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Alimentary Tract

Incidence and prevalence of eosinophilic oesophagitis increase continiously in adults and children in Central Spain: A 12-year population-based study

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ABSTRACT

Objectives: To update population-based incidence, prevalence and trends for eosinophilic oesophagitis (EoE) in children and adults over the past decade.
Methods: All patients referred to our EoE unit and living in the study area up to December 2017 were prospectively registered. Endoscopy and pathology databases and clinical charts were manually reviewed. Diagnosis of EoE was confirmed upon symptoms of oesophageal dysfunction and eosinophilia >15 eos/HPF. Annual incidence rates and prevalence were estimated with confidence intervals (CI) of 95%.
Results: A total of 117 patients, including 19 children, were diagnosed with EoE in the 2006–2017 period. In 2017, the prevalence of EoE in children was 111.9 (95%CI, 67.4–174.6) cases/100,000 inhabitants and in adults 111.9 (95%CI, 90.8–136.5) also, and in both cases was significantly higher for male patients. The highest prevalences were observed in ages ranging between 20 and 24 and 35–39 years old. Mean incidence rates of the study period were 10.6 and 9.1 new cases/100,000 inhabitants/year in children and adults, respectively. Rise in the appearance of EoE during the study period exceeded that for endoscopic procedures. No seasonal variation was observed in the diagnosis of EoE.
Conclusion: The incidence and prevalence of EoE has increased sharply in central Spain, beyond previous estimations, with one out of every 893 inhabitants now being diagnosed.

1. Introduction

Eosinophilic oesophagitis (EoE) is an immune-mediated, oesophageal chronic disease, clinically characterized by symptoms of oesophageal dysfunction and histopathologically by the presence of oesophageal eosinophilia [1]. EoE constitutes a particular allergic condition triggered and maintained by food allergens [2], with a potential role for aeroallergen exposure in the genesis and exacerbations of EoE which is not supported by most of the current evidence [3,4].

First described in the early 1990s, and after years of being overlooked, the awareness of EoE has increased substantially in the last decade, to the point that it is currently the second cause of chronic oesophageal inflammation after gastro-oesophageal reflux disease (GORD) and the most common cause of dysphagia and food impaction among children and young adults [1]. A continuous increase in incidence rates and prevalence of EoE has been reported during recent years, which were summarized in 2016 in a systematic review with meta-analysis on population-based studies. The analysis gave a pooled incidence of 3.7 per 100,000 inhabitants/year and prevalence of EoE of 22.7 cases per 100,000 [5], but with a high inconsistency (I^2 99.9%) among the studies documented. EoE however still has a significant diagnostic delay [6,7], which does not seem to decrease despite the cumulative knowledge on the disease [8]. The initial doubts on whether the EoE epidemic could be fully explained by a growth in endoscopic examinations or improved detection and recognition of the disease by endoscopists and pathologists have been clarified by demonstrating a true increase in disease incidence that exceeds the expanding use of endoscopy [9–11]. Apart from a true increase in the cumulative incidence of the disease in multiple settings, the variations reported in the frequency of EoE in several studies has been as a

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result of differences in the methodological approaches used (from population-based research to studies defining the frequency of EoE in series of endoscopies and databases of biopsies) and/or variations in the diagnostic criteria considered [12,13]. Differences in the threshold of eosinophil count that define EoE and in how patients with a response to proton pump inhibitors (PPIs) were characterized were the most relevant variations. With regard to this latter issue, guidelines for EoE published between 2007 and 2013 systematically recommended ruling out EoE, and providing a diagnosis of PPI-responsive oesophageal eosinophilia (PPI-REE) for those patients with clinical, endoscopic and histological features characteristic of EoE who achieved remission on PPI therapy [14–16]. Cumulative evidence later showed that EoE patients who did or did not respond to PPI therapy were genetically, molecularly, mechanistically, and phenotypically indistinguishable from each other, and radically different from those with conventional GORD [17–20]. Clinical and pathological features also remit after dietary or topic steroid therapy in PPI-REE patients [21,22], eliminating the therapeutic differences between both groups of patients. An international consensus report [23] and updated evidence-based guidelines [1] now consider PPI-REE as true EoE patients. Some previous research excluded the former, likely underestimating the burden of the disease.

Finally, all previous research evaluating the frequency of EoE exclusively analyzed paediatric or adult patients from different populations [5], which represents an additional limitation when evaluating the overall epidemiology of the disease in a given setting.

The aims of this study are (i) to assess the overall incidence and prevalence of EoE along the different ages in a central region of Spain for the period 2006–2017; and (ii) to analyze trends in epidemiological figures over time.

2. Methods

2.1. Study setting

This study was conducted in a health area located in the autonomous region of Castilla-La Mancha, in central Spain. It provides an update on previous research on EoE prevalence for the period up to 2011 [24]. The study area is predominantly rural, with an overall reference population of 104,737 inhabitants in 2017 with no relevant demographic changes in the study period (the variation coefficient between 2006 and 2017 was 3.6%). The area is covered by two neighbouring public hospitals belonging to the regional health service: Hospital General of Tomelloso and Hospital Virgen de Altagracia. Both hospitals offer universal coverage for specialized services, and their Departments of Gastroenterology and Paediatrics act as referral centres in the area since no additional private gastroenterology, endoscopy, paediatric, nor pathology clinics exist. The Hospital General de Tomelloso acts as a reference centre for EoE cases in the region, and centralizes all cases diagnosed at both centres. All patients included in the study or their parents gave their informed consent for endoscopic procedures to be undertaken and for inclusion in the EoE registry. The investigation was conducted according to the principles expressed in the Declaration of Helsinki and the registry supporting the study was approved by the Institutional Review Board at Hospital General La Mancha Centro.

Reference populations of the areas studied were obtained from official databases from the National Institute of Statistics for the same study period, according to which 87,753 (83.8%) adults older than 16 year-olds and 16,984 (16.2%) children, were living there. Gender percentages (%) distributions (M/F) in 2017 were 49.9/50.1 and 51.3/49.7 for children and adults, respectively.

2.2. Diagnostic criteria and case identification

The diagnosis of EoE was based on the presence of gastrointestinal symptoms suggestive of oesophageal dysfunction (e.g. dysphagia, food impaction, heartburn, reflux, chest pain, vomiting, epigastric/abdominal pain) and infiltration of oesophageal biopsies by 15 or more eosinophils per high-powered field (eos/HPF), in agreement with the criteria established in evidence-based clinical guidelines on EoE [1]. Other potential causes of oesophageal eosinophilia, including eosinophilic gastroenteritis, Crohn's disease, drug hypersensitivity, parasites, oesophageal caustications, hypereosinophilic syndrome, vasculitis, pemphigoid, connective tissue disorder, and graft-versus-host disease were ruled out based on medical records. Patients with EoE responding to an eight-week PPI therapy were also included.

All patients newly diagnosed with EoE at either of the two hospitals between 1 January 2006 and 31 December 2017 were prospectively included in the EoE case registry at our centre. Clinical records, endoscopic registries and histological databases were manually reanalyzed to ensure an EoE diagnosis. A patient was considered to be an adult if he or she was 16 years of age or older.

2.3. Data extraction

Demographic and allergologic data, age at diagnosis, type of symptoms, endoscopic features and peak eosinophil counts in baseline biopsies were recorded. Duration of symptoms before achieving a diagnosis was defined as "overall time of evolution"; time from first consultation with a physician (generally a primary care or general practitioner/paediatrician) to EoE diagnosis was defined as "diagnostic delay". Seasonal distribution of EoE diagnoses along the year was defined according to aerobiological information provided by the Spanish Society of Allergy and Clinical Immunology for the Ciudad Real province [25]. The pollen season in our region was defined from March to July, according to pollen count information.

2.4. Incidence and prevalence analyses

The annual incidence of EoE was calculated as the number of new patients identified for each year of study divided by the overall population in the study area of the corresponding year. Prevalence was estimated as the cumulative number of patients with EoE for each year divided by total population of our area of the corresponding year. Subgroup analyses by children and adults were performed. Confidence intervals (CI) of 95% were estimated for each value.

2.5. Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) and categorical variables as percentages. A comparison between children and adults were performed; t student test or U-Mann Whitney test were used for continuous variables and χ square test for categorical variables. A parametric correlation test (Pearson's r) was used for analysing the association between the overall number of cases diagnosed from EoE each year and the annual rate of upper endoscopy exam performed in the recruiting hospitals during the study period.

The binomial test was used to evaluate the deviations in distribution of observed EoE patients diagnosed within a time interval (season) to a theoretically expected distribution, assuming a probability of 0.25. Analyses and summaries were produced with the PASW statistical program, version 18.0 (SPSS, Inc, Chicago, Ill). A 0.05 level of significance was used throughout.

3. Results

3.1. Baseline characteristics

During the study, an overall of 234 patients attending our centres were diagnosed with EoE. 117 (50%) of these were living in our health area and constituted the study cohort (Fig. 1).

Baseline characteristics of the included patients are summarized in Table 1. The mean age ± SD at diagnosis was 29.8 ± 14 (range 5–82) years old. The percentage of males was 87.2% (male/female ratio: 6.8/1). Main symptoms leading to diagnosis in both children and adults were dysphagia (63.2% and 75.3%, respectively; p ns) and food impaction (47.4% and 77.3%, respectively; p = 0.008). By contrast, children presented more commonly with vomiting (36.8% vs. 6.2%; p = 0.001), and weight loss (21.1% vs. 3.1%; p = 0.013).

Median diagnostic delay was 6.2 ± 10.8 months, with no significant differences observed between children and adults (5.9 vs. 8.5 months, respectively; p = 0.185). Significant differences were observed however in overall time of evolution (12 vs. 36 months, respectively; p = 0.007) and length of symptoms before first consultation (4 vs. 37.2 month, respectively; p = 0.002), when children were compared to adults (Table 1).

3.2. Paediatric patients

3.2.1. Incidence

Nineteen children were diagnosed with EoE during the study period, including 15 boys and 4 girls. The first child diagnosed with EoE in our area was in 2008. Incidence subsequently increased, peaking at 28.4 new cases per 100,000 inhabitants in 2015. Apart for this, it remained stable at around 10 cases per 100,000 annually, except for the years 2009 and 2011, when no children were diagnosed at all. The mean annual incidence rate in children during the study period was 10.6 cases per 100,000 inhabitants, being higher in boys (16.1 cases per 100,000/year) than in girls (4.7 cases per 100,000/year) (Table 2).

3.2.2. Prevalence

Consequently, the prevalence of EoE in children rapidly increased in our area during the years covered by our research, up to a period cumulative prevalence of 105.1 cases (95%CI, 67.4–174.6) per 100,000 inhabitants, and peaking at 111.9 cases per 100,000 inhabitants in 2017. The prevalence was almost three times higher in boys than in girls, being respectively 172 (95% CI, 96.3–283.5) and 48.4 (95% CI, 13.2–123.9) cases per 100,000 inhabitants (Table 2).

3.3. Adult patients

3.3.1. Incidence

Ninety eight adults (including 87 men and 11 women) were diagnosed with EoE in our region, the first being in 2006. The average overall incidence was 9.1 new cases per 100,000/year, with significantly higher numbers of male (16 per 100,000 annually) than female cases (2.1 per 100,000/year) (Table 3).

3.3.2. Prevalence

The period cumulative prevalence from 2006 to 2017 was 107.7 cases diagnosed per 100,000 adult inhabitants, with a peak for prevalence adjusted by effective population in 2017 of 111.9 (95% CI, 90.8–136.5) cases per 100,000 inhabitants. For males, the period prevalence in 2017 was 199.7 (95% CI, 159.8–246.6) per 100,000 and in females, it was 25.2 (95% CI, 12.6–45.1) per 100,000 (Table 3).

3.4. Prevalence by aged groups

The prevalence and incidence values were similar in children and adults (Fig. 1). A peak of prevalence was observed in the group of patients 20–24 years old followed by that of 35–39 years old, with 300 and 264 cases/100,000 inhabitants, respectively (Fig. 2). Up to half of the cases affected people aged between 20 to 39 years old.

3.5. Seasonality and upper endoscopies

No seasonal variation at the moment of diagnosis of EoE was found in our research, with similar incidence rates throughout the year: 25.6% of patients were diagnosed each spring, autumn and winter, while the remaining 23.2% of patients were diagnosed in summer (p = ns). A similar number of patients were diagnosed during the pollen and no-pollen seasons (45.3% vs. 54.7%, p = 0.191) (Supplementary Table 1).

Finally, no relationship between the increasing onset of EoE cases and the number of upper endoscopies carried out in the hospitals attending the study area was found (Pearson's r = 0.05 and p = 0.884) (Fig. 3).

4. Discussion

This population-based study documents a dramatic increase in the epidemiology of EoE in our region over the 12 last years to the point that it has doubled from the previous estimations provided in 2011, when a prevalence of 44.6 cases per 100,000 inhabitants and a mean annual incidence of 6.37 new cases per 100,000 was estimated [24]. Our results confirm the escalating epidemiologic trends reported for EoE in multiple settings, [9,26–28] according to which the prevalence of the disease has been increasing continuously since studies published before 2008, to represent a 5-fold increase in only one decade [5].

We have now documented a mean annual incidence of 9.1 new cases per 100,000 inhabitants, exceeding the overall incidence rate of 7.2 that was provided by a recent meta-analysis summarizing studies carried out between 2008 and 2015 [5]. The prevalence of EoE among adult patients of 111.9 cases per 100,000 inhabitants parallels figures recently reported from mid-western Spain for the 2007–2016 period (81.73 patients per 100,000 inhabitants) [10] and constitutes the highest prevalence for EoE reported so far. The incidence rate documented here for EoE currently equals that reported for Crohn's disease in European Countries, including Spain, which ranges between 8.6 and 9.9 new cases per 100,000/year [29–32], while prevalence almost equals the figures recently provided for Spain of 137.17 per 100,000 inhabitants [29].

As for children, an average incidence rate of 10.6 new EoE cases per 100,000 inhabitants, provides evidence that there is an increase, which has grown progressively over time, in the appearance of new EoE cases for this age group also. Population studies carried out before 2008 showed an overall annual incidence for paediatric EoE of 3.3 cases per 100,000 inhabitants, which increased to 7.3 for studies published after this date [5]. It should be remembered, however, that the very first cases of EoE were reported less than 4 decades ago [33–35] and the disease was characterized as a distinct clinico-pathological disorder only in the early 1990s [36,37]. Since then, EoE has increased to the point that 1 out of 893 people are currently suffering from the disease in our region. Considering its chronic nature, the usual recurrence of symptoms and inflammation after treatment withdrawal [38] and the increasingly younger age of affected patients who will suffer from the disease for decades after being diagnosed, the burden of EoE for the national health services will be huge. Efforts to identify risk factors in order to

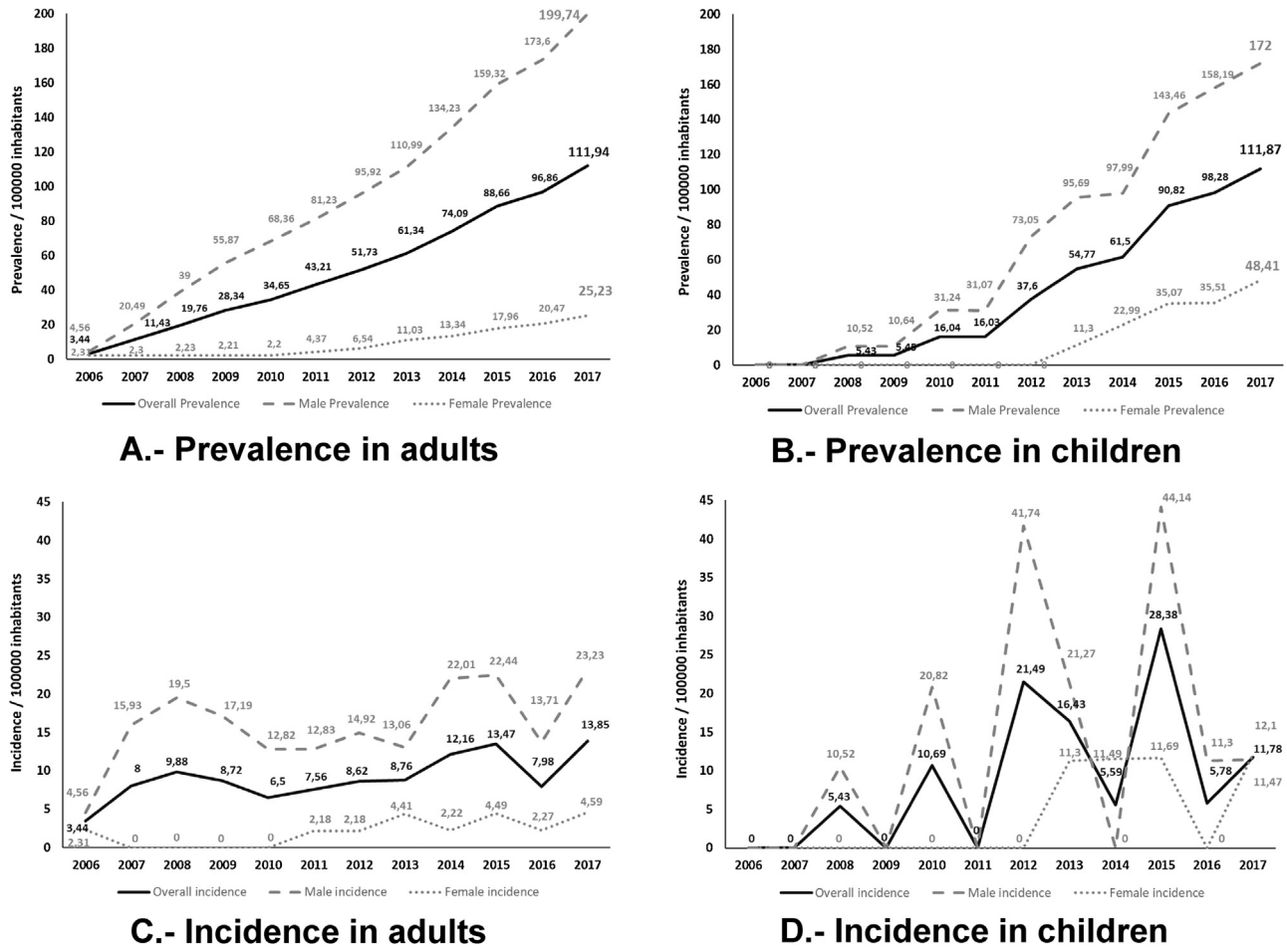

Fig. 1. Diagnostic incidence and cumulative prevalence of EoE per 100,000 inhabitants per year in adult and paediatric patients diagnosed in two hospitals in a central region of Spain during the period 2006–2017, according to evidence-based guidelines diagnostic criteria.

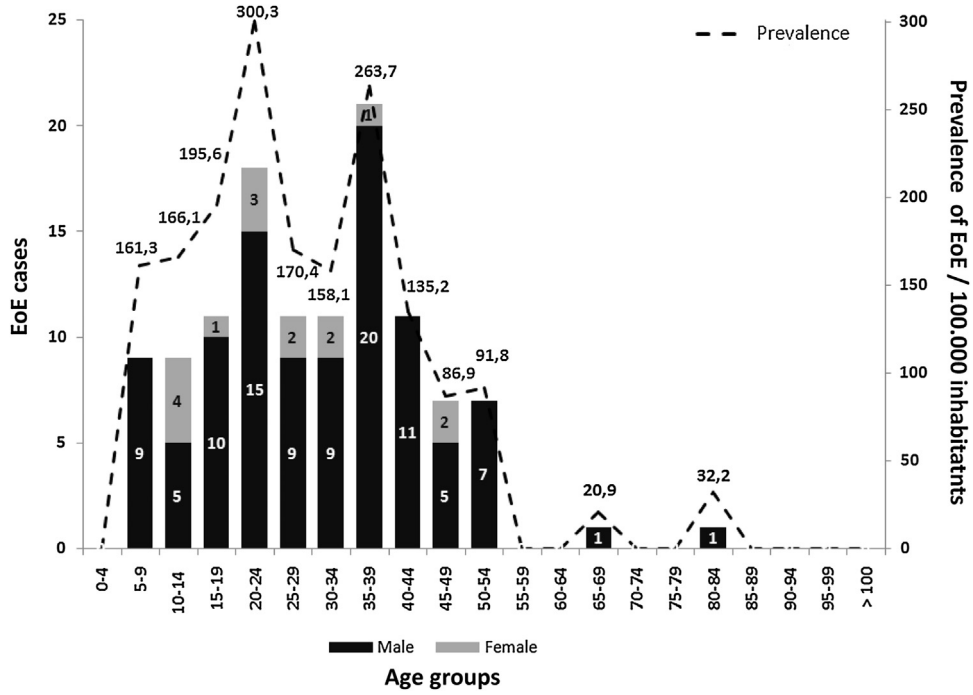

Fig. 2. New cases and prevalence rates of EoE, stratified by age group and gender, in patients diagnosed in a central region of Spain along a 12-year period.

Table 1
Baseline clinical and demographic characteristics of adult eosinophilic oesophagitis patients from two Spanish hospitals included in our study.

	Overall (n = 117)	Adults (n = 98)	Children (n = 19)	p
Mean age (SD; rank)	**29.8 (14; 5–82)**	33.8 (11.7; 16–82)	9.6 (2.8; 5–15)	**<0.001**
Male gender (%)	**102 (87.2%)**	87 (88.8%)	15 (78.9%)	0.263
Symptoms (%)				
Food impaction	**84 (72.4%)**	75 (77.3%)	9 (47.4%)	**0.008**
Dysphagia	**85 (73.3%)**	73 (75.3%)	12 (63.2%)	0.276
Abdominal pain	**31 (26.7%)**	25 (25.8%)	6 (31.6%)	0.601
Vomiting	**13 (11.2%)**	6 (6.2%)	7 (36.8%)	**0.001**
Heartburn	**27 (23.3%)**	21 (21.6%)	6 (31.6%)	0.378
Weight loss	**7 (6%)**	3 (3.1%)	4 (21.1%)	**0.013**
Reduced calibre (%)	**20 (17.1%)**	18 (18.8%)	2 (10.5%)	0.520
Mucosal appearance (%)				
Normal	**14 (12.3%)**	10 (10.5%)	4 (21.1%)	0.247
Longitudinal furrows	**85 (74.6%)**	72 (75.8%)	13 (68.4%)	0.566
Crepe-paper appearance	**24 (21.1%)**	20 (21.1%)	4 (21.1%)	>0.999
Rings	**56 (49.1%)**	55 (57.9%)	1 (5.3%)	**<0.001**
Exudates	**52 (45.6%)**	43 (45.3%)	8 (47.4%)	0.866
Atopic personal history (%)				
Rhinoconjunctivitis	**74 (63.8%)**	63 (64.9%)	11 (57.9%)	0.559
Asthma	**47 (40.5%)**	41 (42.3%)	6 (31.6%)	0.385
Food allergy	**29 (25%)**	20 (20.6%)	9 (47.4%)	**0.021**
Dermatitis	**7 (6%)**	5 (5.2%)	2 (10.5%)	0.322
Drug sensitivity	**10 (8.6%)**	9 (9.3%)	1 (5.3%)	>0.999
Atopic familiar history (%)				
Rhinoconjunctivitis	**23 (20%)**	20 (20.6%)	3 (16.7%)	>0.999
Bronchial asthma	**23 (20%)**	20 (20.6%)	3 (16.7%)	>0.999
Food allergy	**19 (16.5%)**	16 (16.5%)	3 (16.7%)	>0.999
Dermatitis	**2 (1.7%)**	2 (2.1%)	0	>0.999
Drug sensitivity	**5 (4.3%)**	4 (4.1%)	1 (5.6%)	>0.999
Mean peak eosinophils (SD; rank)	**58.1 (46.2; 15–300)**	59.5 (48; 15–300)	51.1 (36.1; 15–140)	0.467
Median overall time of evolution (IQR; rank), months	**36 (63; 0–360)**	36 (70.5; 0–360)	12 (27; 0–92)	**0.007**
Median Diagnosis Delay (IQR; rank), months	**6.2 (10,8; 0.2–128.7)**	5.9 (10.8; 0.2–128.7)	8.5 (18.2; 0.2–41.8)	0.185
Median length of symptoms before first consultation (IQR; rank), months	**31.8 (57.3; 0.6–343.1)**	37.2 (66.3; 1.4–343.1)	4 (20.1; 0.6–51.9)	**0.002**

Bold values denote statistically significant differences among children and adults.

Table 2
Annual incidence and cumulative prevalence for paediatric patients with EoE in two hospitals in central Spain between 2006 and 2017, broken down by gender. Incidence and prevalence are expressed in cases per 100,000 inhabitants.

Year	Overall	Male	Female	Overall population	Male population	Female population	Overall incidence	Male incidence	Female incidence	Overall prevalence	Male prevalence	Female prevalence
2008	1	1	0	18,419	9502	8917	**5.43**	10.52	0	**5.43**	10.52	0
2009	0	0	0	18,343	9402	8941	**0**	0	0	**5.45**	10.64	0
2010	2	2	0	18,703	9604	9099	**10.69**	20.82	0	**16.04**	31.24	0
2011	0	0	0	18,716	9655	9061	**0**	0	0	**16.03**	31.07	0
2012	4	4	0	18,616	9583	9033	**21.49**	41.74	0	**37.60**	73.05	0
2013	3	2	1	18,257	9405	8852	**16.43**	21.27	11.30	**54.77**	95.69	11.30
2014	1	0	1	17,885	9185	8700	**5.59**	0	11.49	**61.50**	97.99	22.99
2015	5	4	1	17,617	9062	8555	**28.38**	44.14	11.69	**90.82**	143.46	35.07
2016	1	1	0	17,298	8850	8448	**5.78**	11.30	0	**98.28**	158.19	35.51
2017	2	1	1	16,984	8721	8263	**11.78**	11.47	12.1	**111.87**	172	48.41
Overall	19	15	4	Mean 18084	9296.9	8786.9	Incidence **10.56**	16.13	4.66	Prevalence **49.78**	82.38	15.33

Bold values denote overall population-based annual incidence and cumulative prevalence figures.

implement preventive strategies to face EoE in future years are urgently needed therefore.

The rising prevalence of the disease cannot be attributed only to the accumulation of cases over time, but also to a continuous and ongoing increase in incidence rates. The reasons behind this increase have not been clarified but their identification is urgently needed. The true expansion in the prevalence and incidence of EoE in our area in respect to previous estimations in 2011, has not been adequately explained. It has been argued for example, that most of the previous population-based studies underestimated the magnitude of EoE by excluding patients with a response to PPIs [10]. All patients included in our research had EoE diagnosed by the current evidence-based criteria [1], according to which a response to PPI does not preclude a diagnosis of EoE, contrary to previous consensus guidelines [14,15]. However, and despite up to half of patients with EoE possibly responding to PPIs [39], most population-based studies carried out previously, both in the early literature [40–43] and in that published after the proposal of the so called PPI-REE in 2011 [9,26,27,44,45] did not exclude response to PPIs as a diagnostic requirement for EoE. As such, we can consider that previous literature assessing the prevalence and incidence rates for EoE did so by using equivalent criteria, as we used in the present research. An increasing generalization in the use of endoscopy for the diagnosis and management of gastroenterological disorders was also proposed as an explanation for an increasing frequency of EoE, together with a greater awareness by clinicians that now consider EoE within the differential diagnosis of oesophageal dysfunction symptoms [46,47]. However, recent studies have demonstrated that the increase in new EoE cases outpaces the use of endoscopy with biopsy [10,11]. Our research also documented that the expan-

Table 3
Annual incidence and cumulative prevalence of eosinophilic esophagitis in adult patients attended in two hospitals in central Spain between 2006 and 2017, broken down by gender. Incidence and prevalence are expressed in cases per 100 000 inhabitants.

Year	Overall	Male	Female	Overall population	Male population	Female population	Overall incidence	Male incidence	Female incidence	Overall Prevalence	Male Prevalence	Female Prevalence
2006	3	2	1	87274	43893	43381	**3.44**	4.56	2.31	**3.44**	4.56	2.31
2007	7	7	0	87477	43930	43547	**8**	15.93	0	**11.43**	20.49	2.30
2008	9	9	0	91071	46155	44916	**9.88**	19.50	0	**19.76**	39	2.23
2009	8	8	0	91744	46541	45204	**8.72**	17.19	0	**28.34**	55.87	2.21
2010	6	6	0	92340	46809	45531	**6.50**	12.82	0	**34.65**	68.36	2.20
2011	7	6	1	92564	46781	45783	**7.56**	12.83	2.18	**43.21**	81.23	4.37
2012	8	7	1	92781	46912	45869	**8.62**	14.92	2.18	**51.73**	95.92	6.54
2013	8	6	2	91294	45950	45344	**8.76**	13.06	4.41	**61.34**	110.99	11.03
2014	11	10	1	90436	45444	44992	**12.16**	22.01	2.22	**74.09**	134.23	13.34
2015	12	10	2	89102	44565	44537	**13.47**	22.44	4.49	**88.66**	159.32	17.96
2016	7	6	1	87753	43779	43974	**7.98**	13.71	2.27	**96.86**	173.60	20.47
2017	12	10	2	86652	43055	43597	**13.85**	23.23	4.59	**111.94**	199.74	25.23
					Mean			Mean Incidence			Mean Prevalence	
Overall	98	87	11	90041	45318	44723	**9.08**	16.01	2.05	**52.12**	95.78	9.18

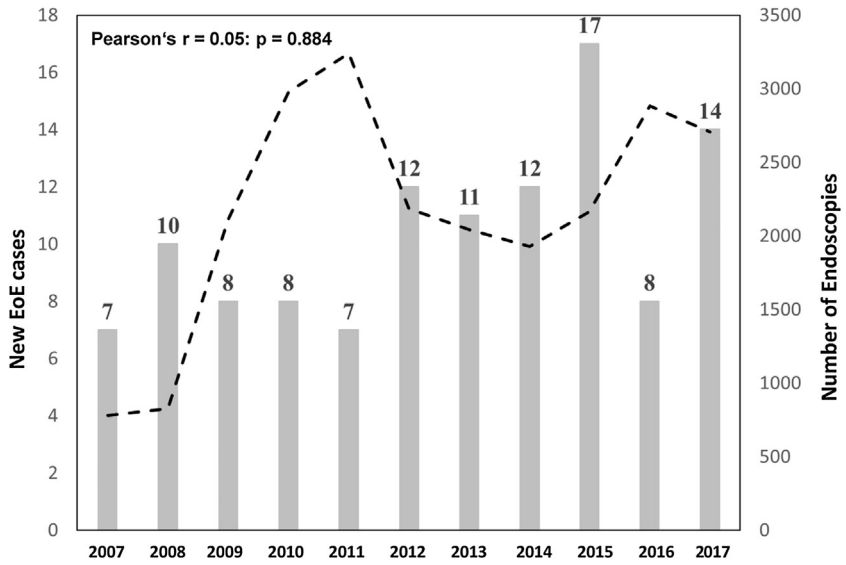

Fig. 3. Yearly overall new EoE cases diagnosed in children and adults in a central region of Spain between 2006 and 2017, compared to the annual rate of upper endoscopic exams performed in our hospitals during the same study period.

sion in the number of new EoE diagnoses during the study period exceeded that of upper endoscopic examations, thus providing additional evidence of a true expansion of the disease in our setting over the last decade.

Some of our results deserve additional comments. To begin with and in line with previous findings [10,27] the prevalence of EoE in our series steadily increased from childhood to adolescence, to peaks in the age groups 20–24 years old and 35–39 years old, which were the ages with the highest number of EoE diagnoses in our cohort. After 45 years old, the number of EoE cases sharply decreased, with only a scattering of patients being diagnosed at older ages. This finding confirms EoE as predominantly a disease of young adults, and invites speculation as to the moment that the as yet to be identified potential risk factors leading to EoE became active. At present, only early-life factors, including caesarean delivery, antibiotic or acid suppressant use in infancy and not having a pet in the home, have been related with an increased risk of suffering from EoE [48]. Considering the more common ages of disease diagnosis after early childhood, two conclusions can be drawn: (a) the latency period between exposure and disease diagnosis (but not onset) ranged between 20 and 40 years for the majority of patients; (b) the most pronounced effect of such factors started after the 1980s. Secondly, our results provided additional evidence on the lack of a seasonal predominance in the appearance of EoE [10], with a similar number of cases being diagnosed throughout the four seasons and with no significant effect of the pollen season on the number of new cases identified. In fact, a previous meta-analysis with meta-regression already demonstrated no seasonal distribution at the moment of diagnosis or clinical recrudescence of EoE [4]. It attributed the increased recognition of EoE during spring and summer to a greater opportunity for establishing a diagnosis in patients with mild, chronic oesophageal symptoms, instead of implicating outdoor antigens as potential EoE triggers. Finally, our mean diagnostic delay of only 6.2 ± 10.8 months from first consultation to definitive EoE diagnosis was significantly shorter than in previous research [6,8,10,49]. Overall time of evolution was also significantly shorter than that reported by other authors, which lasted around 5 years. The limited size of our area and easy access to specialized facilities, the fact of being a reference unit for EoE and the well established awareness of EoE among the staff of our recruiting area might have contributed to a greatly reduced diagnostic delay.

Our study has several strengths, such as the systematic and prospective identification of a large number of new EoE cases in patients of all ages. These patients consecutively attended a referral centre over a long period of time, for whom registered data

were cross-checked with endoscopy and pathology databases. The systematic inclusion of patients with EoE who responded to PPI therapy in accordance with current consensus [23] and evidence-based diagnostic criteria [1] should also be considered. The lack of alternative private clinics able to provide endoscopy services in our study area avoided the loss of potential EoE cases.

Some limitations should also be acknowledged, such as the fact that our data was obtained from patients who sought assistance because of the symptoms of oesophageal dysfunction, and were diagnosed after referral to the gastroenterology or paediatrics departments at our hospitals. In most of the previous research, diagnostic delay in EoE was considerable, significantly higher to that documented in ours [6,8,10,49], probably due to the fact that symptoms can fluctuate over time and are frequently unspecific. Thus, it can be assumed that only the most symptomatic patients would have been seen by primary care physicians and referred to hospital for additional studies. It is even likely that some young patients, with no alarming GORD-related symptoms and responding to empiric antisecretive therapy, were never referred for endoscopy. In this scenario, the finding of a pathological eosinophilic infiltration over the EoE diagnostic threshold described in Sweden during the Kalixandra study [50], would really reflect the actual magnitude of EoE. The study area is exclusively rural, with the local economy based mainly on agriculture, farming processing industries and community services. Therefore, caution should be taken before directly extrapolating our results to urban populations. Conflicting results have been shown regarding the differences in EoE frequency and living areas, with early research showing that EoE was spread homogeneously according to population distribution, with no urban–rural gradient [40]. An American epidemiological study later documented higher prevalence of EoE in urban areas compared with suburban and rural settings [51], and more recently population density has been strongly and inversely associated with oesophageal eosinophilia and EoE [52] suggesting that environmental exposures that are more prominent in rural areas may be relevant to the pathogenesis of EoE, a fact that we should also have considered.

In conclusion, the incidence and prevalence of EoE in our region, located in central Spain, has increased sharply throughout the last 12 years in patient of all ages. The present study reports the highest prevalence seen so far for paediatric and adult EoE and provides evidence of the markedly increasing trend in the frequency of EoE documented in several settings. In view of these results, efforts to investigate the causes of EoE and its increasing frequency in order to propose preventive strategies, are urgently needed.

Conflict of interest

None declared.

Guarantor of the article

Alfredo J. Lucendo.

Disclaimers

None.

Writing assistance

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.07.016.

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