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# Patch test results to the Spanish baseline patch test series according to age groups: A multicentric prospective study from 2019 to 2023

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## Abstract

**Introduction:** Patch test results may be influenced by age-related factors. However, there is still discordant evidence between age and patch test results.

**Objectives:** We aim to evaluate the patch test results reflecting skin sensitisation, their relevance and association with clinical features by age group.

**Methods:** Prospective multicentric study of all patients patch tested with the Spanish baseline series in participating centres. Age groups were pre-defined as children (0- to 11-years), adolescents (12- to 18-years), young adults (19- to 30-years), middle-aged adults (31- to 65-years) and older adults (≥66-years). Occurrence of sensitisation, relevance and clinical features were compared by age group. Factors associated with skin sensitisation were investigated with multivariate logistic regression.

**Results:** A total of 13 368 patients were patch-tested. Differences in positive patch test results and relevance by age were detected with the highest proportion in middle-aged adults. Age-related trend differences were found for nickel, potassium dichromate,

For affiliations refer to page 128

caines, colophony, *Myroxylon pereirae* resin, 2-hydroxyethyl methacrylate and limonene hydroperoxide. The multivariate logistic analysis (adjusted for sex, atopic dermatitis, body location and occupational dermatitis) showed an association between the age group of 31–65 (OR: 1.41, 95% CI: 1.26–1.58) and above 66-years (OR: 1.15, 95% CI: 1.01–1.32) with a higher proportion of positive results, compared with young adults.

**Conclusions:** Positive patch test results vary according to age, with the highest occurrence in middle-aged adults. Most haptens did not present age-related differences, reinforcing the use of baseline series regardless of age.

**KEYWORDS**
age, contact dermatitis, patch test, skin sensitisation

## 1 | INTRODUCTION

Contact dermatitis arises from the skin sensitisation to external substances. Sensitisation is influenced by a myriad of factors, including genetics, skin barrier, gender, occupation and sociodemographic habits, among others.[1,2] Some of these factors are age-related, which raises the question as to whether skin sensitisation differs between age strata. Sensitisation to contact haptens may begin at an early age, but the occurrence of age-related differences in prevalence of contact dermatitis between age groups and their trends have yielded divergent results.[2–7] Thus, increasing prevalence with age,[3] similar prevalence ratios,[2] or even a decrease in prevalence in elderly patients in comparison to young adults or paediatric patients have been described.[4–7] Furthermore, the identification of specific age patterns has occurred for some haptens, including nickel[6] and other haptens.[3,8,9] Occasionally, no prevalence differences have been found between the most frequent haptens when comparing cohorts of children/adolescents and/or adults.[2,10] The analysis of patch testing features (relevance, degree of positivity) by age has seldom been evaluated, even if it has been suggested that the probability of a positive reaction being relevant is lower for children[11] as well as less intense reactions when patch testing elderly patients.[12] Furthermore, the existence of gender differences in terms of sensitisation has been suggested, with women becoming sensitised at a younger age.[13]

To date, age-related studies of skin sensitisation have mainly been limited to retrospective analyses of prevalence across patch-testing cohorts of adults, sometimes considering only specific age frames. In addition, the comparison with cases of paediatric contact dermatitis, may be difficult due to variation in terms of patch test materials and selection of haptens. Therefore, the aim of this article is to evaluate whether belonging to difference age group influences the patch test reactions to 31 of the Spanish baseline series, their relevance, and their association with clinical features.

## 2 | METHODS

A prospective multicentric study of the Spanish Contact Dermatitis Register (REIDAC) was conducted. All consecutive patients attending to the participating contact allergy units who were patch-tested with the Spanish baseline series from January 2019 to December 2023 were included. Allergens were commercially obtained from Chemotechnique (Vellinge, Sweden), allergEAZE, SmartPractice (Calgary, Canada) and TrueTest (Hillerød, Denmark) depending on the availability of each centre. Patch test performance and readings (days 2, 4 and, variably, on day 7) were performed in accordance with the ESCD guidelines.[14] Relevance was evaluated after clinical examination and history of previous exposures. Current relevance was diagnosed if sensitisation could explain or contribute to the dermatitis. Skin sensitisation was considered when a patient presented at least one positive patch test reaction. Nature of the reaction (positive and its grade, negative or indetermined), its relevance (current, past, unknown), age, gender, occupational dermatitis (source of exposure in the work area or occupational setting), atopic dermatitis, affected site(s) (face, hands, legs and others) and symptoms duration were collected. Age groups were pre-defined according to the following cut-offs: 0–11 years (children), 12–18 years (adolescents), 19–30 years (young adults), 31–65 years (middle-aged adults) and ≥66 years (older adults). Polysensitisation (PS) was defined as positivity to three or more haptens[15] of the Spanish baseline series. The diagnosis of atopic dermatitis was performed by REIDAC dermatologists according to guidelines.[16] The registry was approved by the Complejo Hospitalario Universitario Insular-Materno Infantil Ethics Committee (2017/964) and its operation complies with the Declaration of Helsinki. All patients signed informed consent to participate. REIDAC collects online data using the REDCap platform (RRID: SCR_003445).

### 2.1 | Statistics

Continuous non-normally distributed variables are reported as medians (interquartile range), and categorical variables are reported as absolute numbers (proportions). Significance was calculated with Chi-squared test or Kruskal–Wallis depending on the nature of the variable and the number of groups. Additionally, a trend test was performed to compare the occurrence of positive patch test results and relevance (current and past) for each allergen across age groups.

**TABLE 1** Demographic and clinical features of the cohort according to age group.

| Years | 0–11 years | 12–18 years | 19–30 years | 31–65 years | ≥66 years | Total | *p*-value |
|---|---|---|---|---|---|---|---|
| Total by group | 229 | 484 | 1741 | 8241 | 2673 | 13 368 | — |
| Clinical and epidemiologic factors | | | | | | | |
| Women (*n*, %) | 140 (61.1) | 306 (63.2) | 1317 (75.6) | 5811 (70.5) | 1748 (65.4) | 9322 (69.7) | <0.001 |
| Occupational (*n*, %) | 0 (0) | 5 (1.0) | 248 (14.2) | 920 (11.2) | 39 (1.5) | 1212 (9.1) | <0.001 |
| Atopic dermatitis (*n*, %) | 84 (36.7) | 235 (48.6) | 745 (42.8) | 1232 (14.9) | 130 (4.9) | 2426 (18.1) | <0.001 |
| Hands (*n*, %) | 50 (21.8) | 118 (24.4) | 751 (43.1) | 2876 (34.9) | 336 (12.6) | 4131 (30.9) | <0.001 |
| Legs (*n*, %) | 18 (7.9) | 26 (5.4) | 30 (1.7) | 322 (3.9) | 265 (9.9) | 661 (4.9) | <0.001 |
| Face (*n*, %) | 56 (24.5) | 130 (26.9) | 429 (24.6) | 1972 (23.9) | 586 (21.9) | 3173 (23.7) | 0.07 |
| PS (*n*, %) | 22 (9.6) | 27 (5.6) | 116 (6.7) | 773 (9.4) | 223 (8.3) | 1161 (8.7) | <0.001 |
| Symptoms duration, median (IQR) | 12.0 (6–24) | 12.0 (6–24) | 12.0 (6–36) | 12.0 (6–36) | 12.0 (6–36) | 12.0 (6–36) | <0.001 |
| Skin sensitisation and relevance (current and past) | | | | | | | |
| Positive patch test (1+/2++/3+++) (*n*, %) | 79 (34.5) | 151 (31.2) | 716 (41.1) | 4016 (48.7) | 1107 (41.4) | 6069 (45.4) | <0.001 |
| 1+ (*n*, %) | 27 (11.8) | 62 (12.8) | 209 (12.0) | 1072 (13.0) | 328 (12.3) | 1698 (12.7) | <0.001 |
| 2+ (*n*, %) | 27 (11.8) | 58 (12.0) | 370 (21.3) | 2061 (25.0) | 584 (21.8) | 3100 (23.2) | <0.001 |
| 3+ (*n*, %) | 25 (10.9) | 31 (6.4) | 137 (7.9) | 883 (10.7) | 195 (7.3) | 1271 (9.5) | <0.001 |
| Relevance (*n*, %) | 59 (25.8) | 118 (24.4) | 570 (32.7) | 3329 (40.4) | 861 (32.2) | 4937 (36.9) | <0.001 |

*Note*: 1+/2++/3+++ refer to the intensity of the positive reaction according to ESCD guidelines.
Abbreviations: IQR, interquartile range; PS, polysensitisation.

Both univariate and multivariate analyses of factors associated with the occurrence of positive patch test result(s) (vs. absence of positive patch test result(s)) were performed with logistic regression. For multivariate logistic regression, variables were included in the model if the *p*-value was ≤0.1 in the univariate model. Results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI). Results were considered significant when the *p*-value was 0.05 or lower. In the case of multiple comparisons (trend test) for haptens sensitisation and relevance (current and past), the *p*-value was adjusted according to the number of patch-tested haptens and considered significant if it was 0.0016 (0.05/31) or lower (Bonferroni correction). In polysensitised patients, the degree of sensitisation and the relevance were based on the maximum degree presented by the patients considering all positive haptens. Furthermore, to evaluate the relative importance of each relevance, an adaptation of the Significance-Prevalence Index Number (SPIN) was used.[17] In this case, the value was obtained with the formula (proportion of sensitisation) * (1 * current relevance + 0.66 * past relevance + 0.33 * unknown relevance) and called SPIN adapted value. All analyses were performed using STATA v.17.0 (Stata Corp. 2021. Stata Statistical Software: Release 17).

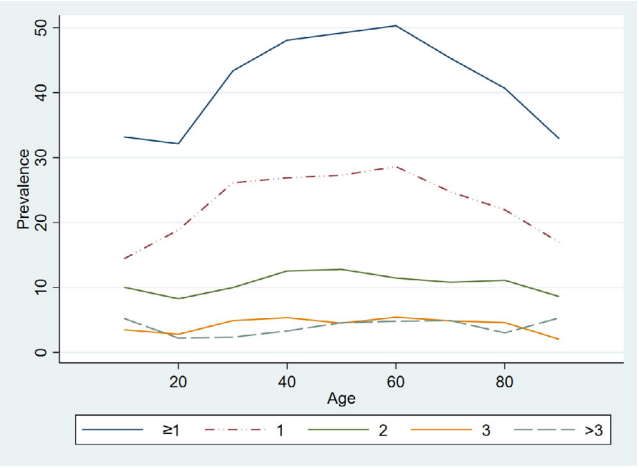


**FIGURE 1** Prevalence of skin sensitisation in the cohort according to age. Blue line indicates total proportion of skin sensitisation (positive patch test to at least one allergen) in the cohort and all other lines indicate the proportion of sensitisation by number of allergens.

## 3 | RESULTS

### 3.1 | Characteristics of the cohort

A total of 13 368 patients were patch-tested during this period (January 2019–December 2023) with the Spanish baseline series. The MOAHLFA values were: male ($n = 4046$, 30.3%), occupational dermatitis ($n = 1212$, 9.1%), atopic dermatitis ($n = 2426$, 18.1%), hand dermatitis ($n = 4131$, 30.9%), leg dermatitis ($n = 661$, 4.9%), facial dermatitis ($n = 3173$, 23.7%) and age > 40 ($n = 9066$, 67.8%). By age group, the distribution corresponded to: 0–11 years ($n = 229$; 1.71%), 12–18 years ($n = 484$; 3.62%), 19–30 years ($n = 1741$; 13.02%), 31–65 years ($n = 8241$; 61.65%) and ≥66 years ($n = 2673$; 20.0%). A total of 6069 patients (45.4%) presented with at least one positive reaction. Differences between age groups were found for most demographic

**TABLE 2** Positive patch test reactions in baseline series by age strata.

| Allergen positivity (*n*, %) | 0–11 years | 12–18 years | 19–30 years | 31–65 years | ≥66 years | *p*-value |
|---|---|---|---|---|---|---|
| Nickel sulphate | 19 (8.3) | 31 (6.4) | 338 (19.5) | 2183 (26.6) | 490 (18.4) | 0.0000* |
| Lanolin | 1 (0.4) | 1 (0.2) | 9 (0.5) | 49 (0.6) | 21 (0.8) | 0.10700 |
| Neomycin sulphate | 5 (2.2) | 0 (0.0) | 5 (0.3) | 67 (0.8) | 30 (1.1) | 0.05200 |
| Potassium dichromate | 8 (3.4) | 8 (1.7) | 18 (1.0) | 288 (3.5) | 94 (3.5) | 0.00002* |
| Caine mix | 1 (0.6) | 0 (0.0) | 3 (0.2) | 55 (0.9) | 44 (2.2) | 0.0000* |
| FM I | 7 (3.1) | 12 (2.5) | 47 (2.7) | 357 (4.3) | 121 (4.5) | 0.00190 |
| Colophonium | 5 (2.2) | 16 (3.3) | 26 (1.5) | 109 (1.3) | 27 (1.0) | 0.0003* |
| Paraben mix | 3 (1.3) | 3 (0.6) | 5 (0.3) | 23 (0.3) | 18 (0.7) | 0.8801 |
| *Myroxylon pereirae* resin | 5 (2.2) | 6 (1.2) | 34 (2.0) | 268 (3.3) | 119 (4.5) | 0.0000* |
| Cobalt chloride | 11 (4.7) | 20 (4.1) | 76 (4.4) | 407 (5.0) | 122 (4.6) | 0.6741 |
| PTBP | 3 (1.3) | 2 (0.4) | 24 (1.4) | 121 (1.5) | 41 (1.5) | 0.1809 |
| Epoxy resin | 1 (0.4) | 3 (0.6) | 10 (0.6) | 88 (1.1) | 21 (0.8) | 0.3152 |
| Carba mix | 3 (1.3) | 3 (0.6) | 22 (1.3) | 158 (1.9) | 39 (1.5) | 0.3381 |
| IPPD | 4 (1.7) | 5 (1.0) | 8 (0.5) | 60 (0.7) | 25 (0.9) | 0.9351 |
| MCI/MI | 6 (3.1) | 15 (3.7) | 50 (3.5) | 330 (4.8) | 78 (3.6) | 0.6026 |
| Quaternium-15 | 3 (1.3) | 4 (0.8) | 12 (0.7) | 60 (0.7) | 27 (1.0) | 0.6343 |
| PPD | 7 (3.0) | 11 (2.3) | 47 (2.7) | 331 (4.0) | 80 (3.0) | 0.3355 |
| Formaldehyde | 5 (2.4) | 15 (3.5) | 40 (2.6) | 166 (2.3) | 54 (2.4) | 0.3375 |
| Mercapto mix | 0 (0.0) | 1 (0.2) | 6 (0.3) | 35 (0.4) | 4 (0.2) | 0.7854 |
| Thiuram mix | 1 (0.4) | 3 (0.6) | 15 (0.9) | 152 (1.9) | 30 (1.1) | 0.2064 |
| Diazolidinyl urea | 2 (0.9) | 5 (1.0) | 6 (0.3) | 21 (0.3) | 23 (0.9) | 0.4871 |
| Tixocortol pivalate | 1 (0.4) | 1 (0.2) | 4 (0.2) | 20 (0.2) | 13 (0.5) | 0.2143 |
| Imidazolidinyl urea | 1 (0.4) | 4 (0.8) | 9 (0.5) | 30 (0.4) | 14 (0.5) | 0.6426 |
| Budesonide | 3 (1.3) | 2 (0.4) | 6 (0.3) | 57 (0.7) | 30 (1.1) | 0.0360 |
| MBT | 0 (0.0) | 1 (0.2) | 7 (0.4) | 31 (0.4) | 4 (0.2) | 0.6142 |
| MI | 14 (6.6) | 34 (7.7) | 88 (5.6) | 532 (7.1) | 140 (5.9) | 0.7242 |
| FM II | 6 (2.8) | 14 (3.2) | 27 (1.7) | 247 (3.3) | 95 (4.0) | 0.0050 |
| 2-HEMA | 3 (1.8) | 5 (1.5) | 84 (7.3) | 262 (4.8) | 25 (1.4) | 0.0006* |
| Textile dye mix | 4 (2.4) | 9 (2.6) | 30 (2.6) | 178 (3.3) | 53 (3.1) | 0.3519 |
| Linalool hydroperoxide | 19 (10.9) | 18 (5.2) | 57 (4.9) | 272 (4.9) | 92 (5.2) | 0.0770 |
| Limonene hydroperoxide | 17 (9.7) | 16 (4.7) | 67 (5.7) | 213 (3.8) | 61 (3.4) | 0.0000* |

Abbreviations: 2-HEMA, 2-hydroxyethyl methacrylate; FM I, fragrance mix I; FMII, fragrance mix II; IPPD, *N*-isopropyl-*N*′-phenylenediamine; MBT, 2-mercaptobenzothiazole; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MI, methylisothiazolinone; PPD, *p*-phenylenediamine; PTBP, para-tertiary-butylphenol-formaldehyde resin.

*Statistically significant differences.

and clinical variables. Women and the occurrence of occupational dermatitis were more frequent in adult age groups. In children and adolescent age groups, there was less hand involvement. Furthermore, adolescent patients had the highest prevalence of atopic dermatitis and face involvement. Both the highest frequency of sensitisation and relevance of reactions were seen in 31- to 65-year-old adults (48.7% and 40.4%, respectively). In contrast, the group with the highest percentage of extreme positive (3+) reactions corresponded to children (10.9%). Table 1 presents the detailed demographic and clinical features of patch test results of the cohort. Figure 1 shows the occurrence of skin sensitisation according to both age and number of haptens.

## 3.2 | Allergen sensitisation and relevance analysis by age group

The study of the 31 haptens composing the baseline series by age group revealed trend differences in sensitisation for 7, including nickel, potassium dichromate, caines, colophony, *Myroxylon pereirae* resin, 2-hydroxyethyl methacrylate (2-HEMA) and limonene hydroperoxide. Among these haptens, nickel, caines, *Myroxylon pereirae* resin and 2-HEMA frequency of sensitisation was higher in adult age groups, while limonene hydroperoxide and colophony were very frequent in the paediatric and adolescent groups, respectively. In regard to potassium dichromate, both paediatric and ≥66-year-old adults had

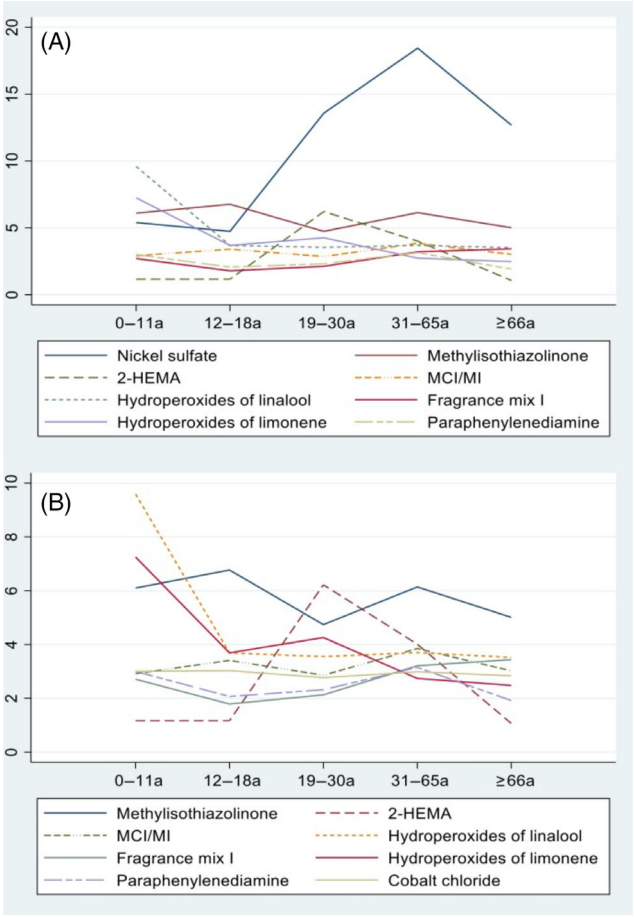


**FIGURE 2** Main allergens according to their SPIN adapted values. (A) Main allergens according to their SPIN-adapted value by age group. (B) Main allergens (excluding nickel) according to their SPIN adapted value by age group.

a higher burden of positivity. Table 2 shows the exact distribution of allergen positivity by age groups. Among the haptens with significant trend differences, nickel, 2-HEMA and limonene hydroperoxide had specific patterns of distribution with age. Nickel had a plateau at middle-aged adulthood, while 2-HEMA at early adulthood. In contrast, limonene hydroperoxide had a descending pattern with its peak in children. Figure S1 shows the aforementioned patterns for these haptens.

Relevance (including current and past relevance) differences were found for eight haptens, including nickel, potassium dichromate, caines, colophony, *Myroxylon pereirae* resin, diazolidinyl urea, 2-HEMA and linalool hydroperoxide. Most haptens with trend differences in relevance also associated differences in frequency of skin sensitisation pattern by age group. Furthermore, diazolidinyl urea relevance had a pattern involving infants/adolescents or ≥66-year-old adults, while linalool hydroperoxide relevance was higher in the paediatric and adolescent groups. Table S1 shows the exact distribution of relevance by age groups.

The most clinically important haptens, considering the SPIN adapted values, were nickel sulphate, linalool hydroperoxide and methylisothiazolinone. However, their SPIN-adapted value varied considerably depending on age spectra, with nickel reaching its highest values in adults (of any group) and linalool hydroperoxide in children. Furthermore, limonene hydroperoxide was also among the most clinically relevant in children, adolescents and young adults. Other haptens presenting with high SPIN adapted value in different age strata include methylchloroisothiazolinone, methylchloroisothiazolinone/methylisothiazolinone, 2-HEMA and both fragrance mix I and II. Figure 2 represents the main haptens in the cohort according to their SPIN-adapted value by age group. The performance of all haptens by age group and SPIN-adapted value is represented in Figure 3 and Tables S1 and S2.

### 3.3 | Factors associated with positive patch test results

Patients sensitised to at least one baseline series allergen were more frequently women, and presented with a higher burden of occupational disease and hand dermatitis. In our cohort, less atopic dermatitis and leg involvement were found among sensitised individuals. No differences could be found for symptoms duration. In terms of the clinical features associated with skin sensitisation in the multivariate logistic analysis, different degrees of association with positive patch test results and age, when considering all the variables of the multivariate model (age, body location, atopic dermatitis, occupational dermatitis and sex), were found. In comparison to 19- to 30-year-old patients, both 31 to 65 (OR: 1.41, 95% CI: 1.26–1.58) and ≥66-year-old age groups (OR: 1.15, 95% CI: 1.01–1.32) were associated with a higher proportion of positive patch-test results in the multivariate analysis. In contrast, 12- to 18-year-old patients were associated with a reduced proportion of positive patch-test results (OR: 0.79, 95% CI: 0.63–0.98) and no significant differences could be found for 0- to 11-year-old patients (OR: 0.88, 95% CI: 0.66–1.19). In terms of other variables of the model (body location, atopic dermatitis, occupational dermatitis and sex), male sex (OR: 0.55, 95% CI: 0.50–0.59), atopic dermatitis (OR: 0.87, 95% CI: 0.79–0.96) and facial (vs. hands) dermatitis (OR: 0.86, 95% CI: 0.78–0.96), were associated with a reduced proportion of positive patch-test results. Furthermore, occupational dermatitis was associated with a higher proportion of positive patch-test results (OR: 2.14, 95% CI: 1.87–2.45). All the results of the univariate and multivariate logistic analysis can be found in Table 3.

## 4 | DISCUSSION

In successively patch-tested patients with the Spanish baseline series in different contact allergy units, differences in skin sensitisation prevalence among age groups were found, with the lowest prevalence found in adolescents and children, and the highest burden of sensitisation found in middle-aged adults. Both young and older adults had similar proportions of positive patch tests and intensity of the reactions. Furthermore, the multivariate logistic analysis has identified


**FIGURE 3** Bump chart showing baseline allergens rank according to the SPIN adapted value. 2-HEMA, 2-hydroxyethyl methacrylate; FM I, fragrance mix I; FMII, fragrance mix II; IPPD, *N*-isopropyl-*N*′-phenylenediamine; MBT, 2-mercaptobenzothiazole; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MI, methylisothiazolinone; PPD, *p*-phenylenediamine; PTBP, para-tertiary-butylphenol-formaldehyde resin.

different age groups that are associated with positive patch test results. In this regard, age between 31- and 65-years (vs. 19- to 30-years) has been associated with a higher proportion of sensitisation cases. To a lesser extent, the same finding was evidenced for age above 66-years (vs. 19- to 30-years). In contrast, age between 12 and 18 years (vs. 19–30 years) was associated with a lesser occurrence of skin sensitisation. Therefore, these results may reinforce the progressive increase in prevalence of skin sensitisation with age, with a plateau in middle-aged adulthood and a subsequent reduction in older adults. An increased cumulative lifetime exposure of haptens as well as different exposure patterns between age groups could explain the increase from adolescence to adulthood. In fact, it is frequent to detect skin sensitisation in adults to a hapten to which the patient has been exposed intermittently thorough life, without any previous reaction.[18] In addition, this is complemented by both occupational factors and sociodemographic habits that may be altered over the course of adulthood. In this regard, cosmetic exposure to facial[19] and nail cosmetics, use of certain topical drugs and medical devices in relation to comorbidity,[4,20] increase use of over-the-counter emollients with fragrances,[21] and exposure to allergens in the occupational site[22] have been described to present principally, but not exclusively, an adulthood onset. In contrast, in the ≥66-year-old group, sensitisation and the degree of intensity of patch test reactions, were similar to young adults but lower than middle-aged adults. These results may show that skin sensitisation does not constantly increase over time but tends to decrease in older patients. The occurrence of this decline in skin sensitisation with advancing age may be explained by immunosenescence[23] in the context of age-related alterations in immune function that may result in a declining susceptibility of sensitisation.[3] However, our results show a still high burden of patch test positivity, indicating that this group is indeed susceptible to skin sensitisation despite the plausible alterations of T-cell-mediated immunity. The still important degree of sensitisation may also be explained by barrier impairment with age or the loss of "low-zone tolerance" phenomenon, by which there is an age-related reduction of Treg-cell responses.[24,25] This is also supported by previous studies indicating that contact

**TABLE 3** Univariate and multivariate analysis for factors associated with skin sensitisation.

| | Positive patch test | | Univariate model | | | Multivariate model | | |
|---|---|---|---|---|---|---|---|---|
| Variable | No | Yes | OR | 95% CI | *p*-value | OR | 95% CI | *p*-value |
| Sex | | | | | | | | |
| Women (%) | 64.4 | 76.3 | Ref | — | | Ref | — | |
| Men (%) | 35.6 | 23.7 | 0.56 | 0.52–0.61 | <0.0001 | 0.55 | 0.50–0.59 | <0.0001 |
| Occupational | | | | | | | | |
| No (%) | 93.6 | 86.8 | Ref | — | | Ref | — | |
| Yes (%) | 6.4 | 13.2 | 2.23 | 1.98–2.53 | <0.0001 | 2.14 | 1.87–2.45 | 0.0014 |
| Atopic dermatitis | | | | | | | | |
| No (%) | 80.0 | 83.7 | Ref | — | | Ref | — | |
| Yes (%) | 20.0 | 16.3 | 0.78 | 0.71–0.85 | <0.0001 | 0.87 | 0.79–0.96 | 0.005 |
| Location | | | | | | | | |
| Hands (%) | 29.0 | 33.6 | Ref | — | | Ref | — | |
| Legs (%) | 5.3 | 4.6 | 0.74 | 0.63–0.88 | 0.0004 | 1.00 | 0.84–1.20 | 0.985 |
| Face (%) | 24.7 | 22.9 | 0.80 | 0.73–0.88 | <0.0001 | 0.86 | 0.78–0.96 | 0.005 |
| Others (%) | 41.0 | 38.9 | 0.82 | 0.76–0.89 | <0.0001 | 0.99 | 0.91–1.09 | 0.896 |
| Age group | | | | | | | | |
| 0–11 years (%) | 2.1 | 1.3 | 0.75 | 0.56–0.99 | 0.0480 | 0.88 | 0.66–1.19 | 0.4180 |
| 12–18 years (%) | 4.6 | 2.5 | 0.65 | 0.52–0.80 | <0.0001 | 0.79 | 0.63–0.98 | 0.0340 |
| 19–30 years (%) | 14.0 | 11.8 | Ref | — | | Ref | — | |
| 31–65 years (%) | 57.9 | 66.2 | 1.36 | 1.23–1.51 | <0.0001 | 1.41 | 1.26–1.58 | <0.0001 |
| ≥66 years (%) | 21.4 | 18.2 | 1.01 | 0.90–1.14 | 0.850 | 1.15 | 1.01–1.32 | 0.0480 |
| Symptoms duration (months) | 12 (6–36) | 12 (6–36) | 1.00 | 1.00–1.00 | 0.341 | | | |

Abbreviations: CI, confidence interval; OR, odds-ratio; Ref, reference.

dermatitis in the elderly may be associated with more fragrance and preservative allergy than other age groups[4] and to PS.[26] In terms of PS, which is considered a marker of susceptibility for skin sensitisation as well as of high allergen exposure,[27,28] children, middle-aged adults and older adults presented the highest PS prevalence, possibly suggesting factors or habits associated with an increased exposure to allergens in these groups. In contrast, age between 12 and 18 years (vs. 19–30 years) was associated with a lesser probability of skin sensitisation. It is important to note that children and adolescents accounted for a small fraction of the cohort (e.g., 1.7% and 3.6%, respectively). It is unclear whether this is a reflection of lower susceptibility to sensitisation or less referral to contact allergy units by paediatricians and general dermatologists.

Apart from age, the evaluation of clinical characteristics (sex, occupational dermatitis, atopic dermatitis and location) related to skin sensitisation has identified several factors that may be associated. In terms of gender, male sex was associated with less occurrence of positive patch-test results, which is in line with previous research suggesting female sex as a risk factor for allergic contact dermatitis, particularly in the paediatric age.[29–31] Despite sensitisation being described to occur earlier in women,[13] sensitisation occurrence was more frequent in women of any age group, with lower proportions in paediatric and adolescent age groups. Atopic dermatitis was also associated with a lower occurrence of skin sensitisation. To date, it is unclear whether atopic dermatitis influences the risk for developing contact allergy, with several studies showing discordant findings. These results reinforce previous observations, including a systematic review, that do not suggest atopic dermatitis as a risk factor for skin sensitisation.[32] There is rationale for the occupational nature of a dermatitis as a risk factor for skin sensitisation due to the contact with materials that contain allergens within the workplace.[33] In terms of body location(s), face (vs. hands) was associated with lower skin sensitisation, which is possibly in accordance with studies suggesting hand dermatitis as a risk factor of PS[26,34] and reflects the high interaction of hands with many allergens in comparison to other body areas.[26]

The comparison of the prevalence of sensitisation for each allergen by age group has indicated that there are no significant age-related trend differences for the majority of baseline haptens (e.g., in 24/31, 77.4%). Despite possible lifespan differences in exposures, and subsequent contact with haptens, patch test positive results for most haptens did not significantly vary according to age group, suggesting both a widespread presence of some haptens and their potential to sensitise individuals with different skin characteristics (e.g., thinner stratum corneum in infants,[35] impaired skin barrier at early or older ages,[36] immunosenescent immune system in older adults,[23] etc.) This observation also reinforces the importance of baseline series haptens

for any patient with the suspicion of allergic contact dermatitis regardless of age. However, the positivity to seven haptens (or hapten mixes), including nickel, potassium dichromate, caine mix, colophonium, *Myroxylon pereirae* resin, 2-HEMA and limonene hydroperoxide, presented significant trend prevalence variation throughout different age groups. Occasionally, age-related patterns of sensitisation have been described for some haptens (e.g., paraphenylenediamine, nickel), which have been mostly attributed to specific patterns of exposure.[6–8]

Among these seven haptens, four-including nickel, 2-HEMA, *Myroxylon pereirae* resin and caine mix-presented a significant trend to increase in adult groups. There is rationale for the age-pattern of sensitisation observed in the case of 2-HEMA since sensitisation to acrylates occurs due to the (occupational) exposure in nail products used from early adulthood on.[37] In this study, 2-HEMA sensitisation proportion had its plateau during early adulthood, reinforcing the existence of this early exposure (Figure S1). In terms of caine haptens, previous investigations have proposed exposure to topical drugs (e.g., pain relief creams and haemorrhoid treatments) as an important source of sensitisation.[38] These creams are mostly destined for adults, taking into account drug data sheets. Nickel was the most common hapten for all adult age groups despite current nickel regulations. Despite lower skin sensitisation prevalence has been previously detected in older adults,[6] prevalence of nickel contact allergy in adults has been described as higher than in the paediatric population.[39] It is not known whether the differences observed between age groups could be a result of nickel regulations or are in line with age-related exposures and variations in other clinical–epidemiological factors. In this study, nickel presented its peak during middle-adulthood and presented a subsequent descent in older adults (Figure S1). In regard to *Myroxylon pereirae* resin, its sensitisation has also been described predominantly in middle-aged adults and also associated with Fragrance mix I.[40] In line with this, contact allergy to fragrances has been described as being more common in older adults in previous studies.[40] In the present study, middle-aged and older adults presented the highest proportions of fragrance mix I and II sensitisation, but no trend differences by age group for fragrance mix I or II could be found. In terms of relevance for nickel, 2-HEMA, *Myroxylon pereirae* resin and caine mix, the SPIN adapted value denoted increased clinical relevance in adult age groups.

In relation to children and adolescent-specific haptens, there are two haptens with clear-cut importance: limonene hydroperoxide and colophonium. In our cohort, sensitisation was significantly more common in the paediatric and adolescent groups, highlighting an early pattern of exposure to these haptens, with its peak among children and then a descending pattern (Figure S1). Moreover, linalool hydroperoxide was more common in children and adolescents—without reaching significance—and its relevance was higher in comparison to adults. Both hydroperoxides in paediatric allergic contact dermatitis have proved to be frequent and relevant haptens in paediatric series,[41–43] and our results reinforce the burden of sensitisation associated to limonene hydroperoxide in the paediatric group. Fragrances are important haptens in the paediatric population due to their presence in a wide spectrum of products, including personal care products, cosmetics—even commercialised as toys—, essential oils and diffusers, among others.[41] Despite fragrance mix (I and II) has been suggested as recommended patch-testing allergens for paediatric patients,[44,45] these results also enhance limonene (and linalool, to a lesser extent) as important haptens to test in this group. In regard to colophonium, the biggest sensitisation frequency was found among adolescents. Previous studies have shown sensitisation proportions between 1.0% and 2.04% in paediatric series.[46–48] However, an Italian study revealed an increased risk of sensitisation among students, with a similar sensitisation proportion.[49] These authors proposed as sources of sensitisation the use of materials such as rubbers, glues and adhesives during schooling. Finally, potassium dichromate had an irregular distribution of sensitisation proportion with increased frequency in different age groups, particularly in children and adults (31–65 and ≥66 years). This is consistent with the multiple chromium exposure sources, including leather goods, tattoo ink, cosmetics and implants.[50] In terms of relevance, the SPIN-adapted value for both hydroperoxides and colophonium was higher among children and adolescents. For other relevant haptens, including methylisothiazolinone or both fragrance mixes, relevance was similar to adult groups.

## 5 | LIMITATIONS AND STRENGTHS

This research is part of a multicentre REIDAC study with a large sample of consecutive patients, which could be considered representative of the Spanish population. Patch testing has been performed in different Contact Dermatitis units, which may result in heterogeneity in the interpretation of patch test reactions. An inherent limitation is the difficulty in differentiating age-related inherent susceptibility to sensitisation from age-related patterns of exposure and possible age-dependent patterns for consultation, as mentioned before. Furthermore, the use of the adapted SPIN value is an approximation to categorise the relevance of allergens but has not been validated.

## 6 | CONCLUSION

Skin sensitisation and relevance of positive patch tests vary according to age. Patients who belong to age periods of 30–65 or ≥66 years may associate an increased probability of skin sensitisation to baseline haptens, possibly due to increased cumulative lifetime exposure plus sociodemographic habits. No age-related differences in skin sensitisation tendency and relevance were detected for most haptens, reinforcing the importance of baseline series in any patient with suspected contact dermatitis regardless of age. However, some haptens showed an age-related pattern of sensitisation either in adults (nickel sulphate, 2-HEMA, *Myroxylon pereirae* resin and caines) or children/adolescents (colophonium, limonene hydroperoxide).

### AUTHOR CONTRIBUTIONS

**David Pesqué:** Writing – original draft; writing – review and editing; investigation; methodology; data curation. **Nidia Planella-Fontanillas:**

Writing – review and editing; methodology; data curation. **Leopoldo Borrego:** Conceptualization; investigation; methodology; writing – review and editing; data curation. **Tatiana Sanz-Sánchez:** Writing – review and editing; investigation; conceptualization; methodology; data curation. **Violeta Zaragoza-Ninet:** Writing – review and editing; methodology; data curation. **Esther Serra-Baldrich:** Writing – review and editing; methodology; data curation. **Francisco Javier Miquel-Miquel:** Writing – review and editing; methodology; data curation. **Juan Francisco Silvestre-Salvador:** Writing – review and editing; methodology; data curation. **Susana Córdoba-Guijarro:** Writing – review and editing; methodology; data curation. **Araceli Sánchez-Gilo:** Writing – review and editing; methodology; data curation. **Pedro Mercader-García:** Conceptualization; investigation; writing – review and editing; methodology; data curation. **Francisco José Navarro-Triviño:** Writing – review and editing; methodology; data curation. **Francisco Javier Ortiz-de-Frutos:** Conceptualization; investigation; writing – review and editing; methodology; data curation. **Fátima Tous-Romero:** Writing – review and editing; methodology; data curation. **Mercedes Rodríguez-Serna:** Writing – review and editing; methodology; data curation. **Gemma Melé-Ninot:** Writing – review and editing; methodology; data curation. **Cristina Barrabés-Torrella:** Writing – review and editing; methodology; data curation. **Inmaculada Ruiz-González:** Methodology; writing – review and editing; data curation. **María Antonia Pastor-Nieto:** Methodology; writing – review and editing; data curation. **José Manuel Carrascosa-Carrillo:** Methodology; writing – review and editing; data curation. **Enrique Gómez-de-la-Fuente:** Methodology; writing – review and editing; data curation. **Paloma Sánchez-Pedreño-Guillén:** Methodology; writing – review and editing; data curation. **Javier Sánchez-Pérez:** Methodology; writing – review and editing; data curation. **José Juan Pereyra-Rodríguez:** Methodology; writing – review and editing; data curation. **María Elena Gatica-Ortega:** Methodology; writing – review and editing; data curation. **Ricardo González-Pérez:** Methodology; writing – review and editing; data curation. **Ramon Maria Pujol:** Methodology; writing – review and editing; data curation. **Miguel Ángel Gallego Descalzo:** Methodology; writing – review and editing; data curation; software; investigation; conceptualization; formal analysis. **Ignacio García-Doval:** Project administration; methodology; conceptualization; investigation; formal analysis; writing – review and editing. **Ana María Giménez-Arnau:** Writing – review and editing; methodology; data curation.

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## CONFLICT OF INTEREST STATEMENT

DP has received research fundings from LEO Foundation and has received funding for congress attendance from Novartis and Almirall, outside the submitted work. FJMM received fees as speaker from Lilly, Leo-Pharma, Novartis, Abbvie, Amgen, Pfizer and Janssen, has been Principal Investigator in clinical trials sponsored by Amgen, Novartis, Abbvie, and Almirall and has participated in Advisory Boards organised by Sanofi, Novartis, Leo-Pharma, Pfizer, Almirall, and Abbvie, outside the submitted work. PMG reports lectures and advisory boards from Sanofi, Leo Pharma, Lilly, Almirall and AbbVie outside of the scope of the submitted work. GMN has been Medical Advisor for Abbvie, Leo Pharma, Lilly, Sanofi, and Novartis and has participated in educational activities for Almirall, Avène, Abbvie, Laboratorio Reig Jofre, Leo Pharma, Lilly, Meda, Novartis, Sanofi, and Uriage, outside the submitted work. IGD has received funding for congress attendance from Abbvie, MSD, Pfizer and Sanofi, outside the submitted work. AGA is or recently was a speaker and/or advisor for and/or has received research funding from Almirall, Amgen, AstraZeneca, Avene, Celldex, Escient Pharmaceuticals, Genentech, GSK, Instituto Carlos III-FEDER, Leo Pharma, Menarini, Mitsubishi Tanabe Pharma, Novartis, Sanofi-Regeneron, Servier, Thermo Fisher Scientific, Uriach Pharma, Noucor, outside the submitted work.

## DATA AVAILABILITY STATEMENT

Data cannot be shared due to ownership restrictions.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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