

Clinical aspects of allergic disease

Relationships between total serum IgE, atopy, and smoking: A twenty-year follow-up analysis

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Background: A number of cross-sectional studies have demonstrated that higher levels of IgE are found in subjects who currently smoke cigarettes and/or who are atopic and that IgE levels decline with age.

Objective: This report examines the interactions among atopic status, smoking, and IgE with longitudinal data and methods.

Methods: Subjects were participants in the Tucson Epidemiological Study of Airways Obstructive Disease and were 6 years of age and older. Total serum IgE measures and allergen skin test results were obtained during three surveys spanning a period of up to 20 years.

Results: The results showed no significant gender differences between nonatopic nonsmoking subjects, who were considered the reference group. Nonatopic current smokers had IgE levels similar to those of the reference subjects initially, but IgE levels did not decline with age at the same rate as in the reference subjects, causing significant differences at older ages. There was a significant relationship between number of cigarettes smoked and IgE level.

Conclusions: Atopy and smoking are both associated with elevated total serum IgE levels. Although the exact mechanism for elevated IgE levels in smokers is not known, the significant dose relationship is suggestive of a causal association. (*J ALLERGY CLIN IMMUNOL* 1994;94:954-62.)

Key words: Allergy skin test, atopy, immunoglobulin, longitudinal, total serum IgE

A number of cross-sectional studies have demonstrated higher levels of IgE in subjects who currently smoke cigarettes and/or who are atopic¹⁻²¹ and that IgE levels change with age, with peak levels occurring in the first or second decades of life followed by decreasing levels thereafter. In addition, sex differences for smoking effects on IgE have been reported, with some studies reporting increased IgE levels in both sexes¹⁷⁻¹⁹ and others finding differences only in male subjects.²⁰⁻²¹ The mechanisms responsible for these elevated IgE levels in smokers are not well understood. Determining whether a dose-

Abbreviation used

REM: Random effects model

response relationship exists between IgE and amount smoked, however, would further address the possibility of a causal association and the potential for using IgE as a biologic marker of susceptibility to chronic obstructive pulmonary disease. Because cross-sectional studies are not able to distinguish or remove age cohort effects, it is important that these results be verified with longitudinal data and methods.

In this study by using longitudinal IgE data, we examine the relationship between IgE level and age and test for differences in subjects who are atopic and/or currently smoke cigarettes. In addition, these findings are compared with cross-sectional results previously reported on this²⁰ and other populations.¹⁶⁻¹⁹ What makes this study unique is that we have longitudinal IgE data taken during three surveys that span a period of

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TABLE 1. Distribution of IgE measurements

Gender	Number of surveys			Total
	1	2	3	
Female	841 (61.4)	341 (24.9)	183 (13.7)	1369
Male	645 (65.7)	223 (22.7)	113 (11.5)	981
Total	1486 (63.2)	564 (24.0)	296 (12.8)	2350

up to 20 years. These data were analyzed with recently developed statistical methods that allowed us to include all of each subject's IgE data and to adjust for subjects who change smoking status during the study interval.

METHODS

Study population

Subjects were white non-Mexican-American participants in the Tucson Epidemiological Study of Airways Obstructive Disease, aged 6 years and older. Detailed descriptions of the study design and methods of data collection have been reported previously.²² Briefly, the population in this ongoing study is a random stratified cluster in Tucson, Arizona, including 3805 individuals in 1655 households enrolled from 1972 to 1973, with new enrollees added by marriages and births.

Data were available for this analysis through the twelfth survey, spanning a period of up to 20 years. During the first, sixth, and eleventh surveys, skin testing with commercially available allergens was done, and venous blood was collected for total serum IgE determinations. Because not all subjects were seen at each survey, surveys 2, 7, and 12 were considered catch-up surveys: subjects who came in and had not been seen in the previous survey had skin tests and serum sampling for IgE at that time. This study includes both the surveys in which the testing was scheduled and those considered catch-up surveys. Responses to questions concerning smoking status and respiratory symptoms or diseases and pulmonary function tests were obtained at each survey in conjunction with the total serum IgE measurements. Subjects were considered to have positive skin test results or to be atopic if they responded to any allergen with a wheal size of greater than 1 mm, after the size of the control test was subtracted, in any survey. Subjects were classified as current smokers in any survey in which active cigarette smoking was reported (i.e., more than one cigarette per day) by questionnaire (self-completed). The prevalence of allergen skin test reactivity and comparisons between first and sixth survey IgE levels have been previously reported.²¹

Total serum IgE measurements

In the selected 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 serum

IgE levels were measured in the same laboratory by the paper radioimmunosorbent test (PRIST; Pharmacia Diagnostics, Piscataway, N.J.) technique. Samples were run in duplicate, as was an aliquot of a reference serum in each batch. In this analysis we used the average of the two IgE measures.

Allergen skin testing

During each of the three surveys, allergen prick tests were performed by trained nurses according to the method of Pepys.²³ Details of the skin test procedure have been previously reported.²⁴ The same five antigen mixtures (Hollister-Stier Laboratories, Spokane, Wash.) were applied in the same concentration for each survey: house dust (1:10), mold mix (Dematiaceae) (1:100), Bermuda grass (1:20), tree mix (1:20), and weed mix (1:20). In survey 11 nine additional antigen mixes were added. A control solution of 50% glycerol was also included.

Statistical methods

Because the total serum IgE data set contains missing observations (i.e., not all subjects were observed during each of the three surveys) and observations that were unequally spaced, we used a "mixed longitudinal model" or "random effects model" (REM)²⁵⁻²⁷ to describe the IgE data. The form of the model is identical to that used in ordinary multiple regression, but the methods used to estimate the regression coefficients are modified to account for the correlation between repeated measures for the same subject. This model allows subjects to have an unequal number of observations that can be obtained at different times for different subjects. It can also include time-dependent and fixed covariables. This model has recently been used to describe longitudinal changes in pulmonary function in a number of studies.²⁸⁻³¹

In the REM analyses $\log[\text{IgE}]$ was the dependent variable, skin test reactivity was a dichotomous fixed covariable, and current smoking status (self-reported) and age were time-dependent covariables. Because atopy and smoking may have a synergistic association with IgE, a two-way interaction was also included. All analyses were done for each gender separately. The $\log[\text{IgE}]$ values were used in all analyses, because log transformation of IgE values yields near normal distributions, which otherwise tend to be heavily skewed to the right.¹⁰ The final model includes only those coeffi-

TABLE II. Percent of subjects who were current smokers and/or atopic in at least one survey (1, 6, or 11) by age in survey 1

Age (yr) at survey 1	Current smokers (%)		Atopic (%)	
	Male	Female	Male	Female
< 15	21.8	23.1	28.9	26.4
15-34	34.9	30.5	33.6	29.5
35-54	22.4	24.1	17.3	20.0
≥ 55	20.9	22.3	20.2	24.2

TABLE III. Results for longitudinal random effects analysis of log [IgE] (coefficients ± SEM)

	Male subjects	Female subjects
Age (yr)	-0.031 ± 0.004	-0.028 ± 0.004
Age ² (yr) ²	0.265E - 3 ± 0.485E - 4	0.238E - 3 ± 0.459E - 4
Constant	1.94 ± 0.08	1.82 ± 0.10
Subgroups		
Atopy	0.602 ± 0.057	0.319 ± 0.127
Atopy × age	NS	0.013 ± 0.006
Atopy × age ²	NS	-0.160E - 3 ± 0.618E - 4
Current smoke	-0.397 ± 0.251*	-0.206 ± 0.124
Current smoke × age	0.027 ± 0.012	0.009 ± 0.002
Current smoke × age ²	-0.242E - 3 ± 0.127E - 3	NS
Atopy × smoke	0.521 ± 0.330*	0.275 ± 0.235
Atopy × smoke × age	-0.034 ± 0.016	-0.017 ± 0.010*
Atopy × smoke × age ²	0.380E - 3 ± 0.172E - 3	0.151E - 3 ± 0.10E - 3*

NS, Not statistically significant ($p > 0.05$).* $0.05 < p < 0.1$; all other coefficients $p \leq 0.05$.

cients that have a significant association with IgE, as determined by evaluation of changes in -2 log likelihood values.

RESULTS

There were 3049 subjects who had at least one total serum IgE measurement taken during the study period. Among those participants, 2350 also had the questionnaire responses necessary for smoking classifications and allergen skin testing in at least one survey. There were 1369 female and 981 male subjects, providing 2072 and 1430 IgE measurements (Table I), respectively. There were 296 subjects who had IgE observations in all three surveys, accounting for 26% of the total observations, and 564 who had only two observations, accounting for 32% of the total observations.

The prevalence of subjects who had ever been smokers or who had ever been reactive to skin tests are listed in Table II by age in survey 1 and by gender. There were more male than female current smokers in the 15- to 35-year-old group but the percentages were similar in all other age

categories. Male subjects in this age stratum were more reactive to skin tests than female subjects. The number of reactive subjects peaked in the 15- to 35-year-old group and was lower at subsequent ages for both genders.

The geometric means for the three surveys of total serum IgE measurements are shown in Fig. 1. Subjects were divided into groups on the basis of current smoking status, gender, skin test reaction, and age at survey 1. The plots for nonsmokers (Fig. 1, A and B) show that subjects with skin test reactivity had higher IgE values than the group as a whole at all ages and that IgE decreases in a nonlinear fashion with age, independent of atopic status. This was true both within and between age cohorts. Changes with age in the older nonsmoking subjects (age ≥ 55 years) were negligible, regardless of atopic status. The increased IgE level associated with atopy was also evident in male smokers (Fig. 1, D) but was less pronounced in female smokers (Fig. 1, C). The trend of decreasing IgE levels with age observed in nonsmokers was also apparent in smokers in all but the

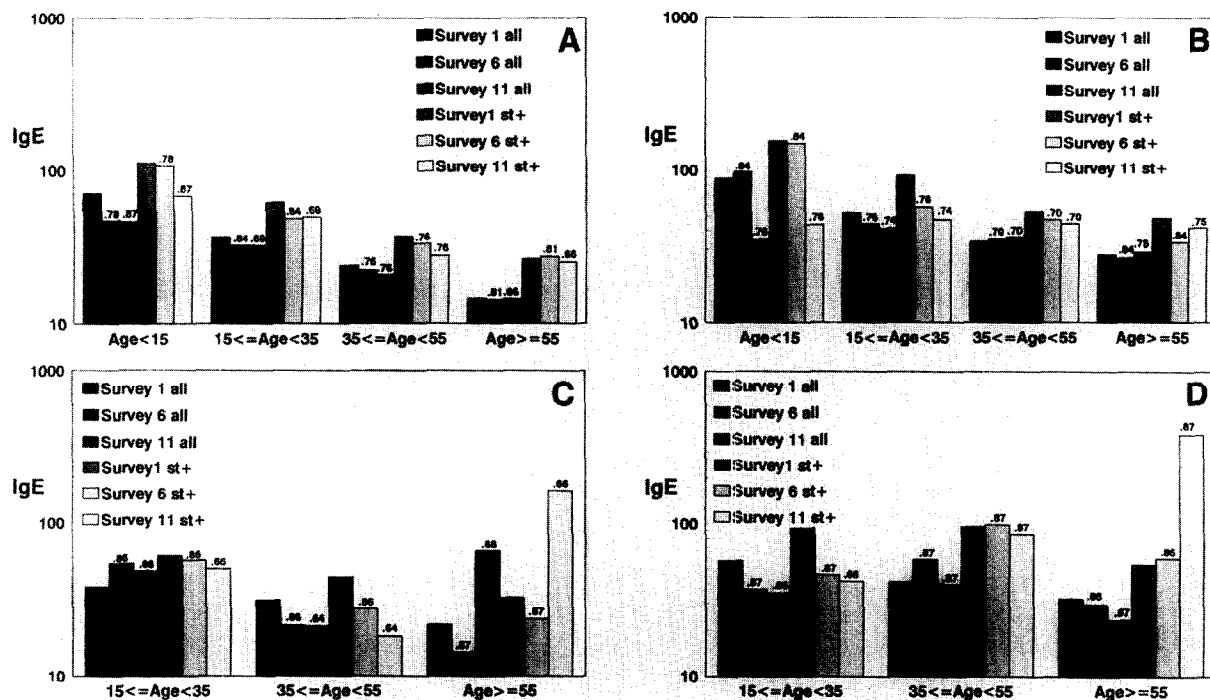


FIG. 1. Geometric means of IgE for participants of Tucson Epidemiological Study of Airways Obstructive Disease (1972 to 1993). Subjects were stratified on the basis of age at the initial survey, gender, skin test allergy response, and current smoking status. A and B display these means for nonsmoking female and male subjects, respectively. C and D display these means for "ever smoking" female and male subjects, respectively. Subjects were classified as skin test positive (*st+*) if they responded to any antigen at any survey with a wheal size greater than 1 mm, after adjusting for control solution. Subjects were classified as smokers if they reported actively smoking during any of the three selected surveys (surveys 1, 6, and 11). Correlation coefficients between IgE measures taken in surveys 1 and 6 and between surveys 1 and 11 are listed above the survey 6 and survey 11 mean bars. These correlations are an index of the degree of tracking associated with serial IgE measurements.

oldest age category. For atopic smokers in this oldest age group (Fig. 1, C and D) this trend was reversed; that is, the IgE level appears to be increasing with age.

Fig. 1 also includes estimates of the correlation between log[IgE] measurements taken during surveys 1 and 6 and surveys 1 and 11 (listed above the histogram bars) for all subjects who had multiple observations. For the correlation estimates, subjects were considered smokers if they reported actively smoking in either survey. These estimates indicate the degree of tracking associated with the IgE measurements over time, which ranged from 0.64 to 0.87, suggesting a strong tracking that did not appear to diminish with increasing age or between age cohorts.

The results of the longitudinal analyses of the total serum IgE data are listed in Table III and plotted in Figs. 2 to 4. Coefficients for the different subgroups and interactions represent differ-

ences from the reference group, which is comprised of all nonatopic and nonsmoking subjects. The best-fitting model for the reference group consists of the constant, age and age² coefficients (Table III). For both male and female subjects, the reference group IgE values had a curvilinear relationship with age as indicated by the significant age² coefficients. Atopic status, current smoking, and their interactions were all statistically significant for both sexes. The pattern of the IgE-age relationships varied from constant shifts in the curves, as seen in atopic male subjects, to quadratic associations, like that found for male current smokers.

Fig. 2 shows the mean total IgE trends with age for nonsmokers who had positive skin test results and for reference subjects. The mean curves and the standard errors were computed with the results of the REM analysis presented in Table III. There were no significant gender differences be-

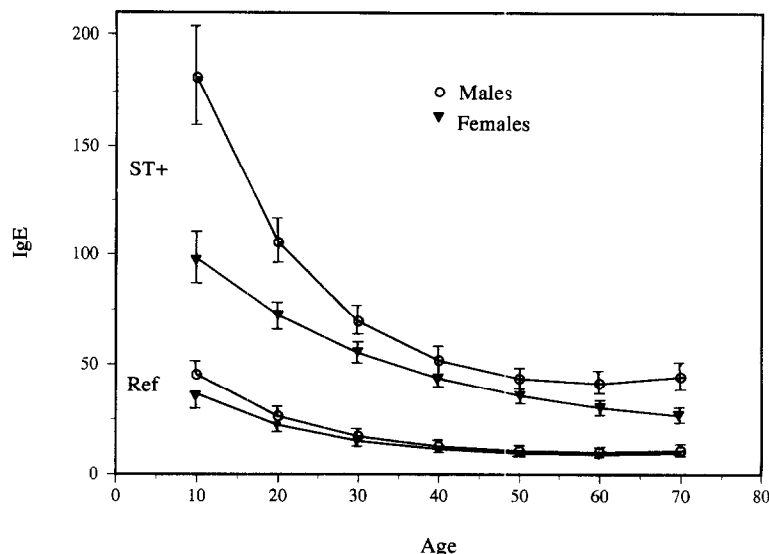


FIG. 2. Mean IgE curves and standard errors of the estimates for *nonsmoking* participants of Tucson Epidemiological Study of Airways Obstructive Disease (1972 to 1993). Means and standard errors were computed with the results of the REM longitudinal analysis presented in Table III. *ST+* indicates subjects who had positive skin test results in one or more of the three selected surveys (two upper mean curves), and *Ref* indicates reference subjects who were nonsmokers and nonresponsive to allergy skin tests in all surveys.

tween reference groups. Both sexes had their highest levels of IgE as children, which fell gradually up to around 40 years of age and remained constant thereafter. In contrast, subjects with positive skin test results had significantly elevated IgE levels at all ages compared with the reference subjects, with male subjects having higher levels than female subjects. For both genders, subjects with positive skin test results experienced declines in IgE with age that lasted throughout most of adulthood but never reached the lower levels of the reference group. Fig. 3 shows the mean plots for nonatopic current smokers, again compared with the reference subjects. For male subjects (Fig. 3, *A*), current smokers have mean IgE levels at age 20 years similar to those of the reference group, but their subsequent rate of decline with age was much less, resulting in significantly elevated IgE levels at most ages. Female current smokers (Fig. 3, *B*) had similar trends up to age 50 years when their IgE levels actually started to increase with age. This upward trend is consistent with the mean trends shown in Fig. 1 for this subgroup. Mean IgE curves for subjects who had positive skin test results and were also current smokers are shown in Fig. 4. Their IgE levels were significantly higher than those of the reference group at all ages, and male subjects had higher levels than female subjects. These subjects also

had increasing IgE levels at older ages, with the largest increases being observed in male subjects.

To examine further the positive trend in total serum IgE levels in older smokers, we reanalyzed the data, adding an indicator variable for subjects who had more severe air flow obstruction (percent predicted forced expiratory volume in 1 second <60%). This new term in the model caused the skin test by current smoke interaction variable to drop out or become nonsignificant, suggesting that at least part of the observed increase in IgE level in older age is limited to the subjects with more serious obstructions. This finding is consistent with that of Dow et al.,¹⁷ who reported significantly reduced ratios of forced expiratory volume in 1 second to forced vital capacity in subjects with higher serum IgE levels (≥ 81 IU/ml) when compared with subjects with lower values (≤ 10 IU/ml). We also included a longitudinal model with pack-years of smoking as a fixed covariate. This was estimated as the number of packs of cigarettes per day subjects reported smoking times the number of years they had been smoking. For example, a subject who had been smoking 1 pack a day for 5 years and a subject who had been smoking 5 packs a day for 1 year would each have a 5 pack-year history. Pack-years of smoking were statistically significant in the model with a positive coefficient, indicating that

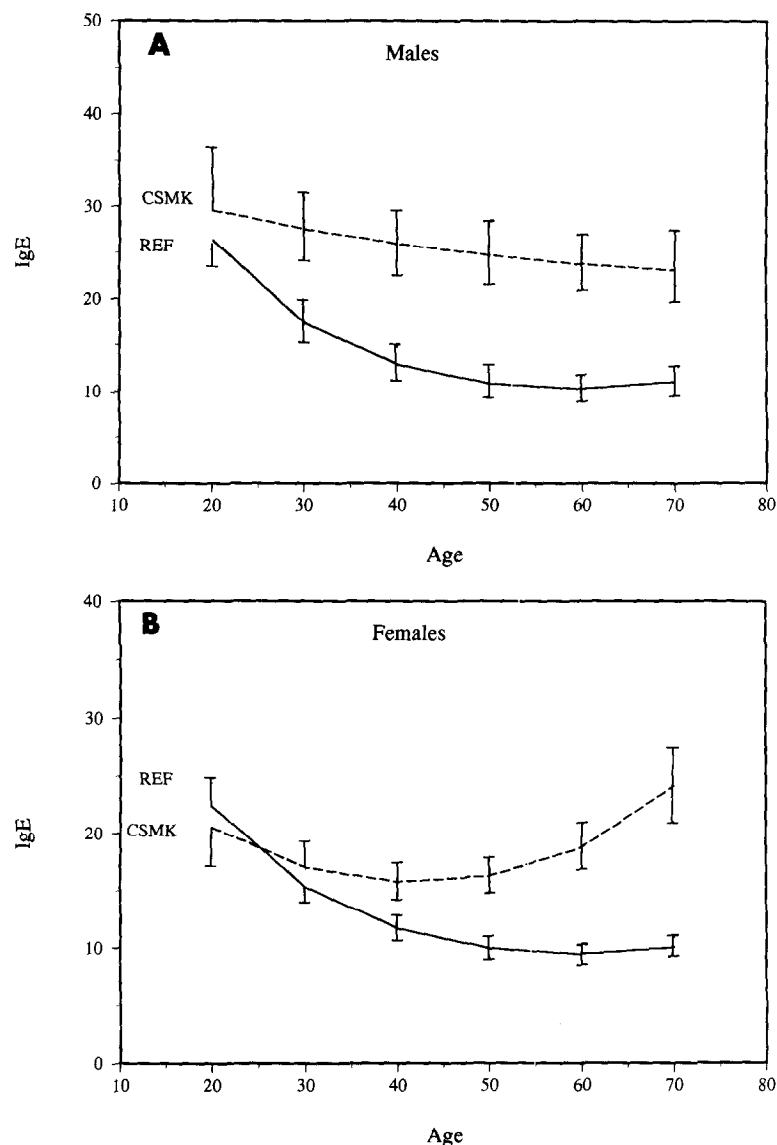


FIG. 3. Mean IgE curves and standard errors of the estimates for male (**A**) and female (**B**) participants of Tucson Epidemiological Study of Airways Obstructive Disease (1972 to 1993). Means and standard errors were computed with the results of the REM longitudinal analysis presented in Table III. Dashed lines represent subjects who had negative *skin test results* in all surveys and current smokers (*CSMK*). The solid lines represent subjects who were nonsmokers and nonresponsive to allergy skin tests in all surveys, considered the reference subjects (*REF*).

subjects with a high pack-year history had significantly higher IgE levels than subjects with low or no pack-year history, for both sexes. Fig. 5 shows the cumulative effect this would have on hypothetical subjects who were current smokers with positive skin test results. For male subjects, we assumed 1 pack per day and for female subjects, 0.8 pack/day smoking habit. Therefore at age 50 the male subjects had a 35 pack-year history, and the female subjects had a 28 pack-year history,

assuming each started smoking at age 15. In this illustration we assumed that there were two male and two female subjects; one subject in each pair continues to smoke at the same rate, thus continuing to increase his or her pack-years, and the other stops smoking at age 50. One can see from these mean plots (Fig. 5) that those subjects who quit smoking subsequently had lower IgE levels than those who continued to smoke in this older age group. The difference was greatest for male

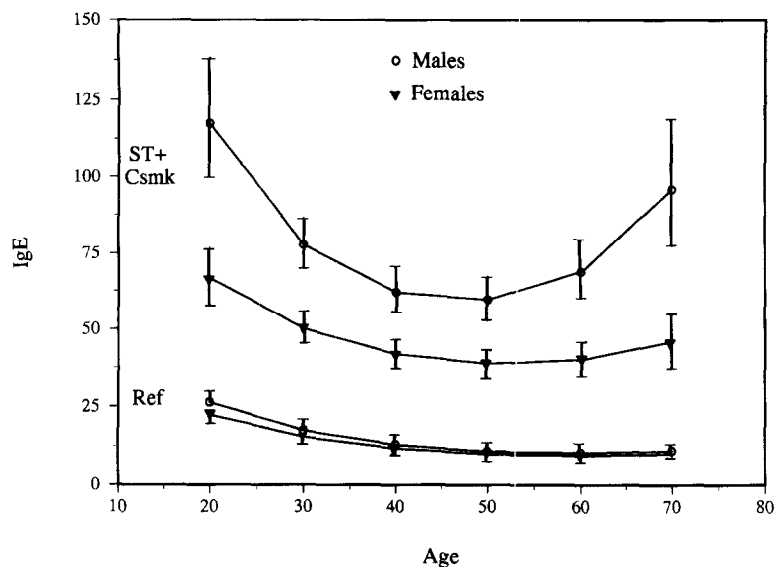


FIG. 4. Mean of IgE curves and standard errors of the estimates for participants of Tucson Epidemiological Study of Airways Obstructive Disease (1972 to 1993). Mean and standard errors were computed with the results of the REM longitudinal analysis presented in Table III. The upper two mean curves represent subjects who had *positive skin test results (SP+)* in one or more of the three selected surveys and *current smokers (Csmk)*. The two lower mean curves are for the reference subjects (*Ref*) who were nonsmokers and nonresponsive to allergy skin tests in all surveys.

subjects, who also had higher pack-year histories of smoking than female subjects; mean pack-years of smoking for subjects older than 55 years was 57.9 for men and 38.0 for women.

DISCUSSION

In this study we have shown that subjects with skin test reactivity have statistically significantly higher levels of total serum IgE than subjects without skin test reactivity and that this relationship was independent of their smoking status (Figs. 2 and 4). Among the subjects with skin test reactivity, male subjects have significantly higher IgE levels than their female counterparts. There were no significant differences between the male and female reference groups, which included nonatopic nonsmokers, although younger boys did have slightly higher levels than girls. Nonatopic current smokers and reference subjects had similar IgE levels at younger ages but did not follow the same time course thereafter (Fig. 3). Instead, IgE levels of current smokers failed to decrease at the same rate as those of nonsmokers, and as a consequence, they had elevated levels throughout adulthood. In female nonatopic smokers there was even a trend toward increasing levels at the older ages (Fig. 3, *B*), a pattern that occurred in both sexes for those who were atopic and current

smokers (Fig. 4). The results of the analyses, which included variables for subjects with some degree of air flow obstruction and pack-years of smoking, suggest that it is the subjects with more severe obstruction or those with significant smoking histories that appeared to drive IgE levels up in the group of older current smokers. However, the mechanisms for this increase in total serum IgE with age in these subjects and those responsible for maintaining elevated IgE levels in all smokers are not known.

Six hundred sixty-three subjects, 392 male and 271 female subjects, were excluded from the longitudinal analyses because they lacked information concerning their current smoking status. To account for potential biases, we examined their atopic status and IgE levels. There were more atopic subjects among those excluded than in the group as a whole (Table II). This was true for both sexes and in every age stratum. Longitudinal analyses of the log[IgE] data of excluded subjects, adjusting only for atopic status, showed no significant differences when compared with the remaining population, except in male subjects with positive skin test results. Their IgE levels were significantly elevated at all ages when compared with atopic nonsmokers (Fig. 2). These results suggest possible underestimation of the IgE levels in this



FIG. 5. An example of mean IgE curves for hypothetical atopic current smokers. Means were computed with the results of the REM longitudinal analysis with pack-years of smoking entered as a fixed covariate. Male subjects were assumed to have a 1 pack per day smoking habit and female subjects, a 0.8 pack per day smoking habit. Solid lines represent subjects who continued to smoke at the same rate from age 15 until age 70. Dashed lines represent subjects who started smoking at age 15 and quit at age 50, thus maintaining their pack-years at a constant level thereafter.

subgroup (Table III), but exact quantification would be difficult because of the lack of smoking information.

Because the REM procedure allows subjects to have an unequal number of data points, subjects with single observations were also included in this analysis. In the REM analysis, the subjects with single observations cannot influence the slope estimates, because there is no slope information contained in a single observation, but they do contribute to the overall position of the fitted line. To determine the contribution of these single observations to the final results (Table III), we reanalyzed the IgE data, excluding all subjects with only one observation (Table I). The results of this REM analysis showed no significant changes in the magnitudes of the estimated coefficients, and only coefficients that were of borderline significance in the original analysis became nonsignificant when single points were removed, indicating some loss of power as a result of the reduced sample size. Another option of the REM analysis is the inclusion of an autoregressive error structure between subjects.²⁶ Because there were so few IgE measurements for each subject, this was not a significant factor in any of the final models.

In a study of 863 subjects drawn from two cohort studies, which were followed up over a

period of 9 to 11 years, Vollmer et al.¹⁹ were not able to show an age-related decline in IgE levels of current smokers. Although they only tested for decreasing trends with age ($p = 0.090$), their plot of $\text{Ln}(\text{IgE})$ (Fig. 2) shows steady increases above age 40, similar to our findings in smokers (Fig. 3, B, and Figs. 4 and 5).

Numerous studies have demonstrated higher IgE levels among smokers than nonsmokers, but none to our knowledge have demonstrated a dose relationship between the amount smoked and level of IgE. Vollmer et al.¹⁹ reported that among smokers, neither amount smoked nor pack-years was correlated with IgE. In contrast, we showed significant associations between pack-years and level of IgE, which were significant in both sexes but strongest in male subjects (Fig. 5). This association was also found cross-sectionally in an earlier study of this population.¹⁰

In this study we have verified earlier cross-sectional findings that atopic subjects and current smokers have elevated total serum IgE levels compared with control subjects. In addition, we found that nonatopic current smokers did not differ from nonatopic nonsmokers at younger ages but did have significantly elevated IgE levels that became apparent before the age of 40. We also demonstrated a significant association with

smoking history (i.e., number of pack-years) that appears to account for most of the IgE increases with age observed in older smokers (Fig. 5). This finding supports the notion of a direct causal relationship; that is, smoking more cigarettes leads to higher levels of total serum IgE. Another important finding was that the elevated IgE levels associated with current smoking after age 40 was detectable in both sexes, with men having higher values than women. Further studies are needed to determine whether the elevated IgE level precedes severe airway obstruction and thus may be useful as a biologic marker of susceptibility to airway obstruction or chronic obstructive pulmonary disease.

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