer system, with the Statistical Package for the Social Sciences programs. Analysis of variance was used to evaluate group differences; the paired t test was used for paired observations. $\log_{10}$ IgE values were used in parametric analyses, and mean values in this article are geometric means.

RESULTS

A number of studies have emphasized that IgE levels are dependent on a variety of factors. Among these factors are age, atopic status, and smoking habits. In some studies, a male versus female difference has also been described. Therefore, the data that follow will be presented in sequential fashion, starting with longitudinal IgE changes in the entire community cohort and then serially controlling for variables that have been said to affect those levels.

The longitudinal IgE data for all 1109 subjects are illustrated by age group in Fig. 1, A. The age groupings are based on age at the time of the initial survey in order that, for example, subjects who were less

than 15 years of age at that time continue to be listed as less than 15 years, although they were, on an average, 8.1 years older at the time of the sixth survey. A significant decrease in IgE with age is demonstrable in both surveys. A large and highly significant decline in serum IgE occurred longitudinally, also, in subjects who were initially aged 6 to 14 years. In survey 1 their geometric mean level was 75.7 IU/ml, compared to only 39.5 IU/ml 8 years later. A smaller, but still significant decline, was also present among 15- to 34-year-old subjects. Virtually no longitudinal change was noted in the older age groups. For the entire cohort the geometric mean level was 28.9 IU/ml in survey 1 and 26.0 IU/ml in survey 6. The same data, broken down by both age and sex, are illustrated in Fig. 1, B. In the youngest age group, survey 1 IgE levels in female subjects were slightly but not significantly higher than for male subjects (81.7 versus 70.0 IU/ml). By the sixth survey the levels for both sexes were essentially identical (39.3 versus 39.5 IU/ml). In young adults (aged 15 to 34 years), male subjects had higher initial levels, but again, there was no dif-

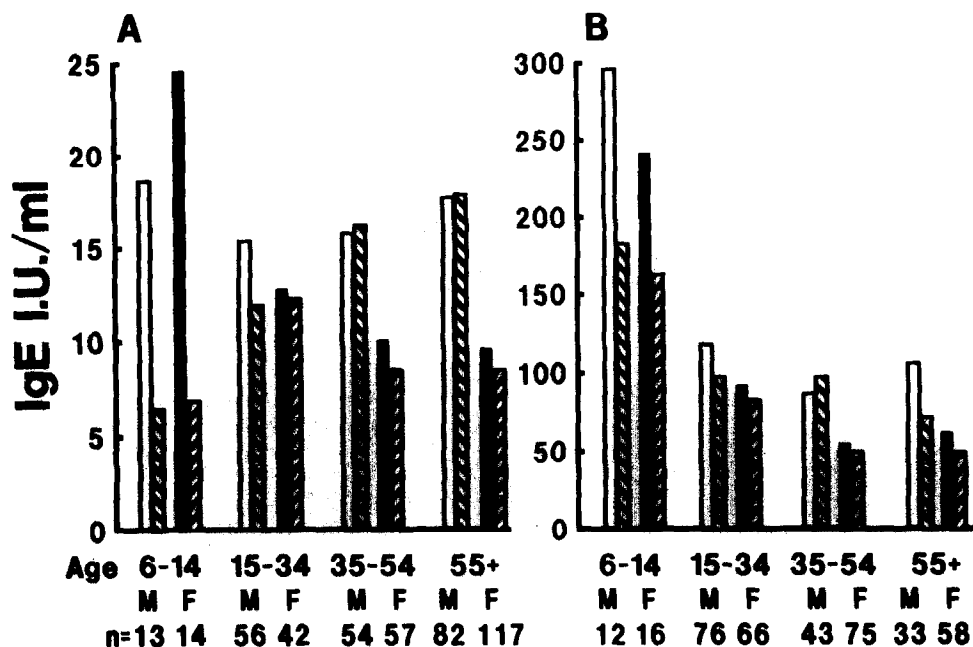


FIG. 2. Effects of sex and age on serum IgE levels in the presence and absence of atopy. **A.** Geometric mean IgE levels for all subjects who are allergen skin test negative in both surveys. Male subjects (□) in survey 1, male subjects (▨) in survey 6, female subjects (■) in survey 1, and female subjects (▩) in survey 6. Age groups for both surveys refer to ages at the time of survey 1. Longitudinal changes from survey 1 to survey 6 in the 6 to 14 years age group are significant. Levels in male subjects are significantly greater than in female subjects in 55 years plus age group in survey 1 and in both older age groups in survey 6. **B.** Geometric mean IgE levels in all subjects who are allergen skin test positive in both surveys. Bars are identified as in **A.** Longitudinal changes in IgE level in the youngest group are not significant. Male subjects have significantly higher IgE levels only in 35 to 54 years age group in survey 6.

ference in survey 6. For both older age groups, IgE levels for male subjects were higher initially and remained higher. Male subjects more than age 55 years, had consistently twice the level (28.9 and 26.6 IU/ml) as female subjects of the same age (13.8 and 13.5 IU/ml). These differences were highly significant ($p < 0.001$).

In Fig. 2, **A** and **B**, IgE data by age and sex according to atopic status are illustrated. Values in Fig. 2, **A** are for subjects who were allergen skin test negative on both surveys. Except for subjects who were initially less than 15 years of age, levels for each sex were quite constant during the 8-year follow-up period. For the entire group, the levels for male subjects in surveys 1 and 6 were 16.6 and 14.6 IU/ml, respectively, and for female subjects, 9.8 and 8.5 IU/ml. In subjects more than 35 years, this male versus female difference is significant. In subjects more than age 55 years, for example, male subject values were 17.7 and 17.9 IU/ml for surveys 1 and 6, respectively. For female subjects of comparable age, the values were 8.4 and 7.9 IU/ml, respectively. These sex differences are highly significant ($p < 0.001$).

Comparable values for the 379 subjects who had at least one positive skin test on both surveys are noted in Fig. 2, **B**. For female subjects, an age decline in IgE levels is apparent through the 35- to 54-year-old age group, both initially and at the time of follow-up. Most longitudinal decline in IgE in female subjects occurred in the 6- to 14-year-old age group, but in the sixth survey, levels still fell progressively with age from 163.3 IU/ml to 50.7 IU/ml in ages 35 to 54 years. IgE levels in young male subjects were slightly higher than in female subjects initially and underwent a similar decline with age up to age 34 years. In the 35- to 54-year-old age group especially, levels in male subjects were higher initially, and by the sixth survey, were almost twice those of female subjects (99.5 versus 50.7 IU). This difference is significant ($p = 0.012$).

It has been suggested that an additional factor that may affect IgE levels is cigarette smoking. To assess this smoking effect, longitudinal IgE data in smokers, exsmokers, and nonsmokers have been examined in both skin test positive and skin test negative male versus female subjects more than age 35 years. These

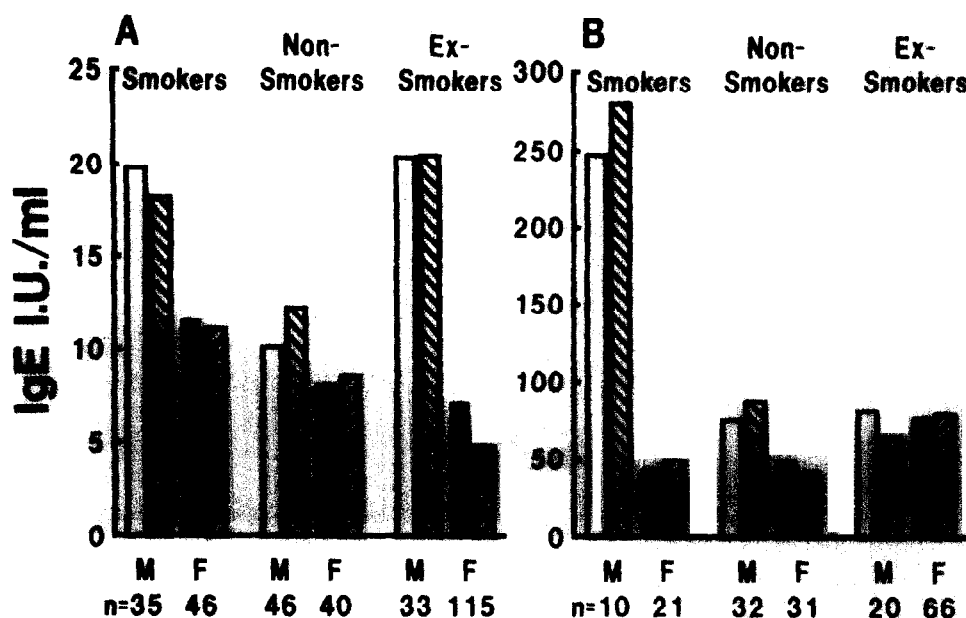


FIG. 3. The relationship of smoking status on serum IgE level in surveys 1 and 6 for subjects 35 years of age and older. **A**, Geometric mean IgE levels for subjects who are allergen skin test negative. Male subjects (□) in survey 1, male subjects (▨) in survey 6, female subjects (■) in survey 1, and female subjects (▩) in survey 6. Male smokers have significantly higher IgE levels than male nonsmokers in survey 1 ($p = 0.045$). The male versus female smoking difference approaches significance ($p = 0.059$) for current smokers and is highly significant in both surveys among exsmokers. **B**, Geometric mean IgE levels for subjects who are allergen skin test positive. Bars are identified as in **A**. IgE levels in male smokers are consistently higher than levels in other male smoking categories and are higher than levels for female smokers. In survey 6, levels in male nonsmokers are also significantly higher than levels for female nonsmokers.

data are presented in Fig. 3, **A** and **B**. Consistent smokers maintained their habit throughout the study period, and nonsmokers denied smoking on both surveys. Exsmokers had stopped the habit before the first survey and remained exsmokers throughout. Similarly, skin test positive and skin test negative subjects were consistent on both surveys.

In skin test negative subjects, an effect of smoking on IgE levels for male but not for female subjects is evident. Survey 1 male smokers had a geometric mean IgE of 19.8 IU/ml compared to only 10.1 IU/ml in nonsmoking male subjects ($p = 0.045$). This smoking effect was somewhat less but still present in survey 6. A significant smoking-related effect was not observed in female subjects in either survey. The mean ages of male and female smokers were virtually identical (53.1 versus 54.2). Exsmoking male subjects had significantly higher IgE levels than exsmoking female subjects on both surveys. Only in survey 1 did the male versus female difference in smokers approach significance ($p = 0.059$).

Thus, although all IgE differences in skin test negative subjects were quite small, what smoking effect there was appeared only among male subjects. A small but not significant male versus female difference in

IgE levels was present in middle-aged and older non-smokers at the end of the follow-up period. Exsmokers, however, demonstrated a significant male versus female difference. In both surveys, exsmoking male subjects had several times the IgE level as exsmoking female subjects. Also, there was no decline in the levels of male subjects despite the fact that they had not smoked for more than 8 years. As illustrated in Fig. 3, **B**, this male-related, smoking-IgE effect is more apparent in skin test positive subjects. Although the number of skin test positive smoking male subjects is small, their IgE levels on both surveys were significantly higher than the levels in female smokers or nonsmoking male subjects. The skin test positive female smokers in this cohort did not demonstrate a smoking-IgE effect. Levels in smokers and nonsmokers were virtually identical. Likewise, exsmoking male and female subjects have similar IgE levels. Levels in male subjects fell somewhat over time, whereas levels in female subjects remained constant.

In Fig. 4, **A** (skin test negative) and **B** (skin test positive), the relationships of age and sex are examined in consistent nonsmokers. Although the numbers of subjects, in the youngest age group especially, are quite small, it is clear in the nonatopic subjects

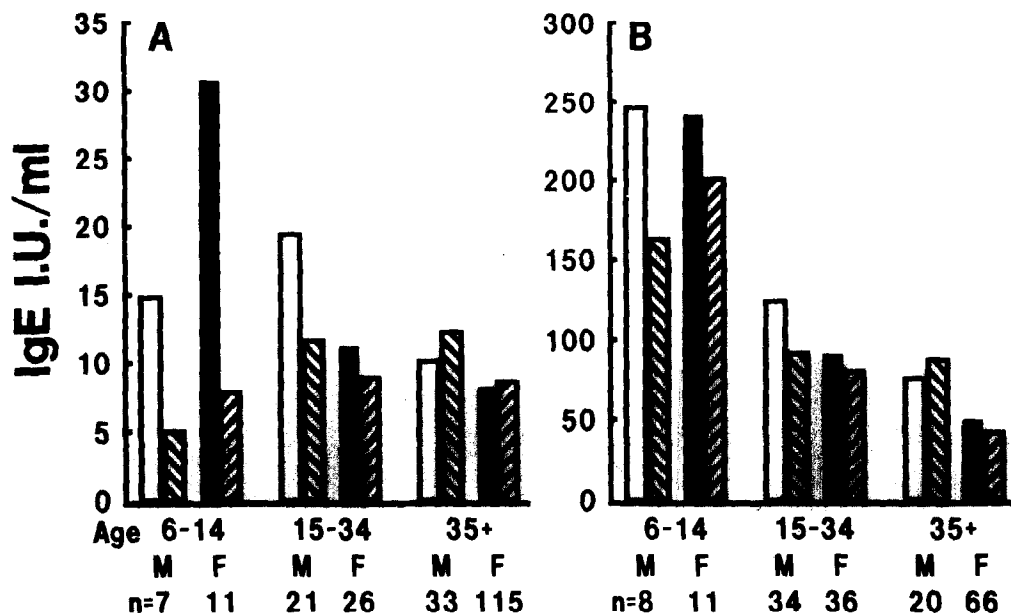


FIG. 4. Effects among nonsmokers of sex and age on serum IgE levels in the presence and absence of atopy. A, Geometric mean IgE levels for nonsmokers who are allergen skin test negative in both surveys. Male subjects (□) in survey 1, male subjects (▨) in survey 6, female subjects (■) in survey 1, and female subjects (▩) in survey 6. Age groups for both surveys refer to ages at the time of survey 1. A significant age relationship exists for female subjects and for both sexes combined in survey 1. No significant sex difference is present in either survey, nor is there an age relationship in survey 6. B, Geometric mean IgE levels for nonsmokers who were allergen skin test positive in both surveys. A significant age relationship exists for female subjects and for both sexes combined in both surveys. Also, for subjects older than 35 years, male IgE levels are significantly higher than female IgE levels in survey 6.

(Fig. 4, A) that the only age-related changes during the follow-up period were in subjects who were initially less than age 15 years. In survey 1, IgE levels for these 18 young subjects were significantly higher than levels of the other two age groups. Geometric mean survey 1 levels for the three age groups were 23.2, 14.3, and 8.6 IU/ml, respectively. By the sixth survey, levels for the same subjects (now 8 years older) were 6.6, 10.0, and 9.3 IU/ml. In the older two age groups, levels changed little, if they changed at all, during the 8-year period. In neither survey was there a significant male versus female difference. For the entire group of 213 nonatopic subjects, the geometric mean IgE level in survey 1 was 10.5 and, in survey 6, 9.2 IU/ml.

Among skin test positive subjects, an age-related decline in IgE levels is more apparent, although, here again, the most notable longitudinal decline occurred in the youngest subjects. However, a significant age relationship was evident in both surveys. Geometric mean levels in survey 1 for the three age groups were 243.6, 105.6, and 54.7 IU/ml, respectively. In survey 6, levels for the same subjects were 183.9, 85.1, and 49.5 IU/ml. In both surveys, levels in male subjects were higher than in female subjects. However,

only in subjects aged 35 years and older was the difference significant.

Because serum IgE levels are closely related to allergen skin test reactivity, it is of interest to examine both initial and follow-up levels in subjects whose skin test status remained constant versus subjects who either became atopic during the study period or, conversely, were positive initially and reverted to negative 8 years later. These data are presented in Table I. As noted previously, consistent skin test negative subjects had low initial IgE levels, and, except for a decline in the 6- to 14-year-old age group, changed little over time. Similarly, skin test positive subjects had initial IgE levels that were several times the level of the nonatopic subjects and, in the young, especially, had somewhat lower levels subsequently. One hundred eighty-five subjects converted from negative in survey 1 to positive by survey 6. For all age categories, the survey 1 IgE levels were significantly higher than levels for subjects who remained skin test negative.

In the youngest age group, the geometric mean initial IgE level among "converters" was 69.8 IU/ml, compared with 21.5 IU/ml in the consistent nonatopic subjects. By the sixth survey, when this age group was skin test positive, the IgE level remained high,

TABLE 1. Serum IgE levels related to consistent versus changing allergen skin test status

Allergen skin test status				Age group (yr)					
Survey		6-14 (yr)		15-35		35-54		55+	
1	6	1	6	1	6	1	6	1	6
Neg	Neg	21.5*	6.5	14.2	12.1	12.6	11.6	10.7	10.4
(n = 485)		(n = 27)		(n = 98)		(n = 111)		(n = 249)	
Neg	Pos	69.8†	65.5†	37.5†	35.5†	28.2†	32.3†	15.2	19.5†
(n = 185)		(n = 15)		(n = 61)		(n = 51)		(n = 58)	
Pos	Neg	—	—	21.8‡	19.1‡	33.6	24.3‡	23.3‡	20.3‡
(n = 60)		(n = 0)		(n = 142)		(n = 19)		(n = 26)	
Pos	Pos	226.7	171.8	106.7	91.0	65.6	65.2	76.7	61.5
(n = 379)		(n = 28)		(n = 142)		(n = 118)		(n = 91)	

Neg = negative; pos = positive.

*Values are given as geometric mean serum IgE in international units per milliliter.

† $p < 0.01$ between converters and consistent negatives.

‡ $p < 0.01$ between reverters and consistent positives.

65.6 IU/ml versus 6.5 IU/ml in the nonatopic group. Similar differences, both initially and at follow-up, were evident through age 54 years. Within the entire skin test conversion group, survey 1 IgE levels appeared to correlate with the degree of atopy that was acquired. The mean initial level for all of the consistently negative subjects was 12.3 IU/ml versus 22.5 IU/ml for subjects who became mildly atopic (a skin test index of 1 to 7) and 60.4 IU/ml for the 37 subjects who were strongly skin test positive (a skin test index of 8 to 20) by the sixth survey.

The reverse was true for subjects who were skin test positive initially and negative 8 years later. Significantly, there were no reverters among the youngest subjects. However, in all other age groups, both initial and follow-up levels in the reverters were significantly lower than in subjects who remained atopic throughout. Thus, among both converters and reverters, survey 1 IgE levels appeared to be predictive of their subsequent atopic status.

To examine further the predictive nature of IgE levels relative to the development of atopy, the 670 subjects who were skin test negative were divided according to their initial IgE level. One hundred fifty-two subjects had levels that were >1 SD below the mean of the Log_{10} IgE values for the entire group. Twenty-seven subjects (17.8%) had at least one positive skin test 8 years later. This compares to a conversion rate of 59.0% (23 of 39) in subjects whose IgE level was >1 SD above the mean. Among subjects whose levels were within the two extremes, the conversion rate was 28.2%. The reverse was true for the 60 subjects who reverted from positive to negative. Only 23 subjects had both positive skin tests initially and IgE levels >1 SD below the group mean. Nine

(39.1%) of those subjects were negative by survey 6. This compares with only 10 reverters (8.5%) of 118 with IgE levels >1 SD above the mean.

DISCUSSION

A number of cross-sectional studies have identified a variety of factors that appear to affect levels of IgE.^{5-10, 14-20} Even with the relatively insensitive methods that were available in the early 1970s, it was apparent that both allergy³ and parasitic disease¹¹ were associated with IgE levels that were severalfold higher than the extremely low levels that characterize normal, nonallergic individuals. More recently, a number of epidemiologic observations on various populations have emphasized the significant age-IgE relationship that exists. Peak levels are reached between ages 8 and 12 years with a fairly rapid decline thereafter. Studies with only adult populations in which most of the decline has already occurred have found less impressive age relationships, especially in nonatopic male subjects.^{5, 16} In two specific areas, disagreement has been evident. Some authors have reported a sex-related IgE difference, wherein levels for male subjects are higher than for female subjects.^{8, 10} Other authors have found such a difference only in atopic subjects, or none at all.^{5, 6} A part of this disagreement may be explained by the observation in some articles that IgE levels are increased by smoking. Therefore, the male versus female differences may be the result of either a higher smoking prevalence among male subjects or because the smoking-IgE effect is only found in male subjects.

Given these somewhat varying observations, two primary functions may be served by longitudinal analysis of a community population cohort. First, an op-

portunity is provided to confirm and/or modify conclusions based on cross-sectional observations by examining the behavior of the same cohort during a number of years. Second, information is provided concerning changes that occur in segments of the cohort that may not be apparent at a single point in time. The data from this population serve both of these functions. For the entire cohort, remarkably little change in geometric mean IgE level was evident during the 8 years of observation. The mean level in survey 1 was 28.9 IU/ml compared with 26.0 IU/ml in survey 6. These mean levels are slightly higher than some authors have reported and may reflect the greater number of skin test positive subjects in the Tucson, Ariz., population. At the time of the initial survey, 439 of the 1109 subjects (39.6%) had at least one allergen prick test reaction greater than control. Eight years later, with a greater number having become positive (185) compared to subjects who appeared to lose their reactivity (60), this percentage had increased to 45.6%. Thus, although there was a small decline in mean IgE level during the follow-up period for the cohort as a whole, three times as many subjects were developing atopic reactivity as were losing it.

In skin test negative subjects, especially, the survey 6 data look very much like those reported by Holford-Strevens et al.⁵ whose youngest subjects were age 20 years. By that age, most of the decline in IgE levels that occurs during teenage years has already taken place. As a result, no significant age relationship is apparent, especially, as will be discussed below, when the smoking effect in male subjects is taken into account. In agreement with some studies,^{5, 15-17} but differing from others,^{10, 13} a definite smoking-IgE relationship is apparent, especially in male subjects. Before controlling for smoking (Fig. 2), IgE levels in male subjects more than age 35 years remain constant or increase over time and are significantly higher than in female subjects who fail to demonstrate a comparable smoking effect. After controlling for this smoking effect (Fig. 4, A), the male-female difference in IgE level among skin test negative subjects disappears. In a study of male and female lung cancer patients, Hallgren et al.¹⁷ noted a similar male versus female difference in the effect of smoking on IgE levels. Except for possible differences in the specific smoking habits between male and female subjects, the explanation for this differing smoking effect between the sexes is unclear. Male smokers, both atopic and non-atopic, smoked a mean of 10 pack-years more than female smokers, but no relationship between IgE level and pack-years was observed.

In contrast to the relatively constant low IgE levels

found in nonatopic adults, a clear age relationship was found in atopic subjects. For both male and female subjects, levels declined progressively up to age 35 years. IgE levels of female but not male subjects continued to fall through middle age and remained quite constant thereafter. In all age groups, even after controlling for smoking, levels in male subjects were higher than in comparably aged female subjects. Thus, in atopic subjects, these data are in agreement with Freidhoff et al.¹⁰ who also noted higher IgE levels in male subjects.

The increase in IgE that has been noted in atopic male smokers is of considerable interest. Recently, Zetterstrom et al.¹⁹ and Venables et al.²⁰ have confirmed this relationship in industrial populations. Both studies demonstrated an increase in specific IgE and allergen skin reactivity to agents with which the workers were in direct close contact. They postulated that this specific sensitization was the result of increased respiratory mucosal permeability, secondary to tobacco smoke. Hulbert et al.²⁸ demonstrated a similar increase in the absorption of horseradish peroxidase in experimental animals immediately after tobacco exposure.

In contrast to a previous article by Burrows et al.¹⁵ based on cross-sectional analyses in this same Tucson, Ariz., population and a similar finding by Hallgren et al.¹⁷ in cancer patients, exsmokers in this cohort did not demonstrate a decline in IgE during the 8-year follow-up period. In the study of Burrows et al., the major decline was noted in younger exsmokers (aged 15 to 34 years). The exsmoking data in the current study were examined in subjects who were older than 35 years at the time of the initial survey. In this age group, up to 20 or more years since quitting cigarettes was required for a decline in IgE to be detectable.¹⁵ Thus, the 8-year follow-up period in our cohort may have been too short for the effect to be observed. A small but not significant fall in IgE level was noted in atopic male exsmokers.

Because of uncertainty in quantifying the degree of change in allergen skin reactivity during an 8-year period, we have, in attempting to assess the predictive nature of initial IgE levels, analyzed only those subjects who changed from negative on survey 1 to positive on survey 6 (converters) and the reverse (reverters). Within this study population there were 185 converters and 60 reverters. Several studies have indicated that IgE levels in nonatopic subjects, especially infants and children, were predictive of subsequent atopic status and/or overt allergic disease.²²⁻²⁴ Specifically, Kjellman,²¹ during an 18-month follow-up period, noted that 75% of subjects whose IgE levels were >1 SD above the group mean devel-

oped symptoms of allergic disease. This was contrasted with only a 6.4% incidence in subjects whose IgE levels were 1 SD below the group mean. In the present study, the initial IgE level of those negative skin test subjects who became skin test positive were significantly higher than the consistent nonatopic subjects. When this finding was analyzed with standard deviations above or below the mean for specific age groups, a similar trend was noted. Only 17.8% of subjects who were 1 SD below the survey 1 mean level became atopic compared to 59.0% of subjects whose levels were >1 SD above the mean level. Reverters demonstrated a trend in the opposite direction.

In most respects, these longitudinal data confirm the findings of cross-sectional studies. It is clear that a number of factors have a significant impact on IgE levels. Among these factors, the age relationship is prominent in children and teenagers. Conversely, especially in skin test negative adults, neither age nor sex has a significant relationship with IgE levels after controlling for smoking habits. In atopic individuals, there is a consistent decline from the initially high levels and an age relationship that exists even after controlling for smoking. Male atopic subjects tend to have higher levels than female subjects. Finally, high initial levels in nonatopic subjects are predictive of the acquisition of atopy. The relationship of these longitudinal changes to the development and/or disappearance of allergic respiratory symptoms will be the subject of future analyses.

We thank B. Boyer and the epidemiologic field staff for data and sample collection, I. C. Lohman and A. M. Dunn for technical assistance, and P. King for manuscript preparation.

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