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Original Article

Minimal Wheal Reactions on Skin Prick Testing Predict Future Aeroallergen Sensitization in Children: A Longitudinal Study

Ezgi Topyıldız, Handan Duman Şenol, Ayşe Pakel, Mehmet Geyik, Figen Gülen, Esen Demir

Ege University Faculty of Medicine, Department of Pediatric Allergy and Immunology, İzmir, Türkiye

ABSTRACT

Aim: Skin prick testing (SPT) provides a rapid, inexpensive, and reliable means of confirming IgE-mediated sensitization in the context of clinical history. This study aimed to evaluate whether baseline SPT reactivity, particularly minimal reactions, predicts the development of new aeroallergen sensitizations during long-term follow-up.

Materials and Methods: In this longitudinal observational study, 121 children who underwent repeat SPT after an interval of at least three years were included. The patients were stratified into four groups based on their baseline maximum wheal diameter and subcutaneous immunotherapy (SCIT) status: Group 1 (0 mm), Group 2 (1-2 mm), Group 3 (≥3 mm), and Group 4 (≥3 mm with SCIT). The primary outcome was new sensitization, defined as a wheal diameter ≥3 mm to an allergen which was previously negative.

Results: A total of 121 patients were included in this study. The rates of new sensitization were significantly higher in Groups 2, 3, and 4 compared with Group 1 ($p<0.001$). New house dust mite sensitization was strikingly more frequent in Group 2 (53.3%) than in all other groups ($p<0.001$). An increase in wheal diameter to the same allergen was most prominent in Group 2 (66.7%). Sensitization to pollens and cat epithelium increased significantly after 10 years of age ($p<0.05$). A history of coronavirus disease-2019 was associated with new sensitizations (odds ratio: 2.97, $p=0.034$).

Conclusion: Minimal SPT reactions (1-2 mm) in symptomatic children are clinically relevant and predict a high risk of developing frank aeroallergen sensitization during follow-up. Repeat SPT should be considered in this population in order to guide timely interventions.

Keywords: Aeroallergen sensitization, skin prick test, minimal wheal reaction, house dust mite, children

Introduction

Allergic rhinitis and asthma are among the most common chronic allergic diseases in childhood, and aeroallergen sensitization plays a key role in their pathogenesis (1,2). Identifying sensitization patterns is essential for diagnosis, environmental control, follow-up, and the selection of candidates for allergen immunotherapy. Skin prick testing (SPT) is widely used as a rapid, inexpensive, and reliable method for detecting IgE-mediated sensitizations (1,3).

However, aeroallergen sensitization in childhood is dynamic. Sensitization profiles evolve under the influence of age, genetics, environmental exposures, and immune maturation (4,5). Longitudinal studies have shown that new sensitizations frequently develop during follow-up,

Corresponding Author
Ezgi Topyıldız, MD, Ege University Faculty of Medicine, Department of Pediatric Allergy and Immunology, İzmir, Türkiye
E-mail: ezgitopyildiz@gmail.com **ORCID:** orcid.org/0000-0002-9260-8157
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with a broadening allergen spectrum and a shift toward outdoor pollens and pet allergens in later childhood (4-8). Environmental factors, including passive smoke, indoor dampness/mold, pet ownership, and cockroach exposure, are linked to allergic sensitization and respiratory morbidity (9-11), yet their role in driving new sensitizations among children with minimal baseline reactivity remains unclear (12).

Although SPT is essential in pediatric allergy practice, indications and optimal timing for repeat testing are poorly defined. The conventional ≥3 mm positivity threshold may miss early or evolving sensitizations in children (13). Repeat testing is often considered for persistent symptoms, changing clinical findings, or borderline initial results (6). The clinical significance of minimal wheal reactions (1-2 mm) which fall below the standard cutoff is particularly uncertain.

Therefore, this study aimed to evaluate the prognostic significance of baseline SPT reactivity, especially minimal (1-2 mm) reactions, on subsequent sensitization patterns in children undergoing repeat SPT after ≥3 years. We also sought to identify any clinical or environmental factors associated with new sensitization developments.

Materials and Methods

Study Design and Patients

This longitudinal observational study included children with a history of allergic disease who were followed up at the pediatric allergy outpatient clinic of a university hospital. Eligible participants had undergone aeroallergen SPT at baseline and were reevaluated with a repeat SPT after an interval of at least 3 years. Exclusion criteria were as follows: (1) the use of antihistamines or systemic corticosteroids within 7 days prior to the SPT; (2) the presence of dermatographism or extensive eczema precluding skin testing; (3) incomplete clinical or laboratory data.

A total of 121 patients were included in this study. According to their baseline skin test reactivity and immunotherapy status, the patients were classified into four groups:

Group 1: Children without sensitization (all allergens with wheal diameter=0 mm; n=30).

Group 2: Children with minimal wheal reactions (wheal diameter of 1-2 mm to at least one allergen, but none ≥3 mm); n=30.

Group 3: Children with established sensitization (wheal diameter of ≥3 mm to at least one allergen); n=30.

Group 4: Children with established sensitization (≥3 mm) who were receiving subcutaneous immunotherapy (SCIT) during follow-up (Note: baseline SPT was performed prior to SCIT initiation); n=31.

Data Collection

Demographic, clinical, environmental, and laboratory data were recorded via a structured case report form. The variables which were collected included age, sex, birth characteristics, family history of atopy (≥1 first-degree relative with physician-diagnosed allergic rhinitis, asthma, or atopic dermatitis), sibling status, diagnoses, body mass index (BMI) z-scores, total and specific IgE, and absolute eosinophil count. The environmental/lifestyle variables included household smoking, open kitchen, residence location (urban/rural), pet exposure, cockroach exposure, indoor dampness/mold, indoor plants, vegetable intake, a history of the coronavirus disease-2019 (COVID-19), and junk food consumption frequency. A history of COVID-19 was recorded based on a parental report and referred to those infections which had occurred between the first and second SPT assessments. Laboratory confirmation was not consistently available. The presence of new sensitizations during follow-up was also recorded.

Skin Prick Testing

Skin prick testing was performed using standardized extracts (ALLERGO®) per the European Academy of Allergy and Clinical Immunology (EAACI) recommendations (14). The volar forearm was cleaned with alcohol, and allergens were applied with negative (saline) and positive (10 mg/mL histamine) controls. A histamine wheal ≥3 mm was required for validity. Reactions were evaluated after 20 minutes, and wheal diameters were measured at their widest point and also perpendicular to it, with the mean of these two measurements recorded in millimeters. The aeroallergen panel included Dermatophagoides farinae, Dermatophagoides pteronyssinus, cat epithelium, weed mix, grass mix preparations, mugwort, ribwort plantain, nettle, meadow fescue/timothy-type grass components, olive tree, ash tree, poplar tree, tree mix, Alternaria, and Aspergillus. The same aeroallergen panel was used for each patient at both their baseline and follow-up SPT assessments.

Outcomes

The primary outcome was a new sensitization (wheal ≥3 mm to an allergen with a baseline <3 mm). Secondary outcomes included increase/decrease in wheal diameter (≥2 mm change) and the loss of prior sensitization (≥3

mm falling to <3 mm). Factors associated with new sensitizations were also evaluated.

Ethical Considerations

This study was approved by the Ege University Medical Research Ethics Committee (approval no.: 23-7.1T/42, date: 27.07.2023) and conducted per the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of the participants, and assent was obtained from the children when appropriate.

Statistical Analysis

Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Normality was assessed using the Shapiro-Wilk test and histograms. Normally distributed variables are presented as mean±standard deviation and were compared using one-way analysis of variance (ANOVA), with Tukey honestly significant difference tests for post-hoc pairwise comparisons. Non-normally distributed variables are presented as median (minimum-maximum) and were compared using the Kruskal-Wallis test; when the overall comparison was statistically significant, exploratory pairwise comparisons were performed using the Mann-Whitney U test. Categorical variables are presented as numbers and percentages and were compared using the chi-square test or Fisher's exact test, as appropriate; when the overall comparison was statistically significant, exploratory pairwise comparisons of proportions were performed. Univariable logistic regression was used to explore predictors of new sensitization, with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A limited multivariable logistic regression model was constructed in order to assess whether the association between COVID-19 history and new sensitizations remained independent after adjustments for age at first SPT, sex, and baseline aeroallergen-specific IgE. Subgroup analysis was conducted in order to examine predictors of wheal increase in Group 2. A p value of <0.05 was considered statistically significant.

Results

A total of 121 children were included in this study. Based on their baseline skin prick test reactivity and subcutaneous immunotherapy status, the patients were allocated into four groups: Group 1 (n=30), Group 2 (n=30), Group 3 (n=30), and Group 4 (n=31). The mean age at the first SPT was 99.4±33.6 months, the mean age at the second SPT was 144.8±34.0 months, and the mean interval between the two tests was 54.9±14.0 months. At baseline, 24 patients (19.8%)

Table I. Baseline demographic, clinical, and laboratory characteristics of the study groups

Variable	Group 1 n=30	Group 2 n=30	Group 3 n=30	Group 4 n=31	p value
Age at first SPT (months) mean±SD	89.6±36.0	104.0±46.0	101.2±33.8	106.6±32.1	0.423
Age at second SPT (months) mean±SD	136.6±33.3	157.6±51.3	160.8±33.2	159.7±31.3	0.058
Interval between tests (months) median (min-max)	43 (36-69)	54.5 (36-101)	57 (36-96)	54 (36-63)	0.057
Male sex, n (%)	17 (56.7)	18 (60)	23 (76.7)	25 (80.6)	0.110
Family history of atopy, n (%)	14 (46.6)	16 (53.3)	16 (53.3)	14 (48.3)	0.935
Cesarean delivery, n (%)	13 (43.3)	12 (40)	13 (43.3)	13 (41.9)	1.000
Presence of siblings, n (%)	15 (50.0)	23 (76.6)	18 (60)	22 (70.9)	0.221
Diagnosis n (%) **Asthma** **AR** **Asthma+AR**	 16 (53.3) 7 (23.3) 7 (23.3)	 9 (30) 14 (46.6) 7 (23.3)	 8 (26.7) 13 (43.3) 9 (30.0)	 11 (35.4) 13 (41.9) 7 (22.5)	0.830
Total IgE (kU/L) median (min-max)	134^{ab} (0-1186)	102^{a} (6.5-1009)	309^{b} (37.3-1222)	517^{c} (51-2940)	**<0.001**
Aeroallergen-specific IgE (kU/L) median (min-max)	0.07^{a} (0-2.23)	0.69^{b} (0-22.4)	12.4^{c} (0.04-88.79)	32.2^{d} (0-180)	**<0.001**
Eosinophil count, (/mm^3) median (min-max)	231^{ab} (11-1050)	200^{a} (10-967)	361^{b} (83-1450)	747^{c} (123-1514)	**<0.001**
Body mass index (kg/m^2) mean±SD	22.06±3.81	20.83±4.03	22.08±3.92	23.50±3.20	0.150

P values were calculated using one-way ANOVA, Kruskal-Wallis test, chi-square test, or Fisher's exact test, as appropriate. For laboratory variables with significant overall differences, superscript letters indicate exploratory post-hoc pairwise comparisons; values sharing at least one superscript letter are not significantly different. Those results shown in bold are statistically significant
Group 1: 0 mm; Group 2: 1-2 mm; Group 3: ≥3 mm; Group 4: ≥3 mm with SCIT
AR: Allergic rhinitis, IgE: Immunoglobulin E, SPT: Skin prick test

were younger than 5 years, 56 (46.3%) were between 5 and 10 years, and 41 (33.9%) were older than 10 years.

The baseline demographic and clinical characteristics were comparable across the four groups (Table I). No significant intergroup differences were observed in terms of age, interval between tests, sex, family history of atopy, cesarean delivery, sibling status, diagnosis, or body mass index between the first and second SPT (p>0.05). However, total IgE, inhalant allergen-specific IgE, and absolute eosinophil counts differed significantly among the groups (p<0.001), with the highest values observed in Group 4 and the lowest in Groups 1 and 2.

The changes in SPT reactivity during follow-up are presented in Table II. The rate of new sensitization was significantly lower in those children with completely negative baseline tests (Group 1, 26.7%) compared to the other three groups (Group 2: 80.0%, Group 3: 66.7%, Group 4: 61.3%; p<0.001). No significant differences were found between Groups 2, 3, and 4 (p>0.05).

An increase in wheal diameter to the same allergen was most prominent in Group 2 (66.7%), and post-hoc analyses confirmed significant differences between Group 2 and both Group 3 (20.0%, p<0.001) and Group 4 (29.0%, p=0.003). A decrease in wheal diameter or the loss of prior sensitization did not differ significantly between the groups (p>0.05).

Newly developed aeroallergen sensitivity patterns are presented in Table III. New house dust mite (HDM) sensitization was strikingly more frequent in Group 2 (53.3%) than in Group 1 (13.3%), Group 3 (20.0%), and Group 4 (6.5%) (p<0.001). Similarly, new cat sensitization was observed more often in Group 2 (36.7%), Group 3 (26.7%) and Group 4 (25.8%) than in Group 1 (3.3%) (p=0.018). New weed pollen sensitization also differed between the groups (p=0.047). In contrast, no significant between-group differences were found for newly developed grass pollen, tree pollen, or mold sensitization (p>0.05).

Potential factors associated with the development of new sensitizations were further examined using univariable logistic regression analyses (Table IV). Among the environmental and clinical variables, a history of COVID-19 was significantly associated with increased odds of new allergen sensitization (OR: 2.97, 95% CI: 1.08-8.15; p=0.034). No significant associations were observed for age at first SPT, the interval between tests, sex, family history of atopy, cesarean delivery, sibling status, baseline total or specific IgE, eosinophil count, residential area, household smoking exposure, open kitchen, pet exposure, mold/dampness, cockroach exposure, indoor live plants, junk food consumption, or vegetable consumption (p>0.05).

A limited multivariable logistic regression model was performed in order to assess whether the association between COVID-19 history and new sensitization remained independent after adjustments for age at first SPT, sex, and baseline aeroallergen-specific IgE. In this model, a history of COVID-19 remained independently associated with the development of new sensitization (adjusted OR: 3.06, 95% CI: 1.01-9.32; p=0.049). Age at first SPT, sex, and baseline aeroallergen-specific IgE were not independently associated with new sensitizations.

In an exploratory subgroup analysis restricted to those children with baseline wheal diameters of 1-2 mm (Group 2), univariable logistic regression did not identify any significant predictors of an increase in wheal diameter to the same allergen during the follow-up (p>0.05).

Age-stratified analyses showed no significant differences in histamine wheal diameters according to age groups or baseline sensitization status (p>0.05). Likewise, there were no significant differences among the age groups in

Table II. Changes in aeroallergen skin prick test reactivity at follow-up according to the study groups

Outcome	Group 1 n=30 (%)	Group 2 n=30 (%)	Group 3 n=30 (%)	Group 4 n=31 (%)	p value
Development of new sensitization to a previously negative allergen	8 (26.7)[a]	24 (80)	20 (66.7)	19 (61.3)	**<0.001**
Increase in wheal diameter to the same allergen	-	20 (66.7)[b]	6 (20.0)	9 (29.0)	**<0.001**
Decrease in wheal diameter to the same allergen	-	8 (26.6)	2 (6.7)	6 (19.4)	0.120
Loss of previous positive sensitization	-	-	9 (33.3)	3 (17.7)	0.059

Overall p values were calculated using the chi-square test or Fisher's exact test, as appropriate. Post-hoc pairwise comparisons were performed using pairwise comparisons of proportions. Group 1 had no baseline sensitization; therefore, changes in wheal diameter to the same allergen and loss of sensitization were not applicable. Group 2 had no baseline positive sensitization (≥3 mm); therefore, loss of sensitization was not applicable. Significant p values are shown in bold.
[a]Post-hoc pairwise comparisons showed significant differences between Group 1 and Group 2 (p<0.001), Group 1 and Group 3 (p=0.002), and Group 1 and Group 4 (p=0.006)
[b]Post-hoc pairwise comparisons showed significant differences between Group 2 and Group 3 (p<0.001) and Group 2 and Group 4 (p=0.003)

Table III. Newly developed aeroallergen sensitizations during follow-up according to the study groups

Allergen group	Group 1 n=30 (%)	Group 2 n=30 (%)	Group 3 n=30 (%)	Group 4 n=31 (%)	p value
House dust mite	4/30 (13.3)	16/30 (53.3)[a]	6/30 (20.0)	2/31 (6.5)	**<0.001**
Cat epithelium	1/30 (3.3)[b]	11/30 (36.7)	8/30 (26.7)	8/31 (25.8)	**0.018**
Grass pollen	5/30 (16.7)	9/30 (30.0)	7/30 (23.3)	3/31 (9.7)	0.232
Weed pollen	0/30 (0.0)[c]	6/30 (20.0)	7/30 (23.3)	4/31 (12.9)	**0.047**
Tree pollen	6/30 (20.0)	10/30 (33.3)	10/30 (33.3)	6/31 (19.4)	0.409
Mold	4/30 (13.3)	7/30 (23.3)	4/30 (13.3)	2/31 (6.5)	0.319

Values are n/N (%) of patients who developed a new sensitization (≥3 mm) to the specified allergen group among those who were negative (<3 mm) at baseline. Overall p values were calculated using Fisher's exact test or chi-square test, as appropriate. For allergen groups with significant overall differences, exploratory post-hoc pairwise comparisons were performed. Significant p values are shown in bold.
[a]Post-hoc pairwise comparisons showed significant differences between Group 2 and Group 1 (p=0.001), Group 2 and Group 3 (p=0.007), and Group 2 and Group 4 (p<0.001)
[b]Post-hoc pairwise comparisons showed significant differences between Group 1 and Group 2 (p=0.001), Group 1 and Group 3 (p=0.026), and Group 1 and Group 4 (p=0.013)
[c]Post-hoc pairwise comparisons showed significant differences between Group 1 and Group 2 (p=0.024) and Group 1 and Group 3 (p=0.011), whereas the difference between Group 1 and Group 4 was not statistically significant (p=0.113)

Table IV. Univariable logistic regression analyses of factors associated with the development of new allergen sensitizations

Variable	OR (95% CI)	p value
Age at first SPT, months	1.004 (0.995-1.013)	0.391
Interval between tests, months	1.020 (0.993-1.048)	0.143
Male sex	1.578 (0.728-3.423)	0.248
Family history of atopy	1.469 (0.655-3.293)	0.350
Cesarean delivery	1.552 (0.671-3.591)	0.304
Not having a sibling	1.326 (0.566-3.105)	0.516
Baseline specific IgE	1.010 (0.996-1.024)	0.161
Baseline total IgE	1.000 (0.999-1.001)	0.950
Baseline eosinophil count	1.001 (1.000-1.002)	0.216
Living in a city	1.492 (0.316-7.056)	0.614
Household smoking exposure	1.707 (0.720-4.048)	0.225
Open kitchen	2.432 (0.772-7.641)	0.128
Pet exposure at home	1.119 (0.453-2.761)	0.807
Mold/dampness at home	2.589 (0.834-8.038)	0.100
Cockroach exposure at home	1.385 (0.562-3.418)	0.479
Indoor live plants	1.655 (0.738-3.709)	0.221
History of COVID-19	2.972 (1.084-8.153)	**0.034**
Junk food consumption (overall)	—	0.291
Vegetable consumption (overall)	—	0.666

For junk food consumption and vegetable consumption, category-specific ORs are not presented because sparse cell counts in some categories resulted in unstable parameter estimates; therefore, only the overall p values for these categorical variables are shown
OR: Odds ratio, CI: Confidence interval, SPT: Skin prick test

Table V. Allergen sensitization profiles according to age groups at the first and second skin prick tests

Allergen group	SPT time	<5 years n=24 (%)	5-10 years n=56 (%)	>10 years n=41 (%)	p value
House dust mite	First	3 (12.5)	16 (28.6)	7 (27.1)	0.190
	Second	6 (25.0)	26 (46.4)	18 (43.9)	0.190
Cat epithelium	First	6 (25.0)	10 (17.9)	10 (24.4)	0.700
	Second	7 (29.2)	15 (27.3)	22 (53.7)	**0.020**
Grass pollen	First	4 (20.0)	5 (11.1)	10 (32.3)	0.070
	Second	7 (29.2)	24 (42.9)	30 (73.2)	**0.010**
Tree pollen	First	5 (20.8)	10 (17.9)	13 (31.7)	0.270
	Second	7 (29.2)	22 (39.3)	27 (65.9)	**0.006**
Weed pollen	First	1 (4.2)	7 (12.5)	8 (19.5)	0.220
	Second	3 (12.5)	11 (19.6)	16 (39.0)	**0.020**
Mold	First	1 (4.2)	4 (7.1)	3 (7.3)	0.900
	Second	7 (29.2)	8 (14.3)	10 (24.4)	0.280

Values are n (%) of patients with a positive SPT (≥3 mm) to the specified allergen group. P values were calculated using chi-square test or Fisher's exact test. Significant p values are shown in bold
SPT: Skin prick test

their baseline sensitization to individual allergen groups (Table V). However, at the second SPT, sensitization to cat epithelium, grass pollen, tree pollen, and weed pollen differed significantly across the age groups, with higher rates observed in those children older than 10 years (p=0.020, p=0.010, p=0.006, and p=0.020, respectively).

Discussion

In this longitudinal observational study, we aimed to evaluate the effects of baseline aeroallergen SPT reactivity on subsequent sensitization patterns in children who underwent repeat SPT after at least three years. Our findings demonstrated that baseline wheal diameter is a significant predictor of new allergen sensitization over time, and they underscore the clinical relevance of minimal wheal reactions (1-2 mm) which fall below the conventional 3-mm positivity threshold. Notably, those children with a baseline reactivity of 1-2 mm (Group 2) developed new sensitizations at a remarkably high rate, with house dust mite sensitization occurring in 53.3% of this group at follow-up.

The prognostic significance of small SPT reactions has been a subject of ongoing debate. Current guidelines from the EAACI and the American Academy of Allergy, Asthma & Immunology generally define a positive SPT as a wheal diameter of ≥3 mm, a threshold primarily validated in adult populations (14,15). However, emerging evidence suggests that lower cutoffs may be more appropriate in children, in whom the immune response is still maturing and evolving (13). Schoos et al. (13) recently demonstrated that the optimal specific IgE cut-off for predicting clinical allergy varies by allergen and is often lower in children, challenging the universal application of adult-derived thresholds. Similarly, Lockey et al. (16) reported that a wheal size as small as 1 mm at age one year was predictive of allergic sensitization by age two. Our findings suggest that minimal wheal reactions (1-2 mm) in symptomatic children should not be dismissed as clinically irrelevant, as they may represent early or incipient sensitizations which can progress to frank positivity over time.

Previous longitudinal studies have reported that sensitization status changes in a substantial proportion of children during follow-up (17,18). In agreement with these reports, our study found that new sensitizations developed in all groups, including those with completely negative baseline tests (Group 1).

The observation that new HDM sensitization was most frequent in Group 2 merits special attention. HDM is a ubiquitous perennial allergen with potent immunostimulatory properties. It is plausible that an initial low-level IgE response to HDM reflects an early phase of the "atopic march" which can rapidly progress to clinical sensitization under conditions of continuous high-dose exposure (19,20). In contrast to pollens, which typically require cumulative seasonal exposure over many years to induce sensitization, HDM sensitization can occur and amplify more quickly in predisposed children (21). This

finding aligns with the longitudinal data from Nokkaew et al. (22) who reported that HDM sensitization had the lowest rate of negative conversion over time, indicating its persistence once established.

Our age-stratified analyses revealed a clear temporal sequence in the acquisition of aeroallergen sensitizations. While HDM sensitization was already prevalent in the younger age groups, sensitizations to cat epithelium, grass pollen, tree pollen, and weed pollen were significantly more common in those children older than 10 years at the second SPT. This pattern is consistent with the natural history of allergic diseases, in which sensitization to indoor allergens often precedes sensitization to outdoor seasonal allergens (21,23). Recent large-scale studies have confirmed this age-dependent shift in sensitization profiles. Shin and Lee (7), in a cross-sectional analysis of over 14,000 individuals, demonstrated that the pattern of aeroallergen sensitization changes markedly across an individual's lifespan, with pollen sensitization peaking in adolescence and early adulthood. Similarly, the longitudinal study by Kölli et al. (8) showed that the prevalence of sensitization to outdoor allergens increases with age, while indoor allergen sensitization remains more stable. These findings reinforce the importance of considering a child's age when interpreting SPT results and when deciding on the timing of repeat testing.

Our exploratory analyses showed that a history of COVID-19 was associated with the development of new sensitizations in univariable analysis and remained independently associated after adjustments for age at first SPT, sex, and baseline aeroallergen-specific IgE. Several studies have reported changes in the aeroallergen sensitization profiles of children during the COVID-19 pandemic, including increased rates of sensitization to HDM and other indoor allergens, as well as higher rates of polysensitization when compared with the pre-pandemic period (24-27). These changes have generally been attributed to pandemic-driven lifestyle modifications, such as increased indoor time, altered ventilation, cleaning practices, and reduced outdoor exposure. However, these factors and a prior SARS-CoV-2 infection were rarely measured directly, limiting causal inference. In our cohort, the positive association with COVID-19 history may therefore serve as a proxy for the intensity of pandemic-related behavioral and environmental changes rather than indicating a direct biological effect of the virus. Furthermore, the absence of systematic laboratory confirmation may have resulted in exposure misclassification, potentially affecting the strength and interpretation of this association. Future studies incorporating detailed exposure assessments and objective biomarkers are needed in order to differentiate the potential effects of the viral infection itself from the broader environmental and behavioral changes which occurred during the pandemic period.

Study Limitations

This study had several limitations. First, its observational design precluded causal inference. Second, the interval between tests was variable, although the mean interval of approximately 4.5 years was consistent across the groups. Third, the relatively small sample sizes in the subgroup analyses may have limited statistical power to detect certain associations.

Despite these limitations, our findings have important clinical implications. For children with persistent allergic symptoms and baseline wheal diameters between 1 and 2 mm, a strategy of watchful waiting may be suboptimal. These children are at high risk of developing frank sensitization, particularly to HDM, within a 3- to 4-year window. Therefore, we suggest that clinicians consider repeat aeroallergen testing after 2-3 years in this specific subgroup, even if the initial test is reported as "negative" based on the conventional 3-mm threshold. Furthermore, given the age-dependent increase in pollen and cat sensitization, repeat testing should also be considered in older children (≥10 years) with new-onset or worsening seasonal/perennial symptoms, as their sensitization profile may have expanded since their initial evaluation.

Conclusion

Baseline aeroallergen SPT reactivity is a strong predictor of subsequent sensitization patterns in children. Minimal wheal reactions (1-2 mm) in symptomatic children are associated with a high risk of developing clinically significant sensitization, particularly to HDM, and should not be dismissed as irrelevant. Repeat SPT after an appropriate interval can provide valuable information in order to guide environmental control measures, pharmacotherapy, and the timely initiation of allergen immunotherapy in this evolving pediatric population.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Medical Research Ethics Committee (approval no.: 23-7.1T/42, date: 27.07.2023).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of the

participants, and assent was obtained from the children when appropriate.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: E.T., H.D.Ş., A.P., M.G., F.G., E.D., Concept: F.G., E.D., Design: H.D.Ş., E.D., Data Collection or Processing: E.T., A.P., M.G., Analysis or Interpretation: E.T., H.D.Ş., F.G., E.D., Literature Search: E.T., H.D.Ş., Writing: E.T., H.D.Ş.

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