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Serum IgE in nonatopic smokers, nonsmokers, and recent exsmokers: Relation to lung function, airway symptoms, and atopic predisposition

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*The influence of smoking on serum IgE (s-IgE) was studied in a selected nonatopic population. The variation in s-IgE was followed during 1 year of smoking abstinence. The study included 287 smokers and 137 never smokers. IgE was higher in smokers compared with IgE in never smokers ($p < 0.005$). Male smokers had higher s-IgE than female smokers ($p < 0.01$). S-IgE was independent of age and claims of atopy among first-degree relatives. Weighted pack-years consumption was defined for cigarette smokers by modifying pack-years consumption by nicotine content of the brand smoked. Weighted pack-years consumption was associated with level of s-IgE ($p < 0.05$). S-IgE was higher in smokers with airway symptoms compared with that in smokers without symptoms ($p < 0.01$). In smokers older than 50 years of age, there tended to be decreased FEV₁ residuals ($0.05 < p < 0.06$), and presence of airway symptoms was ($p < 0.03$) associated with high levels of s-IgE independent of each other. In 92 quitters, s-IgE increased during the first 26 weeks of abstinence ($p < 0.05$), and after 1 year, s-IgE had returned to baseline. The increase was only observed in smokers younger than 40 years and had no relation to variations in FEV₁ during the 1-year follow-up. The increase in s-IgE after smoking cessation was transient, of minor clinical importance, and probably caused by a relief from an immunosuppressive influence. (*J ALLERGY CLIN IMMUNOL* 1992;90:224-9.)*

Key words: Smoking, smoking cessation, IgE, lung function, airway symptoms

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The elevated s-IgE levels found in smokers compared with that in nonsmokers¹⁻⁴ may occur because of genetic predisposition⁵ but more likely develops with time in some smokers because of multiple mechanisms.⁶⁻⁸ A slight association has been found between an elevated s-IgE in elderly smokers and the degree of airway obstruction concurrent with chronic cough and expectoration.^{9, 10} Previous studies have had a risk of including subjects with elevated s-IgE caused by reasons other than smoking.

After smoking cessation, the s-IgE level appears to diminish within years.^{1, 3, 4, 11} The short-term changes in s-IgE and the relation of s-IgE to lung function after smoking cessation have not been investigated previously.

The objectives of the present study were to evaluate the associations between s-IgE, tobacco consumption, lung function, airway symptoms, and atopic predisposition in smokers who had never experienced allergic rhinitis and eczema and/or asthma and to study variations in s-IgE during 1 year after the cessation of smoking.

MATERIAL AND METHODS

Four hundred ninety-six smokers volunteered to participate in a smoking cessation program and were followed for 1 year. The smoking population was recruited through the press. The nonsmoking control group (N = 163) was recruited through requests to local industrial plants and municipal offices and chosen at random. All subjects that had never smoked were included if they met inclusion criteria. Ninety-six percent of the smoking population had professional jobs, and the distribution of industrial and office workers was similar for smokers and nonsmokers (Table I).

FEV₁ and FVC were measured by a dry spirometer (Vitalograph Ltd., Buckingham, England) before start of the trial and in smokers 3, 6, and 12 months after smoking cessation. The best of three reproducible measurements with <5% variation was recorded. Normal values for FEV₁ and FVC were from the European working party on standardization of lung-function tests.¹²

A serum sample was obtained from all participants before smoking cessation and from abstainers and subjects in the smoking reference group after 2, 6, 12, 26, and 52 weeks. Serum samples were stored at -20°C until analysis. IgE was measured with PRIST (Pharmacia Diagnostics AB, Uppsala, Sweden).

All participants underwent an allergologic examination with skin prick test (Soluprick, ALK Laboratories, Copenhagen, Denmark). Allergen extracts were birch, timothy, and mugwort pollen, and horse, cat, dog, and guinea pig dander, *Dermatophagoides pteronyssinus*, *D. farinae* (all 10 histamine-equivalent prick), *Alternaria tenuis* (1:20 wt/vol), and *Cladosporium herbarum* (1:20 wt/vol), and three storage mites (*Acarus siro*, *Lepidoglyphus destructor*, and *Tyrophagus putrescentia*, 10,000 Noon equivalent per milliliter). Histamine, 10 mg/ml, was used as positive and the solvent was used as negative control. A positive reaction

Abbreviations used

s-IgE:	Serum-immunoglobulin E
Ln:	Natural logarithm
WDC:	Weighted daily cigarette consumption
WPC:	Weighted pack-years consumption
PC:	Pack-years consumption
CI:	Confidence interval

TABLE I. Demographic details

	Smokers	Nonsmokers
No.	297	137
Age (yr)	43.5 ± 12.2	45.7 ± 13.11
M/F	146/153	65/72
Industrial office workers	98/199	56/80
Smoking duration (yr)	22.6 ± 7.5	—
DC* (cigarettes/day)	21.9 ± 8.5	—
PC*	25.4 ± 14.4	—
Cigarette smokers	229	—
Weighted PC*	42.6 ± 12.1	—

DC, Daily cigarette consumption.

Mean ± SD is for continuous variables; smokers and nonsmokers were comparable with respect to all relevant variables.

*See text for definition.

was defined as a wheal of at least half the size of the histamine-reaction wheal. Reactions with size wheal same or larger than the wheal of the negative control were confirmed through a test for allergen-specific s-IgE (Phadebas RAST, Pharmacia Diagnostic AB). Subjects with a positive skin test or with a RAST, ≥ 0.35 kU/L, were excluded. All participants completed questionnaires concerning their own and first-degree relative's allergic and asthmatic status. Respiratory symptoms were recorded after smoking cessation at 1, 2, 3, 4, 5, 6, and 12 weeks in a modification of the questionnaire recommended by the British Medical Research Council, Committee on Research into Chronic Bronchitis, 1966.

The smoking history was recorded as duration of smoking (years), kind of tobacco smoked (pipe tobacco, cigarettes, small cigars, and cigars), and name of the brand smoked. Pipe and cigar tobacco was converted into corresponding numbers of cigarettes as follows: one gram of pipe tobacco, one cigarette; one small cigar, three cigarettes; and one cigar, four cigarettes. For cigarette smokers, WDC was defined as the number of cigarettes smoked per day multiplied by a coefficient reflecting the relative nicotine content of the brand smoked. WPC was WDC times years of smoking divided by 20. PC was defined for all smokers as duration of smoking multiplied by the number of cigarettes smoked per day and divided by 20.

Tobacco abstinence was controlled by measuring the concentration of carbon monoxide in expired air (Ecolyzer comonitor, Hawthorne, N.Y.).¹³

The study included 297 smokers and 137 nonsmokers with no history or clinical evidence of asthma or allergic disease. The variation in s-IgE after the cessation of smoking was studied in 92 exsmokers remaining abstinent throughout 1 year (quitters) and 25 smokers with smoking relapse about 3 months after the start of the trial (relapsers). Relapsers were used as a smoking reference group. Quitters and relapsers had comparable age, smoking history, and sex distribution.

Ethics

All participants gave their informed consent to participate. The study had the approval of the ethical committee of Aarhus county.

Statistics

The BMDP statistical software package¹⁴ was used in all calculations. Comparisons of demographic details between groups investigated and control groups were performed with Pearson's chi-square and Student's *t* test. The distribution of s-IgE was not Gaussian, and nonparametric statistics was used to evaluate associations involving s-IgE (Kruskal-Wallis one-way analysis of variance). To obtain expressions for group means, ln-transformed values for s-IgE were used. Student's *t* test was used for comparisons of group means, and the paired *t* test along with tests for repeated measures were used to evaluate variations in s-IgE after smoking cessation. The technique of standardized residuals of FEV₁ and FVC was used to evaluate lung functions.¹⁵

RESULTS

In nonsmokers, s-IgE was independent of age, sex, and lung function.

Mean ln s-IgE in smokers was 2.98 kU/L, and in nonsmokers, 2.60 kU/L ($p < 0.005$). The excess s-IgE was observed in both male ($p < 0.0001$) and female subjects ($p < 0.01$). Among 229 cigarette smokers (98 male and 131 female subjects), male subjects had higher WDC and WPC than female subjects ($p < 0.001$). In cigarette smokers with WPC ≤ 10 ($N = 32$), mean ln s-IgE was lower compared with that in smokers with higher tobacco consumption ($p < 0.05$). Mean ln s-IgE in male and female smokers was 3.26 kU/L and 2.81 kU/L, respectively, and was significantly different after controlling for the difference in WPC ($p < 0.01$).

Ln s-IgE was independent of claims of allergy among first-degree relatives. In the total population, ln s-IgE was independent of FEV₁ residuals. In smokers with ($N = 152$) and without ($N = 135$) chronic cough/expectoration, mean ln s-IgE was 3.18 kU/L and 2.80 kU/L, respectively ($p < 0.01$). In smokers, older than 50 years of age, mean ln s-IgE was 2.43 kU/L in 26 subjects with FEV₁ residuals within the 90% CI and without symptoms from the airways, 3.04 kU/L in 30 subjects with FEV₁ residuals within the 90% CI and with airway symptoms, 2.95 kU/L in

nine subjects with FEV₁ residuals decreased >2 SD and without symptoms from the airways, and 3.46 kU/L in 23 subjects with FEV₁ residuals decreased >2 SD and with chronic cough/expectoration (Fig. 1). Ln s-IgE was higher in the older smokers with airway symptoms, independent of FEV₁ residuals compared with that of older smokers without symptoms ($p < 0.03$). Ln s-IgE tended to be higher in smokers older than 50 years with FEV₁ residuals decreased >2 SD, independent of presence of airway symptoms, compared with that of smokers with higher FEV₁ residuals in the same age group ($0.05 < p < 0.06$) (nonparametric one-way variance analysis for stratified observations). The groups had similar WPC.

Variation in s-IgE during 1 year after smoking cessation

In the 92 quitters and 25 relapsers, differences in s-IgE from baseline at later measurements followed a Gaussian distribution.

In quitters, mean $\pm$ SD increase in s-IgE from baseline at 2, 6, 12, 26, and 52 weeks was 4.28 ± 19.04 kU/L ($p < 0.05$), 7.62 ± 23.79 kU/L ($p < 0.05$), 6.78 ± 21.75 kU/L ($p < 0.05$), 13.08 ± 33.09 kU/L ($p < 0.001$), and 0.46 ± 30.17 kU/L (not significant) (Fig. 2). In relapsers, mean $\pm$ SD increases at the same time points was 4.2 ± 11.8 kU/L ($p < 0.05$), 3.36 ± 12.0 kU/L ($0.05 < p < 0.01$), 9.5 ± 30.6 kU/L ($p < 0.05$), 1.6 ± 9.7 kU/L (not significant), and -1.7 ± 2.28 kU/L (not significant). The increase in s-IgE was different for quitters and relapsers at 26 weeks ($p < 0.05$). In quitters aged 40 years or younger ($N = 48$) and in older quitters ($N = 44$), the mean $\pm$ SD increase in s-IgE from baseline at 26 weeks was 19.4 ± 36.8 kU/L and 3.4 ± 25.1 kU/L ($p < 0.005$). Similar increases in s-IgE were observed in male and female subjects. Analyses of variance for repeated measures demonstrated an increase with time in s-IgE in the 92 quitters ($p < 0.05$). The development was different in quitters aged 40 years or younger and those older than 40 years ($p < 0.05$). The variation in s-IgE within 26 weeks after the cessation of smoking had no association with variations in FEV₁ residuals during that time span. Thirty-four quitters had received nicotine chewing gum during their first 3 months of abstinence.

Their mean $\pm$ SD increase in s-IgE from baseline at 3 months was 2.9 kU/L compared with 9.8 ± 26.8 kU/L in quitters not receiving substitution ($0.1 < p < 0.15$). The variation in s-IgE had no significant association with baseling s-IgE. An improvement in airway symptoms during the first 6 weeks was found in 88.9% of quitters without increase in s-IgE

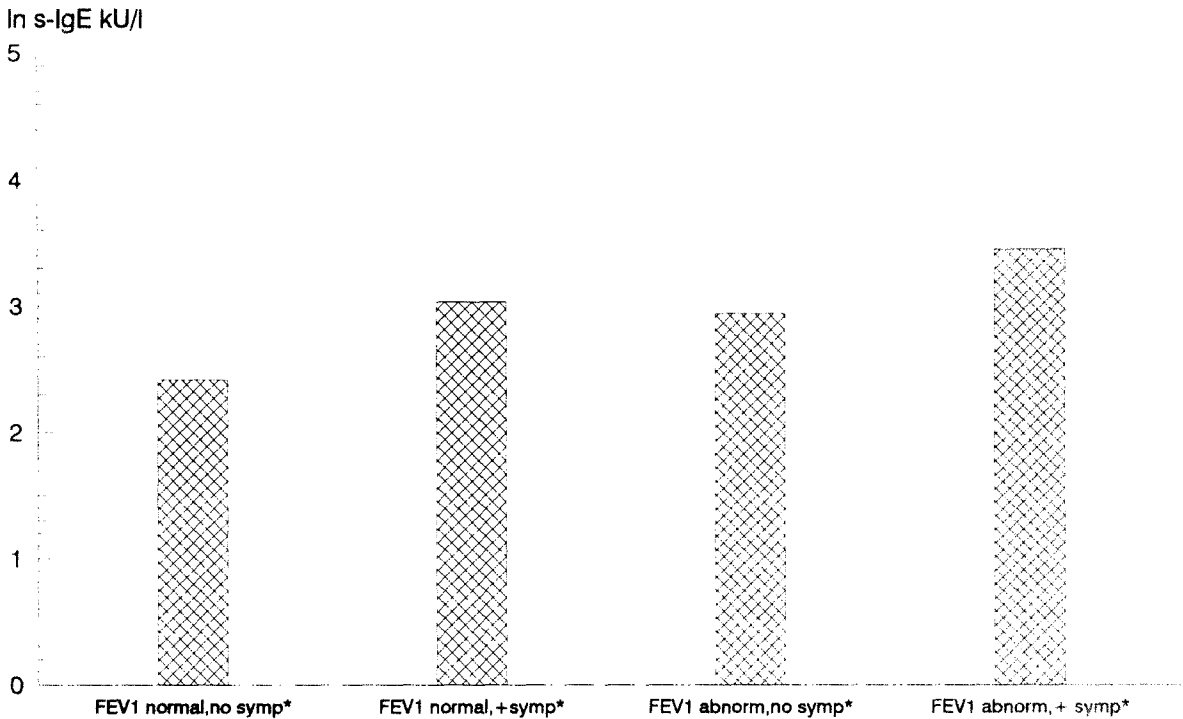


FIG. 1. ln s-IgE; means (▨). FEV₁ normal, residuals within the 90% CI. FEV₁ abnormal, residuals decreased by >2 SD; *symp*, presence of chronic cough/expectoration. High levels of ln s-IgE were associated with presence of airway symptoms independent of FEV₁ residuals ($p < 0.03$) and tended to be associated with decreased FEV₁ residuals ($0.05 < p < 0.06$) independent of presence of airway symptoms.

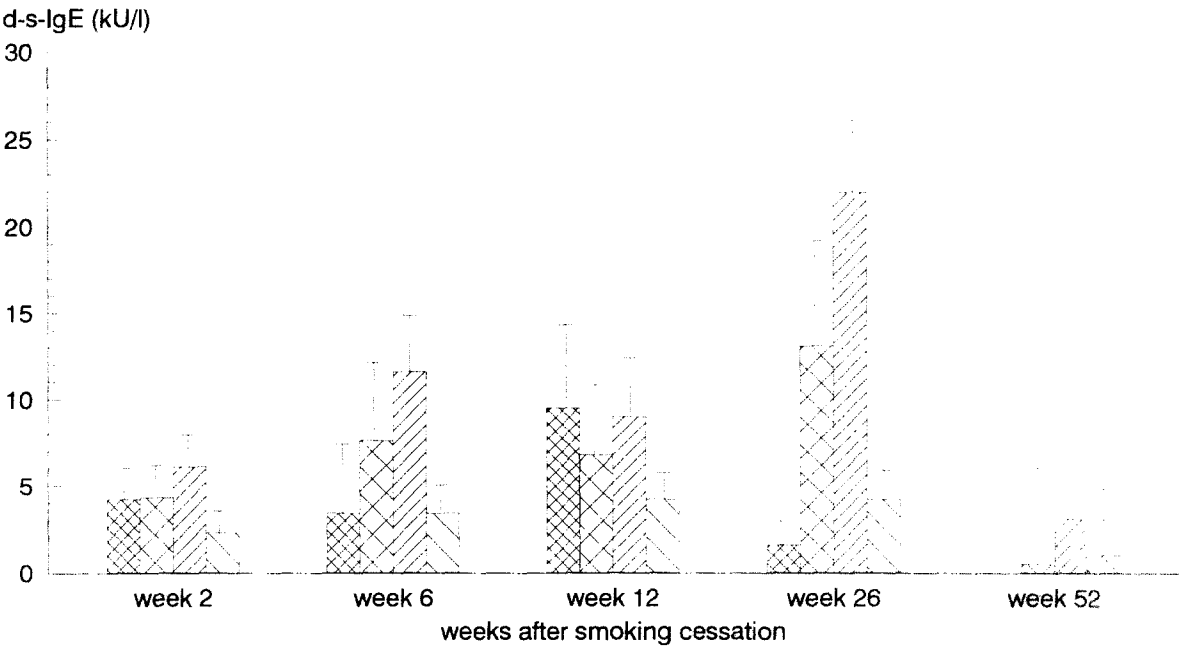


FIG. 2. D-s-IgE, difference in s-IgE from baseline until time of measure, indicated by week number. Means, indicated by *bars*; 1 SD of mean, *vertical lines*; 25 relapsers with smoking relapse between 2 and 3 months after start of trial (▨); 92 quitters who remained abstinent throughout 1 year (▤); 48 quitters 40 years or younger (▥); 44 quitters older than 40 years (▧); d-s-IgE increased with time during first 26 weeks in 92 quitters ($p < 0.05$); different between age groups ($p < 0.05$) and between quitters and relapsers ($p < 0.005$) at week 26.

during 26 weeks of abstinence compared with 53.7% of quitters with an increase in s-IgE ($N = 83$) ($p < 0.05$). None of the quitters developed symptoms compatible with a diagnosis of asthma.

DISCUSSION

This study investigated relations between smoking and s-IgE before and after smoking cessation. No participants had a history or clinical evidence of atopy or allergy. Since the panel of allergens used covered 95% of the local known sensitizers and since parasite infestation is extremely rare in Denmark, a confounding influence from common conditions associated with elevated s-IgE was excluded. Smokers and nonsmokers had identical distribution with respect to sex, proportion of industrial and office workers, and age, and could be compared directly with respect to s-IgE. The groups of smokers had comparable age, smoking history, and sex distribution. An exception to this finding was a difference in smoking history between male and female subjects. Although we confirmed that s-IgE was higher in smokers compared with that in nonsmokers,¹⁻⁴ we were unable to detect an inverse relation between ln s-IgE and daily cigarette consumption.³ Earlier findings of lower s-IgE levels in female smokers compared with that found in male smokers^{9, 11} was also confirmed. As reported by other investigators,¹¹ we found no relation between age and s-IgE in smokers. In contrast with earlier findings,^{9, 11} we were able to detect an influence of PC on the level of s-IgE. This relationship was revealed by standardizing the calculated cigarette consumption by the nicotine content of the brand smoked. This finding indicates that the intake of tobacco constituents by smoking is not well estimated by just considering the number of cigarettes smoked. An even better estimation of the body's tobacco load could be a modification of the cigarette consumption by a coefficient reflecting the content of nicotine metabolites in blood or urine after smoking.

Our results did not support the theory that smokers with elevated s-IgE should have an allergic predisposition since we found no difference in s-IgE between smokers with and without atopic first-degree relatives.

We confirm the association between elevated s-IgE and increased annual FEV₁ loss in older smokers with airway symptoms.^{9, 10} In addition, our results indicated that the presence of airway symptoms and increased annual FEV₁ loss were independently associated with elevated s-IgE. The association between decreased FEV₁ residuals and level of s-IgE did not reach significance, probably caused by a small proportion of smokers with decreased FEV₁ residuals without airway symptoms. The reasons s-IgE is elevated in smokers

compared with elevation in nonsmokers may be the synthesis of IgE specific for microorganisms residing in the lower airways in most smokers,^{6, 7} and the increased permeability of airway epithelium may be a risk for sensitization to various allergens inhaled into the lungs.^{8, 16} S-IgE may also be increased in smokers because of a smoking-induced altered balance between regulating mechanisms for the synthesis of IgE.^{17, 18} Our finding of more airway symptoms in smokers with high levels of s-IgE was consistent with earlier studies and, at least partly, with the finding of a microorganism-induced s-IgE increase in smokers. All subjects with inhalation allergy were excluded in this study, and the possible increased airway epithelial permeability to allergens is likely to have been of minor importance.

This study is the first to investigate the short-term variation in s-IgE after smoking cessation.

The excess s-IgE in exsmokers ceases with time,^{1, 3, 4, 11} and it was surprising that the short-term response to quitting was a further increase in s-IgE.

Smoking is believed to suppress the immune response in some smokers by interfering with the ability of T cells to cooperate with B cells and by depressing B cell function.¹⁹ Lower levels of s-IgG and IgM have been reported in smokers compared with that in nonsmokers,^{20, 21} but specific mechanisms operate in the control of IgE synthesis.¹⁷ The increase in s-IgE after the cessation of smoking may be an acute functional response of IgE-synthesizing cells to removal from a suppressive agent in otherwise immunocompetent individuals. The restriction of this observation to younger subjects is probably caused by the decline in IgE-producing potential with age.^{22, 23} In the present study, no suppression of nicotine on the immune system is demonstrated.

In our opinion this finding should be reinvestigated in a larger population, allowing stratifications according to nicotine chewing gum intake. The clinical relevance of the transient rise in s-IgE after smoking cessation is probably small. Although a weak positive association existed between the variation in s-IgE and the development in airway symptoms after smoking cessation, the variation in s-IgE had no apparent association with lung function, and none of the quitters developed symptoms compatible with asthma.

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