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ORIGINAL RESEARCH

Association of Allergic Sensitivity and Pollination in Allergic Respiratory Disease: The Role of Pollution

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Purpose: To evaluate the association between allergic sensitivity and pollen counts in patients with allergic respiratory disease (ARD) and its relationship with atmospheric pollutants.

Methods: From 2012 to 2018, we evaluated the sensitivity by skin prick test in ARD patients. The pollen counts were analyzed according to international guidelines (2014–2018). The pollutant and meteorological data were obtained at the same time from AIRE-CDMX websites. We analyzed the association between allergic sensitivity and pollen counts using the $\chi 2$ test and stratified by disease allergic rhinitis (AR) and AR with asthma (ARwA), periods (before/after 2015), and pollination seasons (S1:2014–2015), (S2:2015–2016), (S3:2016–2017), (S4:2017–2018). Likewise, we correlated the pollen counts with the concentrations of pollutants using Pearson's correlation. For all analyses, we used SPSS v.21 software, and a *p*-value <0.05 was considered significant.

Results: A total of 520 patients were enrolled, of whom 67.3% had ARwA and 33.7% had AR ($p<0.05$). The frequency of patients allergic to at least one pollen was higher compared with patients sensitive to indoor allergens (55.3% vs 44.6%, $p<0.001$). A total of 46.8% of the patients were only sensitive to trees in comparison to other outdoor allergens ($p<0.001$). The *Fraxinus* sp. and the Cupressaceae family allergens were approximately two times more frequent than the other tree allergens in both diseases ($p<0.05$). These pollens doubled their counts since 2015 ($p<0.001$), which was associated with increases in sensitivity for *Fraxinus* sp. and the Cupressaceae family compared to previous years ($p<0.001$). Regarding pollutants, the most significant correlations were with PM_{10}, NO_2, PM_{CO} for *Fraxinus* sp. pollen concentrations in all seasons ($p\leq0.02$).

Conclusion: The high increases in pollen counts of the *Fraxinus* sp. and Cupressaceae family were associated with increases in the frequency of sensitization to these species, and this phenomenon correlated with increases in PM_{10}, NO_2, and PM_{CO}.

Keywords: air pollutants, airborne particulate matter, pollen, allergy, asthma, rhinitis allergic seasonal

Introduction

The prevalence and incidence of allergic respiratory diseases (ARDs), such as allergic rhinitis (AR) and asthma,[1] are increasing worldwide. AR affects approximately 40% of the world's population[2] and is considered a risk factor for the development of allergic asthma (ARwA),[3] with this being the main phenotype (~80%).[4] It is estimated that 330 million suffer from asthma. Both diseases are health problems due to their impact on the quality of life (sleep quality, outdoor activities, education, occupational performance, etc.).[2,5] House dust mites (HDMs) are the major indoor allergen,[6] while pollen is the predominant cause of outdoor respiratory allergies.[7] Pollen monitoring provides relevant information about the role of this organic pollutant in ARD patients. For example, the description of specific periods of the year when there is an increase or decrease in pollen counts seated in a specific city or region could help the physician to predict the increase in the severity of ARD patients susceptible to pollen and therefore would aid in the prescription of preventive or therapeutic measures for improving the clinical symptoms.[8] Moreover, there is an increase in the prevalence of ARD

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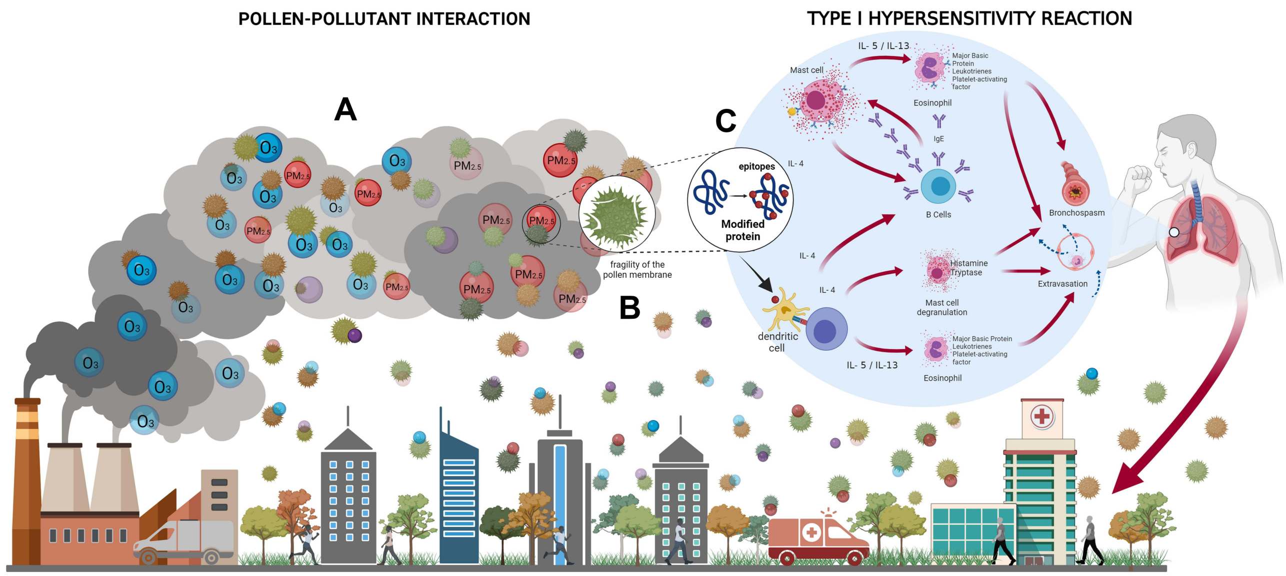

Figure 1 The interaction of pollutants such as $PM_{2.5}$ and O_3 with pollen induces: (**A**) an increase in the production of pollen concentrations, (**B**) a fragile pollen membrane, and (**C**) post-translational modifications in the allergenic protein. In all cases, there are increased levels of allergen proteins, which can be processed by antigen-presenting cells, resulting in a type I hypersensitivity inflammation (mechanism mediated by IL-4, IL-5, and IL-13, and an increase in immunoglobulin E), whose main objective is the degranulation of preformed mediators (histamine or tryptase) contained in mast cells, which promotes mucus secretion by goblet cells and bronchospasm, main symptom of asthma.
Abbreviations: $PM_{2.5}$, particulate matter of 2.5 micrometers or less; O_3, ozone; IL, interleukin.

worldwide, which is related to changes in the concentrations of environmental pollutants, specifically to the increases in pollen counts of various species.[9]

It is well established that pollution facilitates the development of allergic respiratory diseases. Nitrogen dioxide (NO_2), ozone (O_3), and particulate matter (PM_{10} or $PM_{2.5}$) have been associated with asthma exacerbations.[10] This observation is supported by a recent report from the American Thoracic Society Workshop Report showing that air pollution is associated with the onset of both asthma and an increased risk of allergic sensitization.[11] In this context, some pollutants such as $PM_{2.5}$ and O_3 increases pollen counts, leading to a higher concentration of allergenic proteins in the environment.[12] Additionally, $PM_{2.5}$ can induce greater fragility in the exine, causing a collapse of the pollen membrane and a subsequent release of epitopes.[13] These proteins can be up taken and processed by antigen-presenting cells in the respiratory tract mucosa, initiating the type I hypersensitivity-mediated inflammation, whose main objective is the release of preformed mediators (histamine) from mast cells by immunoglobulin E, increasing mucus secretion, vascular permeability and bronchospasm[14] (Figure 1). In the present study, we investigated the association of the allergic sensitivity of ARD patients with the presence of both outdoor aeroallergens and pollution in Mexico City.

Materials and Methods

Geographic Area

Mexico City is the smallest state in Mexico; it represents 7.3% of the national territory and has 9,209,944 inhabitants. It comprises 16 municipalities, Tlalpan being the greatest, with an area of 306.52 km^2, and is located at 19° 09' 57" north latitude and 99° 09' 57" west longitude (http://www.inafed.gob.mx/work/enciclopedia/EMM09DF/delegaciones/09012a.html). This demarcation is the fourth most populated (~700,000 inhabitants) in Mexico City (http://cuentame.inegi.org.mx/monografias/informacion/df/poblacion/). Most of the year, it has a subhumid climate (87%), rain occurs in summer, the total annual precipitation can reach up to 1200 mm per year, and its temperature ranges between 5 °C and 25 °C. (http://www.cuentame.inegi.org.mx/monografias/informacion/df/territorio/clima.aspx?tema=meande=09). This region is the location of the *Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío Villegas*. On its roof (15 m high), a Hirst-type volumetric spore trap (Burkard Manufacturing Co., Ltd., Rickmansworth, UK) is installed.

Subjects of Study

Ethics Statement

All participants provided written informed consent. This study was performed in accordance with the principles stated in the Declaration of Helsinki, and the study protocol was approved by the science and bioethics committee for research of the Instituto Nacional de Enfermedades Respiratorias "Ismael Cosío Villegas" (Approval number: E03-13), before the start of the study (February 20th, 2013).

Patients

The admission criteria to select medical records included: a) the clinical history had to refer to whether the patients lived and carried out their daily activities most of the time in the south of Mexico City, b) AR was diagnosed according to Allergic Rhinitis and its Impact on Asthma-ARIA 2008 guidelines (clinical antecedent of sneezing, itchiness, nasal congestion, and rhinorrhea and evidence of allergic sensitivity by any diagnostic method as skin prick test),[15] c) the asthma was diagnosed according to Global Initiative for Asthma-GINA 2012 guidelines,[5] the presence of suggestive lung symptoms (cough, wheezing, chest tightness, dyspnea) plus reversibility test (an increase of Forced expiratory volume in the first second) by spirometry; being this criterion only apply to the asthma group. From 3520 medical records from AR or ARwA patients attended in our department, only 520 medical records completed these criteria.

Allergen Sensitivity

The allergen sensitivity was evaluated by skin prick test (SPT) using 42 allergens ALK-Abelló (*Port Washington, NY, United States*), distributed as 16 trees (*Acacia* sp., *Morus rubra, Olea europaea, Eucalyptus* sp., *Juniperus californica, Populus tremuloides, Populus alba, Liquidambar styraciflua, Cupressus arizonica, Alnus glutinosa, Ligustrum vulgare, Juniperus virginiana, Schinus molle, Quercus alba, Prosopis* sp., and *Casuarina* sp.); 11 types of grass (*Holcus lanatus, Sorghum halapense, Orchard grass, Lolium perenne, Phleum pretense, Agrostis alba, Anthoxanthum odoratum, Triticum aestivum, Cynodon dactylon, Hordeum vulgare*, and *Bromus pratensis)*; 7 weeds (*Salsola kali, Taraxacum officinale, Artemisia vulgaris, Ambrosia trifida, Amaranthus retroflexus, Rumex crispus*, and *Chenopodium album*); 5 epithelia (*Felis domesticus, Oryctolagus cuniculus, Bos taurus, Canis lupus familiaris*, and *Equus caballus*), 2 mites (*Dermatophagoides pteronyssinus and Dermatophagoides farinae*), and *Blatella germanica*. We used 0.9% saline solution as a negative control and histamine hydrochloride (1:1000) as a positive control. All allergens were applied with a disposable polypropylene duo tip. The diameter of the wheal was recorded in millimeters, and a positive result measured 3 mm more in diameter than the negative control.[16] For pollen counts and pollutants comparisons, we group those allergens that belong to the same family and cannot be distinguished from each other (For example, *Juniperus californica* and *Juniperus virginiana*, conformed to the Cupressaceae family).

Meteorological and Pollutants Data

The meteorological data (wind speed-WSP, temperature-TMP, relative humidity-RH) and information of pollutants (particulate matter of ten micrometers or less-PM_{10}, particulate matter of two point five micrometers or less-$PM_{2.5}$, carbon monoxide-CO, nitrogen monoxide-NO, NO_2, nitrogen oxides-NO_X, O_3, particulate matter coarse fraction-PM_{CO}, sulfur dioxide-SO_2) were extracted from the *Red de Meteorología y Radiación Solar*-REDMET, the *Red Automática de Monitoreo Atmosférico*-RAMA, and the *Red Manual de Monitoreo Atmosférico*-REDMA on the AIRE-CDMX websites.[17] We calculated the averages of these data per day and by week (from 2014 to 2018) for subsequent comparison to the pollen counts.

Pollen Monitoring

Pollen count was measured with a Hirst-type volumetric spore trap-HS *(Burkard Manufacturing Co. Ltd., UK)*, which is an impact suction sampler located at *Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío Villegas*, in Tlalpan Mexico City placed outdoors at a height of 15 m from the ground. The HS mechanism consists of a constant incoming flow of air that impacts the receiving surface continuously and draws in a constant flow of 10 L/min that is arranged tightly around a cylindrical part called a drum that rotates continuously at 2 mm/h. The particles are deposited sequentially on a Melinex tape impregnated with silicone fluid, which is cut into 24 fragments (48 mm) that are mounted on slides using glycerin jelly stained with fuchsine and fixed with phenol, which makes it possible to obtain accurate results with time (gr of pollens-gP/m^3). The tape was analyzed every day by 40x optical microscopy (*Olympus CH 30, Tokyo, Japan*) by an aerobiology technician validated by the Aerobiology Network of *Red Mexicana de Aerobiología*-REMA. The pollen data were registered at the REMA website with PollenCntAdm software.

Pollen Data

We calculated the average of the daily concentrations over seven consecutive days to obtain the weekly mean concentrations to demonstrate the weekly variability in pollination (gP/m^3 per week). Finally, we calculated the annual pollen integral (APIn: sum of the mean daily concentrations of the whole year) of each species to analyze the magnitudes and interannual differences in pollination. For the report of pollination dynamics, we defined the start of the pollination season as the time when the pollen concentration exceeded 2.5% and the finish as when 97.5% of the total annual count had been accumulated.[18] Due to the peculiarities of most tree species in our region, where the flowering phase is in the winter, the start of pollination occurs at the end of the year, and the finish occurs at the beginning of the following year.[19]

Statistical Analysis

We analyzed the general pattern of allergic sensitization by age and disease, and then we compared these results with pollen monitoring (from 2014 to 2018). The association analysis between allergic sensitivity and pollen counts, both general and by period (before and after 2015), was performed with Epi Info v 7.0 (*Division of Health Informatics & Surveillance, DHIS, USA*) and was considered statistically significant with a *p*-value <0.05 and an odds ratio (OR) >1. Clinical quantitative variables and correlations between weather and pollutant variables were performed with SPSS software v.21 (*SPSS software, IBM, New York, USA*). Additionally, the pollen counts and pollutant concentrations were analyzed both per year and during the pollination season [season 1 (S1: 2014–2015), season 2 (S2: 2015–2016), season 3 (S3: 2016–2017), and season 4 (S4: 2017–2018)].

Results

Demographic Data and Allergic Sensitivity

A total of 520 patients without a predominance of sex were analyzed, with a median age of 20 years. 67.3% and 32.7% suffered from ARwA, and AR, respectively. A total of 63.6% had at least 2 allergens in the SPT (Figure 2A), 44.6% were exclusively sensitive to indoor allergens, 15.7% were sensitive to any pollen, and 39.6% were sensitive to both. The frequency of patients who were sensitive to at least one pollen was higher than that of patients who were exclusively indoors (55.3% vs 44.6%, *p*<0.001; OR=1.5) (Figure 2B). A total of 46.8% of the patients were only sensitive to trees, 8.6% to grasses, and 3.8% to weeds. The main intersections were the sensitivities to trees-grasses-weeds (16.3%) and trees-grasses (12.1%) (Figure 2C).

The most frequent pollen allergens were the trees of the Oleaceae family: *Fraxinus excelsior* (18%), *Olea europaea* (15%), and *Ligustrum lucidum* (14.2%), followed by *Betula verrucosa* (14.2%), *Quercus alba* (14%), *Quercus rubra* (14%), *Juniperus californica* (12.1%), *Juniperus virginiana* (10.1%), *Cupressus arizonica* (9.8%), and *Alnus verrucosa* (9.6%). These frequencies did not change when analyzed by disease. When we evaluated the sensitivity of the main tree allergens by specie and family, the frequency did not modify. *Fraxinus excelsior* was the principal allergen, followed by *Quercus* sp. -*Quercus alba* and *Quercus rubra*-, Cupressaceae family -*Juniperus californica, Juniperus virginiana*, and *Cupressus arizonica*-, and *Alnus* sp. However, indoor allergens were ranked first (Figure 3).

Allergic Sensitivity by Disease

We found that patients with allergic respiratory disease were more sensitive to Dermatophagoides or HDMs than to pollens independently if they suffered AR (89.1% vs 53.6%, *p*<0.001, OR=7.1) or ARwA (71.7% vs 50%, *p*<0.001, OR=2.5). In the same context, patients with AR were almost four times more sensitive to trees than to grasses (46.9% vs 18.5%, *p*<0.001, OR=3.8), and patients with ARwA were two times more sensitive (42.3% vs 20.6%, *p*<0.001, OR=2.8). The *Fraxinus* sp. and allergens of the Cupressaceae family were approximately two times more frequent than the other tree allergens in both diseases (Figure 4 and Supplementary Table 1).

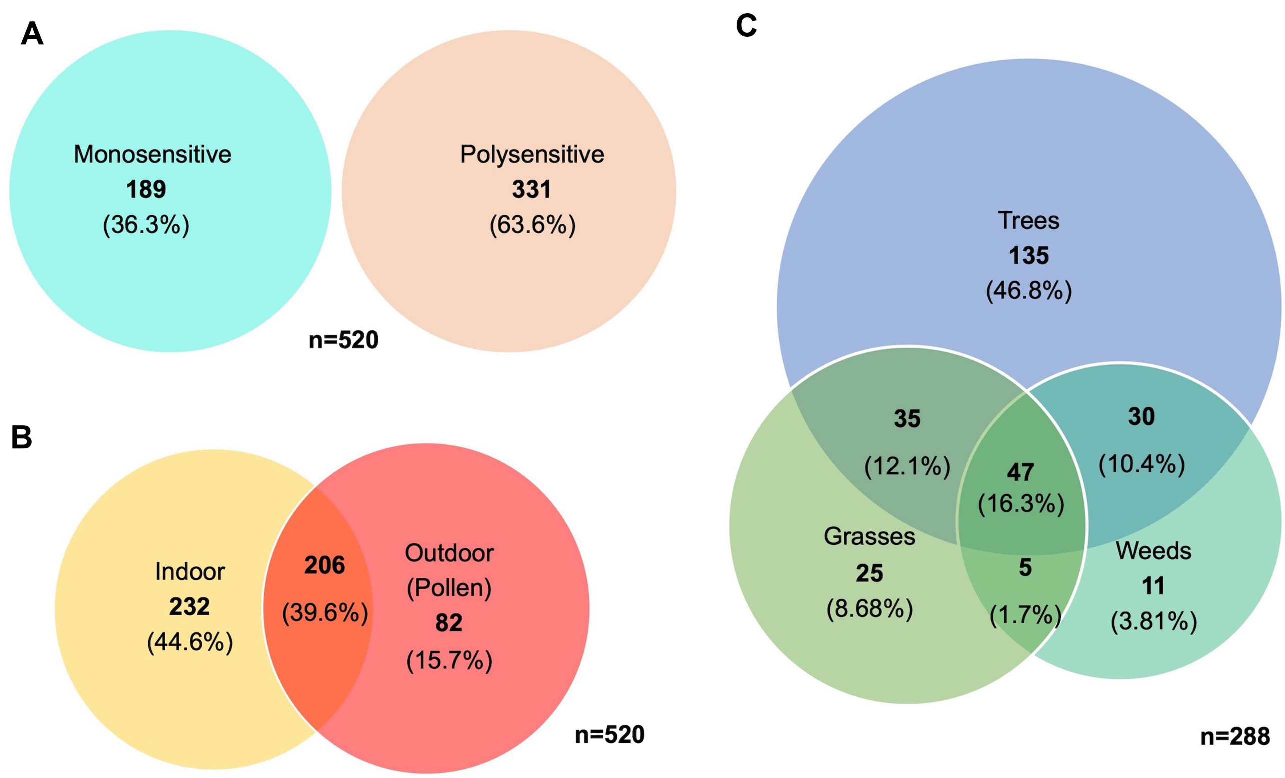

Figure 2 Distribution of allergy sensitivity. (**A**) Venn diagram of patients sensitive to only one allergen (monosensitive) and patients sensitive to two or more (polysensitive), (**B**) Venn diagram of patients sensitive to indoor allergens and/or pollen, (**C**) Venn diagram of patients sensitive to and/or different of pollen (trees and/or grasses and/ or weeds).

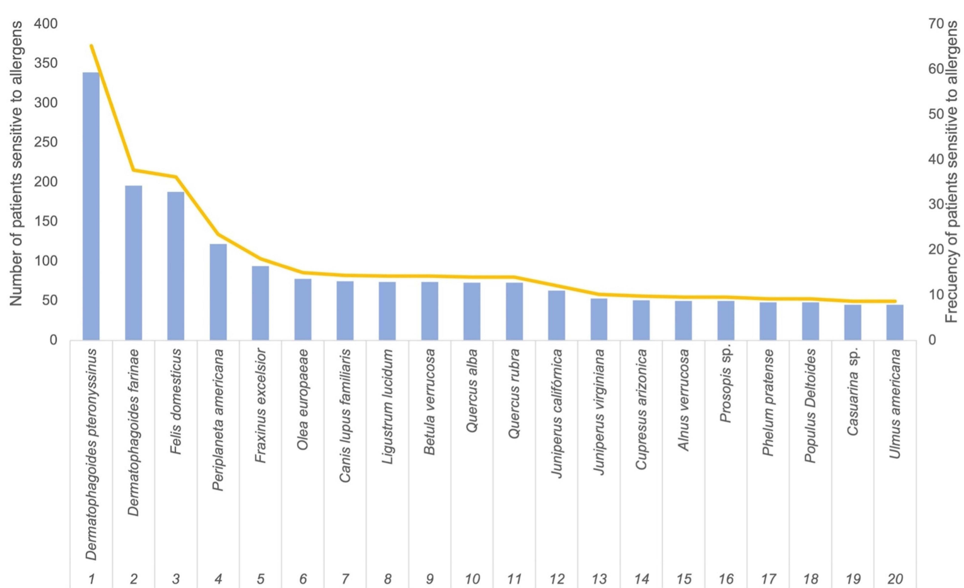

Figure 3 The main sensitization to aeroallergens in skin prick test.

Pollen Monitoring

The main pollens identified during the five years by APIn corresponded to trees, mainly belonging to *Fraxinus* sp. (32.5%), Cupressaceae family (31.1%), *Alnus* sp. (16.1%), *Casuarina* sp. (9.5%), *Pinus* sp. (3.7%), *Quercus* sp. (2.7%), Myrtaceae family (2.6%), Salicilacea family (2.9%), Moraceae family (1.5%), and *Schinus* sp. (1.2%) (Figure 5A, Supplementary Table 2). Interestingly, after 2015, there were increases in the pollen counts of most species, reaching the

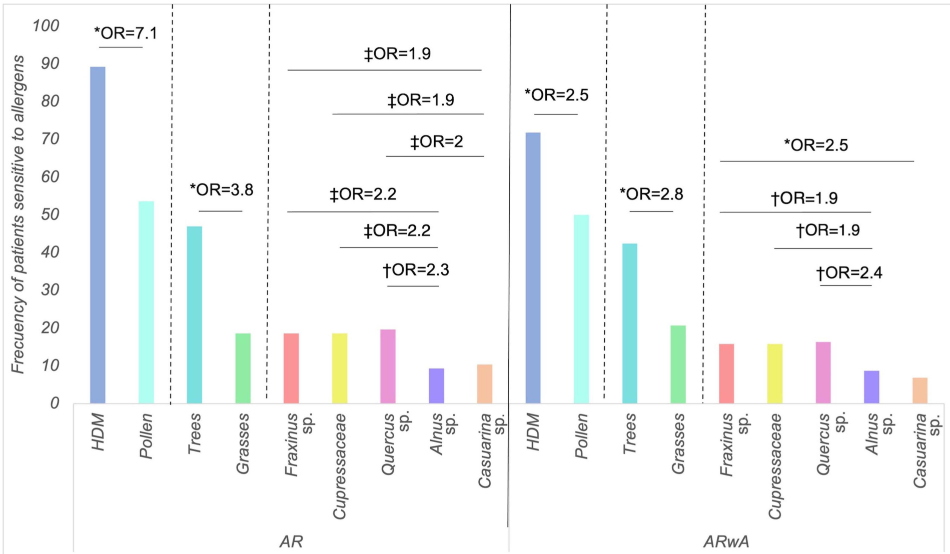

Figure 4 Allergic sensitivity by disease.

Notes: *p<0.001; †p<0.01; ‡p<0.05. Patients were more sensitive to HDM than to pollens. Both groups were more sensitive to trees than grasses (p<0.001). Likewise, *Fraxinus* sp. and Cupressaceae family allergens were twice more prevalent than other tree allergens (p<0.05).

Abbreviations: AR, allergic rhinitis; ARwA, allergic rhinitis with asthma; HDM, house dust mite. OR, odds ratio.

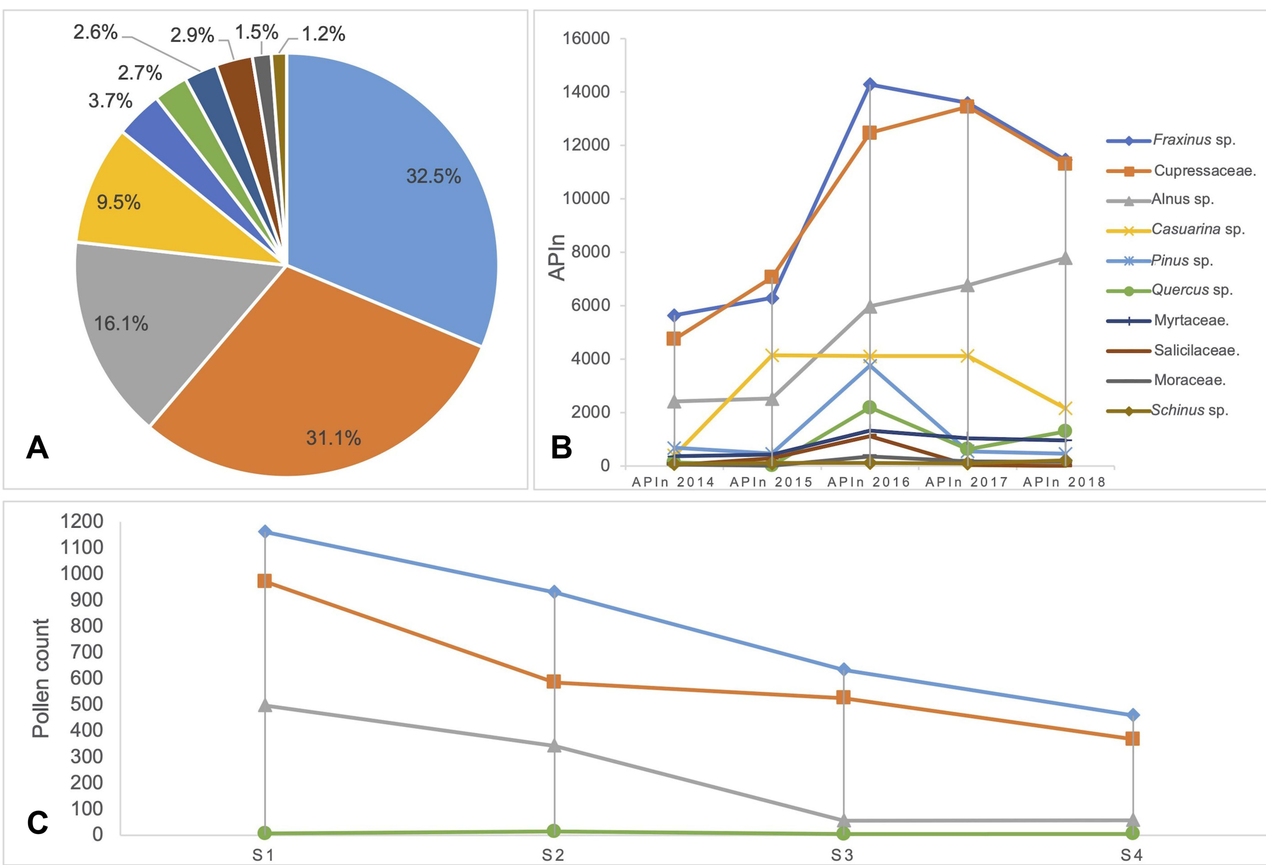

Figure 5 Pollen monitoring (2014–2018). (**A**) Pollen frequency, (**B**) Pollen count measured in annual pollen Integral (APIn), (**C**) Pollen counts by pollination season.
Abbreviations: S1, season 1; S2, season 2; S3, season 3; S4, season 4.

maximum values in 2016, except for *Casuarina* sp. (Figure 5B, Supplementary Table 2). However, when analyzing the main counts by the pollination season of each species (*Fraxinus* sp., Cupressaceae family, and *Alnus* sp.), the first season (2014–2015) had higher concentrations of pollen and was very similar in comparison to the second season (2015–2016), except for *Quercus* sp. However, these pollen gradually decreased in the third (2016–2017) and fourth seasons (2017–2018), reaching the most statistical significance when comparing S1 vs S4 (p<0.001). (Figure 5C and Table 1)

Allergic Sensitivity per Period

When comparing the sensitivity to pollen allergens, taking into consideration the start of the increase in pollen counts (2015), we analyzed the prevalence of sensitization by comparing two periods, the first period (2012 to 2014) and the second period (2015 to 2018). We identified that pollen sensitization significantly increased in the second period two times in AR and four times in ARwA (p<0.01 for each). Regarding specific sensitization by disease, there was an increase in the main sensitizer allergens in the AR group (*Quercus* sp. and *Alnus* sp. OR>3.0, p<0.05; by each), except for the Cupressaceae family. Instead, the ARwA group had increased sensitization frequencies for all allergens (*Quercus* sp. OR=5, Cupressaceae family OR=4, and *Alnus* sp. OR=3; p<0.001 by each). However, the most significant increase was observed for *Fraxinus* sp. in both the AR (OR=5, p<0.001) and ARwA (OR=9, p<0.001) groups. Moreover, HDMs were still the main allergens identified in both periods, and no increase in their frequency was detected (Figure 6 and Supplementary Table 3).

Meteorological Variables and Atmospheric Pollutants

When comparing the weather variables that occurred during the pollination season vs the no-pollination season, the temperature was lower in S1 and S2 (p<0.04), although it decreased in S3 and S4, even though it did not reach statistical significance. The WSP tended to be lower at S1, S2, and S4 but only showed significance at S3 (p=0.01); otherwise, the RH was lower in these seasons (p<0.001), excluding S3.

Regarding the pollutants, PM_{10}, $PM_{2.5}$, PM_{CO}, and NO_X were higher during the four pollination seasons (p<0.01 for each season). NO_2 also had a greater concentration in the pollination seasons (p<0.001); however, it showed a statistical tendency in S4. NO (p=0.001) and SO_2 (p<0.02) were higher in S1, S2, and S4. Meanwhile, CO had increased concentrations in S1 and S2 (p<0.004) (Table 2).

Global Correlations of Weather and Pollutant Correlations with Pollen Counts

When analyzing the counts from 2014 to 2018 of each pollinic season with both meteorological and pollution variables of the same time, we identified that temperature and WSP were the weather variables that correlated with the pollen of *Fraxinus* sp. and Cupressaceae family (r=−0.30, p<0.01 /r=−0.18, p=0.03), respectively. The pollutants (PM_{10}, $PM_{2.5}$, CO, NO, NO_2, NO_X, and PM_{CO}) correlated positively with *Fraxinus* sp., Cupressaceae family, and *Alnus* sp. (r>0.18 and p<0.05 for each). Conversely, *Quercus* sp. pollen only presented significant correlations with $PM_{2.5}$ (r=0.22 and p=0.04), CO (r=0.25 and p=0.01), NO (r=0.2, p=0.03), and NO_X (r=0.20, p=0.03), and it was the only pollen that correlated with SO_2 (r=0.17 and p=0.05). (Table 3 and Supplementary Figure 1).

Correlations by Pollination Season

We analyzed the correlations between air pollution and/or meteorological variables and airborne pollen during the four pollen seasons. The most constant and significant correlations were identified among air pollutants, and pollen concentrations were observed for PM_{10}, NO_2, and PM_{CO} with *Fraxinus* sp. in all seasons (p≤0.02 for each season). However, NO and NO_X concentrations were also related to *Fraxinus* sp. during S2, S3, and S4 (p≤0.02). NO_X was positively correlated with the Cupressaceae family in S2 and S3 (p≤0.01), and NO was positively correlated with the pollen of *Quercus* sp. in S1, S2, and S3 (p<0.04). Additionally, O_3 was related to *Alnus* sp. in S2, S3, and S4 (p≤0.01).

Interestingly, we found a notable increase from S2 in the number of significant correlations with the pollution variables that gradually decrease in the following seasons. Likewise, the contaminants mentioned above, in addition to CO and SO_2 and other meteorological variables (TMP, WSP, and RH), had significant correlations with at least one pollen in some pollination seasons (Figure 7, Supplementary Table 4, and Supplementary Figure 2).

Table 1 Seasons Comparison

Variable	C1			C2			C3		
	Season 1	Season 2	*p*	Season 1	Season 3	*p*	Season 1	Season 4	*p*
Fraxinus sp.	1161.50 (428–2372.25)	930.5 (292–1384.75)	0.06	1161.50 (428–2372.25)	634 (269–1095)	0.01	1161.50 (428–2372.25)	459 (377.75–644.75)	0.001
Alnus sp.	497 (238.5–1294)	342.5 (148.75–809.25)	0.1	497 (238.5–1294)	56 (8–633)	0.001	497 (238.5–1294)	58 (0–510.5)	<0.001
Cupressaceae	971.5 (489–1371.75)	585.50 (403.75–799.5)	0.01	971.5 (489–1371.75)	525 (359–864)	0.009	971.5 (489–1371.75)	368 (159.25–470)	<0.001
Quercus sp.	6.50 (0–34)	15 (0–36.25)	0.43	6.50 (0–34)	5 (0–50)	0.77	6.50 (0–34)	6 (1.25–22.75)	0.59
TMP	15.67 (14.20–16.78)	16.51 (14.93–19.58)	0.13	15.67 (14.20–16.78)	16.34 (15.22–19.21)	0.071	15.67 (14.20–16.78)	17.09 (14.02–18.22)	0.23
WSP	1.90 (1.61–2.11)	1.86 (1.67–2.11)	0.89	1.90 (1.61–2.11)	1.90 (1.74–2.08)	0.81	1.90 (1.61–2.11)	1.93 (1.70–2.22)	0.53
RH	50.26 (43.77–55.77)	43.55 (34.08–52.95)	0.037	50.26 (43.77–55.77)	59.65 (49.39–69.59)	0.001	50.26 (43.77–55.77)	43.69 (41.26–49.49)	0.02
PM_{10}	57.57 (44.50–66.16)	66.71 (53.54–76.64)	0.04	57.57 (44.50–66.16)	56.95 (48.33–67.52)	0.66	57.57 (44.50–66.16)	53.21 (46.33–60.15)	0.39
$PM_{2.5}$	27.85 (22.48–29.71)	33 (27.75–38.35)	0.009	27.85 (22.48–29.71)	26.80 (22.20–31.31)	0.85	27.85 (22.48–29.71)	26.27 (22.59–29.31)	0.54
CO	0.96 (0.89–1.09)	0.92 (0.85–1.07)	0.6	0.96 (0.89–1.09)	0.65 (0.52–0.91)	<0.001	0.96 (0.89–1.09)	0.54 (0.46–0.64)	<0.001
NO	36.21 (30.28–40.02)	31.96 (24.14–41.83)	0.37	36.21 (30.28–40.02)	25.26 (17.31–32.04)	<0.001	36.21 (30.28–40.02)	24.72 (22.29–31.89)	0.001
NO_2	34.99 (31.84–38.41)	37.36 (33.81–41.89)	0.04	34.99 (31.84–38.41)	32.28 (28.73–34.98)	0.04	34.99 (31.84–38.41)	33.91 (29.28–37.65)	0.39
NO_X	70.47 (62.70–77.71)	68.34 (60.32–83.82)	0.98	70.47 (62.70–77.71)	57.76 (45.98–68.97)	0.001	70.47 (62.70–77.71)	58.64 (53.83–70.83)	0.007
O_3	20.11 (16.55–26.26)	23.49 (19.05–36.41)	0.02	20.11 (16.55–26.26)	27.76 (18.69–32.82)	0.006	20.11 (16.55–26.26)	23.63 (20–29.35)	0.02
PM_{CO}	30.77 (19.60–32.63)	32.75 (26.63–38.25)	0.1	30.77 (19.60–32.63)	29.90 (24.06–36.78)	0.67	30.77 (19.60–32.63)	27.87 (23.76–31.82)	0.33
SO_2	8.22 (5.55–10.16)	7.79 (5.31–17.49)	0.69	8.22 (5.55–10.16)	6.95 (4.43–8.53)	0.63	8.22 (5.55–10.16)	9.69 (6.83–13.57)	0.18
Variable	**C4**			**C5**			**C6**		
	Season 2	**Season 3**	***p***	**Season 2**	**Season 4**	***p***	**Season 3**	**Season 4**	***p***
Fraxinus sp.	930.5 (292–1384.75)	634 (269–1095)	0.25	930.5 (292–1384.75)	459 (377.75–644.75)	0.021	634 (269–1095)	459 (377.75–644.75)	0.13
Alnus sp.	342.5 (148.75–809.25)	56 (8–633)	0.001	342.5 (148.75–809.25)	58 (0–510.5)	0.001	56 (8–633)	58 (0–510.5)	0.01
Cupressaceae	585.50 (403.75–799.5)	525 (359–864)	0.83	585.50 (403.75–799.5)	368 (159.25–470)	<0.001	525 (359–864)	368 (159.25–470)	<0.001
Quercus sp.	15 (0–36.25)	5 (0–50)	0.82	15 (0–36.25)	6 (1.25–22.75)	0.74	5 (0–50)	6 (1.25–22.75)	0.65
TMP	16.51 (14.93–19.58)	16.34 (15.22–19.21)	0.92	16.51 (14.93–19.58)	17.09 (14.02–18.22)	0.84	16.34 (15.22–19.21)	17.09 (14.02–18.22)	0.65

WSP	1.86 (1.67–2.11)	1.90 (1.74–2.08)	0.67	1.86 (1.67–2.11)	1.93 (1.70–2.22)	0.35	1.90 (1.74–2.08)	1.93 (1.70–2.22)	0.64
RH	43.55 (34.08–52.95)	59.65 (49.39–69.59)	<0.001	43.55 (34.08–52.95)	43.69 (41.26–49.49)	0.59	59.65 (49.39–69.59)	43.69 (41.26–49.49)	<0.001
PM_{10}	66.71 (53.54–76.64)	56.95 (48.33–67.52)	0.022	66.71 (53.54–76.64)	53.21 (46.33–60.15)	<0.001	56.95 (48.33–67.52)	53.21 (46.33–60.15)	0.13
$PM_{2.5}$	33 (27.75–38.35)	26.80 (22.20–31.31)	0.002	33 (27.75–38.35)	26.27 (22.59–29.31)	<0.001	26.80 (22.20–31.31)	26.27 (22.59–29.31)	0.64
CO	0.92 (0.85–1.07)	0.65 (0.52–0.91)	<0.001	0.92 (0.85–1.07)	0.54 (0.46–0.64)	<0.001	0.65 (0.52–0.91)	0.54 (0.46–0.64)	0.004
NO	31.96 (24.14–41.83)	25.26 (17.31–32.04)	0.003	31.96 (24.14–41.83)	24.72 (22.29–31.89)	0.01	25.26 (17.31–32.04)	24.72 (22.29–31.89)	0.46
NO_2	37.36 (33.81–41.89)	32.28 (28.73–34.98)	<0.001	37.36 (33.81–41.89)	33.91 (29.28–37.65)	0.01	32.28 (28.73–34.98)	33.91 (29.28–37.65)	0.23
NO_X	68.34 (60.32–83.82)	57.76 (45.98–68.97)	0.001	68.34 (60.32–83.82)	58.64 (53.83–70.83)	0.006	57.76 (45.98–68.97)	58.64 (53.83–70.83)	0.31
O_3	23.49 (19.05–36.41)	27.76 (18.69–32.82)	0.54	23.49 (19.05–36.41)	23.63 (20–29.35)	0.8	27.76 (18.69–32.82)	23.63 (20–29.35)	0.18
PM_{CO}	32.75 (26.63–38.25)	29.90 (24.06–36.78)	0.21	32.75 (26.63–38.25)	27.87 (23.76–31.82)	0.003	29.90 (24.06–36.78)	27.87 (23.76–31.82)	0.12
SO_2	7.79 (5.31–17.49)	6.95 (4.43–8.53)	0.08	7.79 (5.31–17.49)	9.69 (6.83–13.57)	0.76	6.95 (4.43–8.53)	9.69 (6.83–13.57)	0.003

Abbreviations: TMP, temperature; WSP, wind speed; RH, relative humidity; PM_{10}, particulate matter of 10 micrometers or less; $PM_{2.5}$, particulate matter of 2.5 micrometers or less; CO, carbon monoxide; NO, nitrogen monoxide; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; O_3, ozone; PM_{CO}, coarse fraction of PM_{10} and $PM_{2.5}$ particles; SO_2, sulfur dioxide; C1, comparison 1 (2014–2015 vs 2015–2016); C2, comparison 2 (2014–2015 vs 2016–2017); C3, comparison 3 (2014–2015 vs 2017–2018); C4, comparison 4 (2015–2016 vs 2016–2017); C5, comparison 5 (2015–2016 vs 2017–2018); C6, comparison 6 (2016–2017 vs 2017–2018).

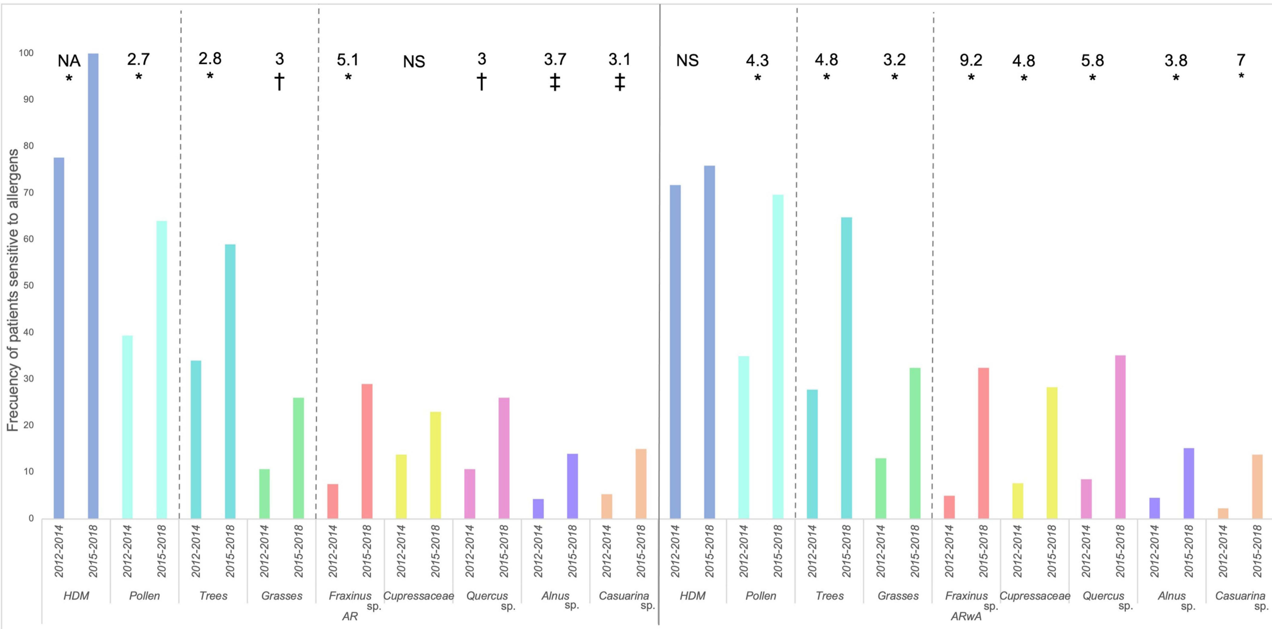

Figure 6 Allergic sensitivity per period by disease.

Notes: *$p<0.001$; †$p<0.01$; ‡$p<0.05$. In the second period (2015–2018), pollen sensitization increased significantly, twice in AR and four times in ARwA ($p<0.01$). *Quercus* sp. and *Alnus* sp. allergens sensitization raised in the AR group ($p<0.05$), whereas the ARwA group increased sensitization frequencies for *Quercus* sp., Cupressaceae family, and *Alnus* sp. ($p<0.001$). However, *Fraxinus* sp. sensitization was the one that increased the most in both groups ($p<0.001$).

Abbreviations: AR, allergic rhinitis; ARwA, allergic rhinitis with asthma; HDM, house dust mite; NS, non-significative; NA, not applicable.

Discussion

In the present study, we associated the sensitivity to aeroallergens in ARD patients with the pollen counts and the possible relationships with atmospheric pollutants. Since 2015, the pollination of trees has augmented for most taxa, especially for *Fraxinus* sp., *Quercus* sp., and the Cupressaceae family, which was associated with increases in sensitization to these species. In particular, some pollutants, such as PM_{10}, NO_2, and $PM_{CO,}$ were directly related to *Fraxinus* sp. pollination.

Pollinosis is the inflammation of the conjunctival, nasal, and/or bronchial mucosa induced by allergens from pollen grains through a type I hypersensitivity mechanism.[20] There is evidence that shows that half of AR patients are sensitive to any kind of pollen;[21] other groups have reported that its prevalence has almost doubled in recent decades.[22] Due to its clinical importance and tendency to increase, some studies have analyzed the factors that could be associated with this phenomenon.[23]

Consistent with previous reports, we identified that our population has a polysensitized pattern,[24] with the most prevalent allergen sensitizer being *Dermatophagoides* sp., plus at least one pollen (members of the Lamiales, Fagales, and Cupressales orders). Interestingly, this study showed tree pollen allergies relegate the grasses to less relevant positions, which indicates that the pattern of allergic sensitivity to pollen in Mexican patients is different from that described in Europe, where grasses are the main sensitizers.[21]

There is evidence that a population is sensitized to the pollen species to which they are more exposed in its geographic localization.[25] In our case, the species that induced greater levels of sensitization were *Fraxinus* sp., *Quercus* sp., and the Cupressaceae family. Some reports refer to the pollens of the Fagales, Cupressales, and Lamiales orders as being among the main sensitizers.[7,21] These observations are supported by other palynological studies developed in Mexico City, which described that the high counts of these pollens are identified during the dry season (from November to May);[19,26] (Supplementary Figure 3). Since 1977, *Pinus* sp. has been reported as the most frequent pollen in Mexico City and traditionally has been considered a non-allergenic pollen[27] for this reason, it was not included in the SPT by our group. However, its sensitivity is increased in populations that live near forested areas.[28] Trees are the dominant species of the forest surrounding this city, particularly in southern Mexico City, which may favor the allergic respiratory diseases in susceptible patients.

Table 2 Meteorological and Pollutants Analysis Between Pollination and No Pollination Seasons

Variables	Season 1			Season 2			Season 3			Season 4		
	Pollination Season	No Pollination Season	*p*	Pollination Season	No Pollination Season	*p*	Pollination Season	No Pollination Season	*p*	Pollination Season	No Pollination Season	*p*
***Fraxinus* sp.**	1161.5 (428–2372.25)	8.50 (1–24.75)	<0.001	930.5 (292–1384)	37 (9.5–37)	<0.001	634 (269–1095)	22 (7.5–44.75)	<0.001	459 (377.75–644.75)	4.5 (2.75–9)	<0.001
***Alnus* sp.**	497 (238.5–1294)	0.000 (0–1)	<0.001	342.5 (148.75–809.25)	18 (1.5–18)	<0.001	56 (8–633)	4 (2–13.5)	<0.001	58 (0–510.5)	0 (0–0)	<0.001
Cupressaceae	971.50 (489–1371.75)	30.50 (22–69.5)	<0.001	585.5 (403.75–799.5)	196 (37.5–196)	<0.001	525 (359–864)	95 (55.75–212)	<0.001	368 (159.25–470)	214.5 (151–366.25)	0.14
***Quercus* sp.**	6.50 (0–34)	0 (0–0)	<0.001	15 (0.0–36.25)	0.0 (0.0–0.0)	<0.001	5 (0.0–50)	0.0 (0.0–0.0)	<0.001	6 (1.25–22.75)	0 (0–0)	<0.001
TMP	15.67 (14.20–16.78)	17.16 (16.31–17.98)	0.003	16.51 (14.93–19.58)	17.8 (17.01–18.31)	0.042	16.34 (15.22–19.21)	17.46 (17.3–18.07)	0.104	17.09 (14.02–18.22)	17.20 (16.60–18.83)	0.24
WSP	1.90 (1.61–2.11)	2.06 (1.83–2.20)	0.095	1.86 (1.67–2.11)	2.02 (1.80–2.28)	0.067	1.90 (1.74–2.08)	2.11 (1.90–2.45)	0.012	1.93 (1.70–2.22)	2.06 (1.91–2.4)	0.09
RH	50.26 (43.77–55.77)	63.83 (59.99–67.05)	<0.001	43.55 (34.08–52.95)	58.83 (55.75–61.96)	<0.001	59.65 (49.39–69.59)	61.25 (57.85–63.45)	0.54	43.69 (41.26–49.49)	61.98 (56.72–68.24)	<0.001
PM_{10}	57.57 (44.50–66.16)	38.57 (38.80–42.64)	<0.001	66.71 (53.64–76.64)	47.92 (44.32–50.92)	<0.001	56.95 (48.33–67.52)	41 (37.41–46.14)	<0.001	53.21 (46.33–60.15)	37.59 (29.46–42.8)	<0.001
$PM_{2.5}$	27.85 (22.48–29.71)	18.16 (17.35–22.21)	0.001	33 (27.75–38.35)	26.57 (23.87–29.89)	0.001	26.8 (22.2–31.31)	20.71 (16.4–21.83)	<0.001	26.27 (22.59–29.31)	19.16 (13.8–23.06)	0.002
CO	0.96 (0.89–1.09)	0.87 (0.77–0.93)	0.004	0.92 (0.85–1.07)	0.81 (0.73–0.91)	0.001	0.65 (0.52–0.91)	0.73 (0.65–0.82)	0.128	0.54 (0.46–0.64)	0.54 (0.48–0.68)	0.71
NO	36.21 (30.28–40.02)	23.64 (21.41–29.57)	<0.001	31.96 (24.14–41.83)	23.62 (20.05–28.66)	0.001	25.26 (17.31–32.04)	20.19 (19.10–22.75)	0.078	24.72 (22.29–31.89)	17.58 (15.41–21.55)	0.005
NO_2	34.99 (31.84–38.41)	26.68 (24.66–29.74)	<0.001	37.36 (33.81–41.89)	29.85 (27.90–33.91)	<0.001	32.28 (28.73–34.98)	26.96 (24.6–29.82)	0.001	33.91 (29.28–37.65)	30.33 (28.07–31.79)	0.06
NO_X	70.47 (62.70–77.61)	51.95 (47.23–57.33)	<0.001	68.34 (60.32–83.82)	55.41 (48.51–59.96)	<0.001	57.76 (45.98–68.97)	49.27 (44.35–53.04)	0.006	58.64 (53.83–70.83)	46.89 (45.77–57.09)	0.007
O_3	20.11 (16.55–26.26)	20.44 (17.17–25.42)	0.905	23.49 (19.05–36.41)	26.42 (22.03–27.83)	0.773	27.76 (18.69–32.82)	25.02 (20.32–28.22)	0.327	23.63 (20–29.35)	21.13 (16.82–24.31)	0.04
PM_{CO}	30.77 (19.60–32.63)	17.76 (15.52–21.08)	0.001	32.75 (26.63–38.25)	20.70 (18.61–23.73)	<0.001	29.90 (24.06–36.78)	22.18 (18.25–23.81)	<0.001	27.87 (23.76–31.82)	17.73 (13.67–19.67)	<0.001
SO_2	8.22 (5.55–10.16)	4.74 (4.20–5.90)	0.002	7.79 (5.31–17.49)	5.89 (5.01–7.49)	0.027	6.95 (4.43–8.53)	5.21 (4.39–7.06)	0.163	9.69 (6.83–13.57)	5.84 (5.15–7.13)	0.001

Abbreviations: TMP, temperature; WSP, wind speed; RH, relative humidity; PM_{10}, particulate matter of 10 micrometers or less; $PM_{2.5}$, particulate matter of 2.5 micrometers or less; CO, carbon monoxide; NO, nitrogen monoxide; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; O_3, ozone; PM_{CO}, coarse fraction of PM_{10} and $PM_{2.5}$ particles; SO_2, sulfur dioxide; Season 1 (2014–2015); Season 2 (2015–2016); Season 3 (2016–2017); Season 4 (2017–2018).

Table 3 Global Correlations Between Meteorological Variables and Pollution with Pollen

Variables	*Fraxinus* sp.		Cupressaceae		*Alnus* sp.		*Quercus* sp.	
	Pearson r	*p*	Pearson r	*p*	Pearson r	*p*	Pearson r	*p*
TMP	−0.31	<0.001	−0.13	0.16	−0.11	0.24	0.11	0.24
WSP	−0.14	0.11	−0.18	0.03	−0.14	0.12	−0.15	0.1
RH	−0.05	0.56	0.05	0.59	−0.06	0.52	0.03	0.75
PM_{10}	0.50	<0.001	0.44	<0.001	0.31	0.001	0.14	0.12
$PM_{2.5}$	0.34	<0.001	0.38	<0.001	0.34	<0.001	0.21	0.02
CO	0.37	<0.001	0.38	<0.001	0.25	0.006	0.25	0.01
NO	0.35	<0.001	0.26	0.004	0.29	0.001	0.20	0.03
NO_2	0.34	<0.001	0.24	0.008	0.18	0.05	0.15	0.11
NO_X	0.37	<0.001	0.27	0.003	0.27	0.003	0.20	0.03
O_3	−0.18	0.06	−0.03	0.78	−0.07	0.45	0.03	0.76
PM_{CO}	0.56	<0.001	0.41	<0.001	0.23	0.01	0.07	0.48
SO_2	0.14	0.13	0.003	0.97	0.01	0.88	0.17	0.05

Abbreviations: TMP, temperature; WSP, wind speed; RH, relative humidity; PM_{10}, particulate matter of 10 micrometers or less; $PM_{2.5}$, particulate matter of 2.5 micrometers or less; CO, carbon monoxide; NO, nitrogen monoxide; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; O_3, ozone; PM_{CO}, coarse fraction of PM_{10} and $PM_{2.5}$ particles; SO_2, sulfur dioxide.

The intensity of pollen exposure has been defined by expert consensus.[29] Currently, there is no specific pollen count associated with sensitization.[30] However, this can also be due to the quantification method used in some studies. Bousquet described that the pollen counts differ if they are analyzed by gP/m^3 or weight (mg/m^3). For example, in France, Cupressaceae were the most abundant by count. However, grasses were the most abundant when the measurements were calculated in mg/m^3 despite its lower counts.[31] In addition, the traditional pollen count also differs from the allergenic proteins suspended in the atmosphere.[32] Therefore, some species can cause symptoms with lower counts.[31] All the above mentioned observations are justified because more than one-third of our population is sensitized to grasses or *Quercus* sp., which is the second sensitizer in our population despite their low counts. Interestingly, the pollens responsible for the main sensitizations have doubled in their counts since 2015. This phenomenon has been reported at other stations of pollen monitoring in Mexico City.[26] Likewise, some reports have described great augmentations of the interannual pollen counts for certain species, such as every three years for *Cryptomeria* sp., from two to four years for the Fagales order (*Betula* sp., *Corylus* sp., *and Alnus* sp.), and every three years for *Fraxinus* sp.[33–35] It is probable that 2015 corresponds to the zenith of pollen due to synchronic mass seeding; however, we need a longer period for identifying the flowering rhythms for the main species in our area. This might be due to the natural phenological behavior of the long-lived plants, which had a synchronic production of seeds at long intervals, where resource matching first had to gain the substrates needed for flowering readiness, and mass seeding reduced levels of loss to seed predators.[36]

The increase in pollen production has been described as a factor involved in the augmentation of sensitization frequency. For example, Lee KS described a positive correlation between the duration of the pollen season and the rates of sensitization to tree pollens in Korea (~0.28% per year, a total of 8295 new patients sensitized to Fagales species over 22 years).[23] Similar cases have been reported in Germany with *Betula* sp. and in Japan with *Cryptomeria japonica*.[37,38] In the same context, Switzerland has reported this phenomenon with the most prevalent species (birch and grasses). In contrast, the prevalence did not increase when there were no changes in pollen counts.[37] In our case, the great

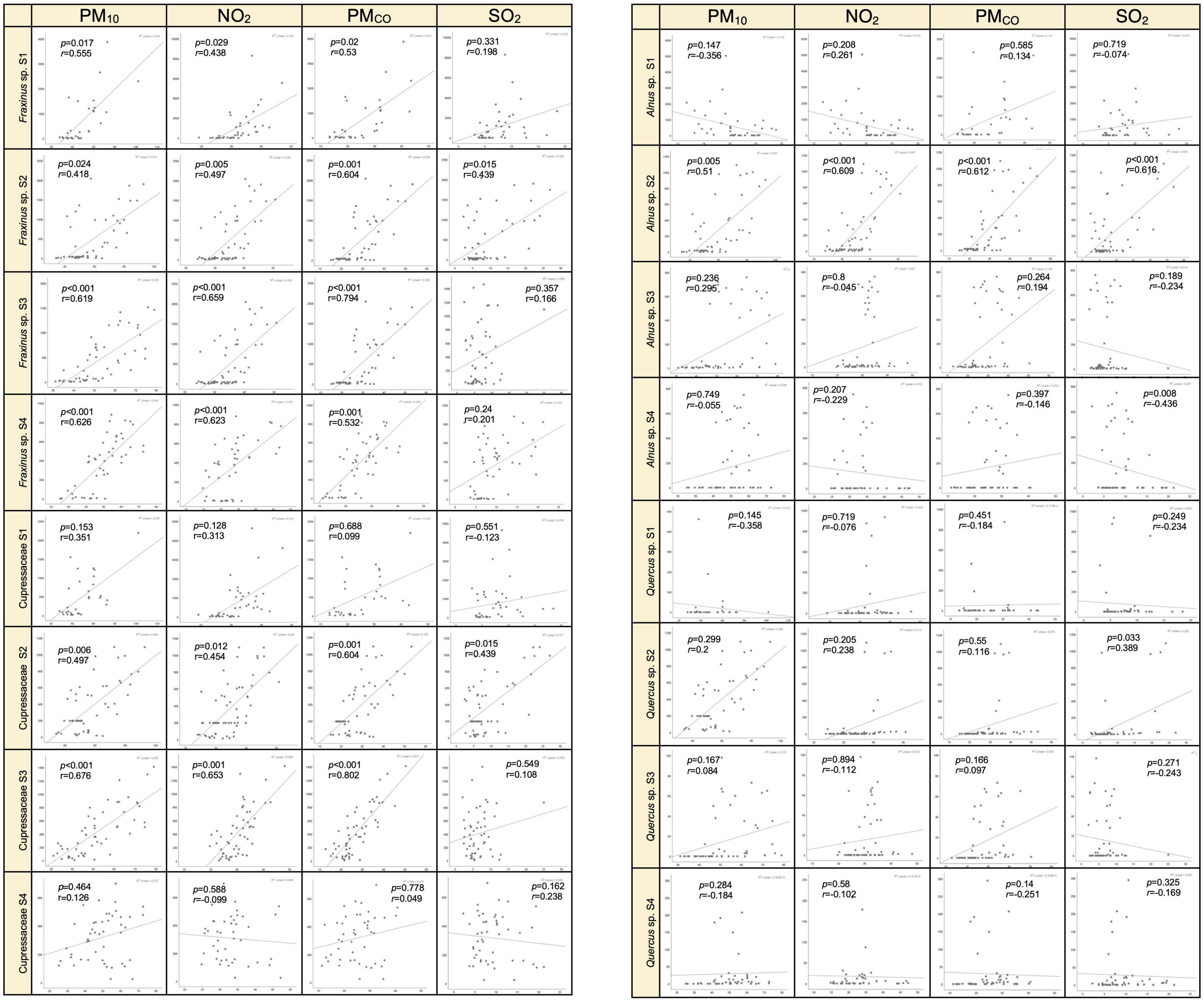

Figure 7 Seasons correlations between significant meteorological variables and pollutants with pollen.

Notes: The number of significant correlations with pollution variables increased significantly from S1 to S2. The most consistent and significant correlations were found between air pollutants and pollen concentrations in all seasons for PM_{10}, NO_2, and PM_{CO} with *Fraxinus* sp. ($p<0.02$).

Abbreviations: PM_{10}, particulate matter of 10 micrometers or less; NO_2, nitrogen dioxide; PM_{CO}, coarse fraction of PM_{10} and $PM_{2.5}$ particles; SO_2, sulfur dioxide; Season 1 (2014–2015); Season 2 (2015–2016); Season 3 (2016–2017); Season 4 (2017–2018).

augmentation in pollen counts was associated with respective increases in sensitization frequency for the main tree species (*Fraxinus* sp., Cupressaceae family, and *Alnus* sp.).

However, as previously mentioned, some pollens (*Quercus* sp. and *Casuarina* sp.) did not show significant increases in their counts, although we reported increases in sensitization to these pollens in our population. This phenomenon has been reported in other countries. Hirsch T. in Germany analyzed two populations located in Dresden and Münich exposed to different pollen amounts. The author described a higher prevalence of sensitization in patients with less exposure and vice versa, suggesting that some environmental factors, such as pollutants, are involved in this phenomenon.[39]

In this sense, we evaluated the role of pollutants in our geographical area. There is evidence that the variation in the concentrations of some pollutants, such as PM_{10}, $PM_{2.5}$, CO, NO, NO_2, NO_X, SO_2, and O_3, is associated with changes in the pollen counts of *Alnus* sp. and *Fraxinus* sp. due to these molecules modifying the flowering and pollination periods.[12,40] In our case, positive correlations of PM_{10}, NO_2, and PM_{CO} were found, mainly to *Fraxinus* sp. in all seasons. NO_2 exposure induces posttranslational modification (S-nitrosylation) of ragweed plants, resulting in an increase in Amb a 1 isoforms and increasing the allergenicity of ragweed pollen.[41] Additionally, the increase in NO_2 and SO_2 during the *Quercus* sp. pollen season can facilitate the bioavailability of airborne pollen allergens.[42] These events may increase the incidence of allergic diseases in contaminated areas. Similarly, ultrafine particles such as PM_{10} bind to pollen, altering its allergic properties, enhancing allergen release, and ultimately acting as an adjuvant, precipitating allergic disease.[13] Likewise, PM_{CO} was related to the variations in the concentrations of some particular pollens in our study. This is likely due to this molecule being a nonspecific classification molecule between $PM_{2.5}$ and PM_{10}. The mechanisms by which pollutants may alter *Fraxinus* sp. pollen allergenicity remain to be shown.

Nevertheless, reforestation has increased pollen counts. Patients become sensitive to at least one species of tree involved in reforestation programs.[43] Although Mexican laws guarantee a healthy environment and population well-being, Mexico City lacks a census of trees utilized in reforestation.[44] Mexico has the highest density and diversity of oaks,[45] which, alongside ash and cedar, are the main species used in reforestation in many cities of Mexico.[46]

In our study, the sensitivity to pollen was not specific to any one particular entity (AR or ARwA). There is evidence that a particular allergic disease could be sensitive to a specific allergen. For example, asthma without AR patients had a greater sensitivity to ragweed,[47] and most of our patients had asthma with AR.

We performed phenological analysis following current international recommendations for aerobiological sampling using standardized instruments and trained professionals. The sample corresponded to patients who undertook their daily activities in the vicinity of the aerobiological sampling area, and the sensitization assessments were carried out following the recommendations of allergic diagnosis using just one brand of allergen kit, avoiding allergenic potency bias. Among the limitations of the present study is that we did not analyze other environmental factors, such as biotic stress (infection), abiotic stress (nutritional deficiency), and other climate data. Interestingly, in 2015, there were increases in regional temperature and precipitation intensity compared to other years.[48] However, is necessary to evaluate these interactions additionally, it is important to describe the morphologic changes or particles adhered to the pollen grains induced by contaminants through scanning electron microscope[13] or analyze isoforms from pollen exposed to pollutants by proteomic technology.[49] Unfortunately, the SARS-CoV-2 pandemic prevented the monitoring of both phenological records and those data inherent to allergic sensitization. Knowing the pollination and the prevalence of pollinosis in patients with ARD is very important in health policy. Pollination can negatively affect lung function.[50] Sensitization to the Oleaceae and Fagaceae families is associated with an asthmatic crisis.[51,52] This phenomenon can be precipitated by meteorological phenomena different from those already analyzed, such as electrical storms, which can interact with the development of clinical outcomes.[51] Finally, we expect these results to help clarify the relationship between pollination and allergic sensitization and to be considered for the development of reforestation policies in both national and international regions.

Conclusion

The high increases in pollen counts of *Fraxinus* sp., Cupressaceae family, and *Alnus* sp. are associated with increases in the frequencies of sensitization to these species in ARD patients. This phenomenon is more related to the correlations of atmospheric pollutants such as PM_{10}, PM_{CO}, and NO_2 with *Fraxinus* sp. pollen.

Abbreviations

ARD, allergic respiratory disease; ARDs; allergic respiratory diseases; AR, allergic rhinitis; ARwA, AR with asthma; APIn, annual pollen integral; CO, carbon monoxide; HS, Hirst-type volumetric spore trap; HDMs, House dust mites; NO_2, Nitrogen dioxide; NO, nitrogen monoxide; NO_X, nitrogen oxides; OR, odds ratio; O_3, ozone; PM_{CO}, particulate matter coarse fraction; $PM_{2.5}$, particulate matter of two point five micrometers or less; PM_{10}, particulate matter of ten micrometers or less; RAMA, Red Automática de Monitoreo Atmosférico; REDMET, Red de Meteorología y Radiación Solar; REDMA, Red Manual de Monitoreo Atmosférico; REMA, Red Mexicana de Aerobiología; RH, relative humidity; S1, season 1; S2, season 2; S3, season 3; season 4; SPT, skin prick test; SO_2, sulfur dioxide; TMP, temperature; WSP, wind speed.

Data Sharing Statement

The pollutant and meteorological data were obtained from AIRE-CDMX websites (http://www.aire.cdmx.gob.mx/default.php), including RAMA, Red Automática de Monitoreo Atmosférico; REDMET, Red de Meteorología y Radiación Solar; REDMA, Red Manual de Monitoreo Atmosférico; REMA, Red Mexicana de Aerobiología.

Ethics Approval and Informed Consent

This study was performed in accordance with the principles stated in the Declaration of Helsinki, and the study protocol was approved by the science and bioethics committee for research of the Instituto Nacional de Enfermedades Respiratorias "Ismael Cosío Villegas" (Approval number: E03-13).

Consent for Publication

All authors have reviewed and approved the present manuscript.

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Author Contributions

All authors have contributed significantly to this work, either in conception, study design, implementation, data acquisition, analysis, and interpretation or in all of these areas. All authors participated in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be responsible for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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