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Sensitizations to aeroallergens in Israel: Prevalences and profiles

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Abstract
Background: Most of the literature on aeroallergen sensitization have been generated in North America and Western Europe.
Objectives: To determine aeroallergen sensitization prevalences and patterns among patients with physician-diagnosed allergic rhinitis (AR) in Israel.
Methods: We conducted a retrospective, observational study of sensitization to 20 aeroallergen extracts in skin prick tests (SPTs) among consecutive pediatric and adult patients with AR attending the allergy clinic at Emek Medical Center (Afula, Israel) and an affiliated regional outpatient clinic (Nazareth, Israel) from 2021 to 2023.
Results: A total of 1993 patients (547 females, 27.4%) were included (median [range] age: 24 [6-82]). The five allergens or groups of allergens with the highest SPT positivity rates were house dust mite (HDM: *Dermatophagoides pteronyssinus* and *D. farinae*; 74.8%), tree pollens (44.3%), olive pollen (34.1%), grass pollens (25.6%), and cat dander (22.6%). Of the 1993 patients, 947 (47.5%) had a positive SPT for just one of the 20 tested extracts. Patients sensitized to cat dander were significantly (12-fold) more likely to be sensitized to dog dander and vice versa. Patients living in an urban environment were more likely to be sensitized to cypress pollen (19.3% vs. 12.0% in a nonurban environment; p = 0.002, chi-squared test) and pellitory pollen (21.6% vs. 15.1%, respectively; p = 0.010, chi-squared test). Our suggestion is that in the Middle East, patients with symptoms of AR can be effectively screened with a standard "European" panel of allergen extracts for SPTs (such as that suggested by the Global Allergy and Asthma European Network [GA2LEN] organization), plus Johnson grass, Bermuda grass, and oak and eucalyptus pollen extracts.

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Introduction

Allergic rhinitis (AR) is a global health issue. However, most of the epidemiological studies in this field have been performed in North America and Western Europe; in contrast, literature on the epidemiology of atopy and allergy in Asia, Africa, and the Middle East are relatively scarce.[1-5] For example, there are relatively few literature on atopy, clinical allergies, and allergy treatments in Israel, although the range of prevalences of AR in the country (from ~10% to ~40%, depending on the age group, the methodology used, and whether the allergy is self-reported or physician-diagnosed) is similar to that observed worldwide, particularly in the Middle East.[4,6-9]

Despite the stereotypical, dry, arid, desert-like image of the Middle East (conventionally defined as encompassing Egypt, Israel, Lebanon, Jordan, Syria, Iran, Iraq, Kuwait, Oman, Qatar, Saudi Arabia, Bahrain, the United Arab Emirates, and Yemen), many of the countries in this part of the world have mountains or coastal regions that experience lower temperatures and/or higher levels of humidity during one or more seasons. Accordingly, a broad range of aeroallergens can be observed in the Middle East, notably in urban zones where people live, travel, and work.[3,10] These aeroallergens include spores from molds (*Alternaria*, *Aspergillus*, *Cladosporium*, and *Penicillium*), cuticle components, and feces from insects (e.g., cockroaches) and arthropods (e.g., house dust mites [HDMs], which are essentially ubiquitous in buildings where humans live, work, or sleep),[11-13] dander from farm animals and pets, and pollen from grasses, weeds, shrubs, and trees.[3,10,14] Sensitization to the two most common HDMs (*D. pteronyssinus* and *D. farinae*) is highly prevalent in both humid and arid areas of Israel.[15] The pollen found in the Middle East comes not only from truly native species (e.g., date palms, oak, olive, cypress) but also from imported species established in the region (e.g., *Ambrosia*).[16]

The prevalence of sensitization and allergy in Israel is thought to vary as a function of ethnic, nutritional, geographic, and even psychological factors.[6-8,15,17-20] However, there are relatively few up-to-date literature on the prevalence of atopy to specific allergens (as assessed with SPTs or specific IgE [immunoglobulin E] assays) in Israel.[15,20-22]

Hence, the objective of this retrospective, observational study was to determine aeroallergen sensitization prevalences and patterns (using SPTs) among patients with physician-diagnosed AR in Israel. We hypothesized that better knowledge of these sensitizations would help optimize an SPT allergen panel for use in the Middle East and potentially reveal unmet treatment needs.

Materials and Methods

Study design and study population

We conducted a noninterventional, retrospective, observational study of data extracted from the medical records of consecutive pediatric and adult patients attending the Allergy Asthma & Immunology Service at Emek Medical Center (Afula, Israel) and the affiliated regional clinic (Nazareth, Israel) from 2021 to 2023. Emek Medical Center is the major allergy referral center for northern Israel. All the patients had been diagnosed with AR (with or without asthma) by a physician. The study inclusion criteria were age between 6 and 80, physician-diagnosed AR (based on clinical symptoms and SPT results) with or without asthma, and a full SPT dataset. The lower age limit was set at 6 because in Israel, allergen immunotherapy (AIT), whether administered as subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT), is usually given only from that age onwards. The patients' demographic and clinical data were extracted from the medical center's electronic medical records or by the Allergy Asthma & Immunology Service's physicians during consultations. The data included age, sex, type of built environment (city, suburb, village, or agricultural community), and geographic region (coastal cities, the Nazareth area, the Galilee region other than Nazareth, or the Jezreel, Beit-She'an, and Jordan valleys). Data on ethnicity were not collected.

The study was approved by the institutional review board at Emek Medical Center on December 21, 2023 (reference: 0060-23-EMC). In line with the national legislation, study participants were not required to consent to research use and publication of their de-identified personal medical data. All study procedures involving human participants were performed in accordance with the tenets of the Declaration of Helsinki.

Sensitization testing

The SPTs were performed in accordance with current guidelines, using allergen extracts produced by anaplastic lymphoma kinase (ALK) (ALK-Abelló Pharmaceutical Company, Hørsholm, Denmark).[23] The allergen panel included 20 extracts: a two-species HDM mix (*D. farineae* and *D. pteronissimus*), cat dander, dog dander, cockroach, feathers, mold (*Alternaria*), Bermuda grass pollen (*Cynodon dactylon*), Johnson grass pollen (*Sorghum halepense*), a seven-grass pollen mix (with timothy [*Phleum pratense*]), orchard grass (*Dactylis glomerata*), Kentucky blue (June) grass (*Poa pratensis*), redtop (*Agrostis alba*), meadow fescue (*Festuca elatior*), perennial rye (*Lolium perenne*), and sweet vernal (*Anthoxanthum odoratum*) pollens), a weed pollen mix comprising cocklebur, rough marsh elder, English plantain, and lamb's quarters, pellitory pollen, ragweed pollen, mugwort pollen, and seven separate tree pollens (pecan, olive, eucalyptus, pine, Australian pine, oak, and cypress). The results for the seven tree pollens were expressed individually but were also pooled and referred to hereafter as "tree pollens"; this was not a physical mixture of extracts but reflected the fact that these tree pollen extracts may be combined when SCIT is administered. All patients were tested with all the allergen extracts in a single session. Each SPT result was defined as either positive/sensitized or negative/non-sensitized. A positive SPT was defined as a wheal (i.e., a raised swelling) with a diameter of 3 mm more than the negative control (saline) and a flare (i.e., the surrounding redness) with a diameter of 5 mm more than the negative control. The test panel also contained a positive control (histamine). The choice of seasonal allergens was based on data on prevalence in Israel.

Statistical analysis

Quantitative variables were described as the mean ± standard deviation (SD) or the median (interquartile range). To compare the types and locations of the place of residence, a univariate analysis of variance or Wilcoxon's test was applied. Categorial variables (e.g., age class, the number of positive SPTs, the urban/nonurban nature of the place of residence, and the region of residence) were expressed as the frequency (percentage) and intergroup differences were examined using a chi-squared test. The strength of an association was assessed with the Phi/Kramer V index or (for segmentation with regard to an urban or nonurban place of residence) an odds ratio. For the purposes of the urban versus nonurban analysis, the former was defined as a city or suburban environment and the latter defined as a village or an agricultural community. For a descriptive analysis, we divided the participants into four 20-year age classes: 6–25, 26–45, 46–65, and 66–85.

All analyses were performed with SAS software (version 9.2, SAS Institute, Cary, NC, USA).

Results

Characteristics of the study population

A total of 1993 patients (547 females, 27.4%) were included in the analysis. By definition, all the included patients had physician-diagnosed AR. Data on age were available for 994 patients: the mean ± SD (range) age of this population was 28 ± 17 (6–82) and the median (interquartile range) age was 24. Children and adolescents (i.e., patients under the age of 18) accounted for 39.3% of the study population.

Data on the place of residence were available for 993 (49.8%) of the 1993 patients: 601 patients were living in an urban area (538 in a city and 63 in a suburb) and 392 in a non-urban area (287 in a village and 105 in an agricultural community, such as a kibbutz). The urban and non-urban dwellers did not differ significantly with regard to the mean ± SD age (27 ± 17 and 29 ± 17, respectively). Data on the region of residence were available for 611 patients: 16 (2.6%) were living in coastal cities, 182 (29.8%) in the Galilee region (except Nazareth), 157 (25.7%) in the valleys, and 256 (41.9%) in Nazareth.

Sensitizations to aeroallergens

For the 20 allergen extracts tested on the 1993 patients, the prevalence of a positive SPT ranged from 1.5% to 74.8% (Figure 1 and Table 1). All the study participants had at least one positive SPT.

Overall, the five highest prevalences of positive SPTs were observed for HDM, followed by tree pollens (i.e., any one of seven individual extracts), olive pollen, grass pollens, and cat dander. The high overall positivity rate (44.3%) for tree pollen was mainly due to the results of the olive pollen (34.1%) and cypress pollen (14.6%) (Figure 1 and Table 1).

We next looked at the proportions of patients with a positive SPT to only one of the 20 tested extracts (947 [47.5%] of the 1993 patients), who we refer to as "monosensitized" patients. The allergen profile mirrored the overall results, with the highest rates for HDM, tree pollens, olive pollen, grass pollen, and cat or dog dander (Figure 2 and Table 1). It is noteworthy that HDM not only predominated as the main sensitizer overall

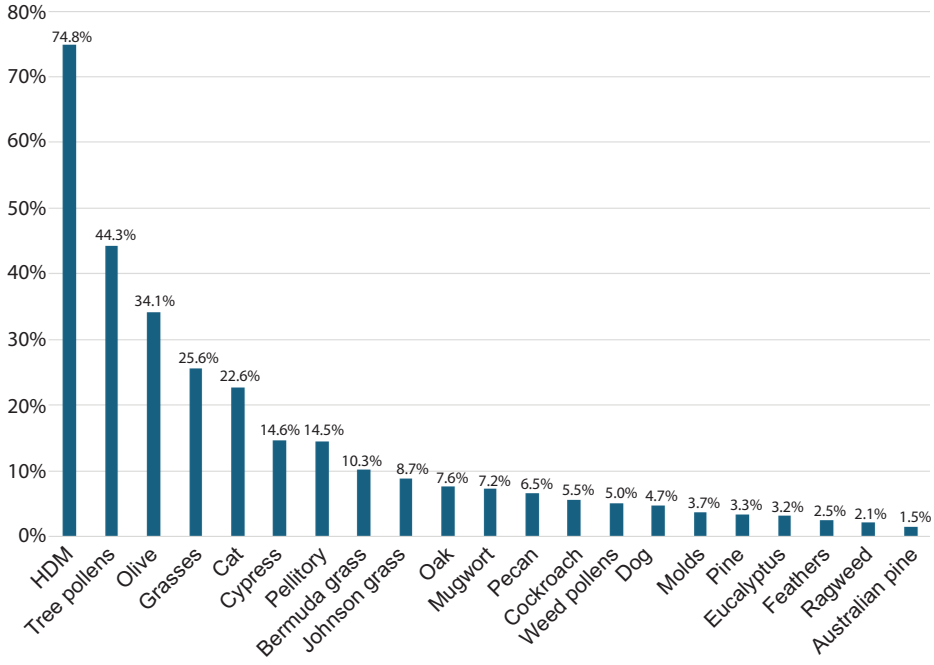

Figure 1 Prevalence of a positive SPT for the extracts tested in the study population (n = 1993).

Table 1 Prevalences of positive SPTs in the sample of patients (n = 1993) with physician-diagnosed AR.

	Overall sensitization		"Monosensitization" (a positive SPT for only one of the extracts or group of extracts)	
Allergen extract or group of extracts	n positive SPTs	Percentage positive SPTs (out of 1993)	n positive SPTs	Percentage positive SPTs (out of 1993)
HDM	1491	74.8%	570	28.60%
Tree pollen	883	44.3%	121	6.07%
Olive pollen	679	34.1%	57	2.86%
Seven-grass mix	510	25.6%	33	1.66%
Cat dander	451	22.6%	32	1.61%
Cypress pollen	291	14.6%	22	1.10%
Pellitory pollen	289	14.5%	33	1.66%
Bermuda grass pollen	206	10.3%	4	0.20%
Johnson grass pollen	174	8.7%	4	0.20%
Oak pollen	151	7.6%	2	0.10%
Mugwort pollen	144	7.2%	9	0.45%
Pecan pollen	130	6.5%	2	0.10%
Cockroach	110	5.5%	9	0.45%
Weed pollens	100	5.0%	2	0.10%
Dog	93	4.7%	3	0.15%
Mold	74	3.7%	4	0.20%
Pine pollen	65	3.3%	1	0.05%
Eucalyptus pollen	63	3.2%	1	0.05%
Feathers	50	2.5%	3	0.15%
Ragweed pollen	41	2.1%	0	0.00%
Australian pine pollen	30	1.5%	0	0.00%

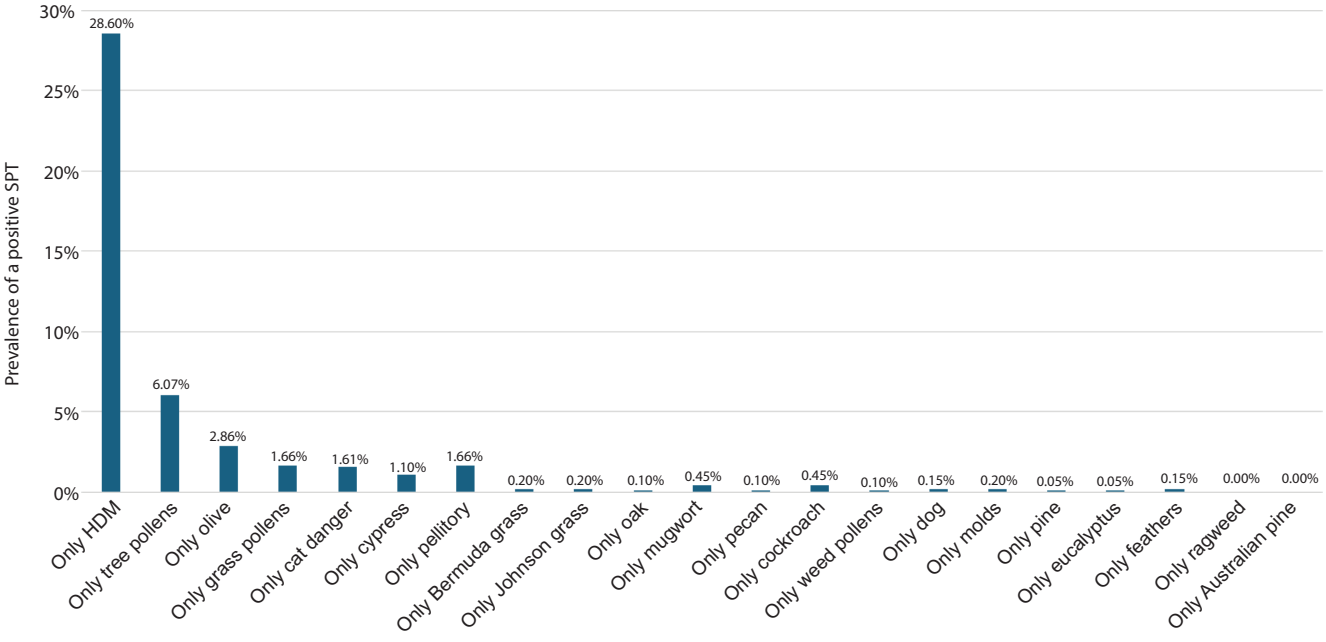

Figure 2 Proportions of "monosensitized" patients (i.e., those with a positive SPT to only one of the extracts tested; n = 1993).

(i.e., in polysensitized individuals) but was also the most common monosensitizer—around a third of HDM-sensitized individuals were solely positive for that extract. A high proportion of patients (44.3%) were sensitized to one or more of the seven individual tree pollen extracts tested (pecan, olive, eucalyptus, pine, Australian pine, oak, and cypress).

Interestingly, we found that patients sensitized to cat dander were significantly more likely to be sensitized to dog dander and vice versa. Of the 93 patients sensitized to dog dander, 70 were also sensitized to cat dander (odds ratio [95% confidence interval]: 12.1 [7.5–19.7]).

There were some significant differences in SPT positivity rates between patients living in an urban setting and those in a nonurban setting (Figure 3); these concerned cypress pollen (19.3% vs. 12.0%, respectively, of patients with data on place of residence; p = 0.002, chi-squared test), pellitory pollen (21.6% vs. 15.1%, respectively; p = 0.010, chi-squared test), and the combined rates for mugwort pollen and pellitory pollen (29.3% vs. 22.2%, respectively; p = 0.013, chi-squared test).

To study the effect of residency, we analyzed different types of residence (city, suburb, village, or agricultural

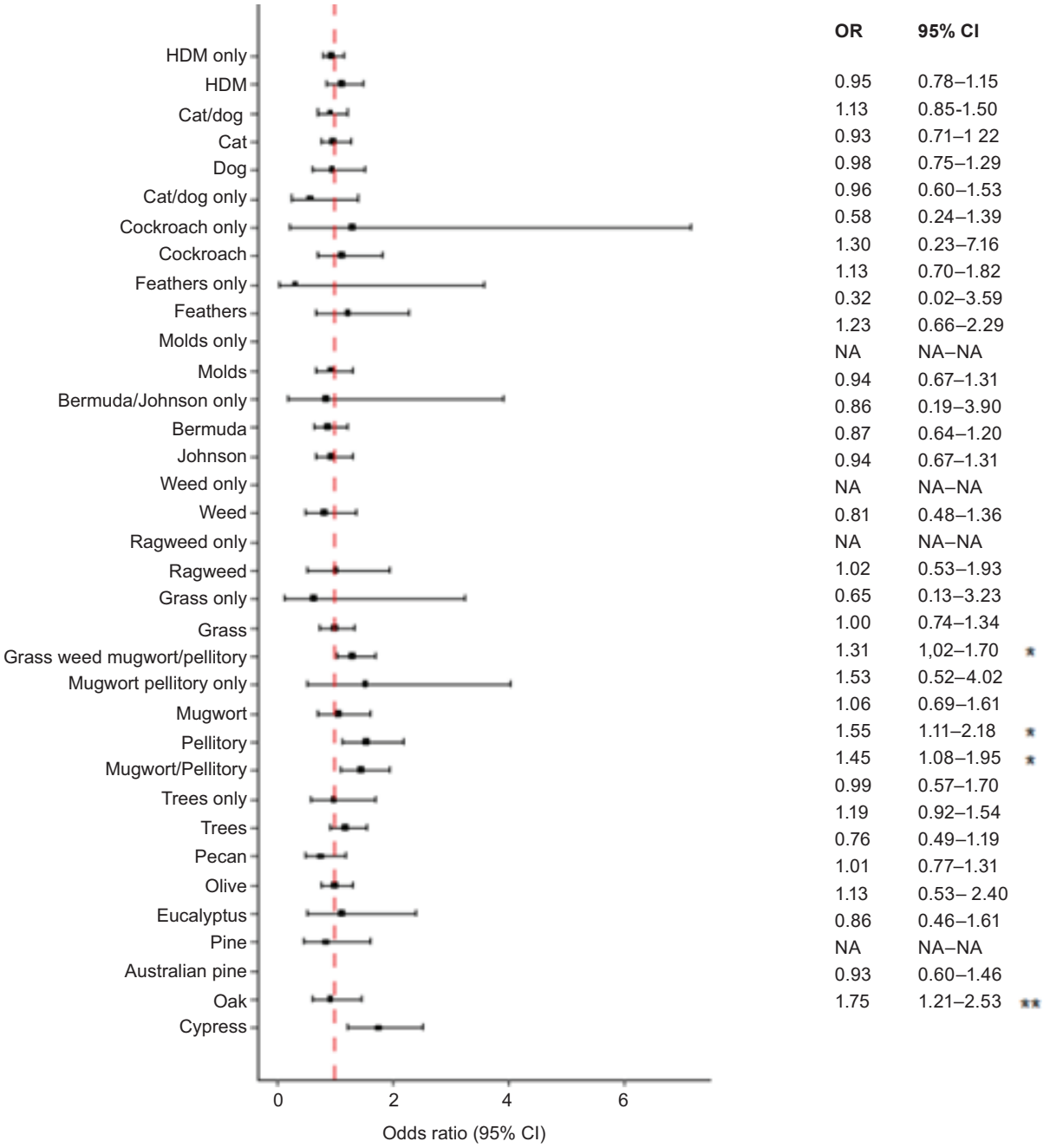

Figure 3 A Forest plot of the odds ratio (95% confidence interval) for a positive SPT in an urban versus nonurban setting. A value above 1 (i.e., to the right of the dotted red line) indicates a protective effect of a nonurban setting. Statistical significance in a chi-squared test is indicated as *: p < 0.01; **: p < 0.001.

community), and found statistically significant differences (using a chi-squared test) between types of residence for HDM (p = 0.024), pellitory pollen (p = 0.002), mugwort or pellitory pollen (p = 0.027), oak pollen (p = 0.003), and cypress pollen (p = 0.001) (Table 2). The prevalences of sensitization to HDM only, oak pollen, and cypress pollen were higher among suburban dwellers than among other patients, and the prevalences of sensitization to mugwort or pellitory and to pellitory pollen were highest among city dwellers.

As mentioned above, data on age were available for 994 of the 1993 patients (49.9%). For a descriptive analysis, we divided the participants into four 20-year age classes: 6–25, 26–45, 46–65, and 66–85 (Table 3). When taking all the extracts to account, the prevalences of a positive SPT were similar in all age classes. The prevalence of a positive SPT fell with age for some extracts (cat or dog dander) and rose with age for others (cockroach, grass mix, and weed mix), but these trends were not statistically significant in a chi-squared test.

Table 2 Statistically significant differences (in a chi-squared test) in the prevalences of positive SPTs among patients with data on the type of built environment in the place of residence (n = 993).

Extract	City (n = 538)	Suburb (n = 63)	Village (n = 287)	Agricultural community (n = 105)	p-value (chi-squared)
HDM only	88 (16.4%)	20 (31.7%)	53 (18.5%)	22 (21.0%)	0.024
Pellitory	124 (23.0%)	6 (9.5%)	48 (16.7%)	11 (10.5%)	0.002
Mugwort or pellitory	163 (30.3%)	13 (20.6%)	66 (23.0%)	21 (20.0%)	0.027
Oak	43 (8.0%)	9 (14.3%)	18 (6.3%)	18 (17.1%)	0.003
Cypress	101 (18.8%)	15 (23.8%)	27 (9.4%)	20 (19.0%)	0.001

Table 3 The prevalences of a positive SPT (n, percentage) by allergen extract and by age class.

Extract	Age 6–25 (n = 424)		Age 26–45 (n = 344)		Age 46–65 (n = 171)		Age 66–85 (n = 55)	
HDM only	85	20.0%	53	15.4%	36	21.1%	9	16.4%
HDM	313	73.8%	256	74.4%	114	66.7%	35	63.6%
Cat or dog only	9	2.1%	5	1.5%	6	3.5%	1	1.8%
Cat or dog	168	39.6%	130	37.8%	42	24.6%	9	16.4%
Cat	163	38.4%	124	36.0%	36	21.1%	8	14.5%
Dog	30	7.1%	31	9.0%	17	9.9%	5	9.1%
Cockroach only	3	0.7%	1	0.3%	1	0.6%	1	1.8%
Cockroach	28	6.6%	26	7.6%	17	9.9%	8	14.5%
Feathers only	1	0.2%	0	0.0%	1	0.6%	1	1.8%
Feathers	19	4.5%	16	4.7%	8	4.7%	3	5.5%
Molds	23	5.4%	19	5.5%	8	4.7%	2	3.6%
Bermuda or Johnson only	1	0.2%	3	0.9%	3	1.8%	0	0.0%
Bermuda	79	18.6%	71	20.6%	44	25.7%	11	20.0%
Johnson	64	15.1%	65	18.9%	34	19.9%	9	16.4%
Weed mix	19	4.5%	20	5.8%	15	8.8%	7	12.7%
Ragweed	17	4.0%	9	2.6%	11	6.4%	4	7.3%
Seven-grass mix only	1	0.2%	1	0.3%	2	1.2%	2	3.6%
Seven-grass mix	101	23.8%	82	23.8%	47	27.5%	21	38.2%
Seven-grass mix, weed mix, mugwort, or pellitory	179	42.2%	160	46.5%	84	49.1%	31	56.4%
Mugwort or pellitory only	7	1.7%	8	2.3%	2	1.2%	3	5.5%
Mugwort	37	8.7%	36	10.5%	27	15.8%	2	3.6%
Pellitory	71	16.7%	74	21.5%	34	19.9%	10	18.2%
Mugwort or pellitory	100	23.6%	96	27.9%	55	32.2%	12	21.8%
Tree pollen only (seven species)	22	5.2%	19	5.5%	13	7.6%	4	7.3%
Tree pollen (seven species)	201	47.4%	181	52.6%	80	46.8%	26	47.3%
Pecan	36	8.5%	24	7.0%	21	12.3%	5	9.1%
Olive	162	38.2%	140	40.7%	51	29.8%	18	32.7%
Eucalyptus	13	3.1%	11	3.2%	6	3.5%	0	0.0%
Pine	21	5.0%	10	2.9%	10	5.8%	1	1.8%
Oak	38	9.0%	29	8.4%	14	8.2%	7	12.7%
Cypress	62	14.6%	59	17.2%	33	19.3%	9	16.4%

Discussion

This study is the first to have examined a large dataset on aeroallergen SPT profiles among patients with physician-diagnosed AR in Israel. Overall, the sensitization profile observed in our center in Israel was in line with and extends the literature on Middle East countries.[3,24]

The highest prevalence of a positive SPT was observed for HDM. This observation is in line with the results of Zeldin et al.'s study of 133 patients (age: 19–34; males: 78%) with AR or asthma and starting AIT at an outpatient allergy clinic in Ashkelon (Israel)—98% were sensitized to HDM.[22] Similarly, in a study of 117 patients aged 16–44 attending an outpatient allergy clinic in Tel Aviv (Israel), Sade et al. found that 81% of the individuals were sensitized to HDM.[21] Data on individual extracts were not provided in Graif et al.'s study of young adults (aged between 18 and 24) attending a defense force clinic.[25] There were 175 participants with confirmed asthma, 150 with suspected asthma, and 100 with no asthma, and the proportions of participants with at least one positive test were 95.4%, 69%, and 54%, respectively.[25]

After HDM, the next highest prevalences of a positive SPT in our study were observed for tree pollens (olive pollen, in particular), grass pollens, and cat dander. The high overall positivity rate (44.3%) for tree pollen was mainly due to the results for olive pollen (34.1%) and cypress pollen (14.6%) (Figure 1 and Table 1). The five individual allergen extracts (i.e., not mixtures or grouped extracts) with the highest positivity rates were olive pollen, cat dander, cypress pollen, pellitory pollen, and Bermuda grass pollen. These results are again in line with Zeldin et al.'s report—after HDM, the highest observed positivity rates were 43% for mixed tree pollen, 34% for mixed grass pollen, and 23% for weed pollen.[22] Likewise, Sade et al. found that 49% of the participants were sensitized to at least one tree, grass, or weed pollen.[21]

The high prevalences of sensitization to HDM and cat dander are typical of a modern, postindustrial lifestyle with relatively humid, climate-controlled dwellings and the presence of pets. Our results indicate that a high proportion of patients with physician-diagnosed AR in this Middle Eastern country are sensitized to predominantly "indoor" allergens, such as HDM. This finding is in line with the report by Sade et al., who considered that HDM proliferation is favored by the climate in many regions of Israel and found that 95.81% of the studied children with AR were sensitized to at least one species of HDM.[21] A lower value was observed in a now somewhat dated study by Kornizky et al. who analyzed the results of 1250 radioallergosorbant tests (RASTs, 776 of which were positive) performed at a medical center in Tel Aviv (Israel) over a 6-year period.[26] Totally, 219 of the 1250 RAST assays were positive for a *D. pteronyssinus* extract; however, some patients underwent more than one RAST assay for a given allergen, and detailed data were not presented. Furthermore, one should not expect IgE assays and SPTs to give identical sensitization rates.[27]

The high positivity rate for HDM has also been observed in Middle Eastern countries other than Israel. In Almogren's retrospective analysis of 105 Saudi nationals with an airway allergy (AR, allergic asthma, or both), the most prevalent sensitizations were observed for HDM (77.8%), *Prosopis juliflora* (72.1%), *C. dactylon* (53.8%), *Chenopodium album* (47.1%), rye grass (36.5%), *Salsola kali* (36.5%), cat dander (33.6%), cockroach (19.2%), and mold (18.2%);[28] three-quarters of the patients were sensitized to at least one allergen.[28] Similar results were obtained in a study of 451 patients (aged between 5 and 60) attending an allergy clinic in Kuwait; the prevalences of sensitization were 76.7% for *S. kali*, 57.6% for *C. album*, and 38.2% for *C. dactylon*.[29] In contrast, Al-Ghamdi et al. reported that sensitization to indoor aeroallergens in Saudi Arabia was not significantly associated with current rhinitis; however, the latter condition was self-reported and not necessarily physician-diagnosed.[30] In a study of 180 children with asthma and AR in Qatar, Zahraldin et al. found high SPT sensitization rates for *D. pteronyssinus* 1 (Der p 1) (38.1%) and *D. farina* 137 (Der f 137) (29.0%).[31] The high prevalence of HDM sensitization in Qatar was confirmed by Thalappil et al., who found SPT positivity rates of 49.5% for *D. pteronyssinus* and 38.6% for *D. farinae* among adult patients attending an allergy clinic.[32]

We observed some significantly higher positivity levels in urban city and suburban settings for five allergens: HDM, pellitory pollen, mugwort, oak pollen, and cypress pollen.

This apparently paradoxical result is in line with some previous observations. In a study of 9-year-old and 12-year-old children with asthma attending a clinic in Ashkelon (Israel), Bibi et al. assessed the prevalence of sensitization (according to SPT results) to a range of allergens: 363 children were living in an urban environment and 85 in a rural environment. The prevalences of positive SPTs, even for outdoor allergens, were significantly higher among urban dwellers than among rural dwellers, with 58.3% and 37.6% for HDM, 46.1% and 31.8% for molds, 17.45% and 5.9% for cat dander, and 26.2% and 15.3% for cypress pollen.[33] The high positivity levels in urban city and suburban settings might reflect the fact that in the Middle East countries, urban environments are often "greener" than country areas as a result of greater per capita water use.[34] Alternatively, one can hypothesize that living in a nonurban setting protects against sensitization to certain allergens, perhaps as a result of earlier or lifelong exposure.

The higher positivity rate for cat dander than for dog dander observed in our study might reflect higher levels of cat ownership than dog ownership in Israel. According to the official registry data from the Israeli Ministry of Agriculture, 245,247 female dogs and 251,291 male dogs were registered in 2020.[35] However, robust data on cat ownership in Israel are scarce. First, dog ownership requires a government permit but cat ownership does not. Second, feral (street) dogs are controlled but street cats are not. Indeed, the Society for the Prevention of Cruelty to Animals in Israel has estimated that there are over two million street cats in the country; this might increase people's levels of exposure to cat dander in general.[36] As mentioned above, we found that patients sensitized to cat dander were significantly (12-fold) more likely to be sensitized to dog dander and vice versa. The underlying mechanism is not clear. There are some reports of allergens in dog dander that cross-react with the major cat allergen Felis Domesticus 1 (Fel d 1), although the clinical relevance of these observations is not yet clear.[37,38] Alternatively, owners of one type of pet might be more likely to own (or have owned in the past) another type of pet.

The sensitization patterns described here for a population of patients with AR in Israel overlap to a fair degree with those documented in Europe, including the Mediterranean region. The most comprehensive multinational European study among people attending an allergy clinic rather than the general population was probably of that carried out by the Global Allergy and Asthma European Network (GA2LEN).[23,39-42] A total of 3034 patients at 17 centers in 14 European countries were screened with a standardized 18-allergen panel (see below).[41] The southern-most centers were located in Coimbra (Portugal), Genoa and Palermo (Italy), and Athens (Greece). The sensitization rates for HDMs were lowest in centers in Central and Western Europe (e.g., 23.5% for *D. pteronyssinus* in Berlin) and much higher in centers in the Mediterranean countries (e.g., 68.8% for *D. pteronyssinus* and 68.0% for *D. farinae* in Coimbra). In this study, we observed an even higher value—albeit for an HDM mixture—of 74.8%. However, values of over 50% were observed in Odense (Denmark); these variations are unlikely to be explained by geographic factors alone. High sensitization rates for Oleaceae pollens were observed not only in the Mediterranean centers (e.g., 35.0% in Athens) but also in Zurich (Switzerland) (45.5%); however, the latter finding was ascribed to the known cross-reactivity between olive pollen and the ash pollen present in Western and Central Europe.[41] In this study, the olive pollen sensitization rate was 34.1%.

Sensitization to cat and dog dander allergens was particularly prevalent in the Nordic countries (e.g., 49.3% for Odense in Denmark vs. 22.6% in the present study in Israel).

With regard to other indoor allergens (e.g., molds and cockroach), the sensitization rates were low in the GA2LEN study and in this study. A few allergens showed a clear north-south geographical gradient in the sensitization rate—possibly reflecting differences in exposure. For example, the cypress tree is essentially absent in Nordic countries; in the GA2LEN study, the cypress pollen sensitization rate was 0.0% in Finland. The highest cypress pollen sensitization rates were found in the Mediterranean Europe and ranged from 5.1% in Coimbra to 8.7% in Montpellier (France).[41] A markedly higher value of 14.7% was found in this study, which suggests that "local" aeroallergens should be added to standard SPT panel for use in the Middle East (see below).

Our study had a number of strengths. First, we tested our consecutive patients with physician-diagnosed allergy; there was no selection bias. Second, we screened our patients against a broad panel of aeroallergen extracts. Third, all the patients were tested with all the allergen extracts. Fourth, we were able to distinguish between monosensitized and polysensitized individuals; when cross-checked against clinical signs and symptoms, this information is important for optimal patient management (i.e., the order in which clinical allergies are treated and the choice of AIT components).[43,44]

This study also had some limitations. First, we purposely surveyed a population of patients with physician-diagnosed AR consulting in an allergy referral center rather than the general population. However, our overall goal was to evaluate and address potentially unmet clinical needs rather than to generate purely epidemiological data on sensitization prevalences in general. Furthermore, the prescription of SPTs to people in the general population not suffering from a suspected allergy raises ethical and financial issues. Second, most of the included patients came from Northern Israel. However, given the large number of patients, the relatively small size of the country (21,000 km^2), and the fact that the patients were from both urban and nonurban areas and from four different types of residence (city, suburb, village, or agricultural communities), we believe that the data presented here are likely to apply to most of Israel. Third, we were not able to assess the clinical relevance of the SPT results in detail (i.e., whether sensitization to a given allergen was associated with clinically relevant signs and symptoms). However, the study by the GA2LEN of 3034 individuals attending allergy clinics in 14 European countries found that the overall clinically relevant sensitization rate of a standard SPT panel was 60%.[40,41] Fourth, the low representation of females meant that our findings may not necessarily be generalizable to other populations of patients with AR. Fifth, the use of a mixed *D. pteronyssinus-D. farinae* extract in the SPT panel prevented us from studying the mites' respective sensitization rates separately. However, this was also the case for the majority of published studies. Sixth, we did not record data on air pollution in the study areas. It is well known that air pollution (e.g., ozone) interacts with pollen levels and has an effect on AR symptoms.[45-47] Hence, geographical differences in the air pollution level might account for some of our findings. Last, data on the type of built environment in the place of residence were missing for around half the patients. Nevertheless, the results of our urban versus nonurban comparisons were highly significant; this at a time when mobility between the place of residence and the place of work (i.e., commuting) tends to reduce differences in aeroallergen exposure and sensitization between urban and nonurban environments.[48-51]

We further suggest that in the Middle East and the Mediterranean region, the treatment of patients with respiratory allergies could be improved by the application of a standard panel of SPT extracts. In Europe, this approach has been promoted by GA2LEN, whose standard SPT panel is described in Table 4.[23,41] With a number of additional components such as extracts of Johnson grass, Bermuda grass, oak and eucalyptus pollen (Table 4), the GA2LEN panel would probably be suitable for use in the Middle East.

Conclusions

This first large study of an SPT dataset from Israel contributes important data on allergen sensitivities in a Middle Eastern country. A two-species HDM allergen mixture was the extract that gave the highest SPT positivity rate. There were few significant differences in SPT positivity rates with regard to age or the type and place of residence, although a nonurban setting appeared to protect against sensitization to cypress, pellitory pollen, and mugwort pollen. In the presence of suggestive signs and symptoms, SPT-based screening with a broad panel of allergen extracts might increase the allergy diagnosis rate and thus guide subsequent AIT in patients with moderate-to-severe AR that is not sufficiently controlled by symptomatic medications. Other perspectives for research and development include the production, testing, and clinical application

Table 4 A suggested panel of extracts for SPTs in the Middle East in comparison with the GA2LEN panel.

Allergen extracts	The GA2LEN panel of allergen extracts for SPTs in patients in Europe[23]	A suggested panel of allergen extracts for SPTs in patients in the Middle East
Corylus avellana (hazel) pollen	✓	✓
Alnus incana (alder) pollen	✓	✓
Betula alba (birch) pollen	✓	✓
Platanus vulgaris (plane) pollen	✓	✓
Cupressus sempervirens (cypress) pollen	✓	✓
Olea europaea (olive) pollen	✓	✓
Quercus calliprinos (common oak) pollen		✓
Eucalyptus camaldulensis (eucalyptus) pollen		✓
Grass pollen mix:		
Poa pratensis (smooth meadow grass)	✓	✓
Dactilis glomerata (cock's-foot grass)		
Lolium perenne (perennial rye grass)		
Phleum pratense (timothy)		
Festuca pratensis (meadow fescue)		
Helictotrichon pretense (meadow oat grass)		
Sorghum halepense (Johnson grass) pollen		✓
Cynodon dactylon (Bermuda grass) pollen		✓
Artemisia vulgaris (mugwort) pollen	✓	✓
Ambrosia artemisiifolia (ragweed) pollen	✓	✓
Alternaria alternata (tenuis)	✓	✓
Cladosporium herbarum	✓	✓
Aspergillus fumigatus	✓	✓
Parietaria (pellitory) pollen	✓	✓
Cat dander	✓	✓
Dog dander	✓	✓
Dermatophagoides pteronyssinus (European house dust mite)	✓	✓
Dermatophagoides farinae (American house dust mite)	✓	✓
Blatella germanica (German cockroach)	✓	✓
Positive control: histamine dihydrochloride 0.1%	✓	✓
Negative control: NaCl 0.9%	✓	✓

of standardized allergen extracts of indigenous Middle Eastern allergens for use in sensitization testing and AIT. The high sensitization rates for grass, pellitory, mugwort, and olive pollen extracts observed in this study suggest that SLIT preparations of these aeroallergens would be a useful addition to the therapeutic armamentarium available in the Middle East.

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Institutional Review Board Statement

This study was approved by the institutional review board at Emek Medical Center on December 21, 2023 (reference: 0060-23-EMC). All study procedures involving human participants were performed in accordance with the tenets of the Declaration of Helsinki.

Informed Consent Statement

In line with the national legislation, study participants were not required to consent to research use and publication of their de-identified personal medical data.

Author Contributions

MB: conceptualization, formal analysis, visualization, writing—original draft—review, and editing. MN, YA: data curation, formal analysis, writing—review and editing.

Conflicts of Interest

MR declares the receipt of speaking fees and travel support from Rafa, Kamada, Sanofi, ALK, and Neopharm. MN and YA declare no competing interests.

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