

Original article

GA²LEN skin test study II: clinical relevance of inhalant allergen sensitizations in Europe

Background: Skin prick testing is the standard for diagnosing IgE-mediated allergies. A positive skin prick reaction, however, does not always correlate with clinical symptoms. A large database from a Global Asthma and Allergy European Network (GA²LEN) study with data on clinical relevance was used to determine the clinical relevance of sensitizations against the 18 most frequent inhalant allergens in Europe. The study population consisted of patients referred to one of the 17 allergy centres in 14 European countries ($n = 3034$, median age = 33 years). The aim of the study was to assess the clinical relevance of positive skin prick test reactions against inhalant allergens considering the predominating type of symptoms in a pan-European population of patients presenting with suspected allergic disease.

Methods: Clinical relevance of skin prick tests was recorded with regard to patient history and optional additional tests. A putative correlation between sensitization and allergic disease was assessed using logistic regression analysis.

Results: While an overall rate of $\geq 60\%$ clinically relevant sensitizations was observed in all countries, a differential distribution of clinically relevant sensitizations was demonstrated depending on type of allergen and country where the prick test was performed. Furthermore, a significant correlation between the presence of allergic disease and the number of sensitizations was demonstrated.

Conclusion: This study strongly emphasizes the importance of evaluating the clinical relevance of positive skin prick tests and calls for further studies, which may, ultimately, help increase the positive predictive value of allergy testing.

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Skin prick testing is the recommended standard technique for detecting type I sensitizations against inhalant allergens. However, a positive skin prick test identifies sensitizations to a particular allergen but does not determine the clinical relevance of this sensitization. While a negative skin prick test response has an excellent negative predictive value for excluding the presence of an immunoglobulin (Ig) E-mediated reaction, an isolated positive skin test cannot be considered as proof of a clinically relevant allergy, but considered as merely indicating the presence of allergen-specific IgE antibodies. Thus, determination of clinical relevance of positive skin prick tests relies on an allergy diagnosis by experienced allergologists taking prick test result, history and optional further tests into consideration. However, only few studies in small populations or patient cohorts have investigated clinical relevance of skin prick test results so far.

The Global Allergy and Asthma European Network (GA²LEN) is a consortium of 24 leading allergy centres with high clinical and experimental research competence across Europe and, thus, an ideal platform for investigating allergy-related problems. A GA²LEN study in 14 European countries aiming at the assessment of sensitization rates against the 18 most frequent inhalant allergens in a patient population of over 3000 individuals (1) had been designed to also record data on clinical relevance of positive sensitizations. Here, we demonstrate that clinically relevant allergy symptoms in sensitized patients may depend on the number of positive sensitizations, the type of allergen, and the country where the prick test was performed. The present study, thus, provides a sound basis for further studies which may aim at identifying further factors that could determine clinical relevance in patients with inhalant allergen sensitizations.

Abbreviations: BE, biologische Einheiten = biological units; G/V, Gewicht/Volumen = weight/volume; GA²LEN, Global allergy and asthma European network; HEP, histamine equivalent prick; IC, index of concentration; IgE, Immunoglobulin E; IR, index of reactivity; SBE, standardisierte biologische Einheiten = standardized biological units.

Methods

The pan-European prick test study, which is described in (1) was designed as a multicentre, open-label study covering a study period of 18 months. The following 17 allergy centres in 14 countries (affiliation and city in brackets) participated: Austria (University of Vienna Medical School, Vienna), Belgium (University Hospital, Ghent), Denmark (University Hospital, Odense), Finland (Helsinki University Central Hospital, Helsinki), France (University Hospital, Montpellier), Germany (Charité University Medicine, Berlin; Ludwig Maximilians University, Munich; Technical University, Munich), Greece (National and Kapodistrian University, Athens), Hungary (Semmelweis Medical University, Budapest), Italy (Consiglio Nazionale delle Ricerche, Palermo; University of Genoa, Genoa), The Netherlands (Academic Medical Centre, Amsterdam), Poland (Medical University of Lodz, Lodz), Portugal (Coimbra University, Coimbra), Switzerland (Children's University Hospital, Zurich) and UK (Royal Brompton Hospital, London).

The following inhalant allergens were tested: alder (50 000 BE/ml), *Alternaria* (1 : 20 G/V), *Ambrosia* (1 : 100 G/V), *Artemisia* (100 IR/ml), *Aspergillus fumigatus* (10 000 BE/ml), cat (10 HEP), birch (50 000 SBE/ml), *Blatella* (1 mg/ml), *Cladosporium herbarum* (10 000 BE/ml), cypress (100 IC/ml), *Dermatophagoides pteronyssinus* (100 IR/ml), *Dermatophagoides farinae* (100 IR/ml), dog (10 HEP), grass mix [10 HEP (smooth meadow grass/*Poa pretensis*, cock's foot grass/*Dactylis glomerata*, perennial rye grass/*Lolium perenne*, timothy grass/*Phleum pratense*, meadow fescue/*Festuca pratensis*, meadow oat grass/*Helictotrichon pratense*)], hazel (50 000 BE/ml), olive (100 IR/ml), *Parietaria* (10 HEP), plane (100 IC/ml). Histamine dihydrochloride 10 mg/ml was used as a positive control, diluent as a negative control. The allergen extracts were donated by the following GA²LEN-sponsors: ALK-Abelló, Hamburg, Germany (grass mix, *Alternaria*, *Parietaria*, cat, dog, *Ambrosia*, positive control, negative control), Allergopharma, Reinbek, Germany (*Cladosporium*, *Aspergillus*, birch, hazel, alder), Leti Pharma, Witten, Germany (*Blatella*), Stallergènes, Antony, France (*D. pteronyssinus*, *D. farinae*, plane, *Artemisia*, olive, cypress).

Results were recorded after 15 min. The largest and perpendicular diameter of the wheal for each of the allergens was measured and the following value calculated: largest + perpendicular diameter/2. A test was regarded positive if the value calculated was ≥ 3 mm in conjunction with a positive histamine control and a negative diluent control. Values calculated for each of the 18 allergens tested were recorded in standardized data collection forms. The clinical relevance of each of the positively tested allergens was assessed for each allergen separately and subdivided into four distinct categories (no clinical relevance, relevant, former relevance and unknown relevance). This assessment was done by an experienced allergologist according to patient history (e.g. season of symptoms, type of

symptoms) and further tests (specific IgE-measurements, provocation tests), if indicated. *Relevant* was stated if the patient's prick test showed positive sensitization against the allergen in question and symptoms were reported if exposed to the allergen. In case of pollen, particular attention was paid to the fact that symptoms had to occur in the corresponding flowering season of the respective plant. Additionally, putative further tests such as positive nasal provocation studies were taken into consideration. For instance, a patient with positive sensitizations against birch and *Ambrosia* and with symptoms during the flowering season of birch but not of *Ambrosia* was categorized as follows: relevant for birch, no relevance for *Ambrosia* (see below). *Former relevance* was stated if the patient had previously had clinically relevant sensitizations. For example, allergic rhinitis with grass pollen as an eliciting agent might have occurred during a patient's childhood or adolescence but may not be present during adulthood any more. *No relevance* was stated if the patient's prick test showed a positive sensitization against the allergen in question and no symptoms were reported if exposed to this particular allergen. *Unknown* was stated if the patient was unable to deny or confirm a positive prick test sensitization by reporting present or nonexistent symptoms during the respective allergen exposure. Unknown was, furthermore, stated if more than one sensitization could have been responsible for the symptoms reported and no provocation tests or other studies were available.

In addition to recording the clinical relevance of sensitizations, the particular type of symptoms if exposed to the allergen in question was noted. Symptoms were categorized into the following disease entities by an experienced allergologist: allergic rhinitis, allergic asthma, atopic dermatitis and food allergy.

Statistical analysis

A total of 3034 valid data sets were analysed. Statistical analysis was performed with STATA 10.0 software (StataCorp LP, College Station, TX, USA). Direct standardization regarding gender and age was used to calculate sensitization rates. The reference population for standardization as well as the demographic characteristics of the study population with regard to patient frequency, gender and age are reported in (1). Adjusted odds ratios (aORs) were calculated using logistic regression. Positive association refers directly to the aORs derived from logistic regression. Adjustment variables were gender, age and region. Robust standard errors, which take into account potential statistical dependence between observations, were used to derive 95% confidence intervals (CIs) and *P*-values for aORs. Reported *P*-values are descriptive; no adjustments were made for multiple testing. As the categorical term for clinical relevance 'unknown' was also used if more than one sensitization could have been responsible for the symptoms reported and no provocation tests or other studies were available, unknowns were included in the analysis of clinically relevant sensitizations.

Results

Clinical relevance of inhalant allergen sensitizations

An overview of clinically relevant inhalant allergen sensitizations is given in Table 1. The allergen with the highest rate of clinical relevance was grass: in 88.4% of all patients sensitized to grasses as determined by prick testing, this sensitization was clinically relevant. The lowest rate was demonstrated for plane (59.9%). For all

Table 1. Clinical relevance of inhalant allergen sensitizations

Allergen	Country	Sensitization rates (%)			
		SSR	CRR	95% CI	% CCR
Outdoor Hazel	Europe	22.8	17.1	15.7–18.4	75.0
	Austria	22.7	13.3	8.2–18.4	58.6
	Belgium	16.6	13.5	8.6–18.4	81.3
	Denmark	49.4	37.8	30.8–44.9	76.5
	Germany	35.9	32.4	27.4–37.8	90.3
	Greece*	10.3	6.5	3.6–10.7	63.1
	Finland	24.7	22.9	16.4–29.4	92.7
	France	11.9	7.4	3.8–11.0	62.2
	Hungary	20.2	15.9	11.3–20.5	78.7
	Italy	9.3	7.2	3.9–10.6	77.4
	the Netherlands	24.8	24.4	19.2–29.6	98.4
	Poland	22.3	13.3	8.3–18.3	59.6
	Portugal	7.4	3.9	1.1–6.8	52.7
	Switzerland*	51.7	24.8	18.0–32.7	48.0
	UK*	15.9	10.3	5.6–17.0	64.8
Alder	Europe	21.2	16.2	14.8–17.5	76.4
	Austria	21.8	12.4	7.6–17.2	56.9
	Belgium	16.1	14.3	9.3–19.4	88.8
	Denmark	47.0	36.2	29.1–43.2	77.0
	Germany	34.8	31.7	26.4–37.1	91.1
	Greece*	8.4	6.5	3.6–10.7	77.4
	Finland	26.3	24.6	17.9–31.3	93.5
	France	10.4	4.8	1.9–7.7	46.2
	Hungary	16.0	12.3	8.2–16.4	76.9
	Italy	3.1	2.3	0.3–4.4	74.2
	the Netherlands	24.5	24.2	19.0–29.4	98.8
	Poland	22.8	13.6	8.5–18.6	59.6
	Portugal	6.8	4.4	1.5–7.4	64.7
	Switzerland*	44.1	22.8	16.2–30.5	51.7
	UK*	16.7	11.1	6.2–17.9	66.5
Birch	Europe	24.2	19.6	18.2–21.0	81.0
	Austria	19.4	9.5	5.1–13.9	49.0
	Belgium	17.6	13.9	9.0–18.9	79.0
	Denmark	57.4	49.1	41.4–56.7	85.5
	Germany	37.6	34.1	28.7–39.5	90.7
	Greece*	9.8	5.1	2.6–9.0	52.0
	Finland	34.0	30.0	23.0–37.0	88.2
	France	8.4	4.0	1.3–6.6	47.6
	Hungary	20.1	16.2	11.6–20.8	80.6
	Italy	9.4	7.7	4.1–11.2	81.9
	the Netherlands	26.9	26.5	21.2–31.8	98.5
	Poland	27.7	19.6	14.0–25.2	70.8
	Portugal	6.8	4.4	1.4–7.3	64.7
	Switzerland*	50.3	43.4	35.2–51.9	86.3
	UK*	19.0	11.9	6.8–18.9	62.6
Plane	Europe	5.6	3.3	2.7–4.0	59.0
	Austria	4.1	0.0	0.0–1.5	0.0
	Belgium	1.2	0.9	0.0–2.5	75.0
	Denmark	8.9	6.2	2.2–10.2	69.7
	Germany	5.3	2.3	0.6–4.0	43.4
	Greece*	6.5	4.2	1.9–7.8	64.6
	Finland	0.9	0.9	0.0–2.5	100.0
	France	7.6	2.7	0.4–4.9	35.5
	Hungary	7.0	5.2	2.5–7.8	74.3
	Italy	3.2	2.5	0.3–4.6	78.1
	the Netherlands	4.7	3.8	1.5–6.1	80.9

Table 1. (Continued)

Allergen	Country	Sensitization rates (%)			
		SSR	CRR	95% CI	% CCR
Cypress	Poland	4.0	2.4	0.5–4.4	60.0
	Portugal	7.0	6.4	1.9–10.9	91.4
	Switzerland*	3.4	2.1	0.4–5.9	61.8
	UK*	15.9	11.9	6.8–18.9	74.8
	Europe	3.9	2.6	2.0–3.1	66.7
	Austria	1.5	0.3	0.0–1.0	20.0
	Belgium	2.0	1.2	0.0–2.7	60.0
	Denmark	5.8	3.7	0.7–6.8	63.8
	Germany	2.8	0.8	0.0–1.6	28.6
	Greece*	5.6	3.7	1.6–7.2	66.1
	Finland	0.0	0.0	0.0–1.5	0.0
	France	8.7	5.3	2.2–8.4	60.9
	Hungary	2.9	2.9	0.9–4.9	100.0
	Italy	8.1	6.0	2.9–9.1	74.1
	the Netherlands	1.5	1.5	0.0–2.9	100.0
	Poland	1.2	0.8	0.0–2.0	66.7
	Portugal	5.1	2.8	0.4–5.2	54.9
	Switzerland*	1.4	1.4	0.2–4.9	100.0
	UK*	11.1	8.7	4.4–15.1	78.4
Olive	Europe	15.0	11.5	10.3–12.6	76.7
	Austria	13.3	5.9	2.5–9.4	44.4
	Belgium	4.0	3.4	0.7–6.1	85.0
	Denmark	9.1	9.1	4.7–13.5	100.0
	Germany	9.7	4.9	2.3–7.6	50.5
	Greece*	35.0	29.9	23.9–36.5	85.4
	Finland	2.0	1.0	0.0–2.8	50.0
	France	18.2	8.9	4.9–12.9	48.9
	Hungary	14.4	12.1	8.0–16.3	84.0
	Italy	23.2	23.0	17.4–28.5	99.1
	the Netherlands	12.3	11.9	7.9–16.0	96.7
	Poland	2.7	2.0	0.3–3.7	74.1
	Portugal	21.3	17.9	11.8–24.0	84.0
	Switzerland*	45.5	32.4	24.9–40.7	71.2
	UK*	15.1	12.7	7.4–19.8	84.1
Grasses	Europe	37.8	33.4	31.7–35.1	88.4
	Austria	30.8	20.2	14.3–26.1	65.6
	Belgium	25.5	24.5	18.4–30.6	96.1
	Denmark	69.9	64.0	56.9–71.1	91.6
	Germany	37.9	34.1	28.7–39.5	90.0
	Greece*	49.5	42.3	35.5–49.2	85.5
	Finland	23.8	18.5	11.9–25.1	77.7
	France	26.4	19.3	13.7–24.8	73.1
	Hungary	40.6	37.3	31.3–43.3	91.9
	Italy	19.5	18.6	13.4–23.7	95.4
	the Netherlands	35.5	34.4	28.8–40.1	96.9
	Poland	38.0	30.8	24.5–37.1	81.1
	Portugal	34.4	31.6	24.6–38.6	91.9
	Switzerland*	78.6	71.0	62.9–78.3	90.3
	UK*	54.0	50.8	41.7–59.8	94.1
Ambrosia	Europe	14.1	10.7	9.6–11.8	75.9
	Austria	8.5	5.3	1.8–8.9	62.4
	Belgium	3.0	3.0	0.3–5.7	100.0
	Denmark	17.1	14.3	8.6–20.1	83.6
	Germany	14.4	9.3	5.6–13.0	64.6
	Greece*	11.7	5.1	2.6–9.0	43.6
	Finland	2.3	1.4	0.0–2.9	60.9
	France	9.0	4.5	1.6–7.4	50.0

Table 1. (Continued)

Allergen	Country	Sensitization rates (%)			
		SSR	CRR	95% CI	% CCR
Artemisia	Hungary	53.8	49.7	43.6–55.9	92.4
	Italy	3.5	3.1	0.8–5.4	88.6
	the Netherlands	18.6	16.7	12.1–21.3	89.8
	Poland	10.8	5.4	1.8–9.0	50.0
	Portugal	12.4	10.8	6.3–15.3	87.1
	Switzerland*	18.6	9.7	5.4–15.7	52.2
	UK*	7.9	7.1	3.3–13.1	89.9
	Europe	16.8	12.6	11.4–13.8	75.0
	Austria	10.6	6.9	2.8–11.0	65.1
	Belgium	4.7	4.7	1.4–8.1	100.0
	Denmark	28.3	23.8	16.8–30.7	84.1
	Germany	22.5	19.1	14.4–23.7	84.9
	Greece*	16.9	11.7	7.7–16.8	69.2
	Finland	17.6	13.0	7.8–18.2	73.9
	France	10.7	3.5	1.0–6.1	32.7
	Hungary	44.3	38.8	32.7–45.0	87.6
	Italy	6.7	5.8	2.7–8.9	86.6
	The Netherlands	6.2	5.8	2.9–8.7	93.5
	Poland	26.2	14.9	9.6–20.2	56.9
Parietaria	Portugal	16.3	14.6	8.8–20.5	89.6
	Switzerland*	17.2	6.2	2.9–11.5	36.0
	UK*	5.6	3.2	0.9–7.9	57.1
	Europe	9.2	7.5	6.6–8.5	81.5
	Austria	2.0	1.0	0.0–2.4	50.0
	Belgium	1.4	0.7	0.0–1.9	50.0
	Denmark	5.6	4.9	1.4–8.5	87.5
	Germany	6.9	3.9	1.3–6.4	56.5
	Greece*	24.8	20.6	15.4–26.6	83.1
	Finland	0.9	0.9	0.0–2.1	100.0
	France	6.5	3.6	1.0–6.2	55.4
	Hungary	3.1	2.0	0.0–4.0	64.5
	Italy	33.2	30.7	24.5–36.8	92.5
	the Netherlands	8.7	8.7	5.2–12.1	100.0
	Poland	3.0	2.2	0.0–4.6	73.3
	Portugal	17.5	14.7	9.6–19.8	84.0
	Switzerland*	2.1	0.7	0.0–3.8	33.3
	UK*	17.5	16.7	10.6–24.3	95.4
Alternaria	Europe	8.9	6.1	5.3–7.0	68.5
	Austria	6.5	2.6	0.0–5.2	40.0
	Belgium	5.3	4.9	1.8–8.1	92.5
	Denmark	8.2	8.2	4.0–12.3	100.0
	Germany	11.0	7.9	4.7–11.2	71.8
	Greece*	23.8	18.7	13.7–24.6	78.6
	Finland	2.0	1.5	0.0–3.4	75.0
	France	10.3	4.2	1.4–7.0	40.8
	Hungary	18.6	10.4	6.6–14.3	55.9
	Italy	3.5	3.0	0.8–5.2	85.7
	the Netherlands	5.5	5.5	2.7–8.3	100.0
	Poland	6.2	3.5	1.3–5.7	56.5
	Portugal	8.5	7.3	3.6–11.0	85.9
	Switzerland*	5.5	4.1	1.5–8.8	74.5
	UK*	0.8	0.0	0.0–2.3	0.0
Cladosporium	Europe	4.9	3.0	2.4–3.6	61.2
	Austria	1.1	0.0	0.0–1.5	0.0
	Belgium	0.8	0.4	0.0–1.2	50.0
	Denmark	7.9	7.0	2.9–11.1	88.6
	Germany	8.0	4.4	1.8–7.1	55.0

Table 1. (Continued)

Allergen	Country	Sensitization rates (%)			
		SSR	CRR	95% CI	% CCR
Indoor Cat	Greece*	7.0	5.1	2.6–9.0	72.9
	Finland	0.5	0.5	0.0–1.3	100.0
	France	3.4	0.0	0.0–1.5	0.0
	Hungary	12.8	8.5	4.8–12.2	66.4
	Italy	0.0	0.0	0.0–1.3	0.0
	the Netherlands	3.9	3.9	1.6–6.2	100.0
	Poland	1.8	0.4	0.0–1.1	22.2
	Portugal	10.3	7.4	3.1–11.7	71.8
	Switzerland*	0.7	0.7	0.0–3.8	100.0
	UK*	7.1	5.6	2.3–11.1	78.9
	Europe	26.3	19.4	18.0–20.8	73.8
	Austria	16.8	11.5	6.7–16.3	68.5
	Belgium	18.4	18.1	12.6–23.7	98.4
	Denmark	49.3	32.0	24.9–39.1	64.9
	Germany	28.1	23.6	18.6–28.5	84.0
	Greece*	29.4	15.4	10.9–21.0	52.4
	Finland	30.4	26.2	19.3–33.2	86.2
	France	23.0	14.8	9.8–19.7	64.3
	Hungary	32.5	22.6	17.3–28.0	69.5
Dog	Italy	21.3	17.6	12.7–22.4	82.6
	the Netherlands	18.5	18.5	13.7–23.3	100.0
	Poland	23.8	16.3	11.0–21.6	68.5
	Portugal	25.4	15.0	9.9–20.0	59.1
	Switzerland*	42.1	24.8	18.0–32.7	58.9
	UK*	31.7	27.8	20.2–36.5	87.7
	Europe	27.2	16.4	15.1–17.7	60.3
	Austria	16.1	8.8	4.7–13.0	54.7
	Belgium	17.8	15.0	9.8–20.2	84.3
	Denmark	56.0	29.4	22.4–36.4	52.5
	Germany	27.4	18.0	13.5–22.5	65.7
	Greece*	29.1	10.8	7.0–15.8	37.1
	Finland	36.5	24.6	17.9–31.4	67.4
	France	24.6	14.2	9.3–19.1	57.7
	Hungary	32.8	20.8	15.6–26.0	63.4
	Italy	17.4	13.4	9.2–17.6	77.0
	the Netherlands	29.9	28.3	22.9–33.8	94.6
	Poland	34.7	12.3	7.3–17.4	35.4
<i>Aspergillus</i>	Portugal	20.7	7.7	3.3–12.2	37.2
	Switzerland*	23.4	13.1	8.1–19.7	56.0
	UK*	21.4	15.9	10.0–23.4	74.3
	Europe	4.4	2.7	2.1–3.2	61.4
	Austria	0.5	0.5	0.0–1.3	100.0
	Belgium	2.4	1.7	0.0–3.7	70.8
	Denmark	4.8	4.3	0.8–7.8	89.6
	Germany	6.2	3.7	1.3–6.1	59.7
	Greece*	10.3	5.6	2.9–9.6	54.4
	Finland	2.5	1.5	0.0–3.1	60.0
	France	4.3	0.5	0.0–1.6	11.6
	Hungary	2.5	1.5	0.0–2.9	60.0
	Italy	0.4	0.0	0.0–1.3	0.0
	the Netherlands	4.6	4.6	2.0–7.2	100.0
	Poland	4.8	2.8	0.1–5.5	58.3
	Portugal	6.9	3.5	0.8–6.1	50.7
	Switzerland*	2.1	2.1	0.4–5.9	100.0
	UK*	7.9	7.1	3.3–13.1	89.9
<i>Dermatophagoides pteronyssinus</i>	Europe	31.3	26.5	24.9–28.0	84.7
	Austria	24.6	12.6	7.9–17.3	51.2

Table 1. (Continued)

Allergen	Country	Sensitization rates (%)			
		SSR	CRR	95% CI	% CCR
	Belgium	29.9	29.9	24.9–38.0	100.0
	Denmark	51.5	40.9	33.5–48.4	79.4
	Germany	23.5	17.0	12.6–21.4	72.3
	Greece*	32.7	26.2	20.4–32.6	80.1
	Finland	16.8	15.2	9.4–21.0	90.5
	France	38.1	29.2	22.9–35.4	76.6
	Hungary	31.3	26.1	20.7–31.5	83.4
	Italy	38.9	34.7	28.5–40.8	89.2
	the Netherlands	29.0	29.0	23.5–34.6	100.0
	Poland	22.2	16.8	11.8–21.8	75.7
	Portugal	68.8	65.3	58.2–72.5	94.9
	Switzerland*	24.8	22.1	15.6–29.7	89.1
	UK*	39.7	31.7	23.7–40.6	79.8
<i>Dermatophagoides farinae</i>	Austria	20.5	11.4	7.0–15.7	55.6
	Belgium	26.4	26.4	21.5–34.2	100.0
	Denmark	51.8	40.7	33.2–48.1	78.6
	Germany	21.1	16.1	11.8–20.5	76.3
	Greece*	26.6	22.9	17.4–29.1	86.1
	Finland	15.5	13.9	8.5–19.4	89.7
	France	31.8	28.8	22.6–35.0	90.6
	Hungary	26.3	20.6	15.5–25.7	78.3
	Italy	35.1	31.9	25.8–37.9	90.9
	the Netherlands	30.9	30.6	25.0–36.2	99.0
	Poland	19.1	15.3	10.4–20.2	80.1
	Portugal	68.0	63.5	56.3–70.8	93.4
	Switzerland*	26.9	22.1	15.6–29.7	82.2
	UK*	34.9	31.0	23.0–39.8	88.8
Blatella	Europe	8.9	5.7	4.9–6.6	64.0
	Austria	4.0	2.2	0.0–4.5	55.0
	Belgium	2.1	1.4	0.0–3.0	66.7
	Denmark	11.1	10.7	5.4–16.1	96.4
	Germany	12.0	6.8	3.7–9.9	56.7
	Greece*	9.8	7.0	4.0–11.3	71.4
	Finland	10.0	3.6	1.3–5.8	36.0
	France	11.4	8.0	4.2–11.9	70.2
	Hungary	4.6	0.6	0.0–1.8	13.0
	Italy	3.4	3.0	0.8–5.2	88.2
	the Netherlands	8.8	8.8	5.3–12.3	100.0
	Poland	8.2	6.8	3.4–10.2	82.9
	Portugal	33.4	21.0	14.5–27.5	62.9
	Switzerland*	1.8	0.9	0.0–4.8	50.0
	UK*	0.8	0.0	0.0–2.3	0.0

SSR, standardized sensitization rates; CCR, clinically relevant sensitization rates; 95% CI, 95% confidence interval; % CRR, percentage of clinically relevant sensitizations rates (CRR) of all sensitizations (SSR).
SSR (% of total population) and CRR (% of total population) are shown for Europe as a whole as well as most countries.
*Because of either age or gender biases, crude sensitizations rates are given for Switzerland, Greece and UK.

other allergens, $\geq 60\%$ of all recorded sensitizations were clinically relevant.

To exemplify the significance of the varying distribution of the reported clinical relevance for outdoor and indoor allergens in the participating countries, graphs for selected allergens are shown in Fig. 1. These histograms illustrate the percentage of allergen sensitizations that were

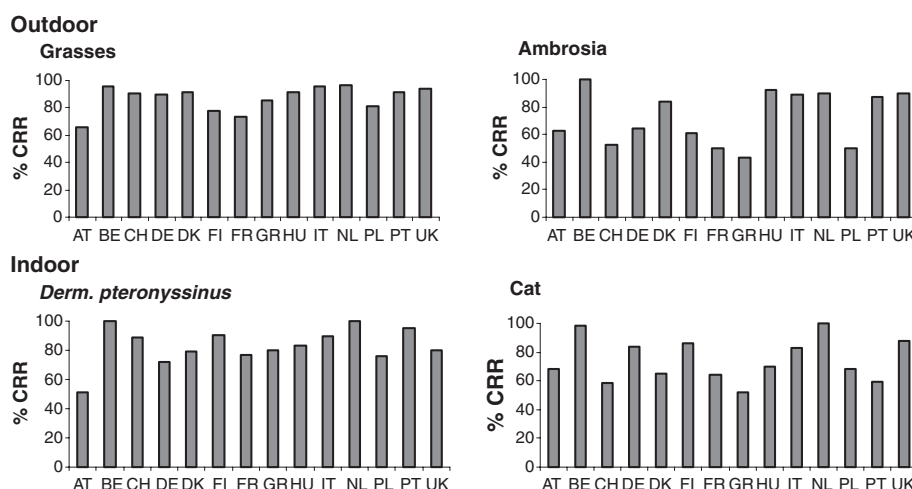


Figure 1. Clinical relevance of sensitizations for selected inhalant allergens. A country-specific analysis is demonstrated for the inhalant outdoor allergens grasses and ambrosia as well as for the indoor allergens *Dermatophagoides pteronyssinus* and cat. Bars represent the percentage of clinically relevant sensitizations (CRR, see Table 1) of all sensitizations (SSR, see Table 1) for the respective country and allergen (% CRR). AT, Austria; BE, Belgium; CH, Switzerland; DE, Germany; DK, Denmark; FI, Finland; FR, France; GR, Greece; HU, Hungary; IT, Italy; NL, the Netherlands; PL, Poland; PT, Portugal; UK, United Kingdom.

clinically relevant. The percentage of sensitizations against grasses that were clinically relevant was evenly distributed with $\geq 80\%$ in almost all countries investigated except Austria, Finland, and France, where $\geq 65\%$ of sensitized patients demonstrated clinical relevance. In contrast, clinically relevant sensitizations against *Ambrosia* were not evenly distributed. Specifically, the percentage of clinically relevant *Ambrosia* sensitizations was $\geq 80\%$ in Belgium, Denmark, Hungary, Italy, the Netherlands, Portugal and UK. However, in both Belgium and Italy, the standardized sensitization rates as a percentage of the total population were low. In other countries, the percentage of clinically relevant *Ambrosia* sensitizations was as low as that demonstrated for Greece ($\geq 43.6\%$).

With regard to indoor allergens, an overall high clinical relevance was seen in house-dust mite (*D. pteronyssinus*)-sensitized patients ($\geq 70\%$ clinically relevant sensitizations except Austria). In contrast, $\geq 80\%$ clinically relevant sensitizations for cat hair were demonstrated for Belgium, Germany, Finland, Italy, the Netherlands and UK. In all other countries, the percentage of clinically relevant sensitizations was $\geq 50\%$.

Increased likelihood of allergic disease with increasing number of sensitizations (Fig. 2)

To assess if the number of positive sensitizations which were reported to be clinically relevant correlated with the prevalent type of allergic disease, logistic regression analysis was performed. Here, a differential pattern was demonstrated for children (≤ 14 years) in comparison with teenagers/adults (≥ 15 years). Both, children and adults were significantly more likely to have allergic rhinitis if ≥ 1 sensitization was present [children: aOR 6.68 (3.71, 12.04);

adults: aOR 4.91 (3.8, 6.35)]. The likelihood of having allergic rhinitis dramatically increased with the number of positive sensitizations being most prominent for children with 5–6 positive sensitizations (aOR 12.73 [4.97, 32.6]) and for adults with ≥ 7 sensitizations [aOR 21.89 (13.08, 36.64)]. Atopic dermatitis was more likely in children [aOR 2.96 (1.37, 6.41)] and adults [aOR 1.77 (1.23, 2.56)] if ≥ 5 positive sensitizations, in children even more likely [aOR 5.8 (2.22, 15.12)] if ≥ 7 sensitizations were recorded. The likelihood of allergic asthma in children and adults was higher with ≥ 1 positive sensitization compared with no positive sensitizations present [children: aOR 1.96 (1.18, 3.25); adults: aOR 2.29 (1.71, 3.06)]. With ≥ 7 positive sensitizations, the likelihood of having allergic asthma was even more prominent in both children [aOR 6.12 (2.02, 18.54)] and adults [aOR 5.65 (4.0, 7.97)]. For food allergy, a significant correlation was demonstrated with ≥ 5 [children: aOR 4.67 (1.89, 11.53); adults: aOR 1.75 (1.19, 2.58)] and ≥ 7 positive sensitizations [children: aOR 6.93 (2.39, 20.13); adults: aOR 2.61 (1.79, 3.8)].

Discussion

Skin prick testing is considered a reliable surrogate for an allergic response in the respective target organ, i.e. skin, nose, lung or gut. However, the clinical relevance of positive sensitizations often remains unclear. Patient history is the first source of information the allergologist turns to allowing a basic assessment of complaints which may be related to allergen exposure. Unfortunately, no conclusive data on this subject have been published so far because mostly, clinical relevance is not recorded in a standardized manner. During the study reported here,

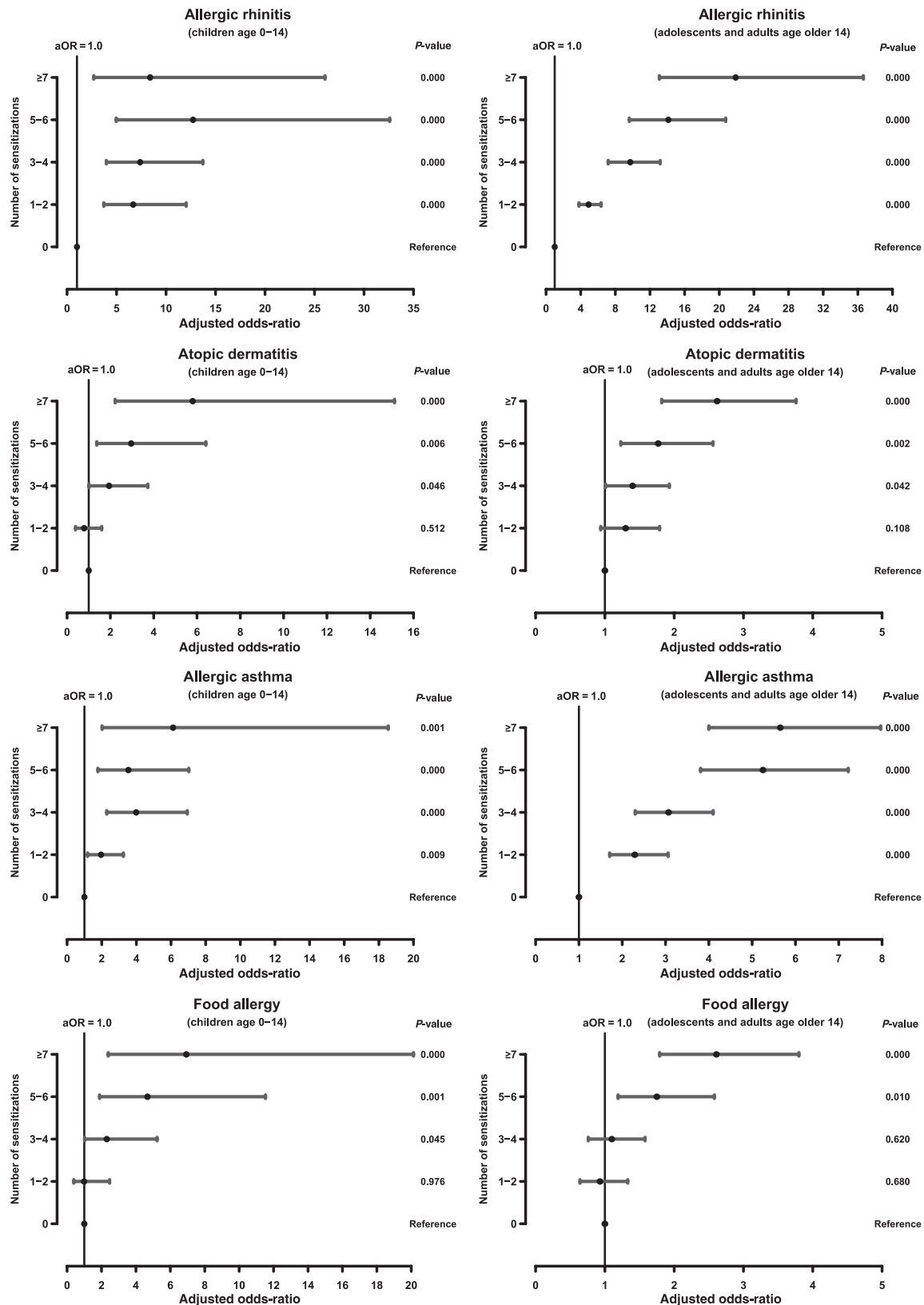


Figure 2. Logistic regression analysis demonstrating an increased likelihood of allergic disease with an increasing number of sensitizations. Data are given as adjusted odds ratios (aORs) in children (age 0–14 years, left row) and adolescents/adults (age older 14 years, right row). *P*-values ≥ 0.05 are regarded statistically non-significant.

clinical relevance was noted for each positive skin prick test sensitization, specific symptoms were assessed and correlated to the putative allergen in question. Looking at the overall rate of clinically relevant sensitizations, approximately $\geq 60\%$ of all sensitizations were clinically relevant. Interestingly, the specific rate of clinically relevant sensitizations varied significantly depending on the allergen and the country where the prick test was performed. We, furthermore, demonstrated that an increasing number of positive skin prick test results were significantly associated with an increasing likelihood of allergic rhinitis, allergic asthma, atopic dermatitis or food allergy.

Clinical relevance of skin prick test sensitizations

During the current study, clinical relevance regarding positive skin prick test reactions was assessed by experienced allergologists. Here, we focused on detailed history taking rather than extensive provocation tests, which were only applied where indicated. Indeed, skin prick testing is easily quantifiable and allows the evaluation of multiple allergens, while mucosal challenge is only possible with one allergen at a time. Furthermore, skin testing correlates well with results of nasal and bronchial challenge (2, 3) and patient history still has to be taken into account if provocation tests are performed.

Interestingly, the percentage of clinically relevant sensitizations was shown to depend on the allergen in question as well as on the country where the skin test was performed. Only few allergens i.e. grasses and house dust mites (*D. pteronyssinus* and *D. farinae*) showed similar rates of clinical relevance in all countries investigated. For all other allergens, a differential distribution was demonstrated among the countries investigated. With particular regard to the country-specific clinically relevant sensitization rates, a bias in reporting clinical relevance for the different allergens could be excluded for almost all countries: While only in the Netherlands, all clinical relevance rates were between 80 and 100%, all other countries demonstrated fluctuations in reporting clinically relevant sensitizations of over 50% (data not shown).

Several factors may have contributed to the differential distribution of clinically relevant sensitizations. The present study demonstrated that the likelihood of a clinically relevant sensitization depends on the type of allergen as well as on the country where the prick test was performed. First, allergens may differ in their allergenicity (4) and, thus, be one of the determining factors in determining clinical relevance. Second, differing climatic factors in the countries investigated may influence pollen production and, thus, pollen amount and exposure as well as allergenicity (5, 6). And third, potential selection biases have to be taken into account: allergy centres may have recruited somewhat different patient populations due to referral of patients to allergy centres in departments of ear, nose and throat-diseases,

respiratory diseases or dermatology. Furthermore, patients who have been evaluated by the investigating allergologist to have an increased likelihood of clinically relevant symptoms were preferentially included into the study and may, thus, not represent a random population of allergy patients.

Number of sensitizations and likelihood of allergic disease

In the current study, clinically relevant symptoms in patients with positive skin prick testing were categorized into four distinct allergic disease entities i.e. allergic rhinitis, allergic asthma, atopic dermatitis and food allergy. While some authors have already suggested that an increasing number of sensitizations to inhalant allergens may be associated with the development of allergic rhinitis or asthma (7–10), detailed studies on this subject are lacking. Here, we could demonstrate that both children and adults are significantly more likely to have allergic rhinitis or asthma if ≥ 1 sensitization was detected by skin prick testing and thus confirm previous studies. We, furthermore, demonstrated that the likelihood of suffering from atopic dermatitis or food allergy was significantly associated with ≥ 5 sensitizations independent of the type of allergen. These findings further support the concept that the term 'atopy' may define a predisposition to develop an allergic disease and may, inter alia, be determined by a prick test response to ≥ 1 allergen (11). While only a higher number of sensitizations might predispose to atopic dermatitis and food allergy, other factors like increased total IgE or specific IgE levels may have, additionally, to be taken into account if evaluating these patients (11).

Conclusion

In summary, this paper demonstrates that the clinical relevance of inhalant allergen sensitizations may differ significantly depending on the allergen as well as the country where the skin prick test was performed. Our study intends to emphasize the importance of evaluating the clinical relevance of positive skin prick tests and proposes additional studies on this topic. The current database provides a basis for identifying further factors that might influence clinical relevance. This may, ultimately, promise to increase the positive predictive value of allergy testing significantly.

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