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Increasing trend in atopy markers prevalence in a Croatian adult population between 1985 and 1999

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Summary

Background Reports about the increasing prevalence of atopy and atopic diseases are common, but recently they have been critically reviewed and the need for relevant research methods has been established.

Objectives This study evaluated a 15-year trend in the prevalence of atopy markers [elevated total IgE, positive skin prick test (SPT) to common aeroallergens and positive atopic symptoms] in Croatian adults, separately for women and men.

Methods The study included 721 subjects (445 men and 276 women), 18–45 years old, examined for allergies within a pre-employment preventive examination. All subjects underwent medical history, SPT with common inhalatory allergens and total serum IgE measurement. The trend analysis of atopy prevalence was performed after stratification of subjects into three consecutive 5-year periods from 1985 to 1999.

Results The prevalence of concurrently elevated total IgE and positive atopic symptoms significantly increased during the studied period in men [odds ratio (OR) 2.44, 95% confidence interval (CI) 1.39–4.29, $P = 0.002$]. Women showed an increased prevalence of positive SPT only, with borderline significance (OR 1.65, 95% CI 1.00–2.71, $P = 0.050$). In women, rural residence was found to be a predictor of elevated total IgE (OR 5.36, 95% CI 2.41–11.93, $P = 0.000$) and smoking to be a predictor of concurrently elevated total IgE and positive SPT (OR 6.20, 95% CI 1.67–23.07, $P = 0.006$).

Conclusions An increasing trend in the prevalence of concurrently elevated total IgE and positive atopic symptoms was found in the Croatian adult male population between 1985 and 1999, but not in the female population. Sex differences responsible for the production and regulation of IgE were suggested.

Keywords atopic symptoms, atopy, sex, skin prick test, time trend, total IgE

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Introduction

The recent revision of nomenclature for allergy [1] defines atopy as 'personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins'. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis or eczema. Therefore, the term atopy or atopic disease should be used when typical respiratory and/or skin symptoms are accompanied by elevated IgE levels and/or a positive skin prick test (SPT) to common allergens.

Since 1960, a number of studies from all over the world have shown a dramatic increase in the prevalence of

atopy and atopic diseases (asthma, rhinitis, eczema), particularly in younger age groups (children and adolescents) and the urban population in the industrialized Western countries [2]. The cause of this 'atopy march' is not yet known, despite considerable scientific effort. Recent studies have raised some doubt about the relevance of the existing epidemiological data on the time trends of atopy prevalence. Wieringa et al. [3] found only nine articles on time trends of atopy and atopic diseases in which objective measures were used at least at two time points in the whole population under study, and only three studies found a consistently significant increase in atopy prevalence. This emphasizes the need for further, methodologically relevant research in the field [4].

The aim of this study was to evaluate a 15-year (1985–1999) trend of atopy markers prevalence in a cohort of adult men and women living in urban and rural regions of northern Croatia, by means of both objective and subjective atopy markers according to the recent WAO/EAACI atopy definition [1]: elevated total IgE, positive SPT and a history of atopic symptoms.

Subjects, study design and methods

Subjects and study design

The cohort was recruited from the register of the Occupational and Environmental Medicine Unit, Institute for Medical Research and Occupational Health, Zagreb, and included all subjects who were examined for allergies during pre-employment examinations for a pharmaceutical manufacturing plant between 1985 and 1999. A pre-employment allergological examination was performed in that period for all workers who applied for the job in a pharmaceutical plant regardless of the applicant's profession, education or job description in the plant. This study was conducted within the national scientific project approved by the authorized ethical committee. The database was designed and the data were analysed in a way to protect subjects' anonymity according to the Helsinki Declaration.

Our analysis of trends in the prevalence of atopy markers was based on cross-sectional data over three consecutive 5-year periods: 1985–1989, 1990–1994 and 1995–1999. The inclusion criterion for this study was completeness of data including address, age, medical history on atopic symptoms, SPT with common inhalatory allergens and total serum IgE levels. Hundred and twenty-eight subjects, i.e. 79 men (mean age 24.6 ± 4.49 years) and 49 women (mean age 22.4 ± 3.24 years), were excluded from the study (Fig. 1): 124 because of missing data regarding address (74 men and 45 women) or atopic

symptoms (five men), and four subjects (three men and one woman) were excluded due to contraindicated SPT. Finally, the study included a total of 721 subjects aged 18–45 years, of whom 276 were women and 445 were men. Excluded subjects did not differ from those included regarding age, gender ratio, proportion of smokers, educational level, proportion of subjects with elevated total IgE, positive SPT and positive atopic symptoms.

Methods

Medical history. Medical history, including address (urban/rural residence), smoking habit and education, was taken in a routine medical interview with all subjects. Data on ever experienced respiratory and/or skin atopic symptoms compatible with diagnoses of rhinitis, asthma and eczema [1] were recorded using a simple questionnaire. Upper airway symptoms compatible with the recent Allergic Rhinitis and its Impact on Asthma Workshop (ARIA) guidelines' definition of allergic rhinitis (AR) included sneezing, rhinorrhoea, nasal itching and nasal obstruction (not related to common cold) [5]. Lower airway symptoms included episodic dry cough (not related to common cold), wheezing, chest tightness and dyspnoea that is compatible with Global Initiative for Asthma (GINA) guidelines for diagnosing asthma [6]. Skin symptoms compatible with diagnoses of urticaria and atopic eczema included itching, erythema, rash, eczema and urticaria [7]. The variable 'positive atopic symptoms' was defined as the presence of at least one upper airway, lower airway or skin symptom.

Smoking habit was analysed as a dichotomous variable (smoker or non-smoker). Only subjects who never smoked were designated as non-smokers.

Education was defined in three categories: low – primary school (8 years), medium – secondary school (8+4 years) and high – university education (more than 12 years of education).

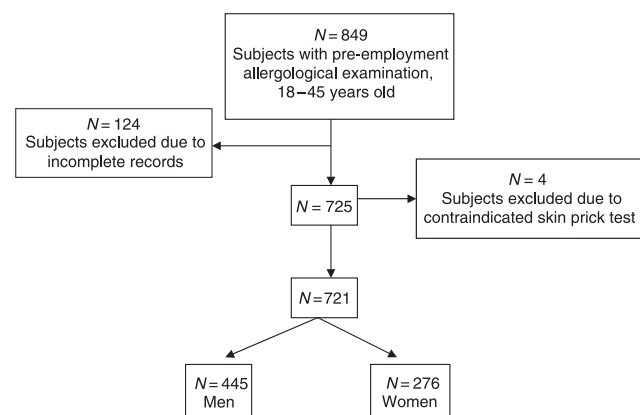


Fig. 1. Selection of the study subjects.

Skin prick testing. SPT was performed using a standard method [8] with the panel of common commercial inhalatory allergens (Epipharm, Austria; ALK, Denmark): grass pollen mixture, birch, hazel, weed (*Ambrosia elatior*, *Artemisia vulgaris*) pollens, mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, moulds *Cladosporium herbarum* and *Alternaria alternata*, cat and dog. SPT included testing with a positive control solution (10 mg/mL of histamine hydrochloride) and a negative control solution (buffer solution). Skin reaction (weal) was evaluated after 15 min. The mean skin reaction (mean weal diameter) was calculated according to the formula $(D+d)/2$, where D represents the largest longitudinal diameter and d its midpoint orthogonal diameter in

millimetres. The results of SPT were considered to be positive when the mean weal diameter to the tested allergens was larger than the negative control by 3 mm or more. The variable 'positive SPT' was defined as a positive SPT to at least one tested allergen.

Total immunoglobulin E. Total serum IgE was measured using the PRIST or the ELISA CAP method (Pharmacia Diagnostics AB, Uppsala, Sweden). PRIST was used in 298 (44%) subjects and ELISA CAP in 373 (56%). In comparative studies, IgE levels obtained with radio- and enzyme-immunoassays were highly comparable, with correlation coefficients usually above 0.95 [9–11].

Values ≥ 125 IU/mL were considered increased. This cut-off value was taken from earlier epidemiological studies that mostly recommended total IgE values between 100 and 150 IU/mL as a cut-off between normal and elevated levels for adults [12–14].

Statistical analysis

Statistical analysis was performed using software Stata/SE 9.0 for Windows (StataCorp LP, Lakeway Drive, College Station, TX, USA) and included descriptive methods and logistic regression. The logistic regression model was used to evaluate the time trend of the prevalence of atopy markers over the three consecutive 5-year periods in the whole sample, and separately in men and women. Each of the three atopy markers, elevated total IgE, positive SPT and positive atopic symptoms, was analysed as a dependent variable. These atopy markers were also combined into the following four dependent variables: elevated

IgE+positive atopic symptoms, elevated IgE+positive SPT, positive SPT+positive atopic symptoms and elevated IgE+positive SPT+positive atopic symptoms. Analyses were controlled for subjects' age, educational level, smoking and urban/rural residence, by introducing these variables into the models as predictors. All variables are described in Tables 1 and 2. The value of $P < 0.05$ was considered to be statistically significant.

Results

Tables 1 and 2 show the profiles of the included subjects and the frequencies of analysed atopy markers and their combinations over the three 5-year periods, separately for men and women. Smokers were more frequent in men (56.9%) than in women (44.8%). However, the prevalence of smokers was similar across the studied periods in both groups. Medium educational level was the most common in both men and women (75.3% and 55.8%, respectively), and across the periods. The frequencies of subjects with elevated total IgE and positive SPT were higher in men than in women (for elevated total IgE 28.1% vs. 13.8%, respectively; for positive SPT 26.1% vs. 18.5%, respectively), as well as the frequencies of subjects with concurrently elevated total IgE and a positive SPT (14.6% in men vs. 5.4% in women). The frequency of subjects with positive atopic symptoms was higher in women than in men (37.0% vs. 25.8%, respectively). The parallel presence of the three analysed atopy markers was shown only in 5.3% of the included subjects.

Tables 3–5 show the results of logistic regression analyses.

Table 1. Characteristics of the subjects according to the three 5-year periods analysed

					Educational level [†]		
	<i>N</i>	Age (years) mean ± SD	Urban/rural residence	Smokers* (%)	Low (%)	Medium (%)	High (%)
Men							
1985–1989	68	24.2 ± 4.50	49/19	44 (66.7)	24 (35.3)	32 (47.1)	12 (17.6)
1990–1994	183	24.3 ± 4.70	125/58	99 (54.1)	11 (6.0)	156 (85.2)	16 (8.7)
1995–1999	194	25.7 ± 5.13	124/70	109 (56.2)	10 (5.2)	147 (75.8)	37 (19.1)
Total	445	24.9 ± 4.91	298/147	252 (56.9)	45 (10.1)	335 (75.3)	65 (14.6)
Women							
1985–1989	56	23.3 ± 4.05	44/12	24 (48.0)	12 (22.2)	30 (55.6)	12 (22.2)
1990–1994	69	24.6 ± 5.21	58/11	30 (43.5)	9 (13.0)	48 (69.6)	12 (17.4)
1995–1999	151	27.3 ± 5.84	124/27	67 (44.4)	19 (12.6)	75 (49.7)	57 (37.7)
Total	276	25.8 ± 5.61	226/50	121 (44.8)	40 (14.6)	153 (55.8)	81 (29.6)
Total							
1985–1989	124	23.8 ± 4.31	93/31	68 (58.6)	36 (29.5)	62 (50.8)	24 (19.7)
1990–1994	252	24.4 ± 4.84	183/69	129 (51.2)	20 (7.9)	204 (81.0)	28 (11.1)
1995–1999	345	26.4 ± 5.50	248/97	176 (51.0)	29 (8.4)	222 (64.3)	94 (27.2)
Total	721	25.2 ± 5.20	524/197	373 (52.3)	85 (11.8)	488 (67.9)	146 (20.3)

*For two men and six women in the first period, smoking data were not available.

†For two women in the first period, data regarding educational level were not available.

Table 2. Markers of atopy in the study subjects according to the three 5-year periods analysed

	<i>N</i>	Elevated total IgE (IgE) (%)	Positive SPT (%)	Positive atopic symptoms (AS) (%)	IgE and AS (%)	SPT and AS (%)	IgE and SPT (%)	IgE, SPT and AS (%)
Men								
1985–1989	68	12 (17.6)	21 (30.9)	13 (19.1)	1 (1.5)	6 (8.8)	9 (13.2)	1 (1.5)
1990–1994	183	48 (26.2)	42 (23.0)	36 (19.7)	14 (7.7)	17 (9.3)	24 (13.1)	12 (6.6)
1995–1999	194	65 (33.5)	53 (27.3)	66 (34.0)	29 (14.9)	24 (12.4)	32 (16.5)	16 (8.2)
Total	445	125 (28.1)	116 (26.1)	115 (25.8)	44 (9.9)	47 (10.6)	65 (14.6)	29 (6.5)
Women								
1985–1989	56	11 (19.6)	8 (14.3)	12 (21.4)	6 (10.7)	5 (8.9)	3 (5.4)	2 (3.6)
1990–1994	69	7 (10.1)	8 (11.6)	30 (43.5)	3 (4.3)	4 (5.8)	2 (2.9)	1 (1.4)
1995–1999	151	20 (13.2)	35 (23.2)	60 (39.7)	9 (6.0)	18 (11.9)	10 (6.6)	6 (4.0)
Total	276	38 (13.8)	51 (18.5)	102 (37.0)	18 (6.5)	27 (9.8)	15 (5.4)	9 (3.3)
Total								
1985–1989	124	23 (18.5)	29 (23.4)	25 (20.2)	7 (5.6)	11 (8.9)	12 (9.7)	3 (2.4)
1990–1994	252	55 (21.8)	50 (19.8)	66 (26.2)	17 (6.7)	21 (8.3)	26 (10.3)	13 (5.2)
1995–1999	345	85 (24.6)	88 (25.5)	126 (36.5)	38 (11.0)	42 (12.2)	42 (12.2)	22 (6.4)
Total	721	163 (22.6)	167 (23.2)	217 (30.1)	62 (8.6)	74 (10.3)	80 (11.1)	38 (5.3)

Elevated total IgE: ≥ 125 IU/mL; positive SPT: positive SPT to at least one of 12 tested standard inhalatory allergens; positive atopic symptoms: ever present at least one upper airway, lower airway or skin symptom.

SPT, skin prick test.

In a total sample (Table 3), logistic model was significant for the following atopy markers and their combinations: elevated total IgE, positive SPT, positive atopic symptoms, concurrently present elevated IgE and atopic symptoms and concurrently present elevated IgE and positive SPT. Elevated total IgE, positive SPT and positive atopic symptoms were significantly predicted with gender, showing a lower risk for the presence of elevated total IgE [odds ratio (OR) 0.44, 95% confidence interval (CI) 0.28–0.67, $P=0.000$] and a positive SPT (OR 0.58, 95% CI 0.39–0.87, $P=0.008$), and a higher risk for the presence of positive atopic symptoms (OR 1.61, 95% CI 1.14–2.28, $P=0.007$) in women. Rural residence significantly predicted only the presence of elevated total IgE (OR 1.99, 95% CI 1.34–2.95, $P=0.001$), and high educational level was found to be predictor of a positive SPT (OR 2.73, 95% CI 1.30–5.76, $P=0.008$). The combination of elevated total IgE and positive SPT was, besides gender, predicted by smoking (OR 1.68, 95% CI 1.00–2.80, $P=0.048$). The prevalence of elevated total IgE, positive atopic symptoms and their combination significantly increased during the 15-year period studied (OR 1.32, 95% CI 1.00–1.74, $P=0.048$, OR 1.54, 95% CI 1.21–1.97, $P=0.001$ and OR 1.71, 95% CI 1.11–2.65, $P=0.015$, respectively). Comparing the first (1985–1989) and the third (1995–1999) 5-year intervals in the total sample, the prevalence of elevated total IgE increased from 18.5% to 24.6%, the prevalence of positive atopic symptoms increased from 20.2% to 36.5% and the prevalence of concurrent presence of both atopy markers doubled (5.6–11%) (Table 2).

In men (Table 4), logistic regression models were significant for elevated total IgE, positive atopic symp-

toms and their combination, and a significant time trend for these atopy markers was found (OR 1.47, 95% CI 1.06–2.05, $P=0.021$, OR 1.59, 95% CI 1.14–2.22, $P=0.007$ and OR 2.44, 95% CI 1.39–4.29, $P=0.002$, respectively). Comparing the first and the third 5-year intervals, the prevalence of elevated total IgE and positive atopic symptoms nearly doubled in men (17.6% vs. 33.5% and 19.1% vs. 34.0%, respectively) (Table 2). Elevated total IgE and positive atopic symptoms did not correlate with age, urban/rural residence, smoking and educational level in men.

In women (Table 5), logistic regression models were significant for elevated total IgE, positive SPT and their combination. Elevated total IgE was highly predicted only with rural residence (OR 5.36, 95% CI 2.41–11.93, $P=0.000$). The combination of elevated total IgE and positive SPT was highly predicted only by smoking (OR 6.20, 95% CI 1.67–23.07, $P=0.006$). The prevalence of a positive SPT was the only atopy marker predicted with the analysed time period, with borderline significance (OR 1.65, 95% CI 1.00–2.71, $P=0.050$). It increased from 14% in the first 5-year period to 23% in the last 5-year period. Elevated total IgE and positive SPT did not correlate with age and educational level in women.

Discussion and conclusion

These are the first data regarding a time trend of atopy for Croatian population. Studies on time trend for atopy prevalence are difficult to compare due to quite different designs, including type of atopy markers analysed, subjects' age and time interval. In order to enable comparison

Table 3. Logistic regression analysis for atopy markers in a total sample

	Elevated total IgE		Positive SPT		Positive atopic symptoms		Elevated total IgE and positive atopic symptoms		Elevated total IgE and positive SPT	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Five-year periods	1.32 (1.00–1.74)	0.048	1.17 (0.90–1.51)	0.245	1.54 (1.21–1.97)	0.001	1.71 (1.11–2.65)	0.015	1.24 (0.86–1.78)	0.250
Gender	0.44 (0.28–0.67)	0.000	0.58 (0.39–0.87)	0.008	1.61 (1.14–2.28)	0.007	0.54 (0.29–1.02)	0.057	0.35 (0.19–0.65)	0.001
Age	0.99 (0.96–1.03)	0.699	0.99 (0.95–1.03)	0.610	1.00 (0.97–1.03)	0.889	0.98 (0.92–1.03)	0.408	0.97 (0.92–1.02)	0.224
Urban/rural residence	1.99 (1.34–2.95)	0.001	0.82 (0.54–1.25)	0.359	0.74 (0.50–1.09)	0.127	1.02 (0.55–1.89)	0.946	1.11 (0.65–1.90)	0.712
Smoking	1.44 (0.98–2.11)	0.065	1.40 (0.96–2.04)	0.078	1.37 (0.97–1.93)	0.073	1.41 (0.80–2.49)	0.232	1.68 (1.00–2.80)	0.048
Educational level (years of education)										
Low (8 years)*	1 (ref)	–	1 (ref)	–	1 (ref)	–	1 (ref)	–	1 (ref)	–
Medium (12 years)	1.51 (0.78–2.91)	0.225	1.55 (0.79–3.02)	0.200	1.15 (0.66–2.01)	0.611	1.38 (0.47–4.09)	0.556	2.31 (0.79–6.74)	0.125
High (> 12 years)	1.22 (0.55–2.69)	0.626	2.73 (1.30–5.76)	0.008	1.24 (0.66–2.33)	0.511	2.10 (0.64–6.91)	0.221	2.91 (0.88–9.63)	0.081
P	0.000		0.0037		0.0001		0.0450		0.0005	
Pseudo R ²	0.062		0.028		0.034		0.0349		0.053	

*Low educational level is set as the reference category.

Number of observations = 711. Logistic regression model was not statistically significant for dependent variables 'positive SPT and atopic symptoms' ($P = 0.0626$, pseudo $R^2 = 0.029$) and 'elevated total IgE, positive SPT and atopic symptoms' ($P = 0.166$; $R^2 = 0.035$).Bold numerals highlight the significant associations, i.e. P -values below 0.05.OR, odds ratio; 95% CI, 95% confidence interval; P , P -value; SPT, skin prick test.

of different studies and to ensure the objectiveness of the studied atopy time trend, Wieringa et al. [3] applied the following inclusion criteria: observation had to be original, with at least two surveys and at least 2 years apart from each other, with similar methods (age groups, areas, sampling) and the same objective atopy prevalence measurements. Our study fulfilled these criteria. The time trend of atopy prevalence was analysed with both objective and subjective atopy markers, taking into account the recent WAO/EAACI definition of atopy [1]. It was based on three 5-year periods, and included population samples selected on the same basis throughout the study.

Increasing time trend for the prevalence of atopy markers during three 5-year periods between 1985 and 1999 was observed in our study. After controlling for age, educational level, smoking habit and type of residence (urban or rural), an increased prevalence of elevated total IgE and ever experienced atopic symptoms was found in men, while in women there was an increase in the prevalence of a positive SPT with borderline significance. The prevalence of elevated total IgE and positive atopic symptoms in men nearly doubled over the 15-year period studied, and the prevalence of a positive skin test in women increased by more than 60% during the same period.

Several studies published in the last 5 years [15–19] also showed a significant increase in the prevalence of atopy over the last 10–30 years among adults, using objective atopy markers and fulfilling the criteria proposed by Wieringa et al. [3]. The increase in the prevalence of atopy based on positive specific IgE to aeroallergens was suggested in adult Greenlanders between 1987 and 1998 (10% vs. 19%, respectively) [15], in adult men from United Kingdom for the period from 1975 to 1998 (30% vs. 42%, respectively) [16] and in the adult Danish population for the period between 1990 and 1998 (26.5% vs. 33.9%, respectively) [17]. The cause of such an increase is not known, but changes in environment and life-style are indicated [2, 20]. In this study, high educational level was associated with the presence of a positive SPT in a total sample, while smoking influenced concurrent occurrence of elevated total IgE and positive SPT in women.

Moreover, we analysed the combined presence of objective and subjective atopy markers to gain a more complete concept of atopy trend in our population. So far, studies have rarely examined the concurrent presence of subjective and objective atopy markers. For example, Linneberg et al. [17] analysed symptoms of AR in combination with specific IgE positivity to aeroallergens and found significantly greater associations between specific IgE positivity and rhinitic symptoms in 1998 compared with 1990. Similar results were obtained in our study. During the first time period (1985–1990), one out of 12 men (8.3%) with elevated total IgE experienced atopic symptoms, while in the last period (1995–1999) the number of male subjects with symptoms increased to

Table 4. Logistic regression analysis for atopy markers in men

	Elevated total IgE		Positive atopic symptoms		Elevated total IgE and positive atopic symptoms	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Five-year periods	1.47 (1.06–2.05)	0.021	1.59 (1.14–2.22)	0.007	2.44 (1.39–4.29)	0.002
Age	1.01 (0.97–1.05)	0.648	1.00 (0.95–1.04)	0.911	1.00 (0.94–1.07)	0.980
Urban/rural residence	1.46 (0.93–2.30)	0.101	0.71 (0.44–1.17)	0.180	0.81 (0.40–1.67)	0.575
Smoking	1.35 (0.86–2.11)	0.194	1.17 (0.74–1.84)	0.510	1.07 (0.55–2.08)	0.848
Educational level (years of education)						
Low (8 years)*	1 (ref)	–	1 (ref)	–	1 (ref)	–
Medium (12 years)	1.48 (0.66–3.30)	0.340	1.44 (0.60–3.46)	0.413	1.54 (0.34–6.89)	0.575
High (>12 years)	0.82 (0.30–2.30)	0.712	2.40 (0.88–6.59)	0.088	2.04 (0.39–10.71)	0.398
P	0.0108		0.0112		0.0249	
Pseudo R ²	0.032		0.033		0.050	

*Low educational level is set as the reference category.

Number of observations = 443.

Logistic regression model was not statistically significant for dependent variables 'positive SPT' ($P=0.1623$; $R^2=0.018$) and 'elevated total IgE and positive SPT' ($P=0.4272$; $R^2=0.016$).

Bold numerals highlight the significant associations, i.e. P-values below 0.05.

OR, odds ratio; 95% CI, 95% confidence interval; P, P-value; SPT, skin prick test.

Table 5. Logistic regression analysis for atopy markers in women

	Elevated total IgE		Positive SPT		Elevated total IgE and positive SPT	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Five-year periods	1.13 (0.67–1.90)	0.638	1.65 (1.00–2.71)	0.050	1.49 (0.64–3.47)	0.350
Age	0.93 (0.86–1.01)	0.106	0.99 (0.93–1.06)	0.839	0.89 (0.76–1.03)	0.125
Urban/rural residence	5.36 (2.41–11.93)	0.000	0.68 (0.26–1.73)	0.417	1.77 (0.44–7.12)	0.421
Smoking	1.62 (0.74–3.54)	0.229	1.38 (0.71–2.69)	0.341	6.20 (1.67–23.07)	0.006
Educational level (years of education)						
Low (8 years)*	1 (ref)	–	1 (ref)	–	1 (ref)	–
Medium (12 years)	1.03 (0.30–3.50)	0.964	0.83 (0.29–2.34)	0.722	1.04 (0.11–9.67)	0.972
High (>12 years)	1.83 (0.49–6.82)	0.367	1.90 (0.67–5.36)	0.228	7.01 (0.73–66.98)	0.091
P	0.0039	0.0440	0.0192			
Pseudo R ²	0.094	0.051	0.138			

*Low educational level is set as the reference category.

Number of observations = 268.

Logistic regression model was not statistically significant for dependent variables 'positive atopic symptoms' ($P=0.0701$; $R^2=0.033$) and 'elevated IgE and positive atopic symptoms' ($P=0.3527$; $R^2=0.055$).

Bold numerals highlight the significant associations, i.e. P-values below 0.05.

OR, odds ratio; 95% CI, 95% confidence interval; P, P-value; SPT, skin prick test.

29 out of 65 men (44.6%) with elevated IgE (Table 2). No such trend was observed in women. However, it must be noted that the prevalences of positive combined atopy markers are rather low in our study, especially in women, and this could have influenced the results.

An often emphasized problem in reporting atopic symptoms is an increase in public awareness of atopic diseases. This issue can exaggerate the incidence and prevalence of atopic symptoms, especially in time-trend evaluation [2, 3]. All subjects in our study were examined for allergies during obligatory pre-employment examinations. The particular-

ity of these preventive examinations is a high motivation for getting a job in potential workers, which makes aggravation of symptoms highly unlikely, and dissimulation more realistic to be expected [21, 22]. Therefore, we assume that underreporting of symptoms is quite possible in these subjects and that the influence of increased awareness of atopic symptoms over time is not likely.

Sex differences in time-trend patterns and predictors among the markers and symptoms analysed were found in this study, suggesting different specificity and sensitivity of analysed atopy markers in women and men. A higher

prevalence of atopic symptoms that was found in women, which was not supported by objective atopy markers, may be partly due to psychological effects. We can speculate that for cultural, social and psychological reasons, women report and discuss their health status, illnesses and symptoms more easily than men. Men, who have to be healthy and strong to be socially acknowledged, will tend to hide their symptoms and diseases. However, differences in the time trends of atopy markers between men and women are more interesting. In men, an increased trend in the prevalence of elevated IgE and atopic symptoms was not followed by a positive SPT, which did not vary considerably across the period studied in this group. In contrast to men, our group of women showed no time trend in the prevalence of elevated total IgE and positive atopic symptoms, with only an indication of increasing prevalence of a positive SPT over the period studied. Elevated total IgE is often considered to be an unreliable and unspecific marker in clinical evaluation of atopy, despite a strong correlation with a positive SPT [23]. The overlapping of total IgE levels between atopics and non-atopics is common [24, 25], which diminishes its clinical specificity. Total IgE level regularly increases in parasitic infections, and depends on other factors, such as age, sex and smoking [26, 27]. However, the clinical relevance of elevated total IgE level in the evaluation of atopic diseases in this study was supported by a significant correlation between elevated total IgE and ever experienced atopic symptoms in our subjects. The proportion of subjects with elevated total IgE, but not other atopy markers analysed, was highly predicted with rural residence only in women, suggesting lower clinical relevance of elevated total IgE as an atopy marker in this group.

Recent studies of time trends in atopy prevalence rarely evaluated sex differences, despite evidence of differently distributed atopy markers in women and men. Our previous study showed a higher prevalence of atopy (based on concomitantly positive SPT and specific IgE to at least one tested inhalatory allergen) in men than in women [21]. It is well established that the total IgE levels, as well as the prevalence of elevated total IgE are higher in men [26, 27]. Our earlier results showed that the total IgE threshold of 125 IU/mL discriminated between positive and negative skin tests in men, but not in women [28]. This is supported by other authors showing different ranges of 'normal' total IgE values between women and men [29]. Some recent studies suggested genetically based sex differences in the expression of total IgE [30, 31]. Although a small number of female subjects with positive atopy markers, especially combined, can hamper the interpretation of sex differences in the prevalence of atopy in our study, our data suggest gender disparities between the clinical expression of atopy and the expression of common objective atopy markers (skin testing, IgE) and support evidence of sex differences in IgE regulatory mechanisms.

In conclusion, our results showed an increasing trend in atopy prevalence between 1985 and 1999 in a Croatian adult male population. They corroborate other findings about the increase in the prevalence and incidence of atopic diseases across several past decades, and they suggest that sex differences in the prevalence of atopy markers should be further investigated.

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