Increasing incidence of paediatric eosinophilic esophagitis in the southwestern of the region of Madrid

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ABSTRACT

Objectives: The incidence of eosinophilic esophagitis is unknown in our area. The aim of our study is to determine the incidence of diagnosis of eosinophilic esophagitis and its possible association with the most frequent absolute annual pollen counts.

Methods: A descriptive retrospective multicenter observational study was designed to calculate the incidence of eosinophilic esophagitis in children under 15 years in the southwest of the region of Madrid in 2002-2013 (provided by the Statistics Institute of Madrid). We collected patient data on age, sex, clinical presentation and date of endoscopic diagnosis. Relative risk estimation was performed (Stata v.11) using negative binomial regression models to assess the association between the incidence and pollen counts (provided by Subiza Clinic).

Results: Two hundred fifty-four patients, 75.6% male (n = 192) aged between 0.5-14.99 years were diagnosed. The clinical presentation was esophageal impaction 23.6%, dysphagia 22%, "*gastroesophageal reflux-like symptoms"* 44.9% and others 9.4%. The annual incidences from 2002 to 2013 per 100,000 children under 15 years / year were respectively: 0.81; 1.5; 0.37; 3.17; 3.07; 4.36; 6.87; 7.19; 8.38; 9.05; 9.14 and 9.68. The incidence of eosinophilic esophagitis increased by an average of 19% annually (RR 1.19, 95% CI: 1.14-1.25, p <0.001). In the overall analysis the relationship between incidence and absolute annual and monthly counts during times of pollination of pollen types analyzed only *Platanus spp* had a RR> 1 (1.17 and 1.06, respectively) (P <0.05).

Conclusion: The incidence of diagnosis of pediatric eosinophilic esophagitis has increased by an average of 19% annually. No significant association was found between the incidence and pollen counts, except for a weak association with *Platanus spp*.

Key words: Pollen. Eosinophilic esophagitis. Epidemiology.

RESUMEN

Objetivo: La incidencia de esofagitis eosinofílica es desconocida en nuestra área. El objetivo de nuestro estudio es determinar la incidencia de diagnóstico de esofagitis eosinofílica y su posible asociación con los recuentos absolutos anuales de los pólenes más frecuentes.

Métodos: Se diseñó un estudio descriptivo multicéntrico retrospectivo para el cálculo de la incidencia de esofagitis eosinofílica en niños menores de 15 años en el suroeste de la Comunidad de Madrid entre 2002-2013 (datos poblacionales obtenidos del Instituto de Estadística de la Comunidad de Madrid). Se recoge de cada paciente: edad, sexo, presentación clínica y fecha de diagnóstico endoscópico. Se estimó la asociación entre la incidencia y los recuentos polínicos (aportados por la Clínica Subiza) mediante cálculo del riesgo relativo usando modelos de regresión binomial negativa (Stata v.11).

Resultados: Se incluyeron 254 pacientes, 75.6% varones (n=192), de edades comprendidas entre 0.5-14.99 años. La presentación clínica fue: impactación esofágica 23.6%, disfagia 22%, síntomas sugerentes de reflujo gastroesofágico 44.9% y otros 9.4%. Las incidencias anuales desde 2002 a 2013 (nº casos/100,000 niños menores de 15 años/año) fueron respectivamente: 0.81; 1.5; 0.37; 3.17; 3.07; 4.36; 6.87; 7.19; 8.38; 9.05; 9.14 y 9.68. La incidencia de esofagitis eosinofílica se incrementó en una media anual de 19% (RR 1.19, 95% IC: 1.14-1.25, p <0.001). En nuestro estudio únicamente existió asociación (RR>1) entre la incidencia y los recuentos polínicos absolutos de *Platanus spp* anuales y durante los meses de máxima polinización (1.17 and 1.06, respectivamente) (P <0.05).

Conclusión: La incidencia de diagnóstico de esofagitis eosinofílica en la edad pediátrica se ha incrementado en una media anual de un 19%. No se encontró una asociación estadísticamente significativa entre la incidencia y los recuentos polínicos, excepto con el *Platanus spp* aunque ésta fue débil.

Palabras clave: Polen. Esofagitis eosinofílica. Epidemiología.

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Summary box:

WHAT IS KNOWN:

- The incidence of eosinophilic esophagitis is increasing in western countries.
- It is unknown if a relationship exists between eosinophilic esophagitis incidence and aeroallergens.
- There is no data of paediatric incidence in our country.

WHAT IS NEW:

- The incidence on the diagnosis of paediatric eosinophilic esophagitis is increasing in our area more than in other European countries over the period 2002-2013.
- The average of annual increase of incidence in paediatric population is 19% in our area.
- This study found no significant association between the incidence of diagnosis and pollen counts except for a weak association with *Platanus spp*.

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INTRODUCTION:

Eosinophilic esophagitis (EoE) is a chronic local immune-mediated inflammatory process characterized clinically by symptoms suggestive of esophageal dysfunction and histologically by eosinophilic infiltration (>15 eosinophils per high-power field) of the esophageal epithelium. The definition of EoE excludes other causes, local or systemic, of esophageal eosinophilia [1]. In young children, typical symptomatology is similar to gastroesophageal reflux (GERD), and, in older children, dysphagia and food impaction [2]. Treatment includes: dietary restriction for certain foods, exclusive PPI (protom pump inhibitor) treatment, topical corticosteroids or other treatments [3,4].

EoE diagnosis is increasing in our surroundings [5]. In addition, the existence of a real increase in the diagnostic incidence, mentioned in other published epidemiological studies, is clear in other areas [6].

Some studies have reported that incidence of EoE is seasonal, though this is not confirmed. Based on this factor and the pathogenic role attributed to food allergens, could be circulating aeroallergens may act as determinants of their incidence and exacerbations by means of cross reactivity [7,8]. However, this aspect is still controversial.

The objective of our study is to describe the incidence of EoE diagnosed in children under 15 years of age in the southwest of the Madrid region in the period between 2002 and 2013. A secondary objective is to describe the clinical presentation pattern and to assess the relationship between the number of cases and the average level of circulating aeroallergens both annually and in the periods of peak pollen count.

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PATIENTS AND METHODS:

A retrospective sampling of all patients under the age of 15 newly diagnosed with EoE during the period between 2002 and 2013 was performed in 11 public hospitals in the southwest of the region of Madrid through review of electronic medical records. Cases were defined as patients with symptoms of esophageal dysfunction associated with presence of esophageal eosinophilic infiltration equal to or greater than 15 eosinophils per high-power field [1] including PPI responders. Patients with other causes of esophageal eosinophilia were excluded, as were those not belonging to the referral area or diagnosed with EoE before 2002. The variables collected from each patient were: sex, month of endoscopic diagnosis, age, diagnostic symptom (grouped into: esophageal impaction, dysphagia, symptoms "*gastroesophageal reflux symptons-like*" and others). This study was approved by Ethical committee.

To assess clinical manifestation as related to age of presentation, the total sample was divided into two groups, consisting of patients younger than 8 years and equal to or older than 8 years. To estimate the annual incidence, we used the referral population under 15 years of age for each hospital/year, provided by the Statistics Institute of the region of Madrid (available at: http://www.madrid.org/iestadis/) (table 1). This estimation was performed in the same way for each age group, taking the respective denominator in each case. The existence of statistically significant differences between the annual incidence by age group (patients <8 years and patients ≥8 years) was analyzed by the Mantel-Haenszel test.

A negative binomial regression model was used to estimate the possible association (RR) between the EoE diagnosed in the pediatric population and the pollen counts.

The average annual absolute pollen counts of the main taxons of Madrid *(Olea spp, Platanus spp, Poaceae, Artemisia, Urticaceae, Cupressaceae and Quercus spp)* provided by the Subiza Clinic was used (available at: https://www.clinicasubiza.com). The analysis included counts of *Alternaria alternata* fungus, as it is the most important

outdoor fungus from an allergy point of view and is present throughout the year (table 1).

The diagnostic period was represented as an indicator variable in groups of one year. From these data, the relative risk (RR) of being diagnosed of EoE was estimated based on the pollen levels using negative binomial regression models [9].

The same calculation with the absolute maximum pollen counts in each pollination period (obtained from the Public Health Technical Paper nº70: "Atmospheric Pollen in Madrid" available for consultation in https://www.madrid.org/polen) taking into account the incidence of cases in each period included. All calculations were performed using the statistical program Stata v.11. This study follows the principles for observational studies outilined in the Declaration of Helsinki.

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RESULTS:

A total of 254 patients were collected, 75.6% male (n = 192), aged between 0.5-14.99 years (mean: 9.24 years, standard deviation: 3.43 years, median: 9.67 years, mode: 6.6 years). Eighty-four were under 8 years and 170 were equal or older 8 years to 15 years old. Clinical presentation was: esophageal impaction 23.6% (n=60), dysphagia / difficulty swallowing 22% (n=56), *gastroesophageal reflux-like symptoms* 44.9% (n=114), casual findings 5.1% (n=13) and other findings (study due to low weight, diarrhea, *H. pylori* infection) 4.3% (n=11). Clinical presentation according to age group (younger and older than 8 years) is presented in figure 1. Statistically significant differences were found between both groups ($p<0.05$).

The overall mean incidence of EoE diagnosis was 6.04 / 100,000 children under 15 years of age/ year. In patients younger than 8 years of age, this was 3.50 and in the equal or older than 8 years to 15 years of age group was 9.41. This difference was statistically significant (RR 2.68, 95% CI 2.09-3.45, $p < 0.001$).

Annual incidences from 2002 to 2013 were, respectively: 0.39; 1.5; 0.37; 3.17; 3.07; 4.36; 6.87; 7.19; 8.38; 9.05; 9.14; 9.68 cases / 100,000 habitants under 15 years / year. This upward trend is presented in overall terms and by age groups in figure 2. It was estimated that, from 2002 to 2013, the incidence of eosinophilic esophagitis increased by an average of 19% annually (RR 1.19, 95% CI: 1.14-1.25, $p <0.001$).

The overall analysis of the relationship between the incidences and the absolute counts of the pollen types, both annually and monthly during peak pollen count period (pollination period) obtained only a statistically significant association ($p<0.05$) with *Platanus spp,* both annually and in the pollination period. However, the strength of this association was weak (RR 1.06 and 1.10 respectively). According to this model, a 6% and 10% increase in the risk of developing eosinophilic esophagitis is expected for every 1,000 unit increase in *Platanus* pollen counts annually and monthly during

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pollination period respectively. There was no relationship with other pollen counts ($p>0.05$).

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DISCUSSION:

The incidence of paediatric eosinophilic esophagitis in our area has increased in last years by an average of 19% annually, being of 9.7/100.000 children/year in 2013. These results corroborate what has been published, although the incidence varies widely according to the geographical area. The systematic review by Soon et al published in 2013 found incidences ranging from 1.6 / 100,000 people / year in Denmark to 10/100,000 people / year in the United States with an average annual increase of 12-17% [10]. Recently, a systematic review of 2016 by Arias et al supports these results, finding a global incidence in children of 5.1 / 100,000 people / year (lower than in adults), with a significant increase in diagnosed disease in studies carried out from 2008. Geographical variations were observed, similar to those described in the Soon et al study, with significant differences between the United States (5.4 /100,000 people / year, 95% CI:1.6-11.5) and Europe (1.7 / 100,000 people / year, 95% CI: 1-2.7) [6]. These values come mostly from retrospective studies [10].

In our country, pediatric EoE series are scarce. There is a retrospective serie from a hospital of Barcelona published in 2005 that presents 11 patients newly diagnosed in the period from January 1997 to November 2003, though with no actual incidence data reported [5]. Another series is from a prospective observational study that includes seventeen patients with a diagnosis of EoE (>20 eosinophils per high-power field) in a hospital of Madrid from 2001 to 2009 [11]. Nevertheless, there are no reported data in our country of incidence in children, and, to our knowledge, our study is the first to provide data on the incidence of diagnosis of EoE in the paediatric age. In this study, there is a clear increase in incidence from 2008-2009 that could be related to an increase in the number of endoscopies performed in paediatric population, an active search for cases with a greater diagnostic suspicion but also with a real increase in incidence of the illness.

In addition, some studies suggest that oral food immunotherapy may be another factor contributing to the increasing incidence of EoE, although we have no data about this topic in our series [12].

Prospective series published in nearby regions include a mixed series of adults and children (age range: 6-63 years, mean age 33.6 years) from 43 patients between 2006 and 2011 [13] and another pediatric series (under 16 years) of 35 patients from January 2011 to December 2015, with a mean age of 9.6 years (4-16 years) [14].The reference population is not included in any of them, so actual incidence calculation is not possible. On the other hand, our incidence data are similar to incidence data of adult population published by Molina et al in our country in the period from 2007 to 2016 that includes PPI responder cases too [15].

The prevalence of males and mean age at diagnosis coincides with that reported in other publications [10].

Clinical presentation is similar to that described in other publications [16] and, as described above, there is a variation in the clinical presentation according to age groups [17], with more frequent occurrence as atypical gastroesophageal reflux-like symptoms that does not respond to usual treatment in patients younger than 8 years of age while, in older than 8 years group, as dysphagia/impaction [10]. Statistically significant differences were found between the annual incidence according to age group. The incidence in the younger group could be really lower or underestimated by unspecified symptoms. The time of onset of the histological alteration is unknown, as is the moment at which the symptomatology begins.

The relationship between EoE and aeroallergens is controversial. A recent systematic review found no significant variations in the seasonal distribution of the incidence of eosinophilic esophagitis [18]. However, seasonality and pollination are not a purely temporal static concept, and they are conditioned by climatic changes (rain patterns ...) or type of vegetation that are variable. Thus, studies such as the one by Moawad et al

[7] or Fahey et al [8] show that there may be a correlation between the incidence of eosinophilic esophagitis and some aeroallergens, though to date it is impossible to distinguish which ones may be responsible. A recent systematic review recognizes that seasonal, geographical and climate-based differences in disease prevalence could be due to multiple environmental exposures although the exact mediators of this process remain elusive [19].

In our study, we found no statistically significant association with any type pollen except with *Platanus spp,* both annually and monthly in peak pollen count period, but the strength of association was weak. According to this model, we could assume that for every 1.000 units increase of this particle, a 10% increase in the risk of eosinophilic esophagitis is expected in a population under 15 years. A study from 1979 to 1993 in Madrid puts the pollen of *Platanus spp* as the second most frequent pollen in this area [20]. There is a high degree of awareness to it and thus it is a major cause of hay fever in our population [21].The theory of cross-reactivity between aeroallergens and food allergens [22, 23] might explain its relationship with EoE. Thus, its massive inhalation in high amounts would exceed the mucociliary clearance and allow arrival into the esophagus. In a situation of increased mucosal permeability, the immunological relationship in deep layers and the recruitment of eosinophils could be triggered [24]. The degree of contamination and suspended particles of the inhaled air could act as a potentiating factor [25, 26].

The limitations of our study are partly a reflection of its retrospective nature. Incidence is probably underestimated due to patients not included in the retrospective review, or others from the catchment area who were diagnosed in other private or public centers not included in the study. Therefore, these data reflect a minimal incidence of diagnosis. On the other hand, we have no data about sensitization to *Platanus sp* and other aeroallergens in these patients, so we can not establish a possible relationship.

We did not evaluate the effect of other environmental factors such as pollutants on the modification of this relation.

Also, due to the retrospective nature of our study, the time of onset of symptoms could not be accurately recorded. The onset of symptoms could more accurately express the onset of the disease, avoiding the time until diagnosis. However, it is known that the disease can be detected as an incidental finding in endoscopies for other causes, that the symptoms may be intermittent, and that inflammation may precede symptoms at onset [27]. This is why it is not possible to analyze whether the symptomatic onset is influenced or not by pollen counts.

Pollen counts were monitored in the centre of Madrid. Although the origin of the data of absolute pollen counts reflects the variations of absolute pollen counts during each year, the quantity of each type of pollen could be different in several places of the same area as it depends of the type of vegetation in each place.

In conclusion, our study is the first of its kind to provide data of incidence of diagnosis of eosinophilic esophagitis in paediatric population residing in an area of Madrid and demonstrates the real increase of this diagnosis along twelve years period. We only observed a weak association between the incidence and annual pollen counts of *Platanus spp.* Well-designed prospective studies are needed to confirm these findings and should account for other factors such as environmental contamination.

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Figure 1. Clinical profile by age group.

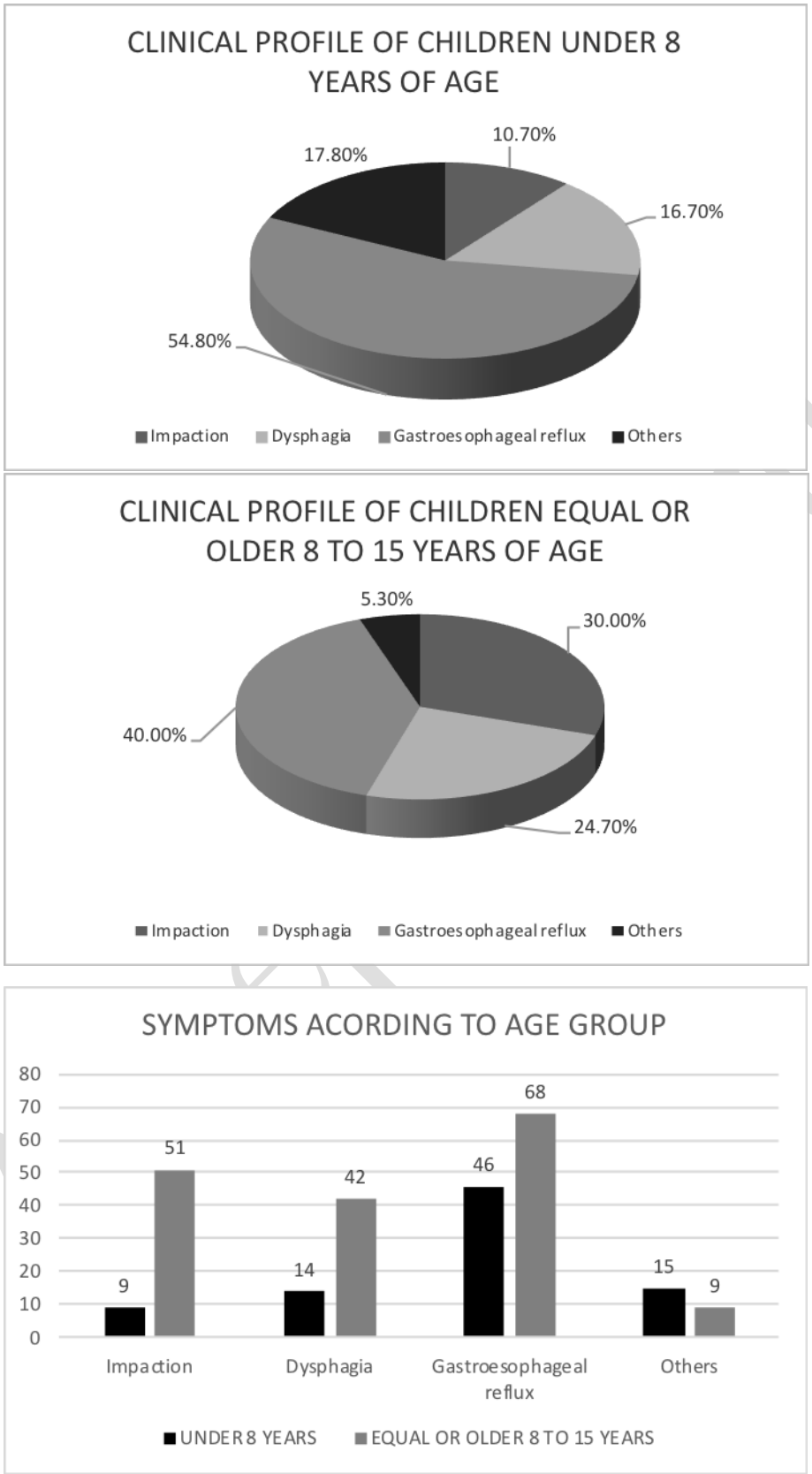

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Figure 2. Annual incidence (number of cases/100000 people/year) both global and in each group of age.

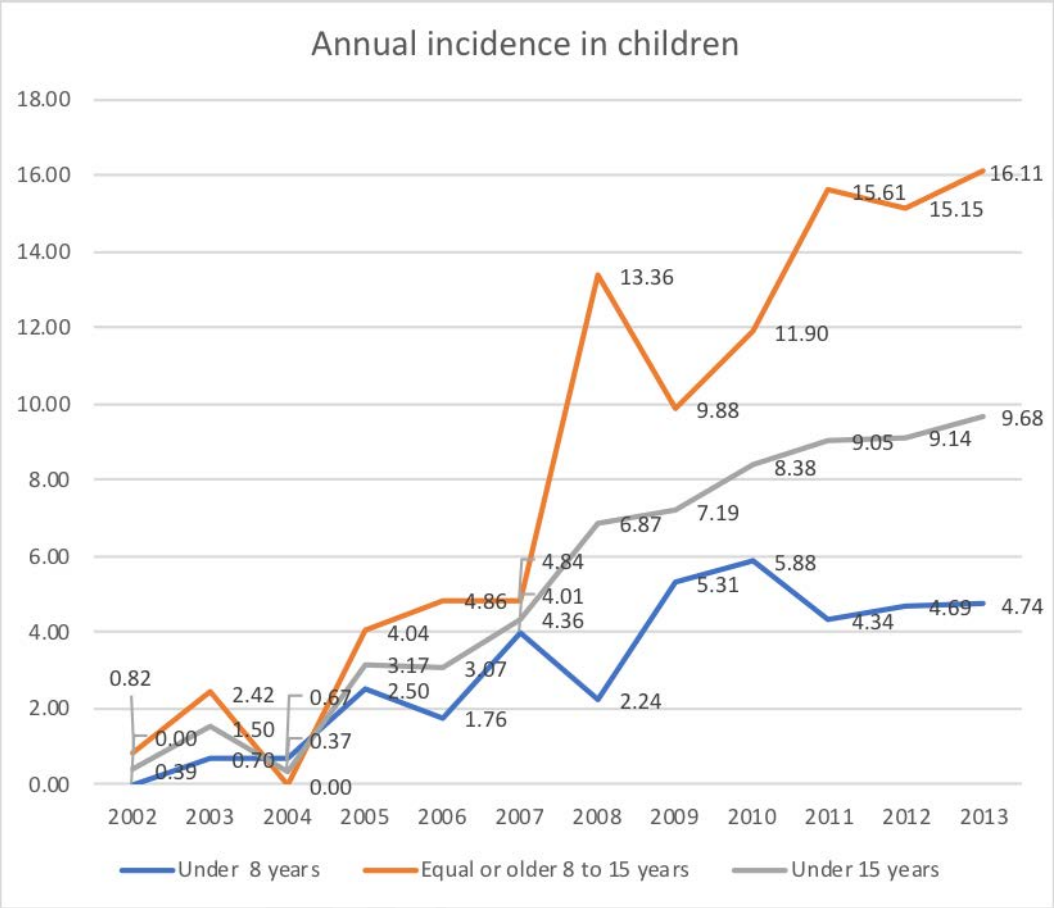

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Table 1. Population under 15 years and absolute pollen counts. Origin: (*) Institute of Statistics of the Madrid region (**) Subiza Clinic. O: *Olea*; P: *Platanus*; Po: *Poaceae*; C: *Cupressaceae*; Q: *Quercus*; A: *Artemisia*; U: *Urticaceae*; AA: *Alternaria alternata*.

Year	N. of cases	Population under 15 years of age (*)			Absolute Pollen Counts (grains/m^3 of air) (**)							
		Under 8 years of age	Equal or older 8 years of age	Total	*O*	*P*	*Po*	*C*	*Q*	*A*	*U*	*AA*
2002	1	132,711	122,541	255,252	2,605	7,612	4,985	9,431	10,886	72	619	3,271
2003	4	142,088	123,787	265,875	2,452	5,850	3,773	4,096	6,430	48	584	1,617
2004	1	150,220	122,957	273,177	801	3,405	2,612	6,027	3,005	58	476	1,130
2005	9	160,060	123,857	283,917	3,581	8,354	1,889	2,906	10,956	47	322	1,198
2006	9	170,119	123,407	293,526	2,782	6,471	5,165	4,456	5,300	36	416	910
2007	13	174,431	123,906	298,337	2,080	7,738	6,860	9,499	7,705	37	423	3,087
2008	21	178,378	127,238	305,616	1,211	10,289	4,425	7,296	7,682	51	519	3,123
2009	23	188,256	131,587	319,843	3,628	7,409	2,560	4,709	8,455	20	503	1,497
2010	39	272,220	193,351	465,571	2,071	11,012	4,176	4,211	7,399	50	385	2,021
2011	43	276,494	198,628	475,122	3,003	15,871	4,120	12,875	10,982	84	574	2,909
2012	44	277,020	204,568	481,588	1,876	13,704	3,487	4,893	16,155	22	428	697
2013	47	274,301	211,054	485,355	5,502	7,149	5,698	7,252	6,201	69	561	929

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