# Impact of environmental factors on the epidemiology of eosinophilic esophagitis in southwestern Europe (2007-2020)

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**Background: Eosinophilic esophagitis (EoE) is a disease characterized by symptoms of esophageal dysfunction and at least 15 eosinophils/hpf in the esophagus. Other systemic and local causes of esophageal eosinophilia should be excluded.**
**Objectives: The study objectives were to examine the annual epidemiology of EoE for 14 consecutive years, investigate whether there is a relationship between the count of aeroallergens and the incidence of EoE for 12 years, evaluate whether there are family ties between the patients with EoE, and determine whether there are cases of EoE that are triggered or exacerbated by pollens.**
**Methods: We conducted a prospective, descriptive, and analytic study in patients with EoE for 14 years (2007-2020). The study variables were age, sex, relatives with EoE, time of evolution of the symptoms until diagnosis of the disease, and symptoms. We examined incidence and prevalence, annual counts of aeroallergens for 12 years, and number of diagnoses per year (in 2007-2020). We studied patients with active EoE (in April-July) and EoE in remission (in August-March) for 2 consecutive years. Exacerbations were investigated by measuring symptoms using a visual analog scale of 1 to 10.**
**Results: Of the 366 patients with EoE (studied from 2007 to 2020), 83.5% were atopic, with respiratory allergy and 28% had a food allergy. Their mean age was 35 years. The time of evolution of the symptoms was more than 6 years. Only 11% of the patients had a degree of kinship. Of the 366 patients, 87% had dysphagia, 27% had had impactions, and 12.5% had other symptoms of esophageal dysfunction. We found a positive correlation between the incidence of EoE and Platanaceae pollens. We did not detect any case of EoE triggered or exacerbated by pollens.**
**Conclusions: The epidemiology of EoE in southwestern Europe continues to grow. We have corroborated the relevant impact of the environment on genetics. Future studies will clarify the possible relevance of Platanaceae pollens in the increased epidemiology of EoE. The role of grass and Oleaceae pollens in triggering EoE is limited by having a short pollination in time. (J Allergy Clin Immunol Global 2023;2:100088.)**

***Key words:*** *Eosinophilic esophagitis, epidemiology, genetic, Platanaceae, aeroallergens*

Eosinophilic esophagitis (EoE) is a chronic local immune-mediated disease characterized by symptoms of esophageal dysfunction and at least 15 eosinophils/hpf in the esophagus. Other systemic and regional causes of esophageal eosinophilia should be excluded.[1] The incidence and prevalence of EoE in central Spain have both increased sharply, beyond previous estimations, interpreted in the context of expanding immune-mediated disorders.[2] This increase is occurring at a rate that is outpacing increased recognition of the disease, indicating the importance of environmental factors to the detriment of genetic factors.[3] This phenomenon is also observed in other atopic diseases.[4]

EoE has a genetic component but does not follow a classic mendelian inheritance pattern. A familial history increases the individual risk of EoE.[5]

In previous studies, the epidemiology of EoE in our region had increased sharply until 2017 in patients of all ages.[2] However, studies from that date onward relating the incidence of EoE with the concentrations of aeroallergens are rare. Most studies evaluating the potential role of aeroallergens in triggering EoE have studied the seasonal variation in EoE diagnosis and symptom onset or worsening, with mixed results.[6-8] Although numerous studies on environmental factors and EoE have been conducted, this field of research remains relatively underdeveloped.

Therefore, the objectives of this study were to study the annual incidence and prevalence of EoE for 14 consecutive years, investigate whether there is a relationship between the count of aeroallergens (pollens and molds) and the incidence of EoE for 12 years; evaluate whether there are family ties between the patients with EoE, and determine whether there are cases of EoE triggered or exacerbated by pollens (grass and Oleaceae) during at least 2 consecutive years.

## METHODS

This was a prospective, descriptive, and analytic study conducted for 14 years (2007-2020) in patients diagnosed with EoE according to consensus guidelines because they had symptoms of esophageal dysfunction (dysphagia, food impaction, chest pain, and heartburn) along with intraepithelial esophageal inflammation of at least 15 eosinophils/hpf. The patients ranged in age from 9 months to 81 years, and they all lived in Central South Spain.

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*Abbreviations used*
EoE: Eosinophilic esophagitis
SPT: Skin prick test

Strictly, in a health area in the autonomous region of Castilla La Mancha covering an average population of 220,000 inhabitants during the years of the study, patients with suspected atopic diseases (including EoE) were referred to the allergology clinic at Hospital General Universitario, which is the referral center for the entire population.

The annual incidence of EoE was calculated as the number of new patients identified each year divided by the average population in the study area during the corresponding year. Prevalence was estimated as the cumulative number of patients with EoE each year divided by the average number of people. The study area's population was supplied to us by the administration service of the hospital that covered the place in which we conducted the study. Analysis with children and adults was performed; 95% CIs were estimated.

Pollen grains (grass, Oleaceae, Cupressaceae, Platanaceae, and Amaranthaceae) and *Alternaria alternata* spore counts were measured in our allergology service by using a Burkard spore trap (Burkard Manufacturing Co, Rickmansworth, Herts, United Kingdom) (Fig 1, *A*). The sampling air flow rate was 10 L per minute, and the size of the spore trap's orifice was 14 × 2 mm. Pollens and fungus were caught on 24-mm-wide transparent tape coated with a thin film of petroleum jelly. This tape was mounted on a cylinder rotating at a speed of 2 mm per hour. To study the pollen and spores caught over 4 hours, a 48-mm sweep (2 mm per hour × 24 hours) was performed with an oil immersion lens (Prior Scientific Instruments Ltd, Cambridge, United Kingdom) (10× ocular, 100× objective, and field diameter of 0.18 mm).

An anesthetist monitored all endoscopic procedures performed on patients under conscious sedation; the monitoring was performed with a 9-mm high-definition flexible endoscope of 9-mm caliber (GIF-H180, Olympus Medical Systems, Hamburg, Germany) and Exera II image processor (Olympus Medical Systems). Biopsy specimens were taken with a conventional needle clamp (Radial Jaw 4, Boston Scientific, Proparck, Costa Rica) from the proximal and distal thirds of the esophagus, with at least 3 samples taken from each section.

Endoscopic signs included in the Endoscopic Reference Score were assessed.[9] Two additional biopsy samples from the antrum and duodenum were taken from all patients. The biopsy samples were fixed with formalin 4% and embedded in paraffin for further staining with hematoxylin and eosin. The samples were examined under a Nikon Eclipse 80i optic microscope (Nikon, Tokyo, Japan) with an hpf (×400) of 0.24 $mm^2$. The samples were also stained with periodic acid–Schiff reagent to exclude the presence of fungi.

All patients underwent a thorough allergic workup. Skin prick tests (SPTs) were performed with a commercial series of aeroallergens (*Lolium perenne*, *Olea europaea*, *Cupressus arizonica*, *Platanus acerifolia*, *Salsola kali*, and *A alternata*). We also served patients a commercial series of foods (milk, wheat, lentils, egg, nuts, pinout, hake, and prawn). The SPTs were carried out following the recommendations of the European Academy of Allergy and Clinical Immunology (EAACI). The allergens used (aeroallergens and food) were supplied by ALK-Abelló Laboratories (Madrid and Leti, Barcelona, Spain). The SPTs were performed on the patients' forearm by puncturing a drop of an extract with standardized disposable lancets. Histamine (10 mg/mL) and normal saline were used as the positive and negative controls, respectively. A wheal with an area of 7 $mm^2$ larger or a diameter of 3 mm larger than those of the negative control (saline solution) was considered positive.

Respiratory allergy was considered if the patients had symptoms compatible with rhinoconjunctivitis and asthma when there were aeroallergens in the air to which the patient was sensitized. Food allergy was considered if the patients had symptoms of oral allergy syndrome, urticaria, angioedema, digestive signs (diarrhea, vomiting, and abdominal pain), respiratory symptoms (nasoocular symptoms, cough, and bronchospasm), and anaphylaxis shortly after the ingestion of any food (<2 hours) to which they had been sensitized.

## Study variables

The study variables were age, sex, relatives with EoE, years of the evolution of symptoms until diagnosis, and symptoms (esophageal impaction, dysphagia, and gastroesophageal reflux–like symptoms). Incidence and prevalence, annual counts of aeroallergens for 12 years, and number of diagnoses of EoE per year (in 2007-2020) were recorded, as were the numbers of patients with active EoE (in April-July) and EoE in remission (in August-March) for 2 consecutive years. Exacerbations were also recorded (the symptoms were measured using a visual analog scale of 1-10). We considered patients' symptoms to have worsened if their score was at least 3 points higher than the baseline score and the eosinophil count was at least 3 times the baseline count (the number of eosinophils outside the pollen season for 2 consecutive years).

## Statistical analysis

Analyses and summaries were produced with the PASW statistical program, version 18.0 (SPSS, Inc, Chicago, Ill). A .05 level of significance was used throughout. Continuous variables were expressed as means and SDs (or medians and interquartile ranges), and categoric variables were expressed as percentages. The Student *t* test or Mann-Whitney *U* test was used for continuous variables, and the chi-square test for was used for categoric variables. A parametric correlation test (Pearson correlation test) was used to analyze the association between the overall number of cases of EoE diagnosed each year and pollen count per year during the study period.

All patients signed forms giving informed consent to participate in the study. This study was approved by our hospital's ethical committee of (C-281) and performed following the principles of the Declaration of Helsinki.

# RESULTS

This study was carried out on 366 patients diagnosed with EoE from 2007 to 2020. The mean age of the patients was 35 years (11% were aged <14 years), 75% were male, 83.5% were atopic, 82% had a respiratory allergy, 11% had atopic dermatitis, and 29% had a food allergy. The time of evolution of the symptoms until the diagnosis was 6 years and 8 months. The average number of diagnoses of EoE per year was 26 (range 1-54); 87% of the patients had dysphagia, 27% had impactions, and 12.5% had other symptoms of esophageal dysfunction (Table I). Only 11 patients in the study (3%) had relatives with EoE (a father and son, 3 brothers, and 3 sets of second cousins). We found only 1 patient with reactivated EoE in the spring (in 2018), but these results were not repeated in 2019. We did not find any patients who experienced exacerbation of their EoE during the spring.

The incidence and prevalence of EoE per year per 100,000 habitats during the 14 consecutive years studied and number of diagnoses of EoE per year are presented in Table II, which shows that the number of EoE diagnoses increased from 15 in 2010 to 54 in 2019 and decreased to 37 in 2020. We believe that the decrease in the number of EoE diagnoses in 2020 was due to the coronavirus disease 2019 (COVID-19) pandemic.

Table III presents the concentration (in $m^3$) of pollen grains of air and mold from different botanic families (Cupressaceae, Plantanaceae, Poaceae, Oleaceae, and Amaranthaceae) and spores of *A alternata* (an environmental fungus) and the number of the total aeroallergens over a 12-year period.

Table IV presents a descriptive summary and correlations of the number of aeroallergens (pollens and fungus [*A alternata*]) per $m^3$ of air per year in patients with EoE. It lists the aeroallergens

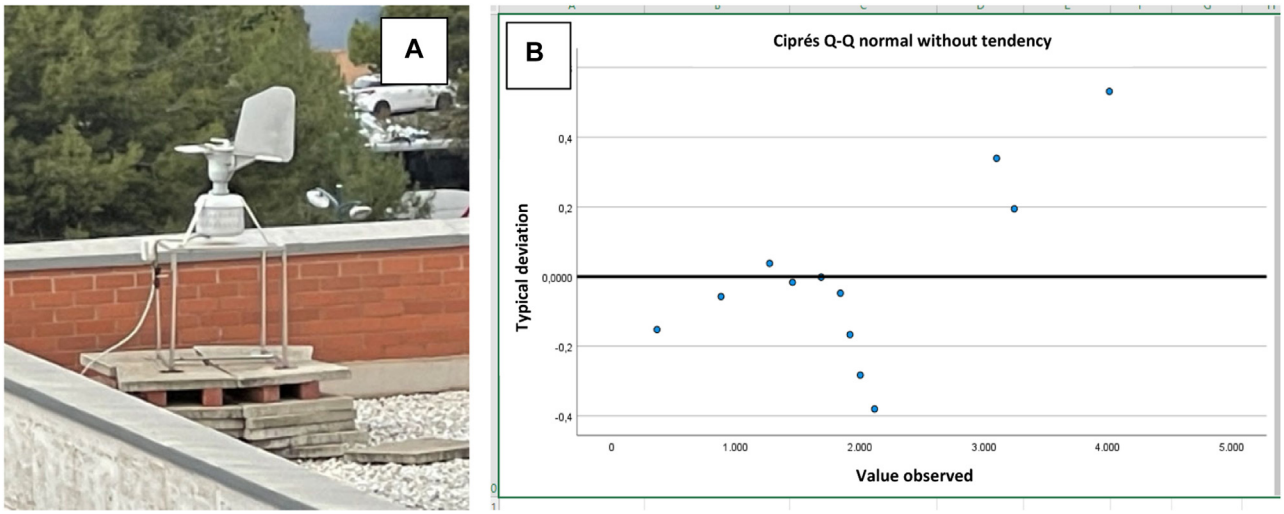


**FIG 1. A,** The situation regarding the pollen catcher (Burkard spore trap) in our hospital in Ciudad Real, Spain. **B,** The correlation is positive between diagnoses of EoE and Platanaceae pollen grains per $m^3$ of air, which is to say that for every 2-unit increase in Platanaceae pollen rises; there is a risk of a diagnosis of EoE.

**TABLE I.** Basic information of the study patients with EoE

| Characteristic | Value |
|---|---|
| Patients with EoE, no. | 386 |
| Median age (y) | 35 |
| Patients younger than 15 y, no. (%) | 43 (11%) |
| Male sex, no. (%) | 290 (75%) |
| Patients with atopy, no. (%) | 322 (83.5%) |
| Patients with respiratory allergy, no. (%) | 317 (82%) |
| Patients with IgE-mediated food allergy, no. (%) | 122 (29%) |
| Patients with atopic dermatitis, no. (%) | 43 (11%) |
| Time of evolution of symptoms (mo) | 80 |
| Diagnoses of EoE/y, average (range) | 26 (1-54) |
| Patients with dysphagia, no. (%) | 336 (87%) |
| Patients with food impactions, no. (%) | 104 (27%) |
| Patients with other symptoms of esophageal dysfunction, no. (%) | 48 (12.5%) |

(pollens and spores) studied, the arithmetic mean of the number of pollens and spores, and the correlation between EoE diagnoses and the number of pollen grains by family. The only positive correlation is with the Platanaceae family, which indicates that the number of Platanaceae pollen grains may be relevant to the number of EoE diagnoses (Fig 1, *B*). On the other hand, a negative correlation means the opposite. Therefore, the pollen grains of other botanic families studied (even though the counts are high) and spores of *A alternata* do not seem to influence the number of EoE diagnoses.

## DISCUSSION

All of the studies that have examined EoE incidence rates over time have concluded that the incidence of EoE is proliferating.[2] It is believed that this is not simply an artifact of increased surveillance and detection.[3] These findings are not explained by knowledge of EoE or the use of endoscopy.[5]

**TABLE II.** Incidence and prevalence of EoE per 100,000 habitats per year during 14 consecutive years and number of diagnoses of EoE per year

| Year | Incidence (100,000/y) | Prevalence (100,000/y) | No. of EoE diagnoses |
|---|---|---|---|
| 2007 | 0.455 | 0.455 | 1 |
| 2008 | 1.818 | 2.273 | 4 |
| 2009 | 5.455 | 7.728 | 12 |
| 2010 | 6.818 | 14.546 | 15 |
| 2011 | 11.364 | 25.91 | 25 |
| 2012 | 19.091 | 45.001 | 42 |
| 2013 | 16.818 | 61.819 | 37 |
| 2014 | 8.636 | 70.455 | 19 |
| 2015 | 17.727 | 88.182 | 39 |
| 2016 | 13.636 | 101.818 | 30 |
| 2017 | 12.727 | 114.545 | 28 |
| 2018 | 10.455 | 125 | 23 |
| 2019 | 24.545 | 149.545 | 54 |
| 2020 | 16.818 | 166.363 | 37 |
| Average (2007-2020) | 11.88 | 69.54 | 26.2 |

95% CIs were estimated.

EoE is a chronic and atopic disease,[7] so the prevalence rates have increased steadily across all sites and over time. The prevalence estimates of EoE vary by location. The prevalence tends to be much higher in developed countries.[3] According to the studies, significant variation is observed between the prevalence of EoE in Western and Eastern countries and is much lower in the latter.[3] How much of this increase is attributable to actual changes in disease incidence is still being determined. In pediatrics, the variation may also be due to the increasing availability and accessibility of pediatric endoscopy equipment and expertise. Also not clear are whether the rates are similar in less developed countries, whether the lack of epidemiologic data in these countries is due to a lack of access to technology and/or health care and to symptoms being reported only as a nuisance and considered of low priority, and whether there is

**TABLE III.** Pollen grains per $m^3$ of air and fungus for 12 years

| Year | Cupresaceae | Platanaceae | Poaceae | Oleaceae | Amaranthaceae | All pollens | *A alternata* | All aeroallergens |
|---|---|---|---|---|---|---|---|---|
| 2009 | 3,102 | 301 | 1,916 | 10,291 | 471 | 18,462 | 6,659 | 25,121 |
| 2010 | 1,458 | 222 | 3,301 | 5,098 | 855 | 13,479 | 6,802 | 20,281 |
| 2011 | 4,011 | 881 | 3,330 | 6,410 | 864 | 20,003 | 9,491 | 29,494 |
| 2012 | 1,689 | 919 | 2,718 | 4,593 | 386 | 13,168 | 9,240 | 22,408 |
| 2013 | 882 | 370 | 3,939 | 5,428 | 355 | 13,040 | 2,092 | 15,132 |
| 2014 | 2,119 | 253 | 2,695 | 1,843 | 253 | 8,820 | 3,702 | 12,522 |
| 2015 | 2,004 | 354 | 2,013 | 6,584 | 90 | 13,814 | 2,168 | 15,982 |
| 2016 | 3,245 | 743 | 2,183 | 7,515 | 847 | 16,978 | 7,077 | 24,055 |
| 2017 | 366 | 627 | 3,273 | 4,042 | 322 | 10,518 | 2,614 | 12,132 |
| 2018 | 1,273 | 1,255 | 2,188 | 7,674 | 477 | 15,819 | 6,940 | 21,759 |
| 2019 | 1,844 | 1,645 | 1,736 | 4,557 | 353 | 12,171 | 2,710 | 14,881 |
| 2020 | 1,921 | 697 | 3,346 | 8,072 | 662 | 16,316 | 4,981 | 21,297 |

**TABLE IV.** Descriptive study of aeroallergens and correlations between the number of aeroallergens/$m^3$ of air per year: Pollens, and fungus (*A alternata*) in patients with EoE

| Aeroallergens | Descriptive summary | Pearson correlation |
|---|---|---|
| Tree pollens (Platanaceae) | Arithmetic mean ± SD: 688.92 ± 437.305<br>Range: 1423<br>Interval: 222-1645 | 0.576 (positive correlation) |
| Oleaceae (*Olea europaea*) | Arithmetic mean ± SD: 608.92 ± 2228.507<br>Range: 8448, I:1843-10291 | –0.168 |
| Cupressaceae | Arithmetic mean ± SD: 1992.83 ± 297611<br>Range: 3645<br>Interval: 366-4011 | –0.111 |
| Grass pollens (Poaceae) | Arithmetic mean ± SD: 2719.83 ± 712.221<br>Range: 2203<br>Interval: 1736-3939 | –0.166 |
| Weed pollens (Amaranthaceae) | Arithmetic mean ± SD: 498.58 ± 256.305<br>Range: 774<br>Interval: 90-864 | –0.289 |
| All pollens | Arithmetic mean ± SD: 14382.33 ± 3246.736<br>Range: 1183<br>Interval: 8820-20003 | –0.139 |
| Mold (*A alternata*) | Arithmetic mean ± SD: 5289.67 ± 2653.227<br>Range: 7399<br>Interval: 2092-9491 | –0.252 |
| All aeroallergens | Arithmetic mean ± SD: 19588.67 ± 5438.072<br>Range: 17262<br>Interval: 12132-29494 | –0.193 |

a real difference in presentation and prevalence outside the developed world.[10,11]

In the future, it will also be essential to more thoroughly assess the incidence and prevalence estimates of EoE in specific patient subgroups to better understand the influence of age, sex, and race on the disease. Further long-term data are needed to clarify whether the increasing incidence and prevalence of EoE result from an increasing recognition and awareness of symptoms or reflect an actual increase in this disease driven by some yet unknown external factor.[10] We discovered that the general frequency of EoE triggered by aeroallergens in our series of patients with EoE is around 1.3%, and the frequency of EoE in response to occupational aeroallergens is about 1%. The frequency of EoE triggered by occupational aeroallergens in patients with occupational allergy respiratory disease is 8%, and the frequency in patients with esophageal dysfunction symptoms and occupational allergy respiratory disease is 57%.[12]

In our study conducted on children and adults, the incidence ranges per 100,000 inhabitants per year were between 0.45 (in 2007) and 16.81 (in 2020), and the prevalence fields per 100,000 inhabitants were between 0.45 (in 2007) and 166.36 (in 2020) (Table II). In this study, the mean incidence of EoE between 2007 and 2020 was 11.88 and the mean prevalence in the same period was 69.54 per 100,000 inhabitants per year. For comparison, the mean incidence in population studies existing in the literature and using national registries is estimated at approximately 10 cases per 100,000 people per year. The prevalence is reported to be between 10 and 57 cases per 100,000 people.[11] Our results are somewhat higher because some of our data are from more recent years.

In another more recent publication, the authors speak of an incidence rate of EoE of 5 to 10 and even 20 new cases per 100,000 inhabitants per year, and the prevalence is higher than 1 per 1,000 people.[13] In a health area close to ours, the mean incidence of EoE (in 2006-2017) was 9.1 in adults, and in 2017, the prevalence was 111.9 cases per 100,000 inhabitants.[2] Our results are somewhat higher, and this slight difference could be explained by the fact that these patients present earlier with other allergic comorbidities and by the fact that we asked all of our atopic patients about upper digestive symptoms.

We think that our finding of an increase in the number of diagnoses has been influenced by the fact that health professionals, especially allergists, are better acquainted with the disease because of introduction of the anamnesis of the patients with allergies to aeroallergens and food and because they ask questions about esophageal dysfunction symptoms such as dysphagia or food impactions if the patients are atopic adults. On the other hand, if the patients are children, we ask about alterations in swallowing or ask them to reveal the use of adaptive habits to solve the said symptoms.[14] In addition, other factors such as the increased awareness among health professionals, the widespread use of endoscopy, and the recognition of proton pump inhibitor–sensitive EoE have raised the epidemiology of this disease.[13]

The etiology of EoE is unknown, and environmental risk factors have been implicated. Many of these have roots in the theoretic framework of the hygiene hypothesis.[15] Exposures in early life, including antibiotic use, acid suppression, and childbirth by cesarean section, may increase the risk of disease.[16-19] Which, if any, of the aforementioned factors underlie the rising frequency of EoE remains to be seen. These factors need not be mutually exclusive, and the cause of EoE may well be multifactorial.[20]

The evidence on the involvement of environmental factors in the etiology of EoE is relatively poorly developed.[17] In a study that was carried out in children in Madrid and examined the incidence of EoE and its possible association with the most frequent annual pollen counts, it was found that pediatric EoE increased by an average of 19% annually. No significant association was found between incidence and pollen counts, except for a weak association with the species *Platanus*.[21] In children and adults, we found a positive correlation between the incidence of EoE per year and the grains per $m^3$ of pollen belonging to the family Platanaceae. *Platanus acerifolia*, a widely planted ornamental tree in urban areas, belongs to this family.[22] Our results indicate that more studies are needed to give relevance to this fact, especially if they are carried out in areas of increased exposure to Platanaceae pollens, such as Madrid and Barcelona because this pollen is higher in these cities than in the area in which our patients live.[23]

Previous studies have reported that warmer and drier weather increases atopic illness and perennial pollen levels, contributing to the higher than expected number of EoE cases recorded.[24] Therefore, a similar climate in recent years in the area in which our study was carried out could have contributed to the increase in incidence and prevalence.[13,25]

EoE occurs in family members with a nonmendelian pattern, indicating complex heritability.[26] As in other studies, we also observed how the environment modulates the genetics of EoE, because only 11 of our patients (3%) had at least 1 other relative with EoE.[27] In our series of patients, there were 5 who were first-degree relatives. EoE is more common among first-degree relatives at higher risk of developing EoE than among the general population. The risk of EoE is approximately 2.4% in siblings with the disease, suggesting a shared perinatal environmental risk factor beyond genetics.[17] The role of grass and Oleaceae pollens in triggering EoE is limited: in our environment, the number of pollen grains per $m^3$ of air is relevant, but the amount of time for they remain in the air is insufficient to trigger EoE because the symptoms usually appear after 2 to 3 weeks of being in contact with the triggering allergen whereas the pollens in the environment begin to decrease in 3 to 4 weeks.

In the literature, there are studies both for and against the seasonality of EoE diagnosis, with most of them correlating EoE with the pollen season. However, some do not find such seasonality in the diagnoses of this disease.[6] A single adult case series demonstrated new-onset EoE after a high burden of exposure to aeroallergens, including dust mites, pollen, and fungi. However, allergic sensitization to the triggering antigen was demonstrated in only 1 patient. In addition, because there has been no follow-up of these 3 patients, nothing is known about the evolution of EoE triggered by aeroallergens. Furthermore, this case series demonstrates that EoE can start after intense exposure to aeroallergens.[20,28] Although this topic is controversial, there is a possibility that inhalant allergen sensitization could play a modifying role in EoE in the context of cross-reacting food allergens.[29]

This study has its limitations. On the one hand, we present data from an allergology service, so it is possible that the results do not coincide with those of other services and other settings with different aerobiology. Also, the methodology is subject to underestimation and inaccurate measurement of the population of the health area because even though health care in Spain is universal and free, a good number of the immigrant population needs to be registered, and the census needs to be updated year by year. On the other hand, the study has strength in that it is a prospective study examining the epidemiology of patients with EoE for 12 to 14 consecutive years.

## Conclusions

The epidemiology of EoE in southwestern Europe continues to grow. Because of the small percentage of our patients with a family history with EoE, we indirectly detected the relevant impact of environmental factors over genetic factors. Future epidemiologic studies will clarify the possible relevance of Platanaceae pollens in the increased epidemiology of EoE. The role of grass and Oleaceae pollens in triggering EoE is limited because in our environment, the number of pollens/$m^3$ of air is relevant. Still, their time in the air is insufficient to trigger EoE.

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**Clinical implications: In view of the continued growth of the epidemiology of EoE, physicians must think about EoE and its triggers, above all in atopic patients, for early and accurate diagnosis and treatment.**

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