doi: 10.1111/cea.12757
Clinical & Experimental Allergy, 46, 1328–1336
ORIGINAL ARTICLE Epidemiology of Allergic Disease

Increase in pollen sensitization in Swedish adults and protective effect of keeping animals in childhood

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Clinical & Experimental Allergy

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Cite this as: A. Bjerg, L. Ekerljung, J. Eriksson, J. Näslund, S. Sjölander, E. Rönmark, Å. Dahl, K. Holmberg, G. Wennergren, K. Torén, M. P. Borres, J. Lötvall and B. Lundbäck, *Clinical & Experimental Allergy*, 2016 (46) 1328–1336.

Summary

Background To date, most studies of the 'allergy epidemic' have been based on self-reported data. There is still limited knowledge on time trends in allergic sensitization, especially among adults.

Objective To study allergic sensitization, its risk factors and time trends in prevalence.

Methods Within West Sweden Asthma Study (WSAS), a population-based sample of 788 adults (17–60 years) underwent skin prick tests (SPTs) for 11 aeroallergens 2009–2012. Specific IgE was analysed in 750 of the participants. Those aged 20–46 years (n = 379) were compared with the European Community Respiratory Health Survey sample aged 20–46 year from the same area (n = 591) in 1991–1992.

Results Among those aged 20–46 years, the prevalence of positive SPT to pollen increased, timothy from 17.1% to 29.0% ($P < 0.001$) and birch from 15.6% to 23.7% ($P = 0.002$) between 1991–1992 and 2009–2012. Measurements of specific IgE confirmed these increases. Prevalence of sensitization to all other tested allergens was unchanged. In the full WSAS sample aged 17–60 years, any positive SPT was seen in 41.9%, and the dominating sensitizers were pollen (34.3%), animals (22.8%) and mites (12.6%). Pollen sensitization was strongly associated with rhinitis, whereas indoor allergens were more associated with asthma. Growing up with livestock or furred pets decreased the risk of sensitization, adjusted odds ratio 0.53 (0.28–0.995) and 0.68 (0.47–0.98), respectively.

Conclusion Pollen sensitization has increased in Swedish adults since the early 1990s, while the prevalence of sensitization to other allergens has remained unchanged. This is one plausible explanation for the increase in rhinitis 1990–2008 in Swedish adults, during which time the prevalence of asthma, which is more associated with perennial allergens, was stable. Contact with animals in childhood seems to reduce the risk of sensitization well into adulthood. One major factor contributing to the rise in pollen allergy is a significant increase in levels of birch and grass pollen over the past three decades.

Keywords adults, allergic sensitization, asthma, epidemiology, farm, skin prick test, specific IgE

Submitted 10 September 2015; revised 26 April 2016; accepted 29 April 2016

Introduction

Allergic diseases such as asthma and rhinitis are today common, following a remarkable increase during the latter half of the 20th century [1–4]. To some extent, this 'allergy epidemic' may reflect increased awareness [5], which has prompted the need to use also objective measures. Compared to studies of prevalence trends in asthma and rhinitis, there have been fewer repeated population-based studies of allergic sensitization, especially in adults.

In children, the prevalence of aeroallergen sensitization increased until the 1990s [6, 7], but later seems to have plateaued in Australia [4] and Europe [1, 8] with the exception of northern Sweden [9]. In contrast, the few available studies of adults have shown continuous increases in sensitization since the 1990s [10–13]. This may reflect a cohort effect, that is a spillover into adults of the previous upward trend in children and adolescents [14, 15]. A levelling off of the previous increasing trend could thus be expected to occur also in adults, although this has not yet been demonstrated.

The increase in allergic sensitization remains largely unexplained. According to the modified hygiene hypothesis, factors related to affluence and a westernized lifestyle result in a Th1/Th2 imbalance and increase the risk of sensitization [16, 17]. The risk of sensitization is decreased in children who have several older siblings, who grow up on a farm and, in some studies, in children exposed to furred pets [16, 18–20]. Much less is known of the impact on sensitization in adults; however, some results suggest that these associations may persist into adulthood. [13, 14].

A study of more than 27000 Swedish adults found an increase in self-reported allergic rhinitis from 21.6% in 1990 to 30.9% in 2008 [2]. The prevalence of allergic sensitization among adults has not been studied in the south-western parts of the country since 1992 [13, 21]. The West Sweden Asthma Study (WSAS) tested a large random sample of adults for allergic sensitization 2009–2012. The aim was to study the prevalence of sensitization and its risk factors, and further to determine time trends in prevalence of sensitization by comparison with a previous study in the same area.

Methods

Study population and questionnaire

The WSAS has been described previously [22]. In short, in 2008 a questionnaire was mailed to 30 000 randomly selected adults (age 16–75 years) living in county of Västra Götaland, Sweden, which includes Sweden's second largest city Gothenburg, and 62% participated. The study flow is described in Fig. 1. The core questionnaire has been described in detail elsewhere [2, 22]. A non-responder study showed high representativeness of the study area's population [23]. A random sample (n = 2000) of the questionnaire respondents was invited to clinical examinations 2009–2012.

Allergic sensitization

Skin prick tests (SPTs) were carried out by a small specifically trained staff following the European Academy of Allergology and Clinical Immunology recommendations [24]. SPTs were performed on the forearm using sterile lancets and a mean wheal diameter ≥ 3 mm after 15 min was considered positive. The tested aeroallergens included three pollen (timothy; birch; mugwort), three animals (cat; dog; horse), two mites (*Dermatophagoides pteronyssinus*; *D. farinae*), two moulds (*Alternaria alternata*; *Cladosporium herbarum*) (ALK-Abelló, Hørsholm, Denmark) and cockroach (*Blatella germanica*) (LETI, Barcelona, Spain). Histamine and glycerol were used as positive and negative controls, respectively. The potency of the allergens was 10 HEP except the moulds (1 : 20 w/v) and cockroach (1 mg/mL).

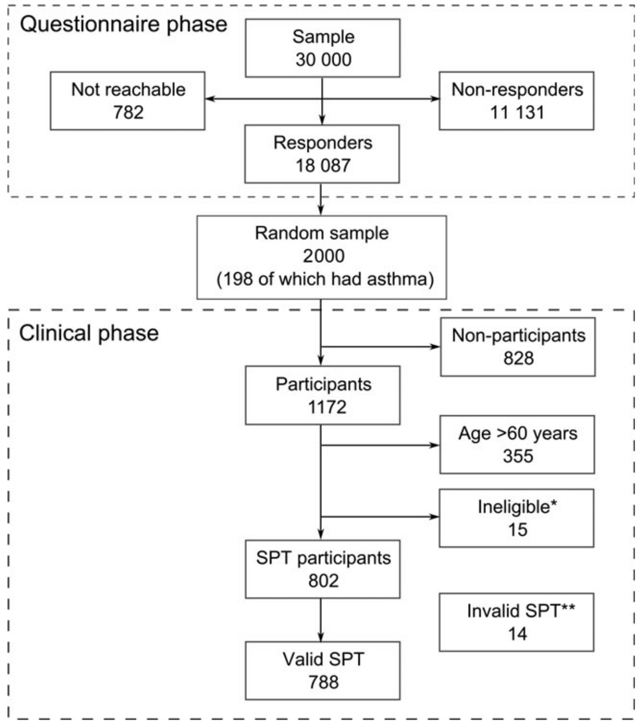

Fig. 1. Study flow in the West Sweden Asthma Study (WSAS). *medical conditions, declined SPT, etc. **Interfering medications, dermographism.

Blood samples were collected and sera stored at −20°C before analysis for IgE using the Phadiatop® test for inhalant allergens (ImmunoCAP, ThermoFisher Scientific, Uppsala, Sweden). All sera with Phadiatop® ≥ 0.35 kU_A/L were analysed for individual allergen-specific IgE to timothy, birch, mugwort, cat, dog, horse, *D. pteronyssinus*, *D. farinae* and *C. herbarum*. Specific IgE ≥ 0.35 kU_A/L was considered positive.

Time trends in allergic sensitization

Data from WSAS were compared to the European Respiratory Health Survey (ECRHS) carried out in 1991–1992 [21]. Owing to the design of the ECRHS, the SPT comparison was limited to subjects aged 20–46 years living in Gothenburg (n = 591 in ECRHS, n = 379 in

WSAS). In ECRHS, SPTs were carried out using Phazet® (Pharmacia Diagnostics, Uppsala, Sweden). Further, ECRHS included specific IgE to birch, timothy, cat and *D. pteronyssinus* analysed by Pharmacia CAP System (Pharmacia Diagnostics). The Phazet® technology utilized single-use lancets pre-coated with freeze-dried allergen.

Pollen data

Pollen data were obtained from the Pollen Laboratory, Gothenburg University. Measurements were made using a Burkard 7-day recording volumetric spore trap, situated on a rooftop 40 metres above ground level at Sahlgrenska University Hospital 'Östra', in eastern Gothenburg (57°43.34′N, 12°3.12′E). The monitoring site is surrounded by residential areas, of woodland in the east and south, and of urban ground in the west. Data were available for the years 1979–2015. The year 1993 was omitted from the analyses as an extreme outlier, due to extreme weather conditions and influx of extraneous pollen to the measurement area.

Statistical analysis

Analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp. Armonk, NY, USA). Bivariate comparisons used the chi-square test and Fisher's exact test where appropriate. Linear trends in ordinal variables were tested using the linear-by-linear test. Two-sided P-values < 0.05 were considered statistically significant. To obtain adjusted odds ratios, the factors significantly ($P < 0.05$) or borderline significantly ($P = 0.05$–0.10) associated with sensitization in univariate analysis were entered into multiple logistic regression models, one model for each group of allergens, yielding adjusted odds ratios (OR). Tests for interactions yielded no significant results and were omitted. Time trends in pollen concentration over time were analysed with simple linear regression models in the application R (R Foundation for Statistical Computing, Vienna, Austria). For birch, the sum of two consecutive years' pollen concentrations was analysed, due to the innate biannual flowering pattern of the species.

Results

Participants

SPT was performed in all 802 eligible subjects aged ≤ 60 years in the random population (Fig. 1). Fourteen invalid SPT readings were excluded, the majority due to dermographism or interfering medications. The remaining 788 subjects with valid SPTs did not differ from the entire WSAS population regarding sex and age distribution (Table 1). Wheeze and physician-diagnosed asthma, but not recurrent wheeze, dyspnoea or rhinitis, were slightly over-represented in the SPT sample.

Prevalence

The prevalence of allergic sensitization, defined as at least one positive SPT, was 41.9% and higher in men than in women (48.1% vs. 37.3%, $P = 0.002$) (Table 2). The dominant sensitizing allergen groups regardless of sex and age were pollen (34.3%) and animals (22.8%) followed by mites (12.6%). Timothy (24.7%) and birch (21.2%) were the most prevalent allergens. The male: female ratio in sensitization prevalence was 1.3 for pollen ($P = 0.021$ for male vs. female) and animals ($P = 0.072$), and 1.6 for mites ($P = 0.010$) and 3.0 for moulds ($P = 0.040$). Subjects aged 16–30 years had the highest prevalence of sensitization to all allergen groups, most pronounced for mites ($P = 0.017$). An inverse linear association with increasing age was seen for the prevalence of sensitization to timothy and birch ($P = 0.002$ and $P = 0.010$, respectively).

In 750 of the subjects with complete SPT results, specific IgE was also analysed for all allergens except cockroach and *alternaria*. In this serum sample, 33.5%

Table 1. Representativeness of the study sample. Questionnaire-based demographic, smoking and respiratory health data in the skin prick test (SPT) sample compared to the entire West Sweden Asthma Study sample of the same age (≤ 60 years). P-values by chi-square test

	WSAS aged ≤ 60 (n = 14030) % (n)	SPT sample (n = 788) % (n)	P
Sex			
Female	55.4 (7707)	57.5 (453)	
Male	44.6 (6216)	42.6 (335)	0.241
Area			
Gothenburg	50.1 (7023)	59.3 (467)	
Västra Götaland County	49.9 (7007)	40.7 (312)	<0.001
Age			
16–30 years	29.5 (4141)	27.5 (217)	
31–45 years	34.7 (4872)	36.4 (287)	
45–60 years	35.8 (5017)	36.0 (284)	0.444
Condition			
Asthma diagnosis	8.6 (1211)	11.7 (92)	0.003
Wheeze last 12 months	16.6 (2329)	21.7 (171)	<0.001
Recurrent wheeze	6.4 (899)	6.6 (52)	0.831
Dyspnoea	5.1 (709)	5.3 (42)	0.731
Rhinitis	29.2 (4098)	32.1 (253)	0.082
Family history of			
Asthma	18.5 (2593)	20.8 (164)	0.102
Rhinitis	31.7 (4443)	36.7 (289)	0.003
Smoking			
Never	61.2 (8542)	59.6 (470)	
Previous	19.5 (2723)	22.0 (173)	
Current	19.3 (2690)	18.0 (142)	0.204

Table 2. Prevalence (%) of allergic sensitization determined by skin prick test (SPT). *P*-values for sex by chi-square test (Fisher's exact test where appropriate) and for age groups by test for trend

		Sex			Age (years)			
Allergen	All (*n* = 788)	Men (*n* = 335)	Women (*n* = 453)	*P*	16–30 (*n* = 173)	31–45 (*n* = 287)	46–60 (*n* = 328)	*P*
Any allergen	41.9	48.1	37.3	0.002	45.1	44.6	37.8	0.077
Timothy	24.7	29.3	21.4	0.012	31.2	27.2	19.2	0.002
Birch	21.2	23.3	19.6	0.217	26.6	22.6	17.1	0.010
Mugwort	10.2	12.2	8.6	0.095	11.0	10.5	9.5	0.569
Any pollen	34.3	38.8	30.9	0.021	38.2	38.7	28.4	0.011
Cat	17.8	19.4	16.6	0.301	20.2	17.4	16.8	0.364
Dog	14.8	17.9	12.6	0.038	16.2	17.1	12.2	0.154
Horse	7.1	7.5	6.9	0.744	7.5	8.0	6.1	0.478
Any animal	22.8	26.0	20.5	0.072	26.0	23.7	20.4	0.141
D. pteronyssinus	11.3	15.2	8.4	0.030	16.8	8.4	11.0	0.126
D. farinae	9.6	12.8	7.3	0.009	15.0	6.6	9.5	0.120
Any mite	12.6	16.1	9.9	0.010	18.5	9.4	12.2	0.111
Alternaria	1.4	2.7	0.4	0.011	0.6	2.4	0.9	0.949
Cladosporium	0.8	0.6	0.9	1.000	0.6	0.3	1.2	0.333
Any mould	2.0	3.3	1.1	0.040	1.2	2.4	2.1	0.545
Cockroach	1.3	2.1	0.7	0.107	2.9	0.3	1.2	0.222

Table 3. Prevalence (%) of respiratory symptoms and indices of asthma and rhinitis, in relation to allergic sensitization. All conditions were strongly associated ($P < 0.01$) with sensitization except the one marked with an asterisk (*)

	Aeroallergen sensitization									
	Any positive SPT		Any pollen		Any animal		Any mite		Any mould	
Condition (prevalence, %)	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Wheeze last 12 months	15.9	29.7	17.8	29.3	16.3	40.0	19.9	34.3	21.2	43.8*
Asthma ever	4.8	23.6	6.2	25.2	6.3	34.4	10.2	30.3	12.0	43.8
Physician-diagnosed asthma	4.6	21.5	6.4	21.9	6.1	30.6	9.4	27.3	11.1	37.5
Asthma medications	5.0	18.8	6.4	19.3	5.9	27.2	8.7	25.3	10.1	43.8
Allergic rhinitis	11.6	64.8	14.1	71.9	21.7	75.0	30.3	58.6	33.0	75.0

had any specific IgE ≥ 0.35 kU_A/L which was lower compared to any positive SPT, 41.3% ($P = 0.002$). The most common allergens with IgE ≥ 0.35 kU_A/L were similar to the results obtained by SPT, albeit at slightly lower prevalences: timothy 20.3%, birch 18.7%, cat 12.8% and *D. pteronyssinus* 12.3%.

Sensitization to any of the tested allergens was strongly associated with upper and lower respiratory conditions such as wheeze, physician-diagnosed asthma, asthma medication use and rhinitis (Table 3). Indices of asthma were particularly associated with sensitization to the indoor allergens (animals, mites, moulds), whereas rhinitis was strongly associated with pollen sensitization.

Trends in prevalence

The subjects aged 20–46 years could be compared with a similar study population examined in the ECRHS study in 1992–1992. In this age group, there was an increase in the prevalence of having at least one positive SPT from 37.7% in 1991–1992 to 45.4% in 2009–2012 ($P = 0.018$) (Fig. 2). This was entirely attributable to an increase in pollen sensitization from 26.1% to 39.3% ($P < 0.001$). Sensitization to the other allergens did not change statistically significantly: any animal from 20.6% to 24.3% ($P = 0.183$), any mould from 3.2% to 1.6% ($P = 0.147$) and *D. pteronyssinus* from 15.9% to 11.9% ($P = 0.080$). The increase in pollen sensitization was seen both for timothy, from 17.1% to 29.0% ($P < 0.001$), and birch, from 15.6% to 23.7% ($P = 0.002$).

The isolated increase in pollen sensitization was confirmed by comparisons of SPT and specific IgE test results. The prevalence of IgE ≥ 0.35 kU_A/L to timothy and birch increased from 17.4% to 24.2% ($P = 0.017$) and from 15.0% to 20.3% ($P = 0.046$), respectively, while cat and *D. pteronyssinus* were unchanged, from 13.1% to 12.7% ($P = 0.893$) and from 12.0% to 14.1% ($P = 0.389$), respectively. In subjects with positive SPT

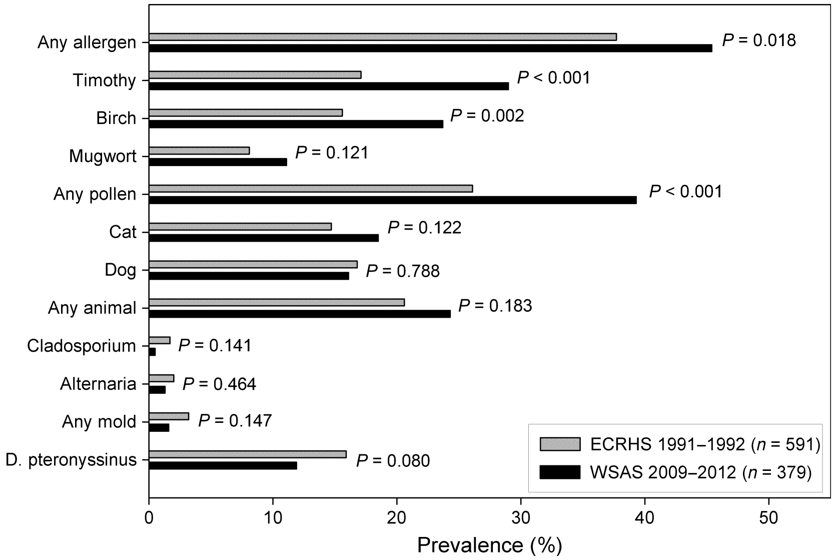

Fig. 2. Trends in the prevalence of allergic sensitization over time. Skin prick test data from the European Respiratory Health Survey (ECRHS) in 1991–1992 were compared within the same age groups (20–46 years) and area (Gothenburg) as in the West Sweden Asthma Study (WSAS) in 2009–2012. *P*-values by chi-square test.

to birch, the proportion with specific IgE $\geq$ 0.35 kU_A/L to birch was similar in ECRHS and WSAS, 77.6% vs. 81.3% ($P = 0.319$). For timothy, the corresponding numbers were 76.0% and 81.9% ($P = 0.495$).

Degree of allergic sensitization

In the skin-tested population ($n = 788$), the degree of allergic sensitization was first analysed by number of positive SPTs (Fig. 3). One positive SPT was seen in 12.4%, while 15.7% had 2–3 positive SPTs and 13.7% had $\geq$ 4 positive SPTs. Sensitization to two or more allergens was more common in males ($P = 0.003$) and in age 16–30 years ($P = 0.028$), respectively.

Of the 327 subjects sensitized to pollen, animal or mite (Figure 4), 54% were sensitized to at least two allergen groups, and 13% were sensitized to all three allergen groups. Almost half of mite-sensitized subjects were sensitized to all three groups, compared to one-fourth of the animal-sensitized and only 16% of pollen-sensitized subjects. Conversely, 39% of pollen-sensitized subjects were neither sensitized to animals

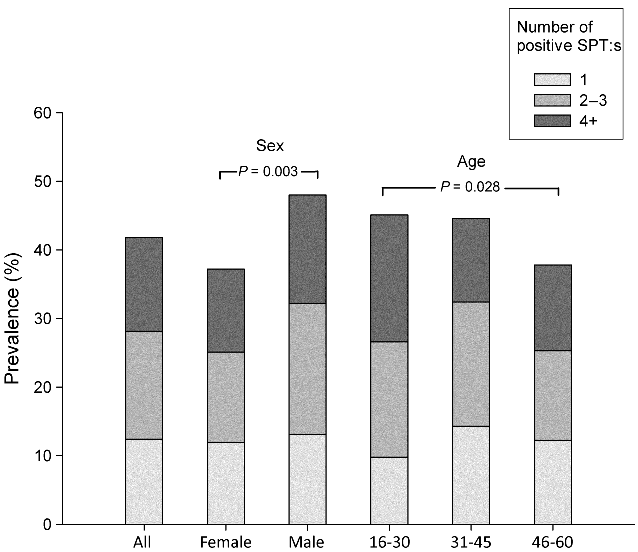

Fig. 3. Degree of allergic sensitization. The number of positive skin prick tests (SPTs) was categorized and stratified by sex and by age. *P*-values by test for trend.

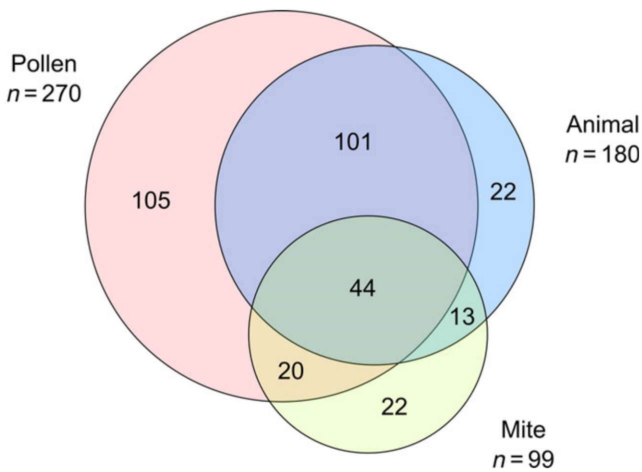

Fig. 4. Proportional Venn diagram of allergic sensitization by groups of allergens (pollen, animals and mites). The number of sensitized subjects (total $n = 327$) is displayed for each allergen group and for each sector in the diagram.

Table 4. Factors associated with positive skin prick test (SPT) in multivariate analysis. Associations are presented as adjusted odds ratios (OR) with 95% confidence intervals (CI). The model included all of the listed factors, and each group of allergens (any positive SPT; any pollen; any animal; any mite) was analysed separately. Statistically significant associations are marked in bold text

	Positive skin prick test							
	Any		Any pollen		Any animal		Any mite	
Risk factor	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Male sex	**1.86**	**1.31–2.64**	**1.58**	**1.10–2.27**	**1.81**	**1.20–2.73**	**2.61**	**1.53–4.43**
Age (vs. 16–30 years)								
31–45 years	1.23	0.78–1.95	1.33	0.83–2.13	1.28	0.76–2.17	**0.45**	**0.24–0.86**
46–60 years	0.83	0.52–1.33	0.83	0.51–1.36	0.88	0.50–1.52	0.53	0.28–1.02
Family history of								
Rhinitis	**2.68**	**1.83–3.93**	**2.67**	**1.81–3.95**	**2.81**	**1.82–4.35**	**1.78**	**1.03–3.08**
Asthma	0.79	0.50–1.24	0.87	0.55–1.39	0.98	0.59–1.63	0.90	0.47–1.73
Older siblings (vs. 0)								
1–2	1.09	0.76–1.56	1.14	0.79–1.67	0.69	0.46–1.06	1.51	0.87–2.65
3+	1.32	0.63–2.73	1.63	0.77–3.44	0.77	0.32–1.85	2.05	0.74–5.69
Severe respiratory infections in childhood	0.97	0.66–1.43	0.85	0.57–1.27	0.80	0.51–1.24	1.14	0.64–2.06
Cat/dog first 5 years of life	**0.68**	**0.47–0.98**	0.90	0.62–1.31	0.83	0.55–1.27	0.79	0.46–1.37
Horse/cow first 5 years of life	**0.53**	**0.28–0.995**	**0.39**	**0.20–0.79**	**0.41**	**0.17–0.97**	0.51	0.18–1.43
Smoking								
Ever	0.68	0.45–1.04	**0.61**	**0.39–0.95**	0.82	0.50–1.35	0.79	0.42–1.50
Current	**0.47**	**0.26–0.84**	**0.49**	**0.26–0.90**	0.86	0.44–1.68	0.61	0.24–1.54

nor to mites (exclusive pollen sensitization), compared to 22% exclusive mite sensitization and 12% exclusive animal sensitization.

Adjusted risk analysis

Risk factors for sensitization identified by univariate analyses (data not shown) were included in multivariate logistic regression models (Table 4). Male sex was associated with having any positive SPT and SPT to pollen, animals or mites, ORs 1.6–2.6. There were no consistent age patterns except for mite sensitization which was associated with lower age. A family history of rhinitis was a strong risk factor, OR 2.7–2.8 for positive SPT to any allergen, any pollen and any animal, and OR 1.8 for any mite. Subjects who had kept cows or horses during their first 5 years of life had a significantly decreased risk of sensitization: OR 0.53 (0.28–0.995) for any SPT; OR 0.39 (0.20–0.79) for any pollen; and OR 0.41 (0.17–0.97) for any animal. Also subjects who had kept cats or dogs in childhood had lower risk of having at least one positive SPT. Current smoking was negatively associated with having any positive SPT, OR 0.47 (0.26–0.84).

Trends in pollen levels

The increment of annual indices of grass pollen over the study period was strongly statistically significant, adjusted $R^2 = 0.50$ ($P < 0.001$). So was the increased duration of the grass pollen season, when all days with more than low values (≥10 pollen/m^3) were considered, adjusted $R^2 = 0.55$ ($P < 0.001$), and also when the period was defined as all days with more than moderate values (≥30 pollen/m^3), adjusted $R^2 = 0.43$ ($P < 0.001$). Likewise, for birch the sum of pollen indices from two consecutive years increased linearly, adjusted $R^2 = 0.27$ ($P = 0.019$). The length of the birch pollen season increased significantly when all days with moderate (≥10 pollen/m^3), high (≥ 100 pollen/m^3) and very high concentration (≥ 1200 pollen/m^3) were considered together, adjusted $R^2 = 0.18$ ($P = 0.005$).

Discussion

In this population-based sample of adults, more than 40% were sensitized to at least one aeroallergen, the most common being pollen and animals. In subjects aged 20–46 years, the prevalence of pollen sensitization had increased significantly since 1991–1992, while in contrast, sensitization to indoor allergens was unchanged. During the last 30 years, levels of grass and birch pollen have increased in the study area. Factors related to farm living and pet keeping during the first 5 years in life were independent negative predictors of allergic sensitization in adulthood.

Grass pollen, represented by timothy in most allergy tests, and birch have repeatedly been identified as the most prevalent sensitizing pollen in Sweden [9, 21, 25]. We found a marked increase in sensitization to these pollen since 1991–1992, while sensitization to animals, mites and moulds was unchanged. The ECRHS in 1991–1992 utilized allergen-coated lancets for the SPT testing. We, however, consider it unlikely that this methodological difference should affect SPTs to pollen exclusively. Moreover, the SPT results were supported by comparison of allergen-specific IgE in ECRHS and WSAS, and the concordance between SPT and IgE was similar in the two studies.

The Swedish part of GA^{2}LEN found an increase in self-reported rhinitis from 21.6% to 30.9% between 1990 and 2008 in ages 20–44 years, which was similar in all centres including WSAS in West Sweden (from 21.7% to 31.5%, $P < 0.001$) [2, 22]. Meanwhile, the prevalence of asthma symptoms remained unchanged. The observation that pollen sensitization is more strongly related to rhinitis than to asthma, especially in the absence of sensitization to indoor allergens such as mites or animals, is in line with several previous studies [26, 27]. Our finding that pollen sensitization increased from 26.1% to 39.3% in the same ages and time frame, with no concurrent increase in sensitization to indoor allergens, thus provides a plausible explanation for the trends in allergic diseases in the Swedish GA^{2}LEN centres.

The isolated increase in sensitization to pollen implies changes in factors associated exclusively with pollen sensitization, rather than with allergic sensitization in general. In Italy, an increase in pollen sensitization was observed between 1981 and 2007, parallel to increased total pollen load and extended pollen season [28]. The increase in indices of birch pollen concentrations in our study is likely a result of the rise in mean summer temperature of ca 1.5°C that has been recorded in Sweden since the mid-1970s [29]. Birch has colonized abandoned pastures in South Sweden since World War II, and the increasing birch pollen amounts might also reflect increased output due to progressing maturity of the trees. In temperate grasses, the severity of the pollen season is determined by temperature and precipitation during the spring [30], and unlike birch, grass flowering intensity in one year is not related to the previous season. The observed increase in grass pollen load is likely due to the increase in mean spring temperatures in the Gothenburg area [29]. It might also be connected with a change in abundance in some species with large pollen production, following changes in land use as well as in deposition of atmospheric nitrogen.

Besides climate change and the associated increments in CO_2 and outdoor temperature which affect pollen production, vehicle combustion products have been shown to increase pollen allergenicity [31, 32]. However, infrastructural changes in the Gothenburg area and lack of long-time data precluded analysis of trends in levels of air pollutants, and the one publication available showed decreasing levels of NO_x [33].

In a previous WSAS publication, farm childhood was negatively associated with self-reported rhinitis in adults [34]. The present study extends these findings and concludes that childhood farm exposure, particularly to livestock, substantially decreases the risk of allergic sensitization, especially to pollen and animals which were the dominant allergens. Unfortunately, the ECRHS study did not report the prevalence of factors pertaining to farm living [21]. In children, similar results have been observed for contact with livestock and forage in stables, but also consumption of unpasteurized milk [20]. The resulting increases in expression of Toll-like receptors and circulating regulatory T cells associated with decreased risk of sensitization stem from stimulation of the innate immune system by microbial products such as endotoxin, a process which seemingly begins already *in utero* [35]. In our study, a similar yet weaker effect was seen for keeping cats or dogs in childhood, in line with several previous studies [3, 14, 19]. Pet keeping increases indoor levels of endotoxin in non-farming homes [36], and the underlying mechanisms may thus share some features with those of farming environments. According to our data, these immune-mediated protective effects of childhood farming environments and pet keeping are lifelong.

The study benefits from its population-based design and large sample size. The study area includes farm lands, smaller communities, medium-sized towns and Gothenburg, Sweden's second largest city. The participation was in line with that seen in other recent studies of unselected adult populations [13, 37]. Representativeness was high in the WSAS questionnaire phase [23]. Subjects with physician-diagnosed asthma were slightly over-represented among the participants in the clinical examinations, which may have affected the prevalence of sensitization to a minor degree. Another methodological advantage was the assessment of both skin reactivity and specific IgE in the same individuals, and concordance between the methods was in line with previous studies [14, 21]. This also strengthens the comparison with ECRHS, although IgE was analysed for fewer allergens 1991–1992. Regarding population stability, the Gothenburg area has since 1991–1992 seen immigration mainly from the Balkans, the Middle East and Africa. The observed results, however, argue against any large impact of immigration since the increases in sensitization were seen for native Swedish plant species and not for, for example, mite, which is a major sensitizer in more temperate parts of the world. The cross-sectional design is a limitation to risk factor analyses, and we thus focused primarily on early-life risk factors to decrease the chance of reverse causation. Further, risk factors for incident sensitization in adults differ from those of prevalent sensitization, which in part reflects the high incidence in childhood [13–15].

Conclusion

This large population-based study of Swedish adults found an isolated increase in sensitization to pollen, but not other aeroallergens, over the last 20 years. This provides an explanation for the increase in rhinitis observed during the same period. The isolated increase in sensitization to pollen points to changes in risk factors associated exclusively with pollen sensitization. A clear increase in pollen concentrations was observed together with a rise in mean temperature during spring and summer. The study further concludes that factors related to animals and farming environments in childhood protect against allergic sensitization well up into adulthood.

Conflict of interest

Sigrid Sjölander and Magnus Borres are employed at ThermoFisher Scientific. Kenneth Holmberg has been paid by MEDA for participating in an educational programme regularly during the last 3 years. None of the other authors declare any conflict of interest.

Funding

The study was funded by the VBG Group Herman Krefting Foundation for Asthma and Allergy Research. Additional funding was received from the Swedish Heart-Lung Foundation, the Swedish Asthma and Allergy Foundation and the Health Authorities of the Västra Götaland Region. ThermoFisher performed the serum analyses.

Author contributions

BL, JL, KT, GW and LE took part in study design. LE coordinated the study and was responsible for the study database. AB, BL, JL and JE were involved in the data collection. AB and JN planned and executed the analyses presented in this paper, and AB wrote the manuscript. ÅD provided and analysed the data on pollen. All authors participated in data interpretation, review and presentation of the results. All authors approved the final manuscript.

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