

Distribution of total serum IgE and specific IgE to common aeroallergens by sex and age, and their relationship to each other in a random sample of the Dutch general population aged 20–70 years*

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To describe the distribution of serum total IgE and specific IgE to common aeroallergens by sex and age and to study their relationship to each other, we measured serum total IgE and specific IgE (CAP) to house-dust mite, timothy grass, cat, birch, and *Cladosporium* in a random sample of 2496 subjects, aged 20–70 years from the Dutch general population. We found that total IgE was higher in men, independently of smoking, and that total IgE had no relationship with age after adjustment for specific IgE and smoking in linear regression analysis. At least one positive specific IgE test was found in 32% in both sexes. Men had higher prevalences of specific IgE to house-dust mite and lower prevalences of specific IgE to birch than women. The proportion with positive specific IgE decreased with age. The mean total IgE increased with the number of positive specific IgE tests. Thus, total IgE is higher in men and has no relationship with age if specific IgE is taken into account. The prevalences of specific IgE to aeroallergens are high and decrease with increasing age. We suggest that sex differences in total IgE should be considered when using total IgE.

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Since the identification of immunoglobulin E (IgE) as the immunoglobulin causing sensitization to allergens, total IgE levels and IgE levels specific to different allergens are frequently measured in

serum, in the clinic as well as in epidemiologic studies. High serum total IgE levels are mainly found in subjects sensitized to allergens, but also in subjects with other diseases (1) or with no disease at all.

Only a small number of studies provide information about the distribution of serum total IgE in adult general populations (2–6). Some studies have found higher serum total IgE levels in men than in women (2, 3), but other studies did not find these differences (7–9). Several studies reported higher serum total IgE levels in smokers (6, 10, 11). However, it is unknown whether any sex differences in serum total IgE levels may be explained by sex differences in smoking habits. It is also

*These results are from a local analysis of data collected for the European Community Respiratory Health Survey. Any final international comparison may use a different form of analysis.

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unclear whether serum total IgE levels decrease with increasing age and whether the relationship with age is different for men and women, as some authors report (4, 5).

Information about the distribution of serum specific IgE to aeroallergens in the adult general population is even more rare. In a sample of the French adult general population, Vervloet et al. (12) found a higher prevalence of positive Phadiatop tests (a test detecting specific IgE to a mixture of common aeroallergens) in men than in women and a decrease of this prevalence with age, mainly in men. No other studies are known that describe the distribution of specific IgE to common aeroallergens in an adult general population.

This study aimed to describe the distribution of total serum IgE and specific IgE to common aeroallergens by sex and age and to study their relationship to each other in a large random sample of the Dutch general population aged 20–70 years.

Material and methods

Subjects

The 2496 subjects studied were aged 20–70 years and were responders from a random sample of 4522 subjects from the general population of three areas in The Netherlands (the city of Groningen in the north and the towns of Roosendaal and Geleen, both with adjacent rural communities, in the southwest and southeast, respectively). The sample was stratified by sex and 10-year age groups. All 4522 subjects were asked to attend for an examination that consisted of the administration of a respiratory questionnaire by a trained interviewer, lung function testing, measurement of bronchial reactivity by methacholine provocation, skin tests with nine aeroallergens, and venous blood collection for IgE and hematology. From 1286 men and 1210 women of these 4522 subjects (55%), data of both serum total and specific IgE were obtained from February 1992 to February 1993. The response rate differed with age; it was relatively low in the age group 20–24 years (47%) and was highest in the age groups 40–44 years (63%) and 50–54 years (63%). Only in the age group 65–70 years was there a significant difference in response between men (57%) and women (44%). The results of a postal screening questionnaire about respiratory symptoms sent to all the subjects before they were invited to the examination showed that there was a tendency for subjects with symptoms of wheeze or cough at night, or symptoms suggestive of nasal allergy to participate more in the examination. Of the responders, 23% reported wheezing in comparison with 19% of the nonresponders. For

cough at night, the proportions were 33% and 30% and for nasal allergy 22% and 17%, respectively.

Study design

In this cross-sectional study, the distribution of total IgE and the relationship of total IgE with age and sex were described as geometric means of total IgE, stratified by 10-year age groups and sex.

The distribution of specific IgE to common aeroallergens was described as the prevalence of a positive specific IgE test to the different aeroallergens, stratified by 10-year age groups and sex. To describe the overlap in sensitization to the various aeroallergens, the prevalences of a single positive specific IgE test to the individual allergens and the prevalences of the most frequent combinations of positive tests in case of more than one positive test were given by 10-year age groups and sex.

To show the effect of specific IgE on the relationship of total IgE with sex, age, and smoking habits, we used two linear regression models, both with the natural logarithm of total IgE as dependent variable. The first model included sex, 10-year age groups, and smoking habits as independent variables. In the second model, the number of positive specific IgE tests and the statistically significant individual specific IgE tests were added to the first model.

Methods of measurement

All measurements were performed according to the protocols of the European Community Respiratory Health Survey (13). To determine the serum IgE levels, blood samples were centrifuged, and the sera were stored at -20°C . Total and specific IgE were measured by the Pharmacia CAP System. The CAP was performed in the laboratories of Pharmacia Diagnostics AB, Uppsala, Sweden. The assay is calibrated against the WHO Standard for IgE, with a range of 0.35–100 kU/l for specific IgE and 2–2000 kU/l for total IgE. A value of 1 kU/l was given to total IgE levels below 2 kU/l. Specific IgE was measured to five common aeroallergens: *Dermatophagoides pteronyssinus* (house-dust mite), cat, timothy grass, birch, and *Cladosporium herbarum*. Specific IgE tests were considered positive at levels of 0.35 kU/l or higher ($\geq$ class 1).

Data on smoking were obtained by questionnaire. Subjects were classified as current smokers or ex-smokers if they had smoked at least 20 packs of cigarettes or 360 g of tobacco in their lifetime or at least one cigarette a day or one cigar a week for 1 year. Never-smokers never smoked this amount. Ex-smokers had stopped smoking at least 1 month

before the survey; current smokers had smoked in the preceding month.

Data analysis

Since total IgE levels follow a log-normal distribution, logarithmic transformation (natural log) of total IgE was applied. Means were calculated after this transformation and expressed as antilogarithms or geometric means. Comparison of mean IgE levels was done by the unpaired Student's *t*-test. The chi-square test was used to compare proportions.

Results

The geometric mean of serum total IgE was higher in men than in women (37 vs. 25 kU/l) (Table 1), and the relationship of total IgE with age was different for both sexes (Fig. 1). For men, the mean serum total IgE in the age group 20–29 years was significantly higher than the means of the other age groups. For women, the total IgE level remained fairly constant until about 40 years of age and slightly decreased with age beyond the age of 40.

Table 1. Characteristics of subjects by sex

	Men (n=1286)	Women (n=1210)
Mean age (years)	45.9	45.2
GM total IgE (95% CI)	37.1 (34.1–40.4) kU/l	25.3 (23.2–27.6) kU/l
Natural logarithm SD	1.55 kU/l	1.53 kU/l
≥ 1 positive specific IgE	32.2 (n=414)	32.1 (n=388)
Current smokers (%)	40.1 (n=500)	32.1 (n=375)
Ex-smokers (%)	34.8 (n=434)	25.0 (n=292)
Never-smokers (%)	25.1 (n=313)	42.8 (n=500)

GM=geometric mean; CI=confidence interval; SD=standard deviation.

A high prevalence of at least one positive specific IgE test (32%) was found, with no sex difference (Table 2). However, sex differences were found in the individual allergens. Men had a higher prevalence of a positive test to house-dust mite (23.8% vs. 19.3%) and a lower prevalence of a positive test to birch (8.2% vs. 13.1%) than women (Table 2).

House-dust-mite-specific IgE was the most prevalent, but timothy grass tests were also frequently found to be positive, especially in the age group 20–29 years. Single positive tests to birch, cat, or *Cladosporium* were rare. The vast majority of the subjects with positive tests to these allergens also had positive tests to house-dust mite or timothy grass (Table 3). In the age group 20–29 years, the combination of a positive test to both timothy grass and house-dust mite had a much higher prevalence (21.0% in men and 18.8% in women) than a positive test to timothy grass alone (4.1% in men

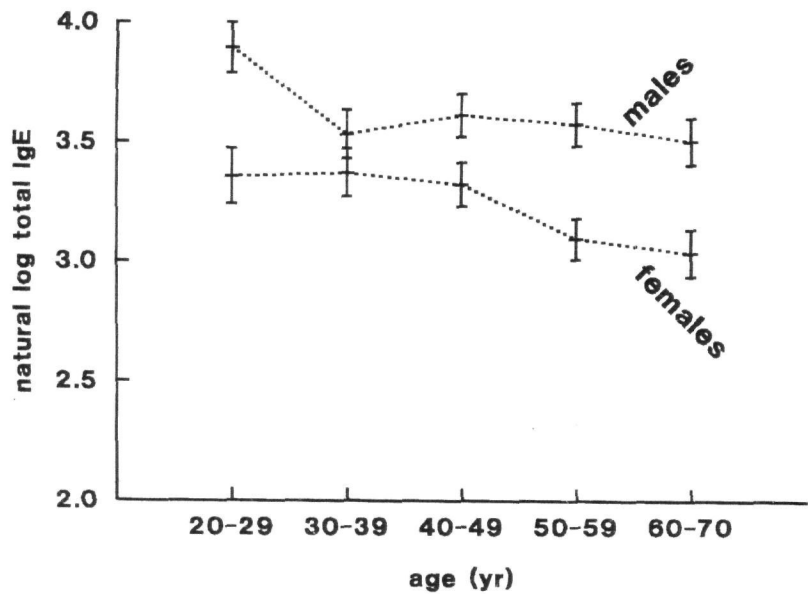


Fig. 1. Mean total IgE levels with standard error by 10-year age groups for men and women separately.

Table 2. Prevalences of positive specific IgE tests to different aeroallergens and prevalences of at least one positive test by 10-year age group and sex

	Percentages (%)											
	20–29 years		30–39 years		40–49 years		50–59 years		60–70 years		20–70 years	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	n=219	n=208	n=239	n=244	n=280	n=266	n=266	n=259	n=282	n=233	n=1286	n=1210
House-dust mite	36.5	27.9	28.0	26.2	21.8	19.2	21.1	15.4	14.9*	8.6*	23.8*	19.3*
Timothy grass	31.1	29.8	18.4	14.8	13.6	11.7	7.1*	12.7*	9.9	9.6	15.3	15.1
Birch	17.4	18.8	8.8	10.7	9.3	13.5	4.1*	11.2*	3.2*	12.0*	8.2*	13.1*
Cat	12.3	12.5	7.9	6.6	5.0	4.9	3.0	3.5	1.8	1.7	5.7	5.6
Cladosporium	5.9	4.8	5.4	3.3	2.9	1.1	2.6	4.6	3.9	1.3	4.0	3.0
≥ 1 positive	48.4	43.8	37.2	36.9	32.1	32.7	28.2	27.4	19.1	21.0	32.2	32.1

* Significantly different between men and women (chi-square test, 1 df; *P*<0.05).

Table 3. Prevalences of single positive specific IgE tests to aeroallergens and prevalences of more than one positive test with specific IgE results for house-dust mite and timothy grass by 10-year age group and sex

	Percentages (%)											
	20–29 years		30–39 years		40–49 years		50–59 years		60–70 years		20–70 years	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	n=219	n=208	n=239	n=244	n=280	n=266	n=266	n=259	n=282	n=233	n=1286	n=1210
1+: House-dust mite +	12.3	5.8	13.4	14.3	11.4	10.5	15.8	7.3	7.4	4.7	12.0	8.7
1+: Timothy grass +	4.1	6.7	2.5	2.9	2.9	1.9	2.6	1.9	1.4	2.6	2.6	3.1
1+: Birch +	0.9	2.9	1.3	2.0	3.2	6.0	0.4	3.5	0	6.4	1.2	4.2
1+: Cat +	0.9	1.0	0.4	1.6	1.1	1.5	0.8	1.5	0	0.4	0.6	1.2
1+: <i>Cladosporium</i> +	0	0.5	0.4	0.8	0.7	0	1.5	0.8	1.1	0	0.8	0.4
>1+: HDM+/Tim+	21.0	18.8	11.3	9.0	8.2	5.6	3.4	6.9	7.1	3.4	9.7	8.4
>1+: HDM+/Tim–	3.2	3.4	3.3	2.9	2.1	3.0	1.9	1.2	0.4	0.4	2.1	2.1
>1+: HDM–/Tim+	5.9	4.3	4.6	2.9	2.5	4.1	1.1	3.9	1.4	3.0	3.0	3.6
>1+: HDM–/Tim–	0	0.5	0	0.8	0	0	0.8	0.4	0.4	0	0.2	0.2

1+ = single test positive; >1+ = more than one test positive; HDM = house-dust mite; Tim = timothy grass.

and 6.7% in women) or house-dust mite alone (12.3% in men and 5.8% in women).

The proportion of subjects with at least one positive specific IgE test decreased with increasing age from 48.4% in men and 43.8% in women in the age group 20–29 years to 19.1% in men and 21.0% in women in the age group 60–70 years (Table 2). In particular, sensitization to more than one allergen was more prevalent in younger age groups than in older age groups (Fig. 2).

Subjects with at least one positive test had much higher mean total IgE levels than subjects with all negative specific IgE tests (Table 4). However, the wide spread of total IgE levels in both groups caused considerable overlap of the distributions. Comparison of the upper limit of the 95% interval of total IgE in specific IgE-negative subjects with the mean total IgE of the specific IgE-positive subjects shows this wide spread and large overlap (for example, the 95% upper limit of specific IgE-negative men aged 20–29 years [285 kU/l] was much higher than the geometric mean of specific IgE-positive men aged 20–29 years [123 kU/l]). In both the specific IgE-negative and the specific IgE-positive groups, 12% of the subjects had a total IgE level above and below the mean of the other group, respectively.

A linear regression model with total IgE as dependent variable and 10-year age groups, smoking habits, and sex as independent variables showed lower total IgE levels in age groups older than 30 years (Table 5, model 1) than in the age group 20–29 years. Current smoking was associated with higher total IgE levels in the age groups older than

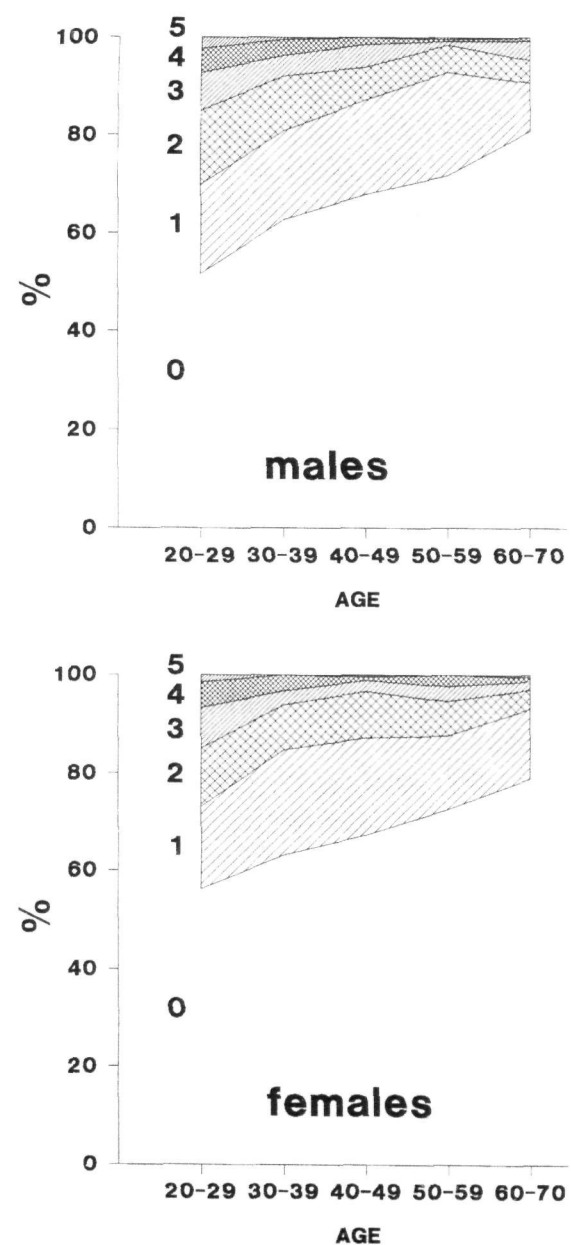


Fig. 2. Relative frequency distribution of number of specific IgE tests positive by 10-year age groups for men and women separately.

Table 4. Geometric mean of total IgE (kU/l) by specific IgE tests, 10-year age group and sex

Age (years)	Sex	0 Specific IgE positive			≥ 1 Specific IgE positive			Total group	
		GM (95%CI)	UL 95%	n	GM (95%CI)	LL 95%	n	GM (95%CI)	n
20–29	M	21 (16–27)	285	113	123 (95–158)	9	106	49 (40–61)	219
30–39	M	17 (14–21)	215	150	114 (90–144)	12	89	34 (28–42)	239
40–49	M	26 (21–31)	380	190	81 (60–108)	5	90	37 (30–43)	280
50–59	M	24 (20–29)	356	191	100 (78–129)	11	75	36 (30–43)	266
60–70	M	24 (20–29)	474	228	130 (91–187)	9	54	33 (28–40)	282
20–70	M	22 (20–25)	352	872	107 (94–121)	9	414	37 (34–40)	1286
20–29	F	12 (9–15)	175	117	86 (66–113)	7	91	28 (22–35)	208
30–39	F	17 (14–21)	271	154	73 (54–98)	5	90	29 (24–36)	244
40–49	F	16 (14–20)	224	179	81 (63–105)	7	87	28 (23–33)	266
50–59	F	16 (14–20)	206	188	48 (35–66)	3	71	22 (19–26)	259
60–70	F	15 (12–18)	216	184	72 (50–105)	5	49	21 (17–25)	233
20–70	F	15 (14–17)	219	822	72 (63–82)	5	388	25 (23–28)	1210

CI = confidence interval; GM = geometric mean; UL 95% = exp (ln[GM] + 1.96 × standard deviation ln[IgE]); LL 95% = exp (ln[GM] – 1.96 × standard deviation ln[IgE]).

Table 5. Linear regression results of two models both with natural logarithm of total IgE as dependent variable and 10-year age groups, sex, and smoking habits as independent variables; in model 2, number of specific IgE tests positive and specific IgE to house-dust mite as independent variables added to model 1

Independent variables	Model 1			Model 2		
	coeff.	SE	P	coeff.	SE	P
Constant	3.87	0.10	0.00	3.00	0.09	0.00
Age 30–39 years (0/1)	–0.34	0.12	0.01	–0.07	0.11	0.54
Age 40–49 years (0/1)	–0.31	0.12	0.01	0.07	0.10	0.53
Age 50–59 years (0/1)	–0.43	0.12	0.00	0.02	0.10	0.88
Age 60–70 years (0/1)	–0.48	0.12	0.00	0.09	0.10	0.42
Female sex (0/1)	–0.36	0.06	0.00	–0.32	0.05	0.00
Current smoking (0/1)	0.20	0.07	0.01	0.21	0.06	0.00
Current smoking and age 20–29 (0/1)	–0.42	0.17	0.02	–0.24	0.15	0.11
1 pos. spec. IgE (0/1)				0.88	0.10	0.00
2 pos. spec. IgE (0/1)				1.34	0.12	0.00
3 pos. spec. IgE (0/1)				1.62	0.17	0.00
4 pos. spec. IgE (0/1)				1.98	0.21	0.00
5 pos. spec. IgE (0/1)				2.52	0.40	0.00
HDM pos. spec. IgE (0/1)				0.55	0.11	0.00

Coeff. = coefficient; SE = standard error; HDM = house-dust mite.

30 years, but with lower total IgE levels in the age group 20–29 years. Women had lower total IgE levels than men independently of smoking habits. Adjustment for the number of positive specific IgE tests changed the relationship of total IgE with age and smoking habits, but had no relevant influence on the relationship with sex (Table 5, model 2). The lower total IgE levels in age groups older than 30 years than in the age group 20–29 years disappeared after adjustment for the number of positive specific IgE tests. The positive association of current smoking with total IgE did not change in age groups older than 30 years, but no association was left in the age group 20–29 years. The level of total IgE increased with the number of positive specific IgE tests. A positive test for house-dust mite was associated with a higher total IgE level,

additionally to the number of positive specific IgE tests. Former smoking was not significantly associated with total IgE. Nor were there significant interactions between the independent variables.

Discussion

This study shows that the mean total IgE is higher in men than in women, independently of smoking habits. In the literature, the findings for sex differences in total IgE are not consistent. Some authors have also observed higher total IgE levels in men than in women (2, 3), whereas others did not find sex differences (4, 7, 9). Omenaas et al. (5) recently found no sex difference in total IgE in the age group 18–54 years, while men above 55 years had higher IgE levels than women. In contrast to our

findings, some authors found that the higher total IgE levels in men could be explained by higher prevalences of current smoking in men (4, 14).

In this study, we found that men in the age group 20–29 years had higher mean total IgE levels than men in the older age groups, whereas women aged 20–49 years had higher mean total IgE levels than women 50–70 years of age. However, multiple linear regression analysis showed that these differences in mean total IgE between age groups could be explained by differences in prevalences of sensitization to aeroallergens and current smoking.

There appears to be no general agreement in the literature as to whether IgE levels decline during adult life. Most authors found a decline in both men and women (2, 4, 8), while others found a decline in women, but not in men (5). However, most authors who studied nonatopic subjects found no relationship with age (3, 4).

This study also shows that 32% of both men and women of the Dutch general population aged 20–70 years has detectable specific IgE antibodies to common aeroallergens, with house-dust mite and timothy grass as the most important allergens and a large overlap in sensitization to the allergens, especially in the age group 20–29 years. Furthermore, men have higher prevalences of house-dust mite and lower prevalences of birch-specific IgE than women.

de Groot et al. (15) also found house-dust mite and grass pollen to be the most frequent sensitizers in The Netherlands. In a recent study, Omenaas et al. (5) found higher prevalences of specific IgE to house-dust mite and cat in men than in women in the Norwegian adult general population, but no sex differences for timothy grass, birch, and *Cladosporium*. In the French population aged 20–60 years, Vervloet et al. (12) found a higher percentage of positive Phadiatop tests in men (22%) than in women (17%). Whether these results agree with our results depends on the nature of the aeroallergens used in the mixture of the Phadiatop test. Sex differences in sensitization might be due to differences in exposure to allergens. However, there is little reason to assume that men are more exposed to house-dust mite and less exposed to birch than women.

Furthermore, we found a decline in the prevalences of positive specific IgE tests with increasing age, especially in the prevalence of more than one positive test with age. In contrast to our findings, Vervloet et al. (12) found a decrease of the percentage with positive Phadiatop tests with age much more sharply in men than in women.

Another finding of this study is that the mean total IgE of subjects with specific IgE to common aeroallergens is much higher than the mean of

those with all specific IgE tests negative, and that total IgE increases with the number of specific IgE tests positive.

The relationship of total IgE with specific IgE might have different directions. One possibility is that the level of total IgE increases as a result of sensitization to allergens. The total IgE level might increase when the amount of exposure to allergens increases in subjects sensitized to the allergens. Our finding that house-dust mite sensitization is associated with higher total IgE levels than other allergens might be due to a more continuous or higher exposure to house-dust mite than to the other allergens.

Another possibility is that a high total IgE level indicates a more general activation of the immune system, resulting in an increased risk of sensitization to specific allergens, especially in younger age groups. This agrees with the results of a longitudinal study with both total IgE and skin prick test measurements at an interval of 5 years. That study showed a very stable total IgE which appeared to be a good predictor of longitudinal changes in skin test results (16).

A limitation of a cross-sectional study of the relationship with age is that changes in risks between generations may cause differences between age groups. Both the relationship of specific IgE and total IgE with age might be influenced by this "cohort effect". A longitudinal study is needed to investigate the course of sensitization to aeroallergens during the lifetime.

Another limitation of this study is the response rate of 55%, which might have caused response bias. Subjects with sensitization to aeroallergens might have responded more to the examination than subjects without sensitization. From 64% of the nonresponders, data on nasal allergy symptoms were known from the previous postal screening questionnaire. The prevalence of nasal allergy symptoms in the screening questionnaire was indeed higher among responders than among non-responders (22% vs. 17%). Thus, the prevalence of positive specific IgE tests in the general population might be somewhat lower than found in our study.

In summary, our results show that serum total IgE is higher in men than in women, independently of smoking habits, and that the differences in mean total IgE between age groups can be explained by differences in prevalences of specific IgE to aeroallergens and differences in current smoking. The prevalences of specific IgE to common aeroallergens are high and decrease with age. Men have a higher prevalence of specific IgE to house-dust mite and a lower prevalence of specific IgE to birch than women, but no sex differences were found in the

total prevalence of specific IgE to common aeroallergens.

The mean total IgE is a useful indicator of the prevalence of sensitization to aeroallergens in a population. When comparing mean total IgE levels, it should be considered that women have substantially lower total IgE levels than men, independently of smoking habits.

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