Contact Dermatitis • **Original Article**

COD
Contact Dermatitis

European Surveillance System on Contact Allergies (ESSCA): polysensitization, 2009–2014

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Summary

Background. Polysensitization, defined as being allergic to three or more haptens from the European baseline series, is considered to reflect increased susceptibility to developing a contact allergy, and is likely to be associated with an impaired quality of life.

Objectives. To evaluate the prevalences of polysensitization across Europe and to analyse factors associated with polysensitization.

Methods. Patch test data collected by the European Surveillance System on Contact Allergies (ESSCA; www.essca-dc.org) in consecutively patch tested patients from January 2009 to December 2014, comprising 11 countries and 57 departments, were retrospectively analysed.

Results. A total of 86 416 patients were available for analysis, showing a standardized prevalence of polysensitization of 7.02%, ranging from 12.7% (Austria) to 4.6% (Italy). Allergen pairs with the strongest association are reported for the total population, for South Europe, and for North/Central Europe. Overall, polysensitized patients showed a higher percentage of extreme (+++) positive patch test reactions than oligosensitized patients. Female sex, occupational dermatitis and age > 40 years were risk factors for polysensitization.

Conclusions. The varying prevalences of polysensitization across Europe most likely reflect differences in patient characteristics and referral patterns between departments. Known risk factors for polysensitization are confirmed in a European dermatitis population.

Key words: clinical epidemiology; contact allergy; patch test; polysensitization.

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Polysensitization, in terms of multiple contact allergies, is currently defined as sensitization to three or more non-related allergens of the European baseline series (EBS) (1). Although arbitrarily defined, this concept is used both to investigate risk factors for developing multiple contact allergies, and to address the topic of increased susceptibility, for example caused by genetic variants (2). For example, polysensitization was shown to be associated with certain genetic markers with links to pathogenetic steps of allergic contact dermatitis (ACD) (3, 4), reflecting increased susceptibility independently from actual haptens (5), which implies that allergen-specific susceptibilities should be considered as well (5, 6). Polysensitization has been extensively reviewed by Carlsen et al. and Schnuch et al. (7, 8). The main cause of acquiring multiple sensitivities is apparently high exposure to environmental allergens, for example by occupational exposure, or pre-existing inflammatory dermatoses conveying 'danger signals' [e.g. in patients with leg (stasis) dermatitis or leg ulcers] (9). Studies have shown, however, that polysensitized individuals, when sensitized in an experimental setting, have a lower elicitation threshold and generally show stronger elicitation reactions than single/double-sensitized individuals, providing arguments for different susceptibilities between these groups (10, 11).

Although quality of life has not been thoroughly investigated in polysensitized patients, one case–control study investigating quality of life in fragrance-allergic dermatitis patients as compared with dermatitis patients with no fragrance allergy found an increase in impairment in quality of life with an increasing number of positive patch test reactions to fragrance allergens (12, 13). Polysensitized individuals have a higher probability of relevant exposure, and therefore it is not difficult to imagine that they suffer more from persistent dermatitis and frequent relapses of their dermatitis.

The reported prevalences of polysensitization in patch test populations depends greatly on the tested population and the length of the tested baseline series, yielding prevalences ranging from 5.0% to almost 20.0% (this last result was based on a baseline series consisting of 73–80 allergens) (1, 11, 14). The prevalence of polysensitization in the largest reported group, that of the Information Network of Departments of Dermatology (IVDK) in Germany, has been found to be stable around 10.0% (15, 16). In one study, the prevalence of polysensitization found in a small general population sample was 0.7% (17).

The objective of this study was to evaluate prevalences of polysensitization in different European countries. We also aimed to evaluate factors associated with polysensitization in patients who were patch tested at departments of the European Surveillance System on Contact Allergies (ESSCA) network in the period from 2009 to 2014.

Methods

The analysis is based on clinical data collected by the ESSCA network, as described in previous publications (18, 19). Briefly, clinical and demographic data, along with patch test results, of all patients patch tested in the departments participating in the ESSCA for suspected ACD caused by various potential exposures are documented electronically in the local departments. These use diverse data capture software and, partly, the multilingual software WINALLDAT/ESSCA provided by the ESSCA (20). Standardized patch testing follows international recommendations (21). The anonymized data delivered by the participants are pooled in the ESSCA data centre in Erlangen for further analysis, (22) with R (version 3.2.3) software (www.r-project.org, last accessed 22 March 2017). Pertinent guidelines for the statistical analysis of patch test data were considered (23, 24).

For analysis, the maximum patch test reactions between day (D) 3 and D5 (inclusive) were aggregated as the patch test outcome. Reactions designated as either +, ++ or +++ were classified as positive (allergic), and the remainder were classified as non-allergic. The study period was January 2009 to December 2014, and included, for the present analysis, 11 European countries and, in total, 57 departments.

Test results obtained with the EBS valid in the study period, during which methylisothiazolinone (MI) 2000 ppm aq. had been added, and the recommended test concentration of methylchloroisothiazolinone (MCI)/MI had been increased from 100 to 200 ppm aq., and that of formaldehyde had been increased from 1% to 2% aq., were analysed (25). Altogether, 86 416 patients were registered who were tested with the EBS and whose tests were read at least between D3 and D5. The TRUE Test® employing a hydrocellulose matrix for the haptens instead of pet. or aq. was used in a relatively small number of consultations, namely 3649, with the vast majority of patients being tested with pet.-based and aq.-based haptens and investigator-loaded chamber systems, respectively. Moreover, two German departments used a 1-day patch test exposure, applied to 2870 patients. As in previous analyses, the impact of these variations of the standard technique was found to be limited, so the results have all been pooled (26).

Concerning the allergens of the EBS, which form the basis of the present analysis of polysensitization, the following rules were applied for counting of the number of individual positive patch test reactions:

- Positive reactions to fragrance mix II and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) were pooled, that is, counted as one reaction if one or the other, or both, were positive.
- The same rule was applied to reactions to mercapto mix 1% and 2% pet. (which were never both tested in one patient) and reactions to 2-mercaptobenzothiazole tested additionally.
- As a marker concerning local anaesthetics, benzocaine is tested in the current EBS, whereas caine mix III is tested by a large number of ESSCA members because of its better diagnostic yield; the positive reaction(s) were counted as one.
- Likewise, sesquiterpene lactone mix is included in the current EBS, but (partly differing versions of) Compositae mix were considered to be equivalent, and positive reaction(s) were counted as one.
- Partly, the mixture of methyldibromo glutaronitrile (MDBGN) and 2-phenoxyethanol 1:4, for example Euxyl® K 400, was tested instead of, or in addition to, MDBGN. All positive reactions were pooled into one.
- In view of corresponding dithiocarbamates and thiurams being redox pairs (27), positive reactions both to zinc diethyldithiocarbamate (ZDEC) or carba mix – which were never both tested in one patient – and thiuram mix were counted as one.
- Although it could be debated whether positive reactions to formaldehyde and various formaldehyde releasers are truly equivalent, as isolated reactions to a releaser might be attributable to the donor molecule, these were also pooled, which concerned quaternium-15, which is presently the only formaldehyde releaser contained in the EBS.

Besides polysensitization, prevalences are also provided for oligosensitization, defined as having one or two positive patch test reactions, but not more, and for 'at least one positive', also known as the 'P' measure (28). For the polysensitized group and for all patients with no positive patch test reactions to the EBS, the MOAHLFA (Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Face dermatitis, Leg dermatitis, Age ≥ 40 years) index is given (29).

To evaluate regional differences for concomitant reactions, that is, pairs of positive reactions contributing to polysensitization (30), or 'oligosensitization', countries were classified into two regions, as previously done by Schuttelaar et al. (31). Two regions were defined: North/Central Europe, comprising Finland, Lithuania, Poland, Germany, Austria, Switzerland, The Netherlands, and the United Kingdom; and South Europe, comprising Spain, Italy, and Slovenia.

Besides descriptive statistics, adjusted multifactorial analyses were employed to quantify the independent association of potentially relevant explanatory factors and oligosensitization and polysensitization, respectively. To this end, log-binomial regression analysis was utilized, which quantifies the association by means of a prevalence ratio (PR), which can be interpreted as a representation of relative risk. Point estimates were accompanied by 95% confidence intervals (CIs) obtained with the profile likelihood method. The set of explanatory variables considered included the country, sex, age (dichotomized as < 40 years versus ≥ 40 years), occupational aetiology of contact dermatitis ('yes' or 'partly' versus 'no' or 'unknown'), atopic dermatitis, past or present, versus no atopic dermatitis, and the anatomical sites hand, leg, face, trunk (as reference), and 'other'. Moreover, the number of allergens in the baseline series tested was used as an adjustment factor, as the likelihood of one (or more) positive reactions depends also on the number of allergens tested (32).

Results

In the years 2009–2014, altogether 86 416 patients were patch tested in the 57 European departments. The characteristics of the patients, and univariate results obtained with the EBS allergens, have been published in a number of publications covering the 2009–2012 study period and the 2013–2014 study period, respectively. For further information, the reader is referred to these (26, 33–38).

Prevalences of polysensitization across Europe

Crude and age- and sex-standardized prevalences for polysensitization and oligosensitization, stratified per country, are presented together with 95%CIs in Table 1. In order to put these results into perspective, prevalences for at least one positive reaction ('P' measure) and for negative patch test results are also given (28). No large differences were seen between crude and standardized prevalences. Overall, the standardized prevalence of polysensitization was 7.05%, with the highest standardized prevalences being seen in Austria (12.7%) and The Netherlands (12.4%), and the lowest in Italy (4.6%) and Lithuania (5.2%). The standardized 'P' measure, presented as 'at least one positive reaction' to the EBS allergens, was 43.0% for the total population, with considerable variation between countries; from 52.9% in The Netherlands to 38.6% in the United Kingdom.

Of the total polysensitized population, the proportion of males aged < 40 years was 6.5%, and the proportion

Table 1. Crude and age- and sex-standardized prevalences of patch tested patients in the European Surveillance System on Contact Allergies database between January 2009 to December 2014 with negative patch test results, at least one positive patch test reaction ('P' measure), oligosensitization, and polysensitization, given per country

		Negative		At least one positive reaction		Oligosensitization		Polysensitization	
Country	n(total)	n (%)	Standardized % (95%CI)	n (%)	Standardized % (95%CI)	n (%)	Standardized % (95%CI)	n (%)	Standardized % (95%CI)
Austria	1622	774 (47.72)	49.32 (46.72–51.93)	848 (52.28)	50.68 (48.07–53.28)	629 (38.78)	37.96 (35.44–40.49)	219 (13.5)	12.71 (11.02–14.41)
Switzerland	7508	3921 (52.22)	52.23 (51.05–53.4)	3587 (47.78)	47.77 (46.6–48.95)	2849 (37.95)	38.34 (37.19–39.5)	738 (9.83)	9.43 (8.75–10.12)
Germany	11 243	6700 (59.59)	59.76 (58.77–60.75)	4543 (40.41)	40.24 (39.25–41.23)	3722 (33.11)	33.46 (32.5–34.42)	821 (7.3)	6.79 (6.3–7.28)
Spain	6567	3614 (55.03)	56.04 (54.79–57.28)	2953 (44.97)	43.96 (42.72–45.21)	2523 (38.42)	37.63 (36.42–38.85)	430 (6.55)	6.33 (5.72–6.94)
Finland	1289	651 (50.5)	50.13 (47.39–52.87)	638 (49.5)	49.87 (47.13–52.61)	526 (40.81)	41.26 (38.54–43.98)	112 (8.69)	8.61 (7.08–10.15)
Italy	12 893	7444 (57.74)	58.08 (57.23–58.92)	5449 (42.26)	41.92 (41.08–42.77)	4855 (37.66)	37.36 (36.53–38.18)	594 (4.61)	4.56 (4.21–4.92)
Lithuania	1424	780 (54.78)	56.67 (53.9–59.43)	644 (45.22)	43.33 (40.57–46.1)	559 (39.26)	38.13 (35.39–40.86)	85 (5.97)	5.21 (4.07–6.34)
The Netherlands	7001	3243 (46.32)	47.12 (45.94–48.29)	3758 (53.68)	52.88 (51.71–54.06)	2854 (40.77)	40.44 (39.29–41.6)	904 (12.91)	12.44 (11.67–13.2)
Poland	5527	2668 (48.27)	49.06 (47.73–50.38)	2859 (51.73)	50.94 (49.62–52.27)	2273 (41.13)	40.67 (39.36–41.97)	586 (10.6)	10.28 (9.48–11.08)
Slovenia	8640	5185 (60.01)	60.76 (59.73–61.79)	3455 (39.99)	39.24 (38.21–40.27)	2874 (33.26)	32.8 (31.8–33.8)	581 (6.72)	6.44 (5.93–6.95)
United Kingdom	22 702	13 650 (60.13)	61.43 (60.8–62.05)	9052 (39.87)	38.57 (37.95–39.2)	7739 (34.09)	33.12 (32.51–33.73)	1313 (5.78)	5.45 (5.16–5.74)
Total	86 416	48 630 (56.3)	56.98 (56.64–57.31)	37 786 (43.7)	43.02 (42.69–43.36)	31 403 (36.3)	35.97 (35.65–36.29)	6383 (7.4)	7.05 (6.88–7.22)

The 'P' measure is the proportion of patch tested patients with at least one positive patch test reaction. Oligosensitization: the proportion of patch tested patients with one or two positive patch test reactions; Polysensitization: the proportion of patch tested patients with three or more positive patch test reactions to unrelated allergens.

[Correction added on 28 February 2018, after first online publication: The country in Row 4 was wrongly indicated as Estonia and has been corrected to Spain in this version.]

of females aged < 40 years was 24.3% (Table 2). The proportion aged ≥ 40 years and male was 19.9%, and the majority were female and aged ≥ 40 years (49.3%). These proportions were largely similar in the oligosensitized population, except that this population was younger. The MOAHLFA index of the polysensitized population is shown in Table 3, together with the total patch tested population as a reference (29). For most of the categories of the MOAHLFA index, the polysensitized group was similar to the total patch tested population, except that the percentage of females was slightly higher for the polysensitized group, and a higher percentage were aged ≥ 40 years. This difference in age distribution was most pronounced in the United Kingdom, whereas, in Spain and Poland, the percentages were almost the same for the polysensitized and the total patch tested population. The distribution of individuals with (a history of) atopic dermatitis was equal between the totals of both groups; however, country-specific differences could be seen. The primary site of dermatitis seemed to be distributed similarly in both groups overall, as well as for all of the individual countries.

The most common allergen pairs in polysensitized individuals and the strengths of patch test reactions

Within the polysensitized group, odds ratios (ORs) were calculated for all possible allergen pairs to evaluate concomitant positive patch test reactions. This was performed for the total population, and separately for South Europe and North/Central Europe as defined above, in order to observe any differences based on geographical location. The top 10 allergen pairs per region ranked by the highest OR are shown in Table 4. Overall, associations were stronger in South Europe than in North/Central Europe. For both regions, the top two concomitant reactions were those to quaternium-15/formaldehyde and carba mix/thiuram mix. The most probable reason for the concomitant reactions is also suggested in the footnotes to Table 4.

The most commonly positive EBS allergens in polysensitized patients are shown and compared with those in oligosensitized patients in Table S1. There were no large differences regarding which allergens were the most commonly positive between the two groups.

The distribution of grades of positive reactions, from weak positive to extreme positive, in oligosensitized and polysensitized individuals stratified per country is shown in Table 5. Overall, for almost all countries, the polysensitized population had a slightly higher percentage of extreme positive (+++) reactions than the oligosensitized population. The percentage of strong positive (++) reactions was comparable between both populations, except for Finland, where the oligosensitized population had a higher percentage of strong positive reactions than the polysensitized population. Large differences between countries can also be observed; for example, the percentage of weak positive reactions in the polysensitized population in The Netherlands was 81.6%, as compared with only 21.0% in Spain.

The distribution of grades of positive reactions, per number of positive reactions, for the total population is shown as a stacked bar plot in Fig. 1. A clear positive correlation can be seen between the number of positive reactions and the percentage of extreme positive (+++) reactions.

Analysis of risk factors for polysensitization

To assess the influence of country, sex, occupational contact dermatitis (OCD), atopic dermatitis, age ≥ 40 years and primary site of dermatitis on the risk of being polysensitized, a log-binomial regression analysis was performed (Table 6). The same regression analysis was performed on the oligosensitized group for comparison. For quantification of the risk of being either oligo- or polysensitised associated with the country an individual has been patch tested in, Switzerland was chosen as reference, because it is situated between the 2 chosen European regions. The association between country and being oligosensitized was minimal; it was lower in Germany and the United Kingdom (PR = 0.79 and PR = 0.82, respectively) than in the reference country, Switzerland. In contrast, the association between country and being polysensitized was more pronounced. The risk of being polysensitized appeared to be significantly lower for most countries than for Switzerland, and was especially low in Germany (PR = 0.64), Italy (PR = 0.59), and the United Kingdom (PR = 0.54). Conversely, this risk was significantly higher for Austria (PR = 1.71) and The Netherlands (PR = 1.27).

Low PRs for male sex in both the oligosensitized and polysensitized groups (0.7 and 0.59, respectively) indicated that females had a significantly increased risk of being sensitized overall, and of being polysensitized in particular. Also, OCD was significantly associated with both oligosensitization and polysensitization, and again this association was even stronger for polysensitization. For atopic dermatitis, a small, significant association was seen for polysensitization, but not for oligosensitization. The highest PR for polysensitization was observed for age ≥ 40 years (1.71). Of the primary sites of dermatitis, only hand dermatitis (PR = 1.15) was found to be significantly associated with polysensitization when compared withy trunk dermatitis as the reference. Leg dermatitis

Table 2. Age (years) and sex of patch tested patients in the European Surveillance System on Contact Allergies database between January 2009 to December 2014 per country per polysensitized group; n (%)

		Negative				Oligosensitization				Polysensitization			
Country	n(total)	M < 40	M ≥ 40	F < 40	F ≥ 40	M < 40	M ≥ 40	F < 40	F ≥ 40	M < 40	M ≥ 40	F < 40	F ≥ 40
Austria	1622	81 (10.5)	162 (20.9)	196 (25.3)	335 (43.3)	42 (6.7)	100 (15.9)	174 (27.7)	313 (49.8)	12 (5.5)	32 (14.6)	54 (24.7)	121 (55.3)
Switzerland	7508	685 (17.5)	1079 (27.5)	715 (18.2)	1442 (36.8)	275 (9.7)	614 (21.6)	684 (24)	1276 (44.8)	50 (6.8)	163 (22.1)	144 (19.5)	381 (51.6)
Germany	11 243	923 (13.8)	2037 (30.4)	1152 (17.2)	2588 (38.6)	374 (10)	983 (26.4)	732 (19.7)	1633 (43.9)	55 (6.7)	216 (26.3)	115 (14)	435 (53)
Spain	6567	469 (13)	888 (24.6)	853 (23.6)	1404 (38.8)	195 (7.7)	415 (16.4)	659 (26.1)	1254 (49.7)	30 (7)	103 (24)	104 (24.2)	193 (44.9)
Finland	1289	152 (23.3)	157 (24.1)	161 (24.7)	181 (27.8)	78 (14.8)	104 (19.8)	147 (27.9)	197 (37.5)	10 (8.9)	21 (18.8)	23 (20.5)	58 (51.8)
Italy	12 893	1460 (19.6)	1404 (18.9)	2156 (29)	2424 (32.6)	616 (12.7)	581 (12)	1731 (35.7)	1927 (39.7)	55 (9.3)	107 (18)	180 (30.3)	252 (42.4)
Lithuania	1424	76 (9.7)	118 (15.1)	177 (22.7)	409 (52.4)	27 (4.8)	56 (10)	189 (33.8)	287 (51.3)	0 (0)	10 (11.8)	25 (29.4)	50 (58.8)
The Netherlands	7001	555 (17.1)	690 (21.3)	946 (29.2)	1052 (32.4)	314 (11)	515 (18)	869 (30.4)	1156 (40.5)	61 (6.7)	184 (20.4)	238 (26.3)	421 (46.6)
Poland	5527	412 (15.4)	523 (19.6)	713 (26.7)	1020 (38.2)	239 (10.5)	286 (12.6)	815 (35.9)	933 (41)	48 (8.2)	72 (12.3)	197 (33.6)	269 (45.9)
Slovenia	8640	813 (15.7)	1045 (20.2)	1418 (27.3)	1909 (36.8)	288 (10)	402 (14)	907 (31.6)	1277 (44.4)	36 (6.2)	99 (17)	159 (27.4)	287 (49.4)
United Kingdom	22 702	2202 (16.1)	2778 (20.4)	4195 (30.7)	4475 (32.8)	576 (7.4)	1228 (15.9)	2426 (31.3)	3509 (45.3)	58 (4.4)	261 (19.9)	314 (23.9)	680 (51.8)
Total	86 416	7828 (16.1)	10 881 (22.4)	12 682 (26.1)	17 239 (35.4)	11 766 (9.6)	13 237 (16.8)	16 147 (29.7)	19 026 (43.8)	415 (6.5)	1268 (19.9)	1553 (24.3)	3147 (49.3)

F, female; M, male.

Results for patients without positive patch test reactions (negative) and for oligosensitization are also presented as a reference.

Table 3. MOAHLFA index per country of patch tested patients in the European Surveillance System on Contact Allergies database between January 2009 and December 2014 with polysensitization and all patients tested. As Slovenian departments could not contribute information on occupational dermatitis, atopic dermatitis, and anatomical site, these were omitted from the table.

Country	(Sub)group	n (total)	% M	% O	% A	% H	% L	% F	% A
Austria	Polysensitized	219	20.1	19.6	29.2	9.1	2.7	7.3	69.9
	All tested	1622	26.4	16.8	21.3	10.1	1.8	5.4	65.5
Switzerland	Polysensitized	738	28.9	15.7	24.1	8.7	2.2	5.6	73.7
	All tested	7508	38.2	12.9	19.6	9.6	2.2	6.5	66.0
Germany	Polysensitized	821	33.0	35.8	27.9	38.0	5.8	9.4	79.3
	All tested	11 243	40.8	32.4	26.4	36.2	5.1	9.3	70.2
Spain	Polysensitized	430	30.9	19.3	13.0	31.6	7.2	11.9	68.8
	All tested	6567	32.0	13.1	14.4	27.5	7.5	13.9	64.8
Finland	Polysensitized	112	27.7	34.8	31.2	55.4	4.5	0.9	70.5
	All tested	1289	40.5	47.6	30.3	64.2	2.9	4.7	55.7
Italy	Polysensitized	594	27.3	8.4	13.5	26.4	4.5	12.3	60.4
	All tested	12 893	32.8	5.3	16.8	21.6	6.6	11.6	51.9
Lithuania	Polysensitized	85	11.8	14.1	10.6	18.8	22.4	32.9	70.6
	All tested	1424	20.2	12.7	11.5	25.5	11.4	24.9	65.3
The Netherlands	Polysensitized	904	27.1	22.8	38.5	22.5	4.3	18.3	66.9
	All tested	7001	33.1	17.8	34.6	19.7	4.4	18.9	57.4
Poland	Polysensitized	586	20.5	26.3	17.2	22.5	3.4	10.9	58.2
	All tested	5527	28.6	17.7	16.0	22.3	3.4	11.2	56.1
Slovenia	Polysensitized	581	23.2	–	–	–	–	–	66.4
	All tested	8640	31.1	–	–	–	–	–	58.1
United Kingdom	Polysensitized	1313	24.3	9.9	31.6	30.2	4.6	26.2	71.7
	All tested	22 702	31.3	8.7	36.1	26.0	5.4	27.8	57.0
Total	Polysensitized	6383	26.4	21.7	26.1	31.3	5.7	18.0	69.2
	All tested	86 416	33.2	16.3	25.7	29.2	6.1	19.2	59.7

M, Male; O, Occupational aetiology; A, Atopic dermatitis (history of); H, Hand dermatitis; L, leg dermatitis; F, face dermatitis; A, age ≥ 40 years.

was inversely significantly associated with oligosensitization (PR = 0.92).

Discussion

Prevalences of polysensitization

For the first time, prevalences of polysensitization are presented for different countries across Europe. Overall, the standardized prevalence of polysensitization was 7.1%, and the standardized prevalence of oligosensitization was 36.3%. The 'P' measure in this dataset was 43.0%, which is similar to the 43% seen in the ESSCA population patch tested in 2005–2006 (39). Note that the 'P' measure includes, by definition, both oligosensitized and polysensitized patients, so similarities in association patterns are to be expected. There is considerable variation in polysensitization and oligosensitization between countries; besides reflecting actual sensitization frequencies and the differences thereof between countries, it can also mainly be explained by the varying eligibility criteria for patch testing between departments. Differences between countries and departments in relation to selection processes and health systems have been discussed in a previous ESSCA publication (26). Another explanatory variable is the length of the baseline series tested in a department; 'a bigger net catches more fish'. However, in the present analysis, this effect has a ceiling, in the sense that only allergens of the EBS as currently recommended were considered (25), together with possible substitutes or additions as detailed above, but not any length of departmental baseline series. Nevertheless, as some national groups or departments systematically omit haptens from the EBS, some adjustment for, basically, a lower number of allergens tested in patients (from one country and department, respectively) was necessary, and was employed in the regression analysis. However, the putatively lower sensitivity (and thus lower prevalence yielded) in those departments still using 100 ppm MCI/MI and 1% formaldehyde, respectively, has not been separately addressed, as the effect is regarded as being relatively minor.

The high prevalence of polysensitization in Austria and The Netherlands may be explained by more restrictive patch testing (i.e. more selective) and different patterns of referral, for example in The Netherlands. It seems unlikely that these countries actually have a higher prevalence of polysensitization, as it does not seem obvious that individuals in these countries have higher exposure

Table 4. Top 10 allergen pairs defined by the highest odds ratios (OR) for the total population and per 'European region', accompanied by a 95%CI, in patch tested patients in the European Surveillance System on Contact Allergies (ESSCA) database between January 2009 to December 2014 who were polysensitized

Total population		South Europe		North/Central Europe	
Allergen pair	OR (95%CI)	Allergen pair	OR (95%CI)	Allergen pair	OR (95%CI)
Quaternium-15–formaldehyde[a]	56.31 (46.55–68.11)	Quaternium-15–formaldehyde[a]	71.62 (48.36–106.07)	Quaternium-15–formaldehyde[a]	49.75 (40.01–61.86)
Carba mix–thiuram mix[a]	30.84 (26.44–35.97)	Carba mix–thiuram mix[a]	33.77 (22.42–50.86)	Carba mix–thiuram mix[a]	32.44 (27.4–38.4)
Mercaptobenzothiazole/mercapto mix–thiuram mix[b]	13.15 (10.91–15.86)	Primin–clioquinol[c]	24.05 (5.51–104.95)	Primin–tixocortol-21-pivalate[c]	12.66 (7–22.91)
Tixocortol-21-pivalate–budesonide[b]	12.77 (8.91–18.31)	Tixocortol-21-pivalate–clioquinol[b]	23.43 (3.03–181.34)	Mercaptobenzothiazole/mercapto mix–thiuram mix[b]	11.81 (9.59–14.55)
Fragrance mix II/hydroxyisohexyl 3-cyclohexene carboxaldehyde –fragrance mix I[b]	12.21 (11.33–13.16)	Tixocortol-21-pivalate–budesonide[b]	23.29 (8.98–60.39)	Tixocortol-21-pivalate–budesonide[b]	11.38 (7.69–16.84)
Primin–clioquinol[c]	12.12 (4.35–33.75)	Benzocaine/Caine mix–*p*-phenylenediamine[a]	20.60 (15.27–27.79)	Potassium dichromate–cobalt[b]	11.15 (10.11–12.3)
Benzocaine/Caine mix–*p*-phenylenediamine[a]	11.97 (9.92–14.44)	Fragrance mix II/hydroxyisohexyl 3-cyclohexene carboxaldehyde –fragrance mix I[b]	18.11 (15.26–21.49)	Fragrance mix II/hydroxyisohexyl 3-cyclohexene carboxaldehyde–fragrance mix I[b]	11.04 (10.16–12)
Potassium dichromate–cobalt[b]	11.80 (10.91–12.76)	Mercaptobenzothiazole/mercapto mix–thiuram mix[b]	17.17 (11.24–26.24)	Primin–mercaptobenzothiazole/mercapto mix[b]	10.78 (5.56–20.89)
Tixocortol-21-pivalate–clioquinol[b]	10.95 (4.70–25.53)	*N*-isopropyl-*N*′-phenyl-4-phenylenediamine–*p*-phenylenediamine[a]	16.53 (11.26–24.26)	Clioquinol–paraben mix[b]	10.40 (3.67–29.46)
N-isopropyl-*N*′-phenyl-4-phenylenediamine–*p*-phenylenediamine[a]	10.87 (8.55–13.82)	Clioquinol–*Myroxylon pereirae*[b]	14.94 (6.96–32.05)	Neomycin–tixocortol-21-pivalate[b]	9.77 (7.14–13.37)

South Europe: Spain, Italy, and Slovenia. North/Central Europe: Finland, Lithuania, Poland, Germany, Austria, Switzerland, The Netherlands, and the United Kingdom. The most probable reasons for the association are:
[a]cross-reaction.
[b]co-sensitization.
[c]neither cross-reaction-related or exposure-related.

to baseline allergens than, for example, individuals in Italy or the United Kingdom. Additional explanations for variation in polysensitization prevalences seen between countries are variations in the factors described in the MOAHLFA index, that is, variations in proportions of atopic dermatitis, site of dermatitis and OCD in the patch tested population between countries. Many of these factors are positively or inversely related to polysensitization, as discussed below. The effects of age and sex, which certainly have an influence on polysensitization, on differences in prevalences between countries have been eliminated by using age- and sex-standardized prevalences, and by adjusting for these factors in the multifactorial analysis, respectively.

Taking these findings together, it appears that differences in polysensitization prevalences between countries are most likely explained by differences in patch tested populations, possibly patch test methodology, and the length of the baseline series (within the limit of the actual EBS set by the present analysis; see above). Therefore, studies investigating this topic have to take into account these factors when comparing their results with those of studies performed in a different department.

Similarly to what has been found in previous studies, the polysensitized population has a higher proportion of elderly individuals and females than patients with negative patch test results (1, 40). This is further supported by the present regression analysis, which shows that being male is a significant risk-lowering factor for polysensitization, and being aged > 39 years is a significant risk-increasing factor, most likely because of the effect of cumulative lifetime exposure. Furthermore, the present analysis was based on allergens of the EBS for better comparison, and the EBS may include some allergens of old relevance (such as clioquinol, primin, and neomycin) and does not rapidly adopt new allergens. Because of this, the overall yield of the EBS may be higher in the older

Table 5. The distribution of grades of positive reactions (+, ++ versus +++) in oligosensitized and polysensitized patients in the European Surveillance System on Contact Allergies database between January 2009 and December 2014, stratified for country. In this analysis, Slovenia is not included, as the departments only contributed data on reactions being positive or negative; that is, no reaction grades were reported

	Oligosensitized					Polysensitized				
Country	N(pat.)	N(rea.)	% +	% ++	% +++	N(pat.)	N(rea.)	% +	% ++	% +++
Austria	629	866	78.6	20.8	0.6	219	863	81.0	16.7	2.3
Switzerland	2849	3779	57.8	31.3	10.9	738	2791	57.0	28.3	14.8
Germany	3722	4889	66.9	26.1	7.0	821	3135	62.5	26.9	10.7
Spain	2523	3367	21.7	60.8	17.5	430	1588	21.0	57.2	21.9
Finland	526	693	26.4	67.5	6.1	112	401	39.9	54.1	6.0
Italy	4855	6184	53.2	37.9	8.9	594	2025	54.8	34.8	10.5
Lithuania	559	739	48.4	36.7	14.9	85	318	51.3	33.3	15.4
The Netherlands	2854	3871	81.4	16.5	2.1	904	3568	81.6	15.9	2.6
Poland	2273	3167	41.3	39.1	19.6	586	2160	40.7	37.8	21.5
United Kingdom	7739	10 098	59.8	36.9	3.3	1313	4727	60.1	36.1	3.9
Total	28 529	37 653	56.3	35.5	8.2	5802	21 576	58.6	31.5	9.9

N(pat.), number of patients oligosensitized/polysensitized; N(rea.), total number of reactions of any grade, that is, multiple occurrences are possible (up to two identical or different reaction grades in oligosensitized patients, up to the observed maximum of 15, and a minimum of three, in polysensitized patients).

population than in the younger population, and so will the odds of being polysensitized.

Occupational dermatitis

Occupational dermatitis is a known risk factor for polysensitization; this is most likely attributable to increased (work-related) exposure to multiple allergens (15, 41). Another risk factor for occupational dermatitis is wet work, which increases the risk of acquiring contact allergy. After age, OCD was most strongly associated with polysensitization, with a PR of 1.57. Certain countries contributed a higher proportion of OCD than others, for example Germany, Finland, and Poland, all three of which have contributions from departments specialized in occupational dermatology (33). A higher percentage of occupational aetiology of dermatitis in the polysensitized population than in the total patch tested population can be seen in all countries, except for Finland, where only 34.8% of the polysensitized group had OCD, as compared with 47.6% of all tested individuals. It is unclear whether this is simply an anomaly, but, without further investigation, there appears to be no easy explanation.

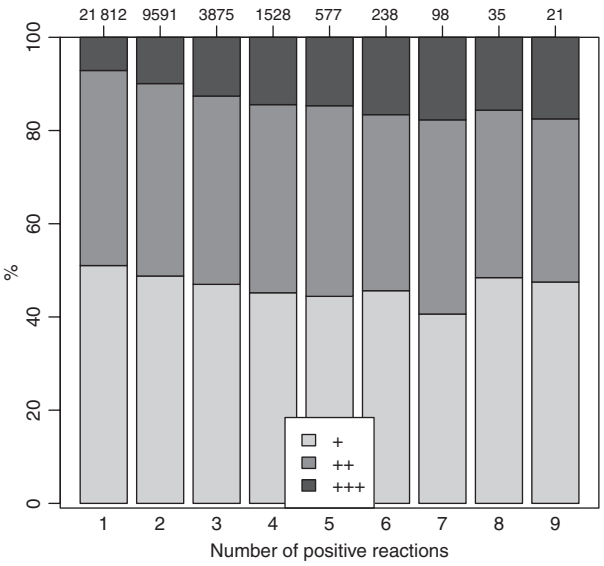

Fig. 1. The distribution of reaction grades according to the number of positive reactions to allergens of the departmental baseline series, each summed up to 100%. The number of patients having one, two and more positive reactions is indicated on the top *x*-axis. One patient each with 15 and 12 positive reactions, 3 patients with 11 positive reactions and 6 patients with 10 positive reactions are omitted for clarity.

Atopic dermatitis

In a case–control questionnaire study focusing on polysensitization, 45.1% of polysensitized individuals had a history of atopic dermatitis, as compared with 31.0% of oligosensitized individuals (40). Another study, however, found similar proportions of atopic dermatitis in polysensitized and oligosensitized populations, which we also found (42). Atopic dermatitis has been reported to be a risk factor for polysensitization (15). Whether atopic dermatitis patients are at higher or lower risk of developing contact allergy has not been completely elucidated yet; because of immunological differences, atopic dermatitis patients are less easy to sensitize in an experimental setting; however, this appears to be mitigated by

Table 6. Log-binomial regression analysis with oligosensitization and polysensitization as outcomes

Factor	%(total)	Oligosensitization PR (95%CI)	Polysensitization PR (95%CI)
Switzerland	8.7	1.00 (reference)	1.00 (reference)
Austria	1.9	1.10 (0.98–1.21)	1.71 (1.36–2.13)
Germany	13.0	0.79 (0.75–0.84)	0.64 (0.55–0.74)
Spain	7.6	0.94 (0.89–1.00)	0.74 (0.63–0.87)
Finland	1.5	0.97 (0.89–1.05)	0.84 (0.67–1.03)
Italy	14.9	0.95 (0.90–1.00)	0.59 (0.51–0.69)
Lithuania	1.6	0.99 (0.91–1.07)	0.72 (0.56–0.93)
The Netherlands	8.1	1.04 (0.98–1.10)	1.27 (1.10–1.47)
Poland	6.4	1.00 (0.94–1.07)	1.22 (1.05–1.44)
United Kingdom	26.3	0.82 (0.78–0.87)	0.54 (0.47–0.62)
Male sex	33.2	0.70 (0.68–0.71)	0.59 (0.55–0.63)
Occupational dermatitis	16.3	1.23 (1.20–1.27)	1.57 (1.45–1.69)
Atopic dermatitis	25.7	0.92 (0.90–0.95)	1.09 (1.02–1.16)
Age ≥ 40 years	59.7	1.10 (1.08–1.13)	1.71 (1.60–1.82)
Site: trunk	9.7	1.00 (reference)	1.00 (reference)
Site: hand	29.2	1.03 (0.99–1.08)	1.15 (1.03–1.29)
Site: leg	6.1	0.92 (0.87–0.97)	0.99 (0.86–1.15)
Site: face	19.2	1.03 (0.99–1.07)	1.03 (0.92–1.16)
Site: other	35.8	0.99 (0.95–1.03)	1.04 (0.93–1.16)

PR, prevalence ratio. As Slovenian departments could not contribute information on anatomical site, these were omitted from the analysis.

easier penetration of allergens, owing to an impaired skin barrier (43), and increased exposure, at least to those haptens encountered in the treatment of atopic eczema. Regarding geographical differences, both Italy and Spain (South Europe) have relatively low percentages of atopic dermatitis. Also of interest is that, in these countries, a lower percentage of atopic dermatitis is seen in the polysensitized population than in all individuals tested. The only other country with this observation is the United Kingdom; in all other countries, the opposite is found.

Sites of dermatitis

Given the findings of previous studies investigating the relationship between primary site of dermatitis and polysensitization, it is perhaps surprising that only one of the sites analysed in the present study was related to polysensitization. One possible explanation might be that only five sites were analysed, as opposed to previous studies, in which between 12 and 19 sites were investigated (15, 44). Some sites previously found to be associated with polysensitization might have been combined with other areas in the present analysis, averaging out the previously found associations. One site of dermatitis that is widely accepted to be a risk factor for polysensitization is the lower leg, because of increased exposure to topical medicaments in patients with leg stasis dermatitis and/or chronic leg ulcers (9). In the present analysis, however, the site 'legs' also included the upper legs, knees, and popliteal fold. Another reason for the lack of association between the legs and polysensitization might be the decline in frequency of contact allergy in patients suffering from chronic leg ulcer/stasis dermatitis (45). Alternatively, or additionally, it might be that polysensitized patients suffer from more generalized dermatitis, as suggested by one study, but not confirmed by later studies (44, 46). Dermatitis of the hands is a well-known risk factor for polysensitization, and this was once again confirmed in the present analysis (15, 30, 44). More interesting, perhaps, are the country-specific differences; especially in Finland and Lithuania, the proportion of patients with hand dermatitis was lower in the polysensitized group than in all patch tested patients in those countries. This might be related to the difference in the proportion of OCD between the polysensitized and oligosensitized patients in Finland (discussed above), as hand dermatitis often has an occupational cause (41).

Concomitant reactions in polysensitized individuals

Concomitant patch test reactions can be explained by various mechanisms; co-sensitization, resulting from concomitant exposure to unrelated allergens, or cross-reactivity, resulting from structural similarities between allergens. Several studies have investigated associations between allergens, most recently in a publication by the IVDK (16, 18, 30, 36). Most pairs can be explained by either co-sensitization through simultaneous exposure (for example, at least historically, cobalt and

potassium dichromate in cement), or by cross-reactivity [*p*-phenylenediamine (PPD)–*N*-isopropyl-*N*′-phenyl-4-phenylenediamine and PPD–benzocaine], or both (8, 47). Co-sensitization can result from either exposure to a product containing different non-related allergens (e.g. topicals containing fragrances or preservatives), or concomitant exposure to different products, for example in specific occupations. The two most common pairs in our analysis, in both North/Central and South Europe, were quaternium-15–formaldehyde and carba mix–thiuram mix, both with high ORs, providing further justification for counting positive reactions to these pairs as one in the analysis of polysensitization. In a previous study, 73% of patients with contact allergy to formaldehyde also reacted to quaternium-15, and, conversely, 59% of quaternium-15-positive patients also reacted to formaldehyde (48). Concomitant reactions between dithiocarbamates and thiurams is a common finding; the OR of reactions to zinc diethyldithiocarbamate being coupled with reactions to thiuram mix was 166.43 (i.e., extremely high) in a previous study (16).

Ingredients of topical medicaments were often seen in the top 10 of both regions. One study showed that a larger proportion of polysensitized patients than of oligosensitized patients suffer from dermatitis, and that the dermatitis is of longer duration (for the group without atopic dermatitis) (1). Therefore, this group might have more intense and longer exposure to several topical medicaments than oligosensitized patients. An interesting observation is that three pairs contain primin, twice together with a topical medicament, and once with mercaptobenzothiazole–mercapto mix. Primin is the main allergen of *Primula obconica* H., and primin allergy occurs mainly in florists and gardeners (49). The relationships with clioquinol, an antiseptic agent used in both topicals and eye drops, and with tixocortol-21-pivalate, a corticosteroid, are not easily explained. The two might both be present together in topicals, or used concomitantly/successively to treat dermatitis. Its relationship with mercaptobenzothiazole–mercapto mix is most likely explained by the use of rubber gloves in florists and gardeners, or by the presence of mercapto compounds in fungicides.

There are no large differences between North/Central and South Europe, and five pairs are present in the top 10 of both regions; quaternium-15–formaldehyde, carba mix–thiuram mix, tixocortol-21-pivalate–budesonide, fragrance mix I–fragrance mix II (together with HICC), and thiuram mix–mercapto mix (together with mercaptobenzothiazole). Some of the variation between the two regions might be explained by the fact that some departments do not test certain allergens in the EBS; for example, clioquinol is only tested in Spain, Lithuania, The Netherlands, Poland, and Slovenia.

It is important to note, however, that although the allergen pairs presented here are often diagnosed together in 1 patient, this does not reflect actual sensitization prevalences of the different allergens. For this, the reader is referred to previous ESSCA publications. For example, the sensitization prevalence of primin in Europe has considerably decreased in the last decade, most likely as a result of the introduction of primin-free cultivars of *P. obconica* H. in 2000 (33, 50). The same is true for clioquinol, with stable low prevalences in the last decade (< 0.5%), so its inclusion in the EBS seems no longer warranted (33, 35, 51).

Strengths of patch test reactions

In the present analysis, a positive correlation was seen between the number of positive patch test reactions and the proportion of extreme positive reactions. Similarly, one study found that individuals with strong or extreme positive patch test reactions were more likely to have additional positive reactions than individuals with weak positive reactions (52). Another study found that an extreme patch test reaction to fragrance mix I was associated with additional positive reactions (16). A possible explanation for our findings could be the often mentioned ‘angry back syndrome’, or ‘excited skin syndrome’, although the actual existence of these phenomena has been disputed, and the occurrence is thought to be rare at best (53, 54). The best explanation for more strong/extreme positive reactions in polysensitized individuals would be that polysensitization is a sign of heightened susceptibility, which is also expressed by increased reactivity. Differences between countries in the distribution of grades of positive reactions are not easily explained. As the distribution within each country was more or less comparable for oligosenitization and polysensitization, a possible explanation could be differences in how reactions were read, or differences in the patch test populations, or differences in the degree of contact sensitization, for example because of varying exposure conditions, as noted before concerning PPD (31).

Limitations

The present analysis is based on only the EBS. As the chance of observing polysensitization increases with the number of allergens tested, the oligosensitized subgroup might include polysensitized individuals, if these had been tested with a more extended baseline series. Comparison of prevalences between countries is also made more difficult by variations in the length of the tested baseline series,

as discussed above, particularly in terms of omissions. For instance, the Austrian, German and Swiss departments mostly use a baseline series that does not include, for example, the two corticosteroid markers budesonide and tixocortol-21-pivalate, as well as benzocaine and neomycin, but includes other allergens considered to be important, although these have been disregarded in the present analysis. In addition, the EBS is prone to contain old allergens, and is in need for an update. The present analysis also does not include D7 readings, possibly leading to an underestimation of single contact allergies (particularly to corticosteroids) (55), and thereby of polysensitization. Another limitation of this study is that inherent differences between departments and countries, for example the mode of reading a patch test and different patterns of referral, make interpretation of the results difficult.

Conclusion

Differences in polysensitization prevalences are seen between different countries in Europe, and while many reasons can be discussed, these differences are not easy to explain. Along with the variation in contact allergy prevalences between countries or even departments, polysensitization varies with the setting, and cannot be regarded as a fixed characteristic of patch tested patients. Known risk factors for polysensitization, such high age and occupational aetiology of dermatitis, were confirmed. Concomitant reactions to allergen pairs were evaluated for both South and North/Central Europe, showing no evidence of strong differences.

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Supporting Information

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

Table S1. The most commonly positive European baseline series allergens in polysensitized (n = 6383) versus oligosensitized (n = 31 403) patients. CI, confidence interval; stand., age-standardized and sex-standardized.

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