

Geographical variation in the prevalence of sensitization to common aeroallergens in adults: the GA²LEN survey

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Abstract

Background: Geographical variation in the prevalence of sensitization to aeroallergens may reflect differences in exposure to risk factors such as having older siblings, being raised on a farm or other unidentified exposures.

Objective: We wanted to measure geographical variation in skin prick test positivity and assess whether it was explained by differences in family size and/or farm exposure. We also compared prevalence in younger and older subjects.

Methods: Within the Global Allergy and Asthma European Network (GA²LEN) survey, we measured the prevalence of skin prick positivity to a panel of allergens, and geometric mean serum total immunoglobulin E (IgE), in 3451 participants aged 18–75 years in 13 areas of Europe. Estimated prevalence was standardized to account for study design. We compared prevalence estimates in younger and older subjects and further adjusted for age, gender, smoking history, farm exposure, number of older siblings and body mass index (BMI).

Results: Skin prick test positivity to any one of the measured allergens varied within Europe from 31.4% to 52.9%. Prevalence of sensitization to single allergens also varied. Variation in serum total IgE was less marked. Younger participants had higher skin prick sensitivity prevalence, but not total IgE, than older participants. Geographical variation remained even after adjustment for confounders.

Conclusion: Geographical variation in the prevalence of skin prick test positivity in Europe is unlikely to be explained by geographical variation in gender, age,

smoking history, farm exposure, family size and BMI. Higher prevalence in younger, compared to older, adults may reflect cohort-associated increases in sensitization or the influence of ageing on immune or tissue responses.

The European Community Respiratory Health Survey (EC-RHS), a largely Europe-based multicentre study, showed that the prevalence of sensitization to common aeroallergens in younger adults was higher in developed countries, particularly 'English-speaking' countries (1, 2). Similar geographical patterns were observed in children in the International Study of Asthma and Allergy in Childhood (3). Adults aged over 45 years were not included in these studies, but single-centre cross-sectional studies suggest the prevalence of sensitization is lower in older participants (4–6). This could reflect remission with ageing (immunosenescence) or increased sensitization in younger cohorts (4, 7, 8).

Although differences in sensitization to specific allergens may be explained by differences in allergen exposure, other factors may explain at least some variation between regions and age groups (cohorts). There is a body of research showing lower sensitization among those with older siblings (9) or raised on farms (10). Although there is evidence that smokers have increased total immunoglobulin E (IgE) (11, 12), associations of smoking with sensitization to environmental (11, 12) and occupational allergens (13, 14) vary between allergens. Nutrition may affect skin prick atopy in children (15), but evidence that obese adults have more atopy than thinner adults is inconsistent (16, 17). Few studies have explored whether these factors could explain the geographical and cohort variation.

The Global Allergy and Asthma European Network (GA²LEN) conducted an international survey to describe prevalence and risk factors for asthma, chronic rhinosinusitis (CRS) and allergy (18, 19). In this survey, adults aged up to 75 years had skin prick testing (SPT) to a common allergen panel. We describe variation in the prevalence of positive SPTs to specific allergens, and total IgE levels, between areas and between younger and older participants. We then ask whether this variation is explained by variation in numbers of older siblings, childhood farm exposure, obesity and smoking.

Methods

Postal survey

In 18 centres (11 countries), a postal questionnaire (telephone interview in Helsinki), asking about symptoms of asthma and

CRS, was sent to representative community-based samples of adults aged 18–75 years. The methods, response rates and results from this postal survey have been described elsewhere (18, 19). At least 2500 (Palermo) but up to 15 000 (Gothenburg) adults were included in the sample in each centre. Response rates varied from 23.2% (Duisburg) to 80.3% (Skopje). Response was higher in women than in men, and in older participants than in younger participants, but was not influenced by the presence of asthma or CRS (18).

Clinical assessment

Participants were recruited to the clinical phase in four groups, based on symptoms reported in the postal survey: (i) asthma but no CRS, (ii) CRS but no asthma, (iii) asthma and CRS and (iv) neither asthma nor CRS. Asthma was defined as a self-report of 'ever having asthma' plus reporting (i) wheeze or whistling in the chest *or* (ii) waking with 'chest tightness' *or* 'cough' *or* 'shortness of breath' in the last 12 months. CRS was defined as suggested by the EP³OS criteria 2007 (20) (presence of at least two of: (i) nasal blockage/obstruction, (ii) nasal discharge, (iii) facial pain/pressure and (iv) reduction or loss of smell, with at least one of these symptoms being nasal blockage or nasal discharge). We invited for clinical assessment a random sample of responders fulfilling the disease definition for each case group, aiming to recruit 40 participants per centre in the asthma and CRS group and 120 participants per centre in the other case groups. Using an interviewer-administered questionnaire, we asked participants about smoking history, sibship and early-childhood farm exposure. We then measured height and weight and performed SPTs and venesection to obtain serum, in which total IgE in kilounits/litre (kU/l) was measured in a single laboratory, using Pharmacia (Uppsala) CAP system. Skin prick test methods, detailed in Data S1, used a mean wheal diameter (MWD) threshold of 0 mm, to reduce observer bias (21) and for consistency with previous reports (2, 22, 23).

Statistical methods

Statistical methods are detailed online in Data S2. Due to the case-control design, proportions of follow-up survey participants with asthma or CRS were higher than those in the postal survey population, so we used sampling probability weights to correct for this. In some centres, the numbers of participants in some case groups were small, so, to avoid such participants having extreme weights, participants from some centres in the same country (Uppsala, Stockholm and Gothenburg in south Sweden; Katowice, Krakow and Lodz in Poland; and London and Southampton in the UK) were combined to form one area. To assess potential participation bias, gender, age and smoking behaviour were compared

Abbreviations

BMI, body mass index; CRS, chronic rhinosinusitis; ECRHS, European Community Respiratory Health Survey; EP³OS, European Position Paper on Rhinosinusitis and Nasal Polyps 2012; GA²LEN, Global Allergy and Asthma European Network; GM, geometric mean; IgE, immunoglobulin E; kU/l, kilounits per litre; MWD, mean wheal diameter; OR, odds ratio; SPT, skin prick test.

between postal survey respondents who did and did not participate in the clinical survey, using Somers' D (24, 25).

The prevalence of a positive SPT to each allergen, to either of the two house dust mite allergens and to any of the allergens, and the geometric mean (GM) total IgE were estimated for the postal survey population in each area, using regression models (logistic or linear), weighting the clinical sample using sampling probability weights. Between-area heterogeneity in unadjusted parameters was measured using the methods of Cochran (26) and the I^2 statistic (27). To measure geographical variation adjusting for gender, age, smoking history, farm exposure, numbers of older siblings and body mass index (BMI), we fitted multivariate models, using additive reference-spline methods (28) and by measuring between-area heterogeneity with Wald chi-squared or F tests.

Results

Of the 56 906 subjects in the 18 centres in the baseline postal survey, 3505 participated in the follow-up survey, of which 3451 (with known gender and age and skin prick test information) were included in the analyses.

Table 1 shows demographics for the clinical survey participants. Age and gender distributions are similar between areas. Compared to the population of postal survey responders, those who took part in the clinical survey were older (Somers' D , 0.08; 95% CI, 0.05–0.11; $P = 2.3 \times 10^{-6}$), but there was no evidence of overrepresentation by gender or smoking. Not all participants provided information on farm exposure or number of older siblings.

Samples from Skopje and Palermo were not tested for total IgE, and skin prick testing for timothy grass (Skopje and

Palermo) and birch (Palermo only) was incomplete. Therefore, no subjects in Skopje and Palermo had values for sensitivity to 'any allergen in the list'.

The prevalence of SPT positivity and total IgE GM in each area are given in Table 2. Heterogeneity tests between areas are given in Table 3, together with lists of areas where prevalence or GM was 'low' (upper 95% confidence limit below the median area prevalence or GM) or 'high' (lower 95% confidence limit above the median area prevalence or GM). The geographical patterns were as follows:

Timothy grass and grass mix

The prevalence and geographical variation of positive SPT to these were similar, both being low in Poland. The prevalence of a positive SPT to timothy grass was highest in the two German centres and south Sweden.

Cat and dog

In most areas, the prevalence of a positive SPT to dog was at least as common as a positive SPT to cat. However, there was stronger evidence for variation between areas for cat sensitization than for dog sensitization, with high prevalence of positive SPT to cat in south Sweden and low levels in Odense and Poland.

House dust mites

Areas with higher prevalence of positive SPT to *Dermatophagoides pteronyssinus* tended to have higher prevalence of positive SPT to *Dermatophagoides farinae*, and there

Table 1 Demographics for clinical survey participants in the 13 areas and in the total sample

Area (Country)	Gender		Age			Childhood farm exposure*		Older siblings	
	Female/Total	Per cent	Min‡	Med	Max‡	Exp/known	Per cent	N known	Mean
Umea (Sweden)	211/360	58.6	18	44	74	47/349	13.5	315	0.97
South Sweden† (Sweden)	524/949	55.2	17	46	76	80/946	8.5	933	1.13
Helsinki (Finland)	98/163	60.1	20	49	75	29/161	18.0	162	0.94
Odense (Denmark)	199/366	54.4	15	49	75	53/365	14.5	302	1.37
Poland‡	148/251	59.0	16	53	76	37/245	15.1	206	0.84
UK‡	107/179	59.8	18	51	75	8/175	4.6	172	1.21
Amsterdam (the Netherlands)	105/218	48.2	18	55	76	14/214	6.5	211	1.46
Ghent (Belgium)	78/150	52.0	18	46	76	8/148	5.4	149	1.11
Brandenburg (Germany)§	111/177	62.7	16	50	75	18/177	10.2	177	1.06
Duisburg (Germany)	118/205	57.6	16	49	75	11/204	5.4	193	0.92
Skopje (Macedonia)	56/111	50.5	16	41	75	0/111	0.0	84	1.02
Palermo (Italy)	24/47	51.1	22	41	72	0/43	0.0	19	1.74
Coimbra (Portugal)	179/275	65.1	18	46	77	27/265	10.2	259	0.98
Total	1958/3451	56.7	15	48	77	332/3403	9.8	3182	1.11

*Self-reported living on a farm in the first 5 years of life.

†South Sweden = Gothenburg, Stockholm and Uppsala; Poland = Krakow, Lodz and Katowice; UK = Southampton and London.

‡Ages were sometimes below 18 years (30 participants) or above 75 years (11 participants) due to time difference between sampling, postal survey and clinical interview dates.

§Rural parts of Brandenburg State in Eastern Germany.

Table 2 Population prevalence (95% CI) of sensitization to each allergen and population geometric mean total immunoglobulin E (IgE; 95% CI) in each area

Subpopulation	Any allergen in list (%)	Grass mix (%)	Timothy grass (%)	Cat (%)	Dog (%)
Umea	39.9 (32.3, 48.1)	21.0 (15.2, 28.3)	21.3 (15.5, 28.5)	17.1 (12.2, 23.5)	19.5 (14.2, 26.2)
South Sweden	44.7 (39.5, 49.9)	23.4 (19.4, 28.1)	24.2 (20.1, 28.9)	18.8 (15.2, 23.0)	19.9 (16.1, 24.2)
Helsinki	44.7 (35.1, 54.6)	22.1 (15.1, 31.2)	18.6 (12.3, 27.3)	11.1 (6.7, 17.7)	20.8 (14.2, 29.4)
Odense	31.4 (24.6, 39.1)	16.9 (11.8, 23.5)	17.3 (12.2, 23.9)	8.3 (5.1, 13.2)	13.1 (8.8, 19.0)
Poland	34.6 (25.8, 44.6)	10.2 (6.2, 16.3)	9.9 (5.9, 16.0)	7.1 (4.0, 12.5)	11.1 (6.8, 17.5)
UK	37.1 (27.1, 48.2)	22.5 (14.8, 32.7)	26.9 (18.3, 37.7)	10.0 (5.7, 17.0)	16.5 (10.1, 25.8)
Amsterdam	46.2 (36.9, 55.8)	22.1 (15.4, 30.8)	19.5 (13.2, 27.8)	15.1 (9.7, 22.8)	17.2 (11.5, 25.1)
Ghent	43.5 (33.8, 53.7)	24.3 (16.9, 33.6)	18.5 (12.2, 26.9)	11.4 (6.7, 18.8)	15.7 (9.7, 24.5)
Brandenburg	49.9 (39.7, 60.2)	29.7 (21.2, 39.8)	28.5 (20.2, 38.5)	17.7 (11.3, 26.8)	20.6 (13.5, 30.1)
Duisburg	52.9 (45.1, 60.6)	28.5 (22.1, 35.9)	28.3 (21.9, 35.7)	13.8 (9.4, 19.9)	12.5 (8.3, 18.5)
Skopje	n/a†	23.8 (15.0, 35.7)	n/a	16.6 (9.3, 27.7)	8.3 (3.6, 17.7)
Palermo	n/a†	12.5 (4.9, 28.4)	n/a	9.7 (3.3, 25.1)	6.4 (1.8, 20.7)
Coimbra	50.4 (42.6, 58.2)	18.2 (13.3, 24.3)	18.6 (13.6, 24.8)	18.3 (13.2, 24.7)	13.8 (9.5, 19.7)

Subpopulation	Any house dust mite (%)	<i>Dermatophagoides pteronyssinus</i> (%)	<i>Dermatophagoides farinae</i> (%)	Birch (%)	Artemisia (%)
Umea	9.3 (5.6, 15.1)	8.2 (4.7, 13.7)	5.4 (2.7, 10.5)	22.3 (16.4, 29.5)	4.3 (2.2, 8.5)
South Sweden	10.2 (7.5, 13.7)	8.6 (6.1, 11.9)	6.4 (4.4, 9.3)	21.7 (17.8, 26.2)	9.6 (7.0, 13.1)
Helsinki	13.9 (8.4, 22.1)	10.4 (5.8, 17.9)	8.8 (4.6, 16.2)	18.7 (12.4, 27.2)	13.4 (8.1, 21.4)
Odense	9.9 (6.3, 15.3)	7.9 (4.7, 12.8)	8.2 (5.0, 13.1)	8.7 (5.3, 13.9)	10.8 (6.9, 16.6)
Poland	13.6 (8.7, 20.5)	11.2 (6.9, 17.6)	10.0 (6.0, 16.1)	8.8 (5.0, 15.0)	11.3 (6.9, 18.1)
UK	22.3 (14.6, 32.5)	21.8 (14.1, 32.0)	17.3 (10.5, 27.0)	9.9 (5.2, 17.9)	3.4 (1.3, 8.6)
Amsterdam	20.8 (14.4, 29.0)	20.0 (13.7, 28.3)	14.2 (9.2, 21.2)	11.5 (6.9, 18.7)	7.9 (4.2, 14.5)
Ghent	27.3 (19.4, 36.9)	27.3 (19.4, 36.9)	20.3 (13.5, 29.2)	9.7 (5.1, 17.8)	4.9 (2.2, 10.7)
Brandenburg	13.0 (7.5, 21.5)	10.4 (5.7, 18.4)	7.9 (3.9, 15.0)	24.8 (17.0, 34.5)	12.8 (7.3, 21.3)
Duisburg	20.5 (14.9, 27.4)	17.2 (12.2, 23.8)	18.7 (13.4, 25.6)	25.5 (19.5, 32.7)	11.4 (7.2, 17.5)
Skopje	21.2 (12.8, 32.9)	15.5 (8.5, 26.7)	13.7 (7.2, 24.5)	11.5 (5.7, 21.7)	11.3 (5.5, 21.9)
Palermo	15.3 (6.8, 31.1)	13.1 (5.3, 28.7)	8.7 (2.9, 22.9)	n/a*	9.1 (2.9, 24.9)
Coimbra	30.6 (24.2, 37.9)	26.9 (20.8, 33.9)	21.7 (16.4, 28.0)	6.8 (3.8, 12.0)	9.6 (5.9, 15.2)

Subpopulation	Olive (%)	Parietaria (%)	Blattella (%)	Alternaria (%)	Total IgE (kU/l; geometric mean)
Umea	3.7 (1.8, 7.1)	2.8 (1.2, 6.6)	3.1 (1.4, 6.7)	2.0 (0.8, 4.8)	28.3 (21.8, 36.7)
South Sweden	3.1 (1.9, 5.3)	1.2 (0.5, 2.6)	4.2 (2.7, 6.7)	2.8 (1.6, 5.0)	33.3 (28.8, 38.6)
Helsinki	4.7 (1.9, 11.3)	1.4 (0.3, 6.6)	2.6 (0.8, 8.2)	3.9 (1.5, 9.9)	41.1 (31.1, 54.2)
Odense	1.2 (0.3, 4.3)	0.2 (0.1, 0.5)	3.0 (1.2, 7.0)	2.5 (1.1, 5.9)	30.9 (25.5, 37.5)
Poland	2.2 (0.8, 5.8)	0.7 (0.3, 1.8)	5.6 (2.5, 12.0)	2.1 (0.7, 5.7)	39.0 (31.2, 48.8)
UK	3.4 (1.3, 8.6)	2.6 (0.8, 8.5)	2.6 (0.8, 8.5)	4.7 (1.8, 11.6)	33.3 (24.3, 45.7)
Amsterdam	8.8 (5.0, 15.3)	0.6 (0.2, 1.6)	5.9 (2.8, 12.2)	2.3 (0.8, 6.3)	40.8 (31.9, 52.2)
Ghent	4.0 (1.5, 9.9)	0.3 (0.0, 1.8)	5.6 (2.2, 13.3)	4.3 (1.5, 11.6)	38.7 (29.4, 51.1)
Brandenburg	4.2 (1.6, 10.9)	0.3 (0.1, 1.0)	5.5 (2.3, 12.6)	3.5 (1.3, 9.1)	37.6 (28.1, 50.3)
Duisburg	13.2 (8.8, 19.5)	2.7 (1.1, 6.3)	6.0 (3.2, 11.0)	5.4 (2.8, 10.2)	43.5 (34.4, 55.0)
Skopje	14.1 (7.6, 24.7)	4.0 (1.2, 12.3)	14.7 (8.0, 25.6)	12.1 (6.1, 22.6)	n/a
Palermo	21.2 (10.7, 37.7)	17.6 (8.3, 33.5)	2.9 (0.4, 18.4)	3.0 (0.4, 18.8)	n/a
Coimbra	9.6 (5.9, 15.2)	9.6 (6.0, 15.0)	12.5 (8.2, 18.6)	8.9 (5.6, 14.0)	38.5 (30.7, 48.2)

n/a = no subjects were tested for timothy grass in Skopje or Palermo – and therefore, positivity to ‘any allergen on list’ is unknown.

*n/a = only two individuals were tested for birch in Palermo (both negatively).

†n/a = the crude prevalence of sensitization to any allergen other than birch and timothy grass was 14/35 in Palermo and 24/70 in Skopje.

was considerable variation in the prevalence of positive SPT to at least one of these. Prevalence was lower in Scandinavia (Umea, south Sweden, Odense) and higher in middle Europe (UK, Amsterdam, Ghent, Duisburg). The highest prevalence of positive SPT to ‘any house dust mite’ was in Coimbra.

Other pollens

A positive SPT to *Artemisia* was less common than a positive SPT to timothy grass in nearly all areas and varied little between areas. The prevalence of a positive SPT to olive,

Table 3 Areas that have a high* and low† population sensitization prevalence or immunoglobulin E (IgE) geometric mean (GM), with tests of heterogeneity in prevalence or GM between areas

Outcome	N of areas	Low areas	High areas	Measures of heterogeneity between areas in the prevalence of sensitization or GM total IgE	
				I^2	Het. P
Any allergen in list (%)	11	Odense, Poland	Duisburg	59.5	0.006
Grass mix (%)	13	Poland		51.3	0.017
Timothy grass (%)	11	Poland	South Sweden, Brandenburg, Duisburg	58.9	0.0068
Cat (%)	13	Odense, Poland	South Sweden	53.8	0.011
Dog (%)	13		South Sweden	38.6	0.076
Any house dust mite (%)	13	Umea, south Sweden, Odense	Ghent, Coimbra	80.2	1.7×10^{-8}
<i>Dermatophagoides pteronyssinus</i> (%)	13	South Sweden, Odense	UK, Amsterdam, Ghent, Coimbra	81.2	4.6×10^{-9}
<i>Dermatophagoides farinae</i> (%)	13	South Sweden	UK, Ghent, Duisburg, Coimbra	77.5	3.5×10^{-7}
Birch (%)	13	Palermo	Umea, south Sweden, Helsinki, Brandenburg, Duisburg	80.3	5.3×10^{-8}
Artemisia (%)	13	Umea, UK		32.6	0.12
Olive (%)	13		Amsterdam, Duisburg, Skopje, Palermo, Coimbra	79.0	7.1×10^{-8}
Parietaria (%)	13	Odense, Brandenburg	Palermo, Coimbra	89.3	1.9×10^{-18}
Blattella (%)	13		Skopje, Coimbra	61.7	0.0018
Alternaria (%)	13		Skopje, Coimbra	57.4	0.0053
Total immunoglobulin E (IgE; kU/l; GM)	11	Umea, Odense		21.0	0.25

*High prevalence = 95% confidence interval around area estimate above and excludes median observed prevalence in all areas.

†Low prevalence = 95% confidence interval around area estimate below and excludes median observed prevalence in all area.

Parietaria and birch varied more, reflecting the distribution of these allergens.

Cockroach and mould

A positive SPT to *Blattella* and *Alternaria* was more common in Skopje and Coimbra than elsewhere.

Any allergen

In areas where all allergens were tested, more than 30% of the population had a positive SPT to at least one.

Total IgE

Differences were no greater than expected by random variation.

Sensitization in younger and older adults, men and women

Table 4 shows overall difference in the prevalence of a positive SPT for each allergen, and the overall GM IgE ratio, between participants aged <45 years and aged 45+ years (presented by area and outcome online in Data S3). Younger adults were

more likely to have a positive SPT to at least one allergen than older adults in all areas except Amsterdam and Brandenburg, where young–old differences were nonsignificantly negative. The overall young–old difference was significantly positive for each allergen, except for *Parietaria* and *Blattella*. The size of the young–old differences varied little between areas, except for house dust mite and olive. For example, younger adults were much more likely than older adults to be sensitized to any house dust mite in Coimbra (difference 38.80, 95% CI 24.86–51.17) and Duisburg (23.65, 95% CI 9.95–36.47), with less difference in Brandenburg (−0.32, 95% CI −14.00–13.37). In contrast, total IgE varied little between age groups.

Gender-specific results are in Data S4. There was no detectable prevalence difference between men and women, but total IgE was lower in women than in men (GM ratio, 0.76; 95% CI, 0.65–0.88).

Prevalence and IgE adjusted for confounders

Table 5 shows that the geographical variations (demonstrated by heterogeneity I^2 and P -values) in the prevalence of positive SPTs remain after adjustment for age, sex, smoking history, number of older siblings, farm exposure in the first 5 years and BMI. After this adjustment, the ranking of areas by prevalence

Table 4 Population levels of atopy measures in younger and older subjects in all areas and their prevalence differences and geometric mean (GM) ratios, with between-subpopulation heterogeneity tests for young–old contrasts

	<45 years		45+ years		<45 vs 45+ years			
	Cases/N	Pop. prev. (%)	Cases/N	Pop. prev. (%)	Diff. (%)	95%, CI	P	Het. P
Skin prick positivity								
Any allergen in list	831/1304	51.0	758/1725	36.9	14.1	8.2, 19.8	2.5×10^{-6}	0.021
Grass mix	530/1396	29.1	361/1794	15.8	13.3	8.8, 17.9	1.3×10^{-8}	0.47
Timothy grass	516/1329	29.1	355/1751	16.3	12.8	8.0, 17.6	2.0×10^{-7}	0.72
Cat	437/1395	19.4	316/1793	12.1	7.3	3.4, 11.2	0.00026	0.47
Dog	433/1394	20.6	361/1794	14.6	6.0	1.8, 10.1	0.0045	0.72
Any house dust mite	384/1395	18.7	269/1794	10.8	7.9	4.3, 11.6	0.000021	0.000032
<i>Dermatophagoides pteronyssinus</i>	341/1396	16.4	227/1794	9.2	7.2	3.8, 10.6	0.00004	0.000049
<i>Dermatophagoides farinae</i>	303/1395	14.5	190/1794	6.1	8.5	5.4, 11.5	8.7×10^{-8}	0.0021
Birch	416/1374	21.5	301/1776	13.9	7.6	3.4, 11.9	0.00047	0.7
Artemisia	221/1394	12.6	156/1794	6.5	6.1	2.9, 9.3	0.00017	0.97
Olive	140/1396	6.3	96/1794	3.5	2.9	0.8, 4.9	0.0058	0.00073
Parietaria	66/1395	2.4	47/1792	1.7	0.8	−0.4, 2.0	0.21	0.13
Blattella	116/1377	5.2	93/1771	4.8	0.4	−1.8, 2.6	0.72	0.056
Alternaria	120/1396	6.1	57/1793	1.6	4.5	2.5, 6.5	9.1×10^{-6}	0.25
Total atopy	N	Pop. GM (kU/l)	N	Pop. GM (kU/l)	Ratio	95%, CI	P	Het. P
Total IgE (kU/l)	1289	34.28	1744	35.40	0.97	0.83, 1.13	0.69	0.37

Table 5 Heterogeneity statistics for geographical variation in the prevalence of positive skin prick tests and geometric mean total immunoglobulin E (IgE) from adjusted* multivariate regression models

Skin prick positivity	Areas	Cases/subjects	Het. $\hat{P}^2$ (%)	Het. P	Disease status range (all areas†)	Min. cases per area‡
Any allergen in list	11	1486/2818	58.0	0.0081	Complete	61
Grass mix	13	827/2922	46.6	0.033	Complete	1
Timothy grass	11	816/2851	57.0	0.0098	Complete	27
Cat	13	703/2921	99.5	$<2.2 \times 10^{-308}$	Incomplete	0
Dog	13	733/2920	99.6	$<2.2 \times 10^{-308}$	Complete	0
Any house dust mite	13	611/2921	82.6	5.0×10^{-10}	Complete	3
<i>Dermatophagoides pteronyssinus</i>	13	530/2922	82.3	7.7×10^{-10}	Complete	2
<i>Dermatophagoides farinae</i>	13	460/2921	80.7	8.8×10^{-9}	Complete	1
Birch	13	671/2906	95.2	2.9×10^{-46}	Incomplete	0
Artemisia	13	358/2921	40.4	0.065	Complete	2
Olive	13	213/2922	78.7	1.0×10^{-7}	Complete	3
Parietaria	13	98/2920	85.0	4.5×10^{-12}	Complete	1
Blattella	13	196/2896	61.5	0.0019	Complete	1
Alternaria	13	165/2922	99.4	$<2.2 \times 10^{-308}$	Complete	0
Total atopy	Areas	Subjects	Het. $\hat{P}^2$ (%)	Het. P	Disease status range (all areas)	
Total IgE (kU/l)	12	2774	0.0	0.74	Incomplete	

*Adjusted for age, gender, smoking status, smoking history, older siblings, farm exposure in childhood and BMI.

†The complete range of disease statuses used in selecting the sample is control, asthma, CRS and asthma + CRS.

‡Minimum number of skin prick test-positive cases in any area for that outcome.

(or GM) was similar to that for the unadjusted parameters. Confounder-adjusted results are online in Data S5. Figure 1 shows the adjusted odds ratios for three common skin prick test outcomes (any allergen, grass mix and any house dust

mite) and GM ratios for total IgE, for each of the included confounders. Even after adjustment, older participants have a lower risk of a positive SPT than younger participants, especially for grass mix, but similar levels of total IgE.

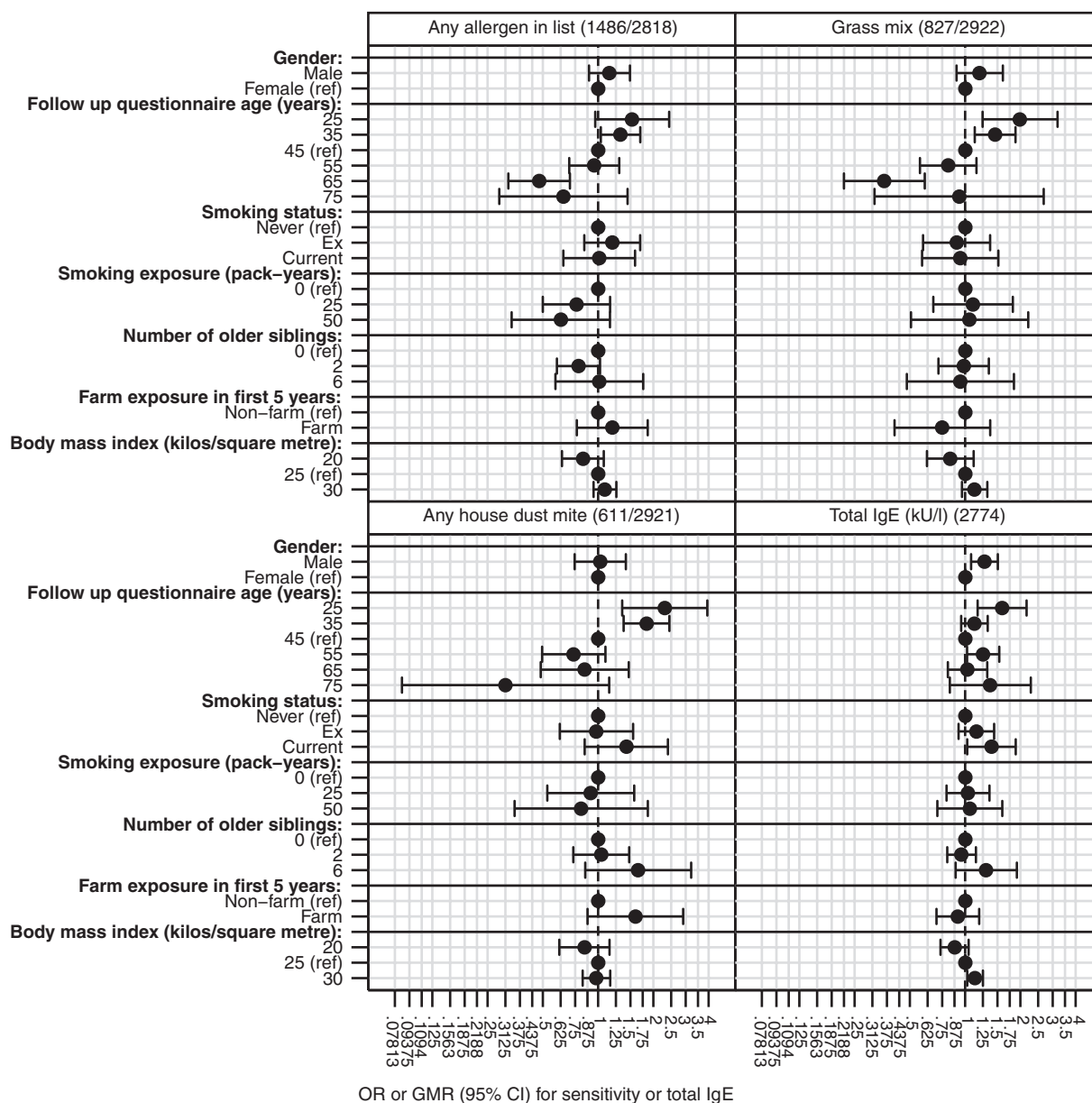


Figure 1 Confounder odds and geometric mean (GM) ratios for common allergen sensitivity and immunoglobulin E (IgE) outcomes.

Discussion

This report describes geographical variation in the prevalence of positive skin prick tests in adults living in Europe, confirming sensitization patterns observed previously in young adults and in children. We extend these findings by including older adults, and we show that variations were not explained by differences in age, gender, early farm exposure, number of older siblings, BMI or smoking. We also show that positive SPTs, for *all* allergens, are common in younger adults than in older adults. Total IgE did not show the same geographical or age-related variation.

This is the fourth major report on international variation in the prevalence of sensitization to common allergens (1–3). In these developed nations, variation in skin prick test positivity was not explained by differences in older sibling numbers, early farm exposure, BMI or smoking. These factors may explain differences in atopy between developed and developing nations, but, within Europe, the variation observed is more likely to be explained by other factors, including variation in allergen exposure.

We have shown that the prevalence of sensitization to each allergen, especially to grass, is higher in younger than in older adults. As this is a cross-sectional study, we cannot be

certain whether these age differences are cohort-related or caused by remission with ageing. There is little evidence that sensitization decreases with ageing (29) and some evidence to the contrary (8). These age differences remained after controlling for confounders, suggesting that if the age differences are cohort-related, then they are unlikely to be explained by trends in family size, movement off farms, smoking or obesity over the last century.

Unlike some other single-centre cross-sectional studies (30, 31), but in line with previous observations in Finland (32), we have shown that older and younger adults have similar total IgE levels. Longitudinal studies suggest that total IgE declines with age (8), but there is cross-sectional (12) and longitudinal evidence (33) that the relationship of age with total IgE may be different between smokers and nonsmokers. We have adjusted for smoking status and smoking history, but there is little evidence of age (or birth cohort) differences in total IgE levels.

We confirm several earlier findings from ECRHS (2). Sensitization to house dust mite, grass and cat is common, but, unlike ECRHS, we have also tested for sensitization to dog and found that it is as common as sensitization to cat in many parts of Europe. We also confirm that Sweden has high sensitization levels to grass, pets and birch, but lower sensitization levels to house dust mite, than the rest of Europe; that urban Belgians have a high prevalence of sensitization to house dust mites; and that olive sensitization is seen in areas where olive trees do not grow, possibly resulting from cross-reactivity with ash (34, 35) (common in northern Europe) or from northern Europeans holidaying in southern Europe.

Participants in our study were responders to a postal survey to a representative population-based sample of adults (18, 19), who were then invited for further clinical tests. These invitations depended on symptoms reported in the postal survey, and participants were recruited in four case groups. We used sampling probability weights to reweight the clinical sample to estimate levels of sensitization and total IgE in the postal survey population. This method inflates confidence limits, but we see no reason why it should materially bias estimates. Prevalence estimates can be biased by differential response, and we know that responders to the postal survey were more likely to be older and/or female than non-responders (18). However, there was no evidence that those with asthma or hay fever were more likely to respond to the postal survey (19), and no evidence that age, gender or smoking influenced response to take part in the clinical survey (when SPTs were performed). It is unlikely that the observed geographical variations are due to response bias.

In this multicentre study, we standardized SPT using a common batch of allergens, centrally purchased for the study. Fieldworkers underwent centralized training, to confirm that the coefficient of variability in histamine testing was less than 20% before they commenced fieldwork. Not all fieldworkers complied with this, and, to reduce the impact of fieldworker variation in the assessment of a positive test, we have reported the prevalence of a SPT wheal greater than 0 mm (21). This is in line with previous epidemiological work, showing that geographical variation observed with this

cut-off was similar to that seen for serum IgE (1, 2) and similar to that seen when a 3-mm cut-off was used (2). In this study, high prevalence of sensitization was observed in Coimbra for many allergens, and we cannot exclude that this is an artefact of sampling or observer variation.

In summary, this study shows marked geographical variation in sensitization to aeroallergens in Europe in 2008–2010, with a similar pattern to that shown over 20 years ago. We have also shown that sensitization is more common in younger adults than older adults. Neither of these patterns seems attributable to differences in gender–age distribution, smoking history, farm exposure, number of older siblings or BMI. If the age gradient is cohort-related, then we would expect sensitization to become more common in older Europeans.

Author contributions

R. B. Newson and D. Jarvis wrote the text of the article. P. G. J. Burney contributed extensively to the analysis plan. R. Van Ree carried out the measurements of total IgE. B. Forsberg, C. Janson, J. Lötvall, S-E Dahlén, E. M. Toskala, J. Bælum, G. M. Brožek, L. Kasper, M. L. Kowalski, D. Jarvis, P. H. Howarth, W. J. Fokkens, C. Bachert, T. Keil, U. Krämer, J. Bislimovska, M. Gjomarkaj and C. Loureiro supervised the work in their respective centres contributing to this multicentre study and commented on the manuscript.

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Conflicts of interest

None.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Supplemental methods for skin prick testing (SPT) and immunoglobulin E (IgE).

Data S2. Statistical methods.

Data S3. Skin prick positivity prevalence and immunoglobulin E (IgE) geometric means by age category and their differences and ratios.

Data S4. Skin prick positivity prevalence and immunoglobulin E (IgE) geometric means by gender and their differences and ratios.

Data S5. Baseline skin prick positivity prevalence and immunoglobulin E (IgE) geometric means by area for a 45-year-old female with no smoking history, farm exposure or elder siblings and a body mass index (BMI) of 25 kilos per square metre, estimated from multivariate models.

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