Received: 25 January 2019 | First decision: 11 February 2019 | Accepted: 25 February 2019

DOI: 10.1111/apt.15231

WILEY AP&T Alimentary Pharmacology & Therapeutics

Systematic review with meta-analysis: the growing incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies

Pilar Navarro[1] | Ángel Arias[2,3] | Laura Arias-González[3,4] | Emilio J. Laserna-Mendieta[4] | Miriam Ruiz-Ponce[4] | Alfredo J. Lucendo[3,4]

[1]School of Public Health, Physiotherapy and Sports Science, University College Dublin, Dublin, Ireland

[2]Research Support Unit, Complejo Hospitalario La Mancha Centro, Alcázar de San Juan, Spain

[3]Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain

[4]Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Spain

Correspondence
Dr Alfredo J. Lucendo, Department of Gastroenterology, Hospital General de Tomelloso, Ciudad Real, Spain.
Email: ajlucendo@hotmail.com

Summary

Background: The frequency of eosinophilic oesophagitis (EoE) occurrence is escalating. Current diagnostic criteria recently proposed for the disease, determine that previous estimates of incidence and prevalence are outdated.

Aim: To gauge the current incidence and prevalence of EoE by performing a systematic review of population-based studies.

Methods: Three electronic databases were searched from their inception dates to September 2018. A total of 2386 documents were screened; 29 studies reported on the prevalence and incidence of EoE in the general population.

Results: The pooled prevalence of EoE was 34.4 cases per 100 000 inhabitants (95% CI, 23.1-47.5), and was higher for adults (42.2; 95% CI, 31.1-55) than for children (34; 95% CI, 22.3-49.2). The pooled EoE incidence rates were 6.6/100 000 person-years (95% CI, 3-11.7) in children and 7.7/100 000 (95% CI, 1.8-17.8) in adults. No differences were found between North American and European studies using varied sources of data (insurance and administrative databases compared to hospital-bases case series). Subgroup analysis according to risk of bias did not change results significantly. A steady rise in EoE incidence and prevalence rates was observed over time, comparing studies conducted under subsequent definitions for EoE. No significant publication bias was found.

Conclusions: In a systematic review and meta-analysis, we found a sharp increase, higher than previous estimates, in the incidence and prevalence of EoE in population based studies. Results from studies carried out in developed countries show broad consistency and provide evidence of increasing pooled prevalence and incidence of EoE rates over time.

Pilar Navarro and Ángel Arias contributed equally to the first authorship.
As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Dr Colin Howden, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Eosinophilic oesophagitis (EoE) is a food-related allergic-mediated condition that triggers an eosinophil-predominant inflammatory response in the oesophageal mucosa leading to oesophageal dysfunction. Dysphagia and food impaction are the most characteristic symptoms in adults, while gastroesophageal reflux disease (GORD)-with similar symptoms and feeding disturbances, predominates in children.[1,2] Despite being a relatively new condition, first described less than 4 decades ago,[3] the expansion of EoE in the last decade has been such that at present it is already described as a common disease in clinical practice.

Several studies have documented the increasing frequency of the disease, some analysing the weight of EoE in series of endoscopies or biopsies, and others trying to establish the epidemiology of the disease in well-defined populations, either by analysing geographically confined regions, or using institutional registry data and electronic medical records.[4] In 2016, a systematic review of these population-based studies summarised an incidence of 0.7-10.0 per 100 000 person-years and a prevalence range of 0.2-43.0 per 100 000 person-years, with an increasing trend over successive years.[5] The time at which each study was developed, differences in the threshold of eosinophil count defining EoE and in how patients with a response to proton pump inhibitors (PPIs) were considered, as well as regional variations, are the most relevant explanations for the broad range of incidence and prevalence provided by this systematic review. The recent consideration that patients who respond to PPIs are within the spectrum of the disease rather than considered a different entity,[1,6] along with new data available from 2018 that provides the highest frequency for the disease reported so far[7–9] (and not included in recent reviews[10]), makes the previously reported prevalence and incidence figures outdated.

After the recent publication of relevant population-based studies providing new data on the current frequency of EoE in patients of all ages, this research aims to conduct a systematic review of the literature in order to update incidence and prevalence rates of EoE in children and adults. Assessing temporal trends in different geographic areas is a secondary aim.

2 | MATERIALS AND METHODS

This systematic review has been registered in the PROSPERO International prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO; register no. CRD42018108756), and has been reported in accordance with the PRISMA statements.[11]

2.1 | Selection of studies

A systematic literature search was performed independently by two researchers (AJL and AA) in three major bibliographic databases (PubMed, EMBASE, and Scopus) for the period up to September 2018. The search was not restricted with regard to date or language of publication. A predetermined protocol was used in accordance with the quality standards for reporting meta-analyses of observational studies in epidemiology.[12] Comprehensive search criteria were used to identify articles dealing with the epidemiology of EoE in children and adults. The following search strategy was used to consult the thesauri for MEDLINE (MESH) and EMBASE (EMTREE): ("eosinophilic esophagitis" OR "eosinophilic oesophagitis") AND ("epidemiology" OR "incidence" OR "prevalence" OR "demography"). As for the SCOPUS database, only free text searches with truncations were carried out. Reference lists from retrieved articles and abstracts of conference proceedings (taken from abstract books from the annual Digestive Diseases Week, American College of Gastroenterology Meetings and the United European Gastroenterology Week for the period between 2014 and 2018) were also examined to identify additional, relevant studies. Four reviewers (PN, AA, LA-G & AJL) independently screened the database search for titles and abstracts. If any of the reviewers felt that a title or abstract met the study eligibility criteria, the full-text of the study was retrieved.

2.2 | Inclusion criteria

A combination of symptoms referred to oesophageal dysfunction and a dense eosinophilic infiltration (≥15 eosinophils per high power field) in oesophageal biopsies was a diagnosis of EoE. Population-based studies including national, provincial/state-wide and local estimations were considered if they provided original data on the prevalence and/or incidence of EoE in children and/or adults, irrespective of the study design or document format.

2.3 | Exclusion criteria

Our study excluded clinical guidelines, consensus documents and reviews that did not provide original epidemiological data. We also excluded studies not carried out on humans, papers providing duplicated information (ie repeated abstracts presented at different congresses or abstracts subsequently published as a full-paper), and studies using subsets of patient cohorts from previously published research by the same group of authors.

2.4 | Risk of bias assessment

Retrieved documents were evaluated for risk of bias only if the article described all the patients' demographical data, the diagnostic criteria used for EoE, and the reported prevalence/incidence with its 95% CI. Risk of bias assessment was checked against The Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data.[13] A study was considered to be at low risk for bias if each of the bias items could be categorised as low risk. Studies were judged to have a high risk of bias however if any one of the items was deemed high risk. Four investigators (AJL, AA, EJLM and LA) independently gave each eligible study an overall rating of high, low or unclear risk of bias; disagreements were resolved by consensus.

2.5 | Data extraction

Four reviewers (AA, AJL, PN and LA) independently extracted relevant information from each eligible study using a standardised data extraction sheet and then proceeded to cross-check the results. The data extracted included the last name of the first author, publication year, study period, study region, level of study (national, state/provincial, local), age and gender of study participants, sample size (total as well as by sex and by number of regional subgroups), reported prevalence and/or incidence with 95% CIs, and prevalence and/or incidence figures by gender and age group, if available. When not directly stated, incidence rates were calculated using the population used to calculate prevalence rates; we estimated the exposure periods, assuming that the reference populations were stable throughout the given study periods.

Methodological design and data indicative of risk of bias assessment for all included studies were also extracted. Disagreements between reviewers regarding data extraction were resolved through discussion.

2.6 | Statistical analysis

Proportions provided by source documents were transformed and calculated with the Freeman-Tukey double arcsine method; estimations of both prevalence and incidence were carried out with the aid of random-effects meta-analyses weighted for inverse variance, following DerSimonian and Laird's method.[14] In studies that reported data for more than one-time point, only data reported at the last time point was included in the primary analysis. Summary estimates, along with their 95% CIs, were calculated for the prevalence and incidence rates of EoE among children and adults. The proportions of male and female patients (where reported) were compared using pooled odds ratio (OR) with a 95% CI.

Heterogeneity between studies was assessed by means of a chi-square test (Cochran Q statistic) and quantified with the I^2 statistic. Generally, I^2 was used to evaluate the level of heterogeneity, assigning the categories low, moderate and high to I^2 values of 25%, 50%, and 75%, respectively.[15] Publication bias was evaluated with the aid of a funnel plot, the asymmetry of which was assessed through Begg-Mazumda's rank test[16] and Harbord's bias test.[17]

For the primary outcomes, planned subgroup analyses were performed based on the diagnostic criteria used in each document to define EoE (ie, those provided by either 2007,[182] or 2017[1] guidelines), the source of data (hospital-based registries or administrative claims databases) and the year in which studies were carried out.

A subgroup analysis was performed with regard to quality (risk of bias). All calculations were made with StatsDirect statistical software version 2.7.9 (StatsDirect Ltd, Cheshire, UK).

3 | RESULTS

3.1 | Literature search

The search strategy yielded 2386 references; 2324 were excluded from the search mainly due to (a) no measure of prevalence or incidence of EoE being given, (b) not being population-based studies, (c) being review articles or (d) the focus not being on EoE. In all, we identified 29 studies that reported on the population-based incidence and prevalence of EoE. Figure 1 summarises the results of the search strategy. Most of the studies of the prevalence of EoE were conducted in United States (US),[8,9,19–29] Canada[30,31] and Europe,[7,32–42] but there were also studies from Western Australia,[43] and South America.[44] Key differences in prevalence rates depended on whether the study population included only children, only adults or individuals of all ages, as well as on the time the study was undertaken and the definition of prevalence such as a point (16 studies[21–32,36,37,42] or a period (11 studies)[7,9,19,33–35,38,40,41,43,44]; and methodology used, such as hospital-based case series (14 studies),[7,8,19,21,32–35,38–,41,43] administrative database (7 studies),[9,20,30,31,36,37,42] or insurance database (8 studies)[22–29] (Table S1). Further variation was related to the definition of EoE considered by the various authors, which differed significantly over the period with regard to the role of pH-monitoring and consideration of PPIs in the diagnostic and therapeutic algorithm of the disease.[1,2,18]

3.2 | Overall prevalence rates and changes according to regional distribution and diagnostic criteria for EoE

The overall prevalence of EoE in the 24 retrieved studies was 34.2 cases per 100 000 inhabitants (95% CI, 23.1-47.5; I^2 = 99.9%; Figure 2A). Differences in the overall prevalence rates were also documented according to study region, being higher for North America (41; 95% CI, 25.7-59.9; I^2 = 99.7%) than for Europe (29; 95% CI, 19.9-39.8; I^2 = 99.6%), although these differences were not statistically significant (P = 0.571).

Subgroup analysis according to risk of bias of source documents (Table S2) did not provide significant changes in the prevalence of EoE (35.5; 95% CI, 25.7-46.8; I^2 = 99.8% vs 32; 95% CI, 16.6-52.4; I^2 = 100%, for studies with low and high risk of bias, respectively; P = 0.710).

When the studies were classified according to the criteria used by their authors to define EoE and its variations over time, the overall prevalence reported for the disease increased progressively, with a fourfold increase from the oldest studies (that considered criteria before the 2007 consensus[18]) and those that used the most up-to-date evidence-based diagnostic criteria provided from 2017 onwards[1,6] (Figure 3). This change in prevalence reached a statistically significant difference (15.4; 95% CI, 10.4-21.2 vs 63.2; 95% CI, 34.6-100.3, respectively; P = 0.011) (Table 1).

3.3 | Prevalence of EoE in children

Fourteen studies reported the prevalence of EoE in children (defined as those aged < 16 years) (Figure 2B). In general, the overall prevalence of EoE in children was up to 34.4 cases/100 000 inhabitants (95% CI, 22.3-49.2; I^2 = 99.7%), with no significant differences between the US and Europe (38.3; 95% CI 23.7-56.4 and 41; 95% CI, 3.2-121.1, respectively). Studies based on insurance and

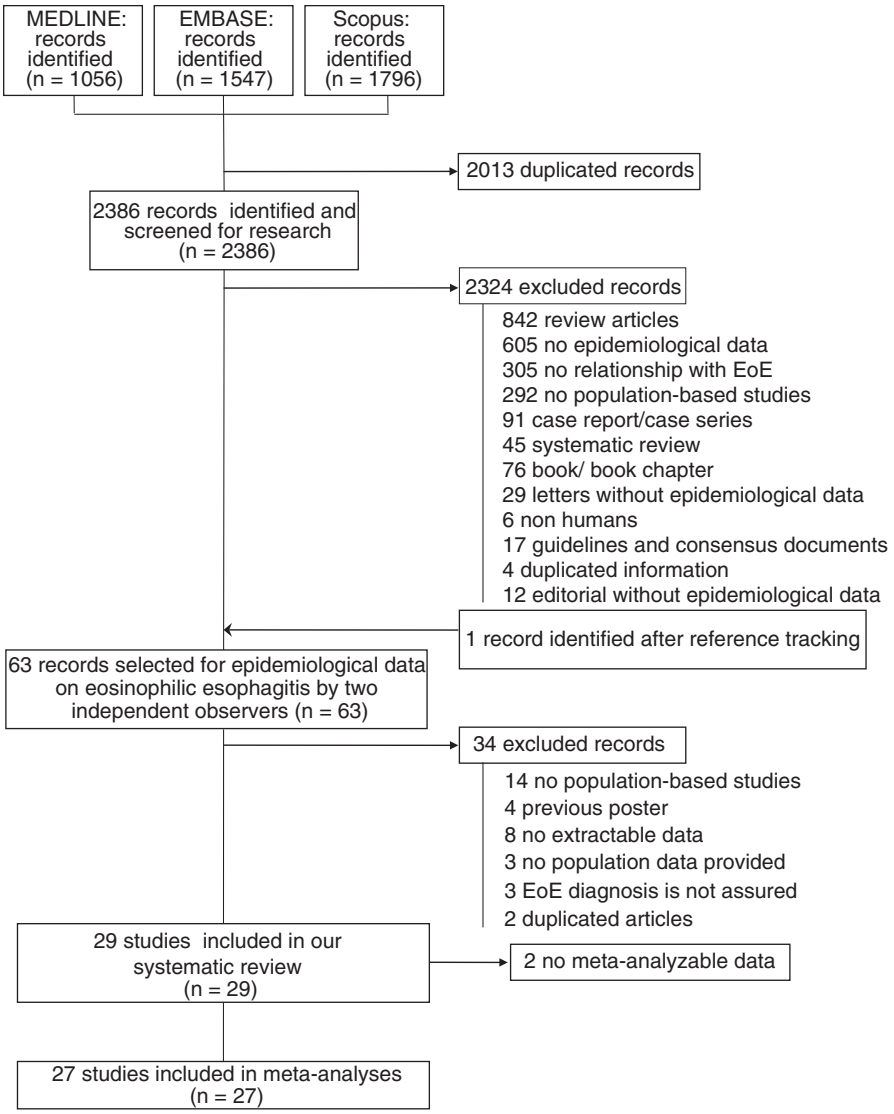

FIGURE 1 Flow chart for the process of identifying studies included in and excluded from the systematic review

administrative databases, confined to those aged under 16 years, reported the same prevalence provided by hospital-based case series (Table 1). According the three most recently published studies[7,40,44] following the most up-to-date diagnostic criteria for EoE, the current prevalence for EoE in children is 53.4 cases/100 000 inhabitants (95% CI, 27.1-88.5; I^2 = 95.6%). There was a nonsignificant trend towards a higher prevalence of EoE among the studies with a lower risk of bias (42.7; 95% CI, 14.1-86.8 vs 28.2; 95% CI, 16.4-43.3)

3.4 | Prevalence of EoE in adults

The nine studies focused on prevalence of EoE in adults (Figure 2C) yielded higher estimates than studies focused on children, with an overall prevalence of 42.2 (95% CI, 31.1-55; I^2 = 99.9%). However, there appeared to be little consistency between countries, with European-based studies providing significantly higher prevalence figures for EoE than American ones (95.8; 95% CI 68.4-127.8 vs 31.9; 95% CI, 21.5-44.3; P = 0.006). In Europe, Spain had the highest consistent estimates reported, with two recent studies on different populations carried out with hospital-based, prospectively maintained databases.[41,7] In contrast, prevalence estimates for EoE in adults in the US and Canada were obtained from insurance and administrative databases, some of them specifically excluding patients with codes related to GORD,[8,27,29,37] which could have resulted in an underestimation of the true magnitude of prevalence (Table 1). No population-based epidemiological study on adults has been published by the US since the release of the AGREE conference paper[6] that supports the elimination of PPI in the diagnostic algorithm of EoE.[1,45] Again source studies with lower risk of bias tended to provide higher prevalence rates than those with some methodological weakness (64.2; 95% CI, 14.9-148.2 vs 34.2; 95% CI, 21.4-49.9; P = 0.167).

3.5 | Overall incidence of EoE and changes according to regional distribution and diagnostic criteria

Eighteen studies examined the incidence of EoE in the general population. These studies were conducted in North America (US,[20,22–24] Canada[30,31]) and Europe (The Netherlands,[36,42] Denmark,[37] Switzerland[38] and Spain[7]) and looked at different groups of the population

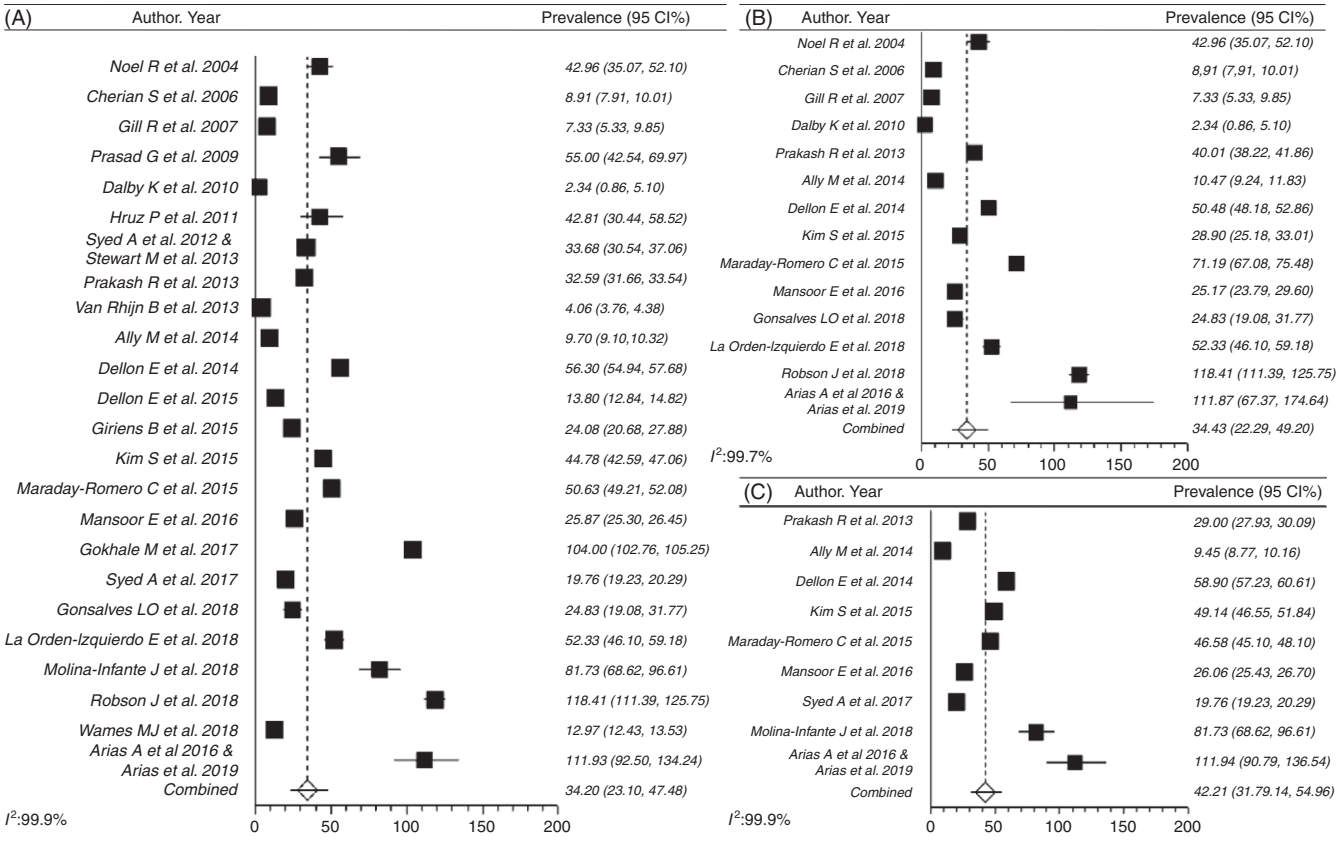

FIGURE 2 Summary estimates for population-based prevalence of EoE, including overall (A) and subgroup analysis of studies conducted in children (B) or adults (C). Summary estimates are expressed as the number of EoE patients/100 000 inhabitants. An I^2 value (statistical heterogeneity) over 75% indicates a high variability in intra-study differences in the overall effect size

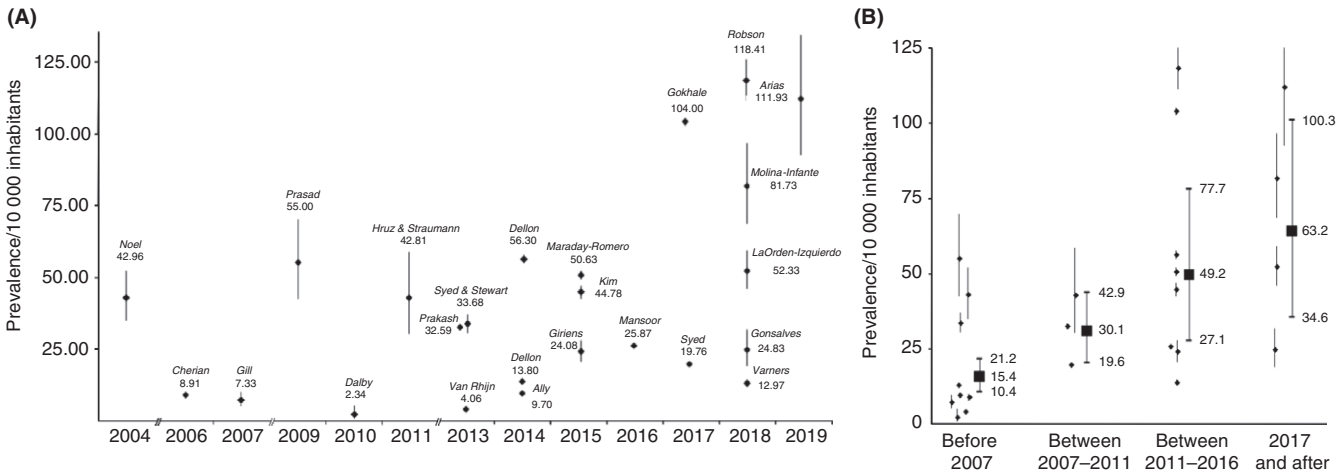

FIGURE 3 Population-based studies that have assessed the prevalence of EoE over time. Graphic representation of the prevalence rates (value per 100 000 inhabitants with 95% CI) of each individual study (identified by first author's name), distributed (A) throughout the years of publication and (B) according to the diagnostic criteria for EoE used in each study. Boxes and whisker plots in B represent summary of prevalence with 95% CIs after meta-analysis of individual studies

(children or adults or all ages) and different time periods. The studies were pooled to give an overall incidence rate estimate of 4.4 (95% CI, 2.8-6.4) new cases of EoE per 100 000 inhabitants/year at risk of EoE based on a random-effects model (I^2 = 99.9%; Table 2; Figure 4A). No significant differences were noted for pooled incidence rates when studies were grouped by geographical origin, despite incidence figures being higher for those conducted in North American compared to European countries (7; 95% CI, 2.6-13.6 vs 2.7; 95% CI, 2-3.6, P = 0.108). No significant differences in incidence of EoE based on the origin of source data (i.e., hospital-based case

TABLE 1 Summary estimates and 95% CIs of population-based prevalence from studies dealing with the epidemiology of eosinophilic oesophagitis in patients of all ages

Prevalence	All patients/100 000	I^2 (%)	n	Adults/100 000	I^2 (%)	n	Children/100 000	I^2 (%)	n
Overall	34.2 (23.1-47.5)	99.9	24	42.2 (31.1-55)	99.9	9	34.4 (22.3-49.2)	99.8	14
Subgroups according to geographical areas									
North America (US and Canada)	41 (25.7-59.9)	99.9	13	31.9 (21.5-44.3)	100	7	38.3 (23.7-56.4)	99.9	9
Europe	29 (19.9-39.8)	99.6	9	95.8 (68.4-127.8)	—	2	41 (3.2-121.1)	92	3
Subgroups according to diagnostic criteria for EoE									
Before 2007 consensus	15.4 (10.4-21.2)	99.8	9	—	—	—	—	—	—
After 2007 consensus	30.1 (19.6-42.9)	—	3	—	—	—	—	—	—
After updated consensus 2011	49.2 (27.1-77.7)	100	8	—	—	—	—	—	—
After 2017 guidelines and AGREE conference 2018	63.2 (34.6-100.3)	97.1	4	95.8 (68.4-127.8)	—	2	53.4 (27.1-88.5)	96.6	3
Subgroups according to study risk of bias									
High risk	32 (16.6-52.4)	100	10	34.2 (21.4-49.9)	100	6	28.2 (16.4-43.3)	99.9	7
Low risk	35.5 (25.7-46.8)	99.8	14	64.2 (14.9-148.2)	—	3	42.7 (14.1-86.8)	99.7	7
According to source of patients' data									
Insurance and administrative databases	31 (17.3-48.6)	100	13	31.9 (21.5-44.3)	100%	7	35 (21.3-52.2)	99.9	6
Hospital-based case series	38.3 (17.7-66.8)	99.6	11	95.8 (68.4-127.8)	—	2	34.9 (11.3-71.6)	99.7	8

TABLE 2 Summary estimates and 95% CIs of population-based incidence from studies dealing with the epidemiology of eosinophilic oesophagitis in patients of all ages

Incidence	All patients/100 000	I^2 (%)	n	Adults/100 000	I^2 (%)	n	Children/100 000	I^2 (%)	n
Overall	4.4 (2.8-6.4)	99.9	18	7.7 (1.8-17.8)	99.9	5	6.6 (3-11.7)	99.8	10
Subgroups according to geographical areas									
North America (US and Canada)	7 (2.6-13.6)	99.9	8	7.2 (0.6-21)	100	3	8.1 (2.7-16.4)	99.9	6
Europe	2.7 (2-3.6)	99.6	9	8.5 (7.5-9.6)	—	2	5.4 (2-10.3)	92	3
Subgroups according to diagnostic criteria for EoE									
Before 2007 consensus	2.6 (1.6-3.9)	99.8	8	—	—	—	—	—	—
After 2007 consensus	2.3 (2.2-2.4)	—	2	—	—	—	—	—	—
After updated consensus 2011	8.7 (0.6-25.9)	100	4	—	—	—	—	—	—
After 2017 guidelines and AGREE conference 2018	6.2 (3.5-9.5)	97.1	4	8.5 (7.5-9.6)	—	2	5.6 (2.6-9.8)	96.6	3
Subgroups according to study risk of bias									
High risk	4.7 (1.4-9.8)	100	6	7.2 (0.6-21)	100	3	5.5 (0.9-14)	99.9	4
Low risk	4.3 (2.9-5.9)	99.8	12	8.5 (7.5-9.6)	—	2	7.4 (1.7-17.2)	99.7	6
According to source of patients' data									
Insurance and administrative databases	3.3 (1.4-5.9)	100	8	7.2 (0.6-21)	100	3	7.3 (1.2-18.5)	99.9	3
Hospital-based case series	5.5 (2.2-10.3)	99.6	10	8.5 (7.5-9.6)	—	2	6.3 (1.5-14.6)	99.7	7

series regarding insurance and administrative databases) were noted, although summaries for incidence tended to be slightly higher in the former (5.5; 95% CI, 2.2-10.3 vs 3.3; 95% CI, 1.4-5.9, respectively).

Subgroup analyses by grouping source studies according to risk of bias, did not show significant differences in overall incidence rate of EoE, being 4.3 (95% CI, 2.9-5.9) and 4.7 (95% CI, 1.4-9.8) new cases per 100 000 persons-year for studies with low and high risk of bias, respectively.

Subgroup analysis according to diagnostic criteria for EoE demonstrated changes through time in incidence rates when comparing studies carried out before 2007 (2.6; 95% CI, 1.6-3.9) and after 2017, with current pooled incidence rates for EoE being 6.2/100 000 inhabitants/year; 95% CI, 3.5-9.5; $P = 0.059$).

3.6 | Incidence of EoE in children

There were 10 studies of the incidence of EoE in children; these were conducted in the US,[8,9,19,21,39] Denmark,[32] Spain[40,7] and Brazil[44] over a 14-year period, with data from 1991 to the end of 2017 (Table S1). It was found that the incidence of EoE in children for the

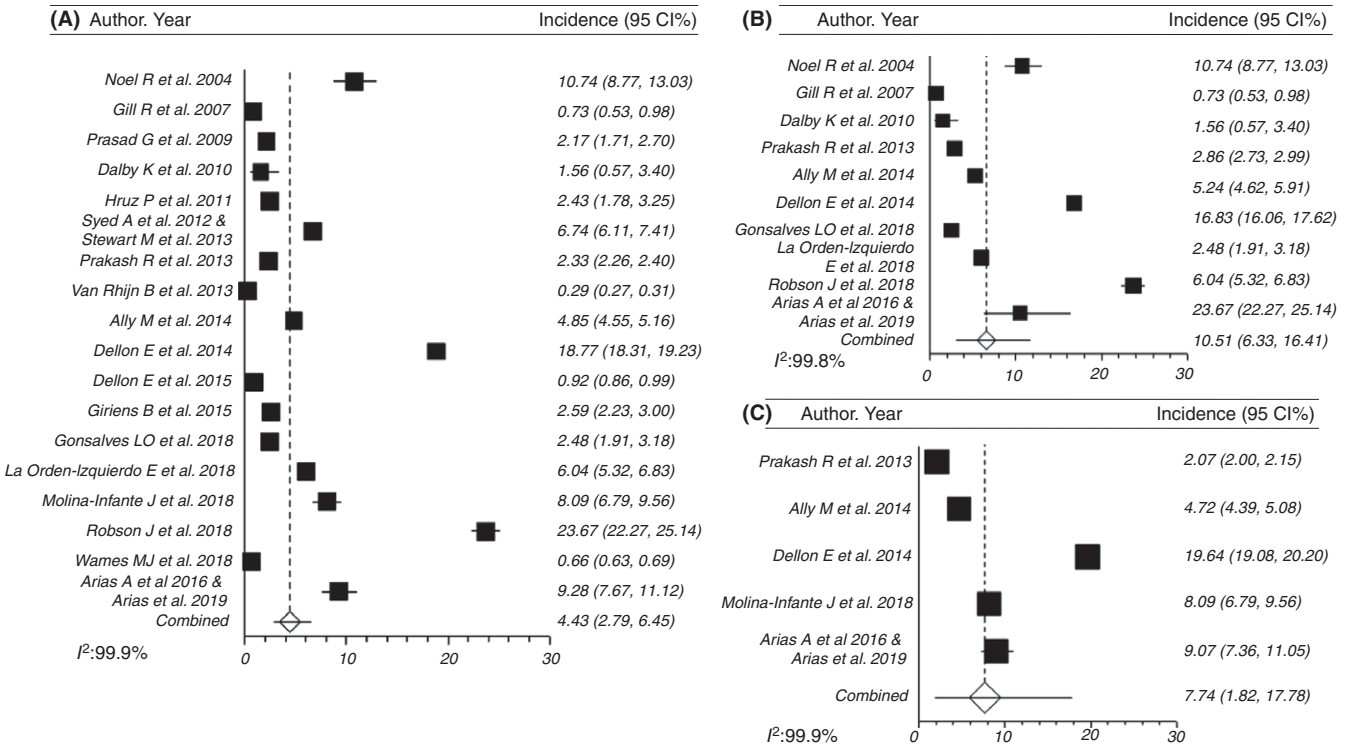

FIGURE 4 Summary estimates for population-based incidence of EoE overall (A), as well as subgroup analysis of studies conducted in children (B) or adults (C). Summary estimates are expressed as the number of EoE patients/100 000 persons-year. An I^2 value (statistical heterogeneity) over 75% indicates a high heterogeneity

whole period was 6.6/100 000 persons-year; 95% CI 3-11.7; I^2 = 99.8%), but 5.6; 95% CI, 2.6-9.8; I^2 = 96.6% when only the most recent studies were considered, thus supporting stable incidence rates for EoE over time (Figure 4B). Subgroup analysis showed no significant differences in incidence rates according to risk of bias or origin of data (Table 2).

3.7 | Incidence of EoE in adults

Five studies reported the incidence of EoE in adults (Table S1)—one from the US[29] and four from Europe[7,33–35]with collective data for the period 1989 to 2017. Overall, the summary estimates for the whole period were 7.7/100 000 person-year (95% CI, 1.8-17.8), with no significant differences between US and European figures (Figure 4C). According to the most recent studies using current diagnostic criteria for EoE,[41,7] the summary incidence for the period 2017 and beyond was 8.5 new cases per 100 000 persons-year (95% CI 7.5-9.6).[41,7] Subgroup analyses according to risk of bias and source of data (administrative or insurance database vs hospital-based cases series) showed no significant differences in incidence rates (Table 2).

3.8 | Prevalence rate ratio for genderss

The prevalence rate ratio by gender was reported in nine studies.[7,20,23–25,27–,29,41] Although a significant heterogeneity in the results was observed, the pooled prevalence of EoE among male patients was 72.1 (95% CI, 41.3-111.5; I^2 = 99.9%) patients per 100 000 inhabitants, while in females it was 29.4 (14.8-48.8; I^2 = 99.9%). Males were thus at greater risk for presenting EoE compared to females, with an OR of 2.22 (95% CI: 2-2.46; Figure S1).

3.9 | Publication bias assessment

Funnel plot analyses of studies assessing the prevalence of EoE revealed no significant publication bias (Begg-Mazumda's rank test P = 0.676; Harbord test P = 0.980). Likewise, studies reporting on the incidence of EoE exhibited no significant publication bias (Begg-Mazumda's rank test P = 0.549; Harbord test P = 0.091). Funnel plots assessing size effect against study precision are shown in Figure S2.

4 | DISCUSSION

This systematic review provides a detailed update of the existing data on the worldwide incidence and prevalence of EoE. Comparison between studies was attempted in relation to geography and age. In addition, we investigated whether observed differences in disease occurrence and changes over time might have been due to varying definitions for the disease. The results from the systematic review confirmed that EoE is a common disease, less common in children than in adults; and identifies its growing frequency.

Prevalence rates for EoE showed a worldwide geographical variation, which probably reflects the fact that EoE is directly related to

socio-demographic development and the recognition of EoE in developed countries. The higher reported prevalence of EoE was in North America and Europe, with most of the studies coming from these countries. Differences in prevalence among studies are widely related to varying case definition (with evolving diagnostic criteria for EoE in the last decade) rather than solely geographic variation.

The main purpose of this investigation, and also the main difference from other reviews, was to analyse data on the general population only and to cluster studies according to their focus, whether adults or children. We also aimed to update the figures provided by our previous systematic review, which summarised publications up to the end of 2014[5]; with the expanding recognition of EoE, a sharp increase in numbers of reported cases, together with the 17 population-based studies released since 2014/5 (which represent half of the documents included in this systematic review), determined that previous results were obsolete. Furthermore, the recent update of diagnostic criteria for EoE, by eliminating proton pump inhibitor-responsive oesophageal eosinophilia (PPI-REE) as a different entity and including these patients within the clinical spectrum of EoE,[1,6,45] required an update of the data in order to reflect the magnitude of the problem, especially since several recent population studies had already applied the new diagnostic criteria.[7,9,40,44]

We are able to confirm the findings from our previous systematic review showing that EoE overall is less common in children than in adults.[5] It is worth noting that there has been a significant increase in the overall prevalence of EoE for both age groups since the summary estimates provided up to the end of 2014 were documented: prevalence rates in children increased from 19.1 (95% CI, 7.9-35.2) to 34.4 (95% CI, 22.3-49.2) patients per 100 000 inhabitants in less than 4 years, while for adults they grew from 32.5 (95% CI, 12.4-62.2) to 42.2 (95% CI, 31.1-55) patients per 100 000 inhabitants. 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. Thus, the overall incidence rate of EoE increased from 3.7 (95% CI, 1.7-6.5) to 4.4 new cases/100 000 persons-year (95% CI, 2.8-6.4) in less than 3 years, with increases both for children (from 5.1; 95% CI, 1.5-10.9 to 6.6; 95% CI, 3-11.7) and for adults (7; 95% CI, 1-18.3 to 7.7; 95% CI, 1.8-17.8), with even higher rates provided by the most recent studies. The reasons behind this increase have not been clarified completely and are urgently needed. 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.[41] Only the most recently published papers included in our review had EoE diagnosed by the current evidence-based criteria,[6,7] according to which, a response to PPI does not preclude a diagnosis of EoE, contrary with previous consensus guidelines.[2,18] However, multiple studies, both in the early literature[19–21,43] and in that published after the proposal of the so called PPI-REE in 2011,[31,36,42] did not exclude response to PPIs as a diagnostic requirement for EoE. In any case, it is clear that the frequency of EoE has progressively increased over the years as the criteria for the disease have been updated, reflecting a change in the epidemiology of the disease beyond that of including patients who previously responded to PPIs within the epidemiological calculations.

A more widespread, general use of endoscopy for the diagnosis and management of gastroenterological disorders was also proposed as an explanation for the 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 goes beyond the use of endoscopy with biopsy,[7,41,48] thus supporting true expansion in the epidemiology of the disease in several settings.

Our review has several strengths, such as: compiling results from an exhaustive literature search of three major databases with no time limit on publication date; critically appraising the studies recovered according to their methodology and risk of bias; different investigators independently extracting the data from the studies which were included; and risk of bias being assessed with a validated document developed for prevalence studies[13] by two independent researchers. We also assessed the potential effect of the changing definition of EoE over the last decade on the epidemiology of the disease, and the accuracy of data obtained from administrative and insurance databases in relation to those extracted from hospital-based case series.

However, some limitations should also be acknowledged, including the possibility of not recovering all the relevant information published on population-based epidemiological data concerning EoE, despite our attempts to minimise this risk. This fact could also affect the lack of significant publication bias found in our Funnel plot analyses. Furthermore, most of the information retrieved comes from retrospective registries of codified diagnoses, and the reliability of this information was not systematically checked. Finally, a high I^2 value may identify estimates with low predictive values, thus limiting the reliability of the results of our meta-analyses.

In conclusion, our results confirm that EoE currently constitutes a highly prevalent disorder, with rising incidence and prevalence rates in recent years. The increasing frequency of EoE overall in population-based studies, which are mainly restricted to US and Europe, have consistently demonstrated the predominance of EoE among adults compared to children. The high, and still ongoing prevalence of EoE in developed countries, should prompt resources to be allocated in order to face the costs associated with the diagnosis and treatment of EoE, and to design sustainable health policies with regard to the chronic nature and impact of the disease on patients' health.

ACKNOWLEDGEMENTS

Declaration of personal interests: None.

AUTHORSHIP

Guarantor of the article: Alfredo J. Lucendo.

Author contributions: Pilar Navarro, study conception and design, data extraction, analysis and interpretation of data, risk of bias

rating, final approval of the manuscript; Ángel Arias, study conception and design, article retrieval, data extraction, analysis and interpretation of data, risk of bias rating, statistical analyses, final approval of the manuscript; Laura Arias González, study conception and design, article retrieval, analysis and interpretation of data, risk of bias rating, final approval of the manuscript; Emilio J. Laserna-Mendieta, data extraction, risk of bias rating, final approval of the manuscript; Miriam Ruiz-Ponce, analysis and interpretation of data, final approval of the manuscript; Alfredo J. Lucendo, study conception and design, data extraction, analysis and interpretation of data, risk of bias rating, manuscript writing, final approval of the manuscript. All authors approved the final version of the manuscript, including the authorship list.

ORCID

Pilar Navarro https://orcid.org/0000-0002-6293-2570
Ángel Arias https://orcid.org/0000-0003-1006-0958
Laura Arias-González https://orcid.org/0000-0003-2132-9350
Emilio J. Laserna-Mendieta https://orcid.org/0000-0002-9039-7667
Miriam Ruiz-Ponce https://orcid.org/0000-0001-8713-7760
Alfredo J. Lucendo https://orcid.org/0000-0003-1183-1072

REFERENCES

1. Lucendo AJ, Molina-Infante J, Arias A, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United Eur Gastroenterol J*. 2017;5:335-358.
2. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128:3-20.
3. Picus D, Frank PH. Eosinophilic esophagitis. *AJR Am J Roentgenol*. 1981;136:1001-1003.
4. Moawad FJ. Eosinophilic esophagitis: incidence and prevalence. *Gastrointest Endosc Clin N Am*. 2018;28:15-25.
5. Arias A, Pérez-Martínez I, Tenías JM, et al. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. *Aliment Pharmacol Ther*. 2016;43:3-15.
6. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. *Gastroenterology*. 2018;155:1022-1033.
7. Arias Á, Lucendo AJ. Incidence and prevalence of eosinophilic oesophagitis increase continiously in adults and children in central Spain: a 12-year population-based study. *Dig Liver Dis*. 2019;51:55-62.
8. Hommeida S, Grothe RM, Hafed Y, et al. Assessing the incidence trend and characteristics of eosinophilic esophagitis in children in Olmsted County, Minnesota. *Dis Esophagus*. 2018;31:doy062.
9. Robson J, O'Gorman M, McClain A, et al. Incidence and prevalence of pediatric eosinophilic esophagitis in Utah based on a 5-year population-based study. *Clin Gastroenterol Hepatol*. 2019;17:107-114.
10. Shaheen NJ, Mukkada V, Eichinger CS, et al. Natural history of eosinophilic esophagitis: a systematic review of epidemiology and disease course. *Dis Esophagus*. 2018;31:doy015.
11. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
12. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008-2012.
13. Munn Z, Aromataris E, Tufanaru C, et al. The development of software to support multiple systematic review types: the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). *Int J Evid Based Healthc*. 2018; [Epub ahead of print]. https://doi: 10.1097/XEB.0000000000000152
14. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials*. 2015;45:139-145.
15. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
16. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088-1101.
17. Harbord RM, Egger M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med*. 2006;25:3443-3457.
18. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology*. 2007;133:1342-1363.
19. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med*. 2004;351:940-941.
20. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol*. 2009;7:1055-1061.
21. Gill R, Durst P, Rewalt M, et al. Eosinophilic esophagitis disease in children from West Virginia: a review of the last decade (1995-2004). *Am J Gastroenterol*. 2007;102:2281-2285.
22. Prakash R, Maradey C, Fas R. Eosinophilic esophagitis is much less common than previously thought: a large nationwide database study. *Am J Gastroenterol*. 2013;108(Suppl 1):S33.
23. Ally MR, Maydonovitch CL, Betteridge JD, et al. Prevalence of eosinophilic esophagitis in a United States military health-care population. *Dis Esophagus*. 2015;28:505-511.
24. Dellon ES, Jensen ET, Martin CF, et al. Prevalence of eosinophilic esophagitis in the United States. *Clin Gastroenterol Hepatol*. 2014;12:589-596.
25. Kim S, Kim S, Sheikh J. Prevalence of eosinophilic esophagitis in a population-based cohort from Southern California. *J Allergy Clin Immunol Pract*. 2015;3:978-979.
26. Maradey-Romero C, Prakash R, Lewis S, et al. The 2011-2014 prevalence of eosinophilic oesophagitis in the elderly amongst 10 million patients in the United States. *Aliment Pharmacol Ther*. 2015;41:1016-1022.
27. Mansoor E, Cooper GS. The 2010–2015 prevalence of eosinophilic esophagitis in the USA: a population-based study. *Dig Dis Sci*. 2016;61:2928-2934.
28. Gokhale M, Bell C, Law M, et al. Implications on patient identification using claims data. *Pharmacoepidemiol Drug Saf*. 2017;26(Suppl 2):67.
29. Syed A, Maradey-Romero C, Fass R. The relationship between eosinophilic esophagitis and esophageal cancer. *Dis Esophagus*. 2017;30:1-5.
30. Syed AAN, Andrews CN, Shaffer E, et al. The rising incidence of eosinophilic oesophagitis is associated with increasing rates: a population-based study. *Aliment Pharmacol Ther*. 2012;36:950-958.
31. Stewart MJ, Shaffer E, Urbanski SJ, et al. The association between celiac disease and eosinophilic esophagitis in children and adults. *BMC Gastroenterol*. 2013;13:96.

32. Dalby K, Nielsen RG, Kruse-Andersen S, et al. Eosinophilic oesophagitis in infants and children in the region of southern Denmark: a prospective study of prevalence and clinical presentation. *J Pediatr Gastroenterol Nutr*. 2010;51:280-282.
33. Hruz P, Straumann A, Bussmann C, et al. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. *J Allergy Clin Immunol*. 2011;128:1349-1350.
34. Straumann A, Simon H-U. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol*. 2005;115:418-419.
35. Arias A, Lucendo AJ. Prevalence of eosinophilic oesophagitis in adult patients in a central region of Spain. *Eur J Gastroenterol Hepatol*. 2013;25:208-212.
36. van Rhijn BD, Verheij J, Smout AJPM, et al. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol Motil*. 2013;25:47-52.
37. Dellon ES, Erichsen R, Baron JA, et al. The increasing incidence and prevalence of eosinophilic oesophagitis outpaces changes in endoscopic and biopsy practice: National population-based estimates from Denmark. *Aliment Pharmacol Ther*. 2015;41:662-670.
38. Giriens B, Yan P, Safroneeva E, et al. Escalating incidence of eosinophilic esophagitis in Canton of Vaud, Switzerland, 1993-2013: a population-based study. *Allergy*. 2015;70:1633-1639.
39. O'Malley A, Keane F, Casey A, et al. Paediatric eosinophilic oesophagitits in Ireland - a 10 year review of incidence, presenting symptoms, phenotype and management at diagnosis. *J Pediatr Gastroenterol Nutr*. 2017;64(Suppl. 1):293.
40. La Orden Izquierdo E, Gutiérrez Junquera C, Mahillo-Fernández I, et al. Increasing incidence of paediatric eosinophilic esophagitis in the southwestern of the region of Madrid. *J Investig Allergol Clin Immunol*. 2019;29:24-29.
41. Molina-Infante J, Gonzalez-Cordero PL, Ferreira-Nossa HC, et al. Rising incidence and prevalence of adult eosinophilic esophagitis in midwestern Spain (2007-2016). *United Eur Gastroenterol J*. 2018;6:29-37.
42. Warners MJ, de Rooij W, van Rhijn BD, et al. Incidence of eosinophilic esophagitis in the Netherlands continues to rise: 20-year results from a nationwide pathology database. *Neurogastroenterol Motil*. 2018;30:e13165.
43. Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. *Arch Dis Child*. 2006;91:1000-1004.
44. Gonçalves LO, Lopes MM, Rezende ER, et al. Incidence of childhood eosinophilic esophagitis in central Brazil: how many are we missing? *J Investig Allergol Clin Immunol*. 2018;28:241-245.
45. Molina-Infante J, Bredenoord AJ, Cheng E, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. *Gut*. 2016;65:521-531.
46. Borowitz KC, Borowitz SM. Feeding problems in infants and children: assessment and etiology. *Pediatr Clin North Am*. 2018;65:59-72.
47. Philpott H, Garg M, Tomic D, et al. Dysphagia: thinking outside the box. *World J Gastroenterol*. 2017;23:6942-6951.
48. Kidambi T, Toto E, Ho N, et al. Temporal trends in the relative prevalence of dysphagia etiologies from 1999-2009. *World J Gastroenterol*. 2012;18:4335-4341.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

How to cite this article: Navarro P, Arias Á, Arias-González L, Laserna-Mendieta EJ, Ruiz-Ponce M, Lucendo AJ. Systematic review with meta-analysis: the growing incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. *Aliment Pharmacol Ther*. 2019;49:1116–1125. https://doi.org/10.1111/apt.15231