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Rising trend in pediatric eosinophilic esophagitis incidence in Spain: Results of a prospective study 2014–16

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Abstract

Objectives: The rate of eosinophilic esophagitis (EoE) diagnosis is increasing. This study aims to determine the incidence of EoE in the pediatric population residing in the southwestern Madrid and to analyze whether absolute monthly pollen counts, modified or not by the principal atmospheric pollutants, are associated with it.

Methods: A cross-sectional study on prospectively recruited patients was designed to calculate the incidence of EoE in children aged under 15 years who were diagnosed between September 2014 and August 2016 in twelve hospitals.

We collected demographic and symptoms data, date of onset of symptoms, date of medical consultation, and date of endoscopic diagnosis of each included patient. Relative risk estimation was performed to assess the association between the incidence of diagnosis and monthly pollen counts and levels of atmospheric pollutants. All these models were adjusted for the number of total patients that underwent endoscopy at first time.

Results: One hundred forty-eight patients were included. The most frequent symptoms were abdominal pain [42.57%], dysphagia [42.57%], and impaction [39%–86%]. The median overall monthly incidence was 1.13 [interquartile rank: 0.97–1.43] cases/100,000 children, and the annual mean was 15.2. The overall analysis of the relationship between incidence and absolute monthly counts, corrected for the number of first-time endoscopies performed, revealed no statistically significant association with pollen and air pollutants. There was a higher frequency of diagnosis during the pollination period of *Cupressaceae* [relative risk 1.647; 95% CI (1.192–2.276) $p < .002$] and during February and November (relative risk 1.67; $p < .01$).

Conclusions: This study confirms the high incidence of eosinophilic esophagitis and also suggests a period of higher incidence of diagnosis in the months of February and November as well as in the period of high pollination of *Cupressaceae*.

Abbreviations: EoE, Eosinophilic esophagitis; eos/HPF, Eosinophils per high-powered field; PPI, Proton pump inhibitors.

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KEYWORDS
eosinophilic esophagitis, epidemiology, pollen

1 | INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic local immune-mediated inflammatory disorder characterized by chronic or recurrent symptoms of esophageal dysfunction and eosinophilic infiltration of the esophageal mucosa in which other causes of tissue eosinophilia, both local and systemic, must be ruled out.[1,2] The rate of EoE diagnosis has been noted to be increasing in children in many studies globally,[3,4] according to geographical area and reference population, with an estimated incidence of 4 cases/100,000 inhabitants/year.[5] Navarro P et al.,[6] in their meta-analysis, described a greater annual incidence in adults (7.7/100,000 inhabitants) than in children (6.6/100,000).

The role played by aeroallergens in the pathogenesis of EoE is controversial.[7–9] Experimental studies have supported this hypothesis, and observational studies describe some seasonality in the presentation and exacerbations of the disease.[10] However, other studies and meta-analyses challenge this hypothesis.[11] Other environmental factors influencing the appearance of EoE have been described, such as the levels of air pollutants,[12] but no studies have quantitatively evaluated this relationship to date. A previous study by our group in the same geographic area also found a weak but statistically significant association between incidence and absolute annual and monthly counts during the *Platanus* spp pollen seasons[13] but without differentiating by period of pollination or correcting for pollutants.

The objective of this study is to describe the incidence of diagnosis of EoE in the pediatric population residing in the southwest of the region of Madrid since September 2014 and August 2016. As a secondary objective, we set out to analyze whether an association exists with the absolute monthly counts of the most frequent pollens in our environment (*Poaceae*, *Platanus* spp, *Cupressaceae*, *Artemisia*, *Olea* spp), modified or not by the principal atmospheric pollutants (NO_2, O_3, PM2,5, PM10) and between periods of high and low pollination of each one.

Key Message

The incidence of eosinophilic esophagitis is increasing in Western countries. It is unknown whether a relationship exists between eosinophilic esophagitis incidence and aeroallergens. There are no prospective data on pediatric incidence in Spain. The incidence of pediatric eosinophilic esophagitis is higher than in other parts of our country and in other European countries independently of number of endoscopies performed. This study found no significant association between diagnosis and monthly pollen counts. We describe a high incidence of diagnosis during the *Cupressaceae* pollination period, a finding not described in previous studies.

2 | METHODS

A cross-sectional study on prospectively recruited patients was designed to calculate the incidence of EoE in children aged under 15 years who were diagnosed between September 2014 and August 2016 in twelve hospitals.

All patients under the age of 15 newly diagnosed with EoE at one of the twelve hospitals located in the southwest of the region of Madrid with a defined catchment area, between September 2014 and August 2016 (total time: 24 months), were prospectively included. Cases were defined in accordance with the criteria established in evidence-based clinical guidelines on EoE, that is, patients with symptoms of esophageal dysfunction (heartburn, retrosternal pain, food impaction, gastroesophageal reflux, abdominal pain, vomiting/regurgitation, dysphagia, refusal to eat, cough, hematemesis) and infiltration on esophageal biopsy by 15 or more eosinophils per high-powered field (eos/HPF) independently of response to proton pump inhibitors (PPI).[1,2]

Patients already diagnosed with other causes of esophageal eosinophilia were excluded, as were those not residing in the health area studied. This investigation was conducted according to the principles set forth in the Declaration of Helsinki, and the registry supporting the study was approved on July 25, 2014, by the Clinical Research Ethics Committee of the Fundación Jiménez Díaz Hospital and it also obtained ethics approval from the remaining recruiting sites.

The variables collected from each patient were as follows: referring hospital, sex, date of birth, date of onset of symptoms, date of medical consultation, date of endoscopic diagnosis, age, place of residence, history of atopy and sensitization of patients to aeroallergens (*Poaceae*, *Platanus* spp, *Cupressaceae* spp, *Artemisia*, *and Olea* spp), and symptoms at diagnosis.

Time length from symptoms onset to the first visit to the specialist was calculated in each patient, as well as the time elapsed from this visit to the endoscopic examination that led to EoE diagnosis by median and interquartile rank.

Incidence was calculated as the number of new patients identified for each period of study (year and month) divided by the overall population under 15 years of age in the study area of each hospital. Demographic data were obtained from the Institute of Statistics of the Community of Madrid (available at http://www.madrid.org/iestadis/fijas/estructu/demograficas/padron/estructupcrd.htm).

The incidence rate was also calculated for sex and for individuals younger than 8 years of age and those over age 8 years. The number of total and first-time endoscopies carried out in the participating hospitals was gathered to assess the effect of this variable on incidence.

The Mantel-Haenszel test was performed to assess the existence of statistically significant differences in annual incidence by age group.

To analyze the relationship between the monthly incidence of EoE diagnosis and absolute monthly pollen counts, we used Poisson regression or regression negative binomial model in cases in which the data presented overdispersion to calculate the relative risk and confidence interval at 95%. All these models were adjusted for the number of total patients who underwent endoscopy at first time (first-time endoscopies) in order to limit the potentially confounding effect of the active search for the disease.

The relationship between the monthly incidence of EoE and the number of first-time endoscopies was performed by calculating the relative risk (RR) (95% confidence interval and p value <.05) using Poisson regression.

To study whether the concentration of air pollutants could enhance the risk associated with the monthly concentration of each pollen (interaction or modification of the effect) regression model that included the concentration of pollen, the concentration of air pollutant, and one term of interaction between both was used.

Absolute monthly counts of the main pollen types in the region of Madrid *(Poaceae*, *Platanus* spp, *Cupressaceae* spp, *Artemisia*, *and Olea* spp) were provided by the Red PalinoCam (available at: https://www.madrid.org/polen). Levels of air pollutants (O_3, NO_2, PM2.5, and PM10) were obtained from the Madrid Air Quality Network (available at https://www.madrid.org/calidaddelaire).

To assess the relative risk of being diagnosed with EoE, negative binomial regression models were applied based on pollen levels and using the diagnostic period as an indicator variable, represented in groups of 1 year. The same calculation was carried out with the mean of the maximum absolute pollen counts in each pollination period obtained from the Technical Document on Public Health, no. 70: "Atmospheric pollen in the Community of Madrid" available for consultation at http://www.madrid.org/bvirtual/BVCM009130.pdf taking into account the incidence of cases in each period. The existence of differences between mean pollen concentrations between both periods was confirmed by Mann-Whitney test. All calculations were performed using the Stata v.11 statistical program.

3 | RESULTS

During the study, a total of 148 patients who presented to the participating hospitals were diagnosed with EoE and were included in the study cohort. The percentage of males was 65.5% [n = 97] (male/female ratio: 1.9/1). The mean age ± SD at diagnosis was [9.7 ± 3.52] years, and the median was 10.43 years [interquartile rank: 7.13–12.66 years]. Of the total of patients, 48 were under 8 years of age and 100 were age between 8 and 15 years. The most frequent symptoms at diagnosis were abdominal pain [42.57%; n = 63], dysphagia [42.57%; n = 63], and food impaction [39.86%; n = 59]. Dysphagia and food impaction were more frequent in the group of patients aged 8–15 years (p < .01). Of all the patients included, 16.89% [n = 25] had a history of atopic dermatitis, 23.65% [n = 35] food allergy, 30.41% [n = 45] asthma, 29.05% [n = 43] allergic rhinoconjunctivitis, and 10.81% [n = 16] history of induction of oral tolerance to some food. There were no statistically significant differences between children aged under 8 years and those 8–15 years of age for these variables. Forty-eight of the 148 patients included (32.43%) did not present concomitant atopies. Allergen sensitization studies were not carried out systematically in all patients. Among those who underwent pollen sensitization tests, IgE sensitization against Poaceae was documented in 53% [43/81], Platanus spp and Olea spp 87.55% [42/48], and Cupressaceae spp in 32.4% [23/71]. This study was not performed in all the cases that were included.

The period between the subjective onset of symptoms and the first visit to the specialist was 10.13 months [median: 4.17 months; interquartile rank: 1.53–12.66 months], and the mean time elapsed from the first consultation to the performance of diagnostic endoscopy was 1.84 months [median: 1.07 months; interquartile rank: 0.47–2.03 months].

From September 2014 to August 2015, 1,356 upper endoscopies were carried out, of which 781 were first-time studies. From September 2015 to August 2016, 1,357 endoscopies were performed, 652 for the first time. The frequency of EoE diagnosis among all first-time endoscopies was [10.32%].

The monthly incidence (cases/100,000 inhabitants) throughout the study period appear in Figure 1 by age group and in Figure 2 by sex group. The number of cases per month and as compared to the reference population by age group is presented in Table 1 and by sex group in Table 2.

The median overall monthly incidence was 1.13 [interquartile rank: 0.97–1.43] cases/100,000 inhabitants under 15 years of age, and the mean of annual incidence was 15.2/100,000 individuals under 15 years of age [2014–15: 15.22; 2015–16: 15.2]. The monthly median incidence was 1.3/100.000 inhabitants/month [interquartile rank: 0.75–1.88] in the group of children under 8 years of age and 2.05 [interquartile rank: 1.38–2.41] in the group of patients aged 8–15 years (p = .016). No relationship was found between the monthly incidence of EoE and the number of first-time endoscopies [RR =1.022, 95% CI 0.998–1.047; p = .073].

We observed a peak in the incidence of diagnosis in February and November, revealing a period of high incidence (February and November) and another period of low incidence (other months). A comparison was made between incidence adjusted for the number of first-time endoscopies for both periods. Using a regression model, a risk ratio of 1.67 (95% CI 1.15–2.40) was estimated, according to which there is a 67% greater likelihood of being diagnosed in this period regardless of the number of endoscopies performed.

There was no statistically significant association between the monthly incidence of disease and mean pollen counts.

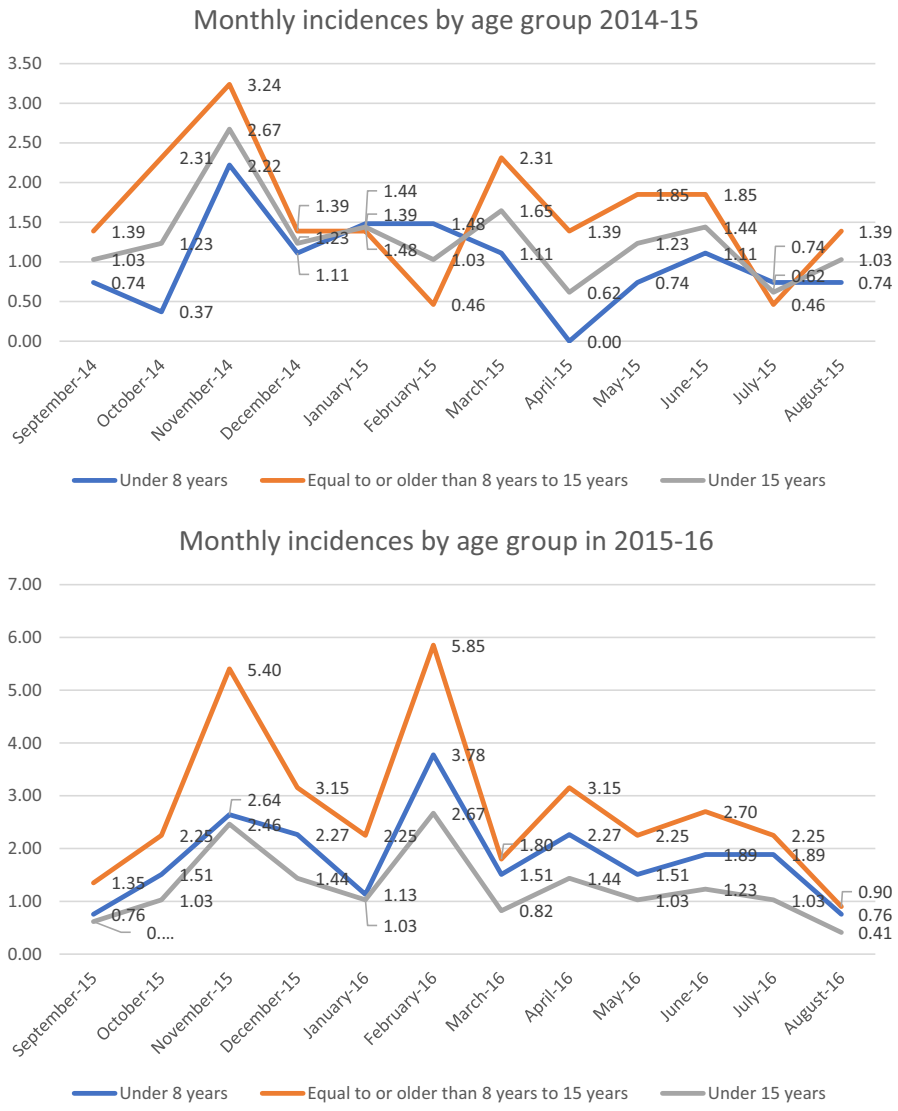

FIGURE 1 Monthly incidences by age group and period

However, comparing the incidence by periods of high and low pollination according to pollen type, a statistically significant association was observed [RR =1.647; 95% CI (1.192–2.276); p = .002] during the period of pollination of the *Cupressaceae* (Table 3). In contrast, a weak but statistically significant association was found between EoE incidence and the concentration of PM10 and NO_2 (Table 4).

4 | DISCUSSION

This study provides evidence that the incidence of EoE among the population under 15 years of age in our sample (minimum incidence of diagnosis, 15.2/100,000 children under 15 years of age/year) exceeds that reported in other international[3] and national [14,15] series. The clinical presentation, history of allergy, and demographic variables described in this study resemble data from other reports.[1,16,17]

Molina-Infante et al describe a progressive increase in incidence from 2007 to 2016, with an annual incidence in the last year of 13.7/100,000 inhabitants and a mean incidence of 8.09/100,000 inhabitants[14] in their prospective cohort of adult patients in our country. The prospective study by Arias et al.[15] with a population base includes a total of 19 cases under the age of 16 diagnoses between 2006 and 2017, with a mean annual pediatric incidence of 10.6 cases/100,000 inhabitants. All other published incidence data, national and international, come from retrospective, population-based studies or endoscopy registries, which do not take into account the number of first-time endoscopies carried out and exclude PPI-responsive cases, so they may be underestimated.[6,18–20]

In our area, a previous retrospective study by our group performed between 2002 and 2013 and which included 254 patients under the age of 15 years using the current diagnostic criteria without excluding cases with response to PPIs [1,2] reported a mean incidence of 6.04/100,000 under 15 years/year[12] with a mean annual increase of 19% [RR, 1.19; 95% CI, 1.14–1.25; p < .001] and a maximum in 2013 of 9.68/100,000 children under 15 years.

This series provides new incidence data through a prospective study of the pediatric population in the same geographic area of

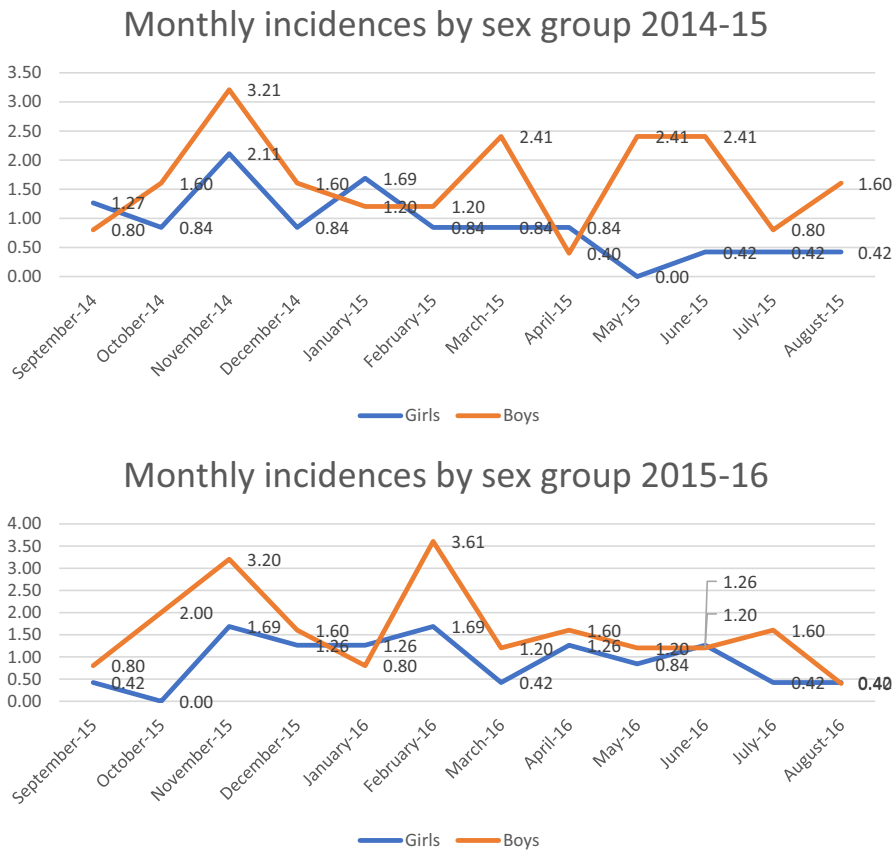

FIGURE 2 Monthly incidences by sex group and period

Spain. The retrospective series may not have included all cases, although the cases that were studied were included regardless of their response to PPI therapy. Therefore, a comparison of the two studies in the same geographic area confirms a real increase in the incidence of the disease across all age groups; this increase is not related to the greater number of first-time endoscopies according to data collected in the present study. The frequency of diagnosis of EoE among children who underwent upper gastroscopy in this study, 10.32%, was similar to that reported by other authors.[21]

In our study, the incidence of EoE in children younger than 8 years of age was lower than in the group of individuals aged 8 to 15 years. A previous retrospective study described a lower incidence in the first [0.55 (0.21–0.89)] compared to the second decade of life [0.95 (0.52–1.38)] without reaching statistical significance.[22] This could be due to a lower real incidence of the disease in children younger than 8 years of age or to a lower symptomatic expression of the disease in this age group, leading to a delay in diagnosis.[23]

Data on seasonal diagnosis of EoE and a causal relationship with aeroallergen exposure are scarce and heterogeneous.[9] The absence of data on the time elapsed between the onset of symptoms and endoscopy makes it difficult to ascertain the onset of the disease and likely influences seasonal variation.[24,25] It is conceivable that aeroallergen exposure could increase the histologic EoE activity that preceded endoscopic and clinical changes.

Studies such as those by Moawad et al and Fahey et al support the etiopathogenic relationship between exposure to aeroallergens and EoE development [26,27] and suggest seasonality of the initial EoE diagnosis. The literature contains descriptions of adult cases who develop EoE after massive exposure to aeroallergens.[28] The incidence study by Molina-Infante et al found no seasonal variations in diagnosis,[14] and the same is true for the prospective incidence by Arias et al.[15] However, periods that were considered in both studies did not attend to pollen periods according to type of aeroallergen and not correlate with local pollen records. In the retrospective study carried out by our group in the same geographic area, an association was found between the incidence of EoE in the pediatric population and the annual pollen counts of *Platanus* sp,[13] though in the study we did not assess the existence of differences in the incidence according to high and low pollination periods for each type of pollen. There are no studies to assess whether environmental pollution could influence this relationship.

Our study describes a period of high incidence of EoE diagnosis (February and November); this difference was statistically significant with respect to the rest of the months (period of low incidence). According to this model, regardless of the number of endoscopies performed in each period, 67% more patients are diagnosed in this high incidence period (RR 1.67%, 95% CI 1.15–2.40; $p < .05$). This seasonal pattern has not been previously described in other publications.

In our study, no statistically significant association was found between the monthly mean counts of the main pollen types registered and the monthly incidence during the 2 years of the study, though we did observe an increased risk of EoE diagnosis during the period

TABLE 1 Number of cases by group of age and month, overall population, and incidence

	Number of cases		Total population		Incidence (cases/100,000 inhab/month)		Incidence (cases/100,000 inhab/year)	
Month	<8 years	8–15 years	<8 years	8–15 years	<8 years	8–15 years	<8 years	8–15 years
September 2014	2	3	270,039	264,850	0.74	1.39	11.85	6.04
October 2014	1	5	270,039	264,850	0.37	2.31		
November 2014	6	7	270,039	264,850	2.22	3.24		
December 2014	3	3	270,039	264,850	1.11	1.39		
January 2015	4	3	270,039	264,850	1.48	1.39		
February 2015	4	1	270,039	264,850	1.48	0.46		
March 2015	3	5	270,039	264,850	1.11	2.31		
April 2015	0	3	270,039	264,850	0.00	1.39		
May 2015	2	4	270,039	264,850	0.74	1.85		
June 2015	3	4	270,039	264,850	1.11	1.85		
July 2015	2	1	270,039	264,850	0.74	0.46		
August 2015	2	3	270,039	264,850	0.74	1.39		
September 2015	1	2	216,133	222,070	0.76	1.35	19.43	26.12
October 2015	1	4	216,133	222,070	1.51	2.25		
November 2015	5	7	216,133	222,070	2.64	5.40		
December 2015	1	6	216,133	222,070	2.27	3.15		
January 2016	2	3	216,133	222,070	1.13	2.25		
February 2016	3	10	216,133	222,070	3.78	5.85		
March 2016	0	4	216,133	222,070	1.51	1.80		
April 2016	1	6	216,133	222,070	2.27	3.15		
May 2016	1	4	216,133	222,070	1.51	2.25		
June 2016	1	5	216,133	222,070	1.89	2.70		
July 2016	0	5	216,133	222,070	1.89	2.25		
August 2016	0	2	216,133	222,070	0.76	0.90		

of high pollination of the *Cupressaceae* (64.7%); this is the first finding of its kind to be published in the literature.

Therefore, there is insufficient evidence to confirm this causal relationship, although it is unknown whether the allergens may play a prominent role in a minority of patients [8–10] so more studies are required.

Seasonality in the EoE diagnosis may be influenced by pollen types, lifestyle habits that determine exposure, geographic area, differences in climate (in temperature and humidity) and masked by the diagnostic delay during the subclinical phase of the disease, overlapping of seasonal aeroallergens, and interannual and geographic variations.[29] Regarding environmental air pollutants, there are no published studies that directly assess their relationship as risk factors associated with the development of EoE.[30,31] In our study, this effect was significant but weak, so more studies are necessary to assess a possible pathogenic relationship.

This study has some strengths as its prospective design that includes data of cases of several hospitals of the same area and provides exhaustive and trustworthy data of pollen and pollutants unlike similar studies related with this topic. However, there are limitations too as its observational design. First, we have studied the possible association between pollen and environmental pollutants and EoE at the moment of endoscopic diagnosis. We are aware that it would be more accurate to relate these factors with the time of onset of symptoms, but this time is not easy to know in practice, as symptoms can be intermittent and initially non-specific. Some patients from the catchment area might have been diagnosed with EoE in other centers and so not be included in the study so the incidence rates that we report could be underestimated. Finally, the study period may have not been long enough to confirm a statistically significant association with pollen counts and air pollutants, so more studies are necessary on this topic.

5 | CONCLUSIONS

Our study confirms high incidence of EoE in the pediatric population residing in the southwest of Madrid, independently of the number of endoscopies carried. We did not find a statistically significant association between the monthly pollen counts and monthly

TABLE 2 Number of cases by group of sex and month, overall population, and incidence

	Number of cases		Total population		Incidence (cases/100,000 inhab/month)		Incidence (cases/100,000 inhab/year)	
Month	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
September 2014	2	3	249,255	236,917	0.80	1.27	19.66	10.55
October 2014	4	2	249,255	236,917	1.60	0.84		
November 2014	8	5	249,255	236,917	3.21	2.11		
December 2014	4	2	249,255	236,917	1.60	0.84		
January 2015	3	4	249,255	236,917	1.20	1.69		
February 2015	3	2	249,255	236,917	1.20	0.84		
March 2015	6	2	249,255	236,917	2.41	0.84		
April 2015	1	2	249,255	236,917	0.40	0.84		
May 2015	6	0	249,255	236,917	2.41	0.00		
June 2015	6	1	249,255	236,917	2.41	0.42		
July 2015	2	1	249,255	236,917	0.80	0.42		
August 2015	4	1	249,255	236,917	1.60	0.42		
September 2015	2	1	249,635	237,285	0.80	0.42	19.23	10.96
October 2015	5	0	249,635	237,285	2.00	0.00		
November 2015	8	4	249,635	237,285	3.20	1.69		
December 2015	4	3	249,635	237,285	1.60	1.26		
January 2016	2	3	249,635	237,285	0.80	1.26		
February 2016	9	4	249,635	237,285	3.61	1.69		
March 2016	3	1	249,635	237,285	1.20	0.42		
April 2016	4	3	249,635	237,285	1.60	1.26		
May 2016	3	2	249,635	237,285	1.20	0.84		
June 2016	3	3	249,635	237,285	1.20	1.26		
July 2016	4	1	249,635	237,285	1.60	0.42		
August 2016	1	1	249,635	237,285	0.40	0.42		

TABLE 3 Comparison of the incidence by periods of high and low pollination according to pollen type

Periods	RR	95% CI	*p*
Poaceae (high vs. low)	0.828	(0.560–1.224)	.343
Platanus (high vs. low)	1.111	(0.773–1.597)	.569
Cupressaceae (high vs. low)	1.647	(1.192–2.276)	.002
Artemisia (high vs. low)	1.269	(0.892–1.806)	.185
Olea (high vs. low)	0.895	(0.610–1.312)	.569

The period of maximum absolute pollen counts in each pollination period was obtained from the Technical Document on Public Health, no. 70: "Atmospheric pollen in the Community of Madrid" available for consultation at http://www.madrid.org/bvirtual/BVCM009130.pdf

TABLE 4 Relative risk estimation between EoE incidence and the concentration of air pollutants

Air Pollutants	RR	(95% CI)	*p*
NO_2	1.025	(1.012–1.037)	<.001
O_3	0.989	(0.981–0.996)	.004
PM2.5	1.011	(0.979–1.045)	.493
PM10	1.037	(1.011–1.063)	.004

Abbreviations: NO_2, Nitric oxide; O_3, ozone; PM10, suspended particles with size less than 2,5 microns; PM2.5, suspended particles with size less than 2,5 microns; RR, Relative Risk.

Levels of air pollutants (O_3, NO_2, PM2.5, and PM10) were obtained from the Madrid Air Quality Network (available at https://www.madrid.org/calidaddelaire).

incidence of EoE, though our findings do suggest a period of higher incidence of diagnosis in the months of February and November as well as in the period of high pollination of *Cupressaceae*. Well-designed prospective studies are needed to confirm this pathogenic hypothesis.

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CONFLICT OF INTEREST

Nothing to declare.

AUTHOR CONTRIBUTIONS

Enrique La Orden Izquierdo: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Project administration (lead); Supervision (lead); Validation (lead); Writing-original draft (lead); Writing-review & editing (lead). **IGNACIO MAHILLO:** Formal analysis (lead); Methodology (lead); Supervision (lead). **Sonia Fernández Fernández:** Investigation (equal). **Josefa Barrio Torres:** Investigation (equal). **Enriqueta Román Riechmann:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (lead); Project administration (equal); Supervision (lead); Writing-review & editing (lead). **Carolina Gutiérrez Junquera:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (lead); Project administration (equal); Supervision (lead); Writing-review & editing (lead).

ETHICAL APPROVAL

This study was approved by the local ethics committee.

CONSENT TO PARTICIPATE

All patients included gave informed consent.

PEER REVIEW

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APPENDIX 1

List of study centers

- Foundation Hospital Alcorcón (01).
- Doce de Octubre University Hospital (02).
- Fuenlabrada University Hospital (03).
- Getafe University Hospital (04).
- Infanta Cristina University Hospital (05).
- Infanta Elena University Hospital (06).
- Puerta de Hierro Madrid-Majadahonda University Hospital (07).
- Rey Juan Carlos University Hospital (08).
- Severo Ochoa University Hospital (09)
- Collado-Villalba General University Hospital (10).
- El Escorial Hospital (11).
- Aranjuez Hospital (12).