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

Á. Arias*, I. Pérez-Martínez†, J. M. Tenías‡ & A. J. Lucendo§

*Research Unit, Complejo Hospitalario La Mancha Centro, Alcázar de San Juan, Spain.
†Department of Gastroenterology, Hospital Universitario Central de Asturias, Oviedo, Spain.
‡Family and Community Medicine Teaching Unit, Escola Valenciana d' Estudis de la Salut, Valencia, Spain.
§Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Spain.

Correspondence to:
Dr A. J. Lucendo, Department of Gastroenterology, Hospital General de Tomelloso, Vereda de Socuéllamos, s/n, Tomelloso, Ciudad Real 13700, Spain.
E-mail: alucendo@vodafone.es

Publication data
Submitted 13 August 2015
First decision 4 September 2015
Resubmitted 28 September 2015
Accepted 4 October 2015
EV Pub Online 28 October 2015

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y. Yuan. This article was accepted for publication after full peer-review.

SUMMARY

Background
The recognition of eosinophilic oesophagitis (EoE) has risen sharply, but its current epidemiology is still under debate.

Aim
To estimate accurately the prevalence and incidence rates of EoE, by a systematic review and meta-analysis.

Methods
MEDLINE, EMBASE and SCOPUS databases were searched for population-based studies on the epidemiology of EoE. Pooled incidence and prevalence rates, male: female and children:adult ratios, and geographical and temporal variations were calculated with random-effects models.

Results
The search yielded 1334 references; the final quantitative summary included 13 population-based studies from North America, Europe and Australia, with the results showing high heterogeneity. The pooled EoE incidence rate was 3.7/100 000 persons/year [95% confidence interval (CI): 1.7–6.5] and was higher for adults (7; 95% CI: 1–18.3) than for children (5.1; 95% CI: 1.5–10.9).
The pooled prevalence of EoE was 22.7 cases/100 000 inhabitants (95% CI: 12.4–36), rising to 28.1 (95% CI: 13–49) when studies with a lower risk of bias were considered; prevalence was higher in adults than in children (43.4; 95% CI: 22.5–71.2 vs. 29.5; 95% CI: 17.5–44.7, respectively), and in American compared to European studies.
A steady rise in EoE incidence and prevalence rates was observed upon comparison of studies conducted before and after 2008. No significant publication bias was found.

Conclusions
Eosinophilic oesophagitis is an increasingly common diagnosis in North America and Europe. The population-based incidence and prevalence of eosinophilic oesophagitis vary widely across individual studies, probably due to variations in diagnosis and risk of bias of research. More prospective, large-scale, multicenter studies are needed to evaluate reported data.

doi:10.1111/apt.13441

INTRODUCTION

Eosinophilic oesophagitis (EoE) is a chronic immune/antigen-mediated inflammatory clinicopathological entity characterised by the presence of large numbers of intraepithelial eosinophils in oesophageal biopsies and recurrent symptoms of oesophageal dysfunction.[1] First characterised as a distinct disorder about 20 years ago,[2, 3] the recognition of EoE in Westernised countries has risen sharply, so that it is now considered to be the most frequent eosinophilic gastrointestinal disorder[4] as well as the second most common cause of dysphagia and chronic oesophagitis after gastroesophageal reflux disease, the main cause of oesophageal symptoms in children and young adults.[5, 6] In fact, EoE currently comprises up to 15% of diagnoses in patients undergoing upper endoscopy for non-obstructive dysphagia.[7, 8]

In recent years, several studies have attempted to define the extent of EoE by estimating its epidemiology in different populations. Different methodological approaches have been employed, from population-based research to studies defining the frequency of EoE in various series of endoscopies and oesophageal biopsies. Although the results vary widely, a gradual increase in the prevalence of EoE in recent years can be observed in figures provided by different authors, who estimate that EoE may currently affect between 45 and 56 patients/100 000 inhabitants.[9–11] However, neither the epidemiology of EoE nor its temporal trends as observed in population-based studies has been systematically evaluated to date, thus hampering a reliable and accurate estimation of the magnitude of the problem.

The aim of this study was to conduct a systematic review of the literature to estimate the incidence and prevalence rates of EoE in children and adults, as well as their temporal trends and geographic variations.

METHODS

This systematic review has been registered in the PROSPERO International prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO; register no. CRD42014014078), and has been reported in accordance with the PRISMA statements.[12]

Selection of studies

A systematic literature search of three major bibliographic databases (PUBMED, EMBASE and Scopus) was performed independently by two researchers (AA and AJL) for the period up to December 2014. The search was not restricted with regard to date or language of publication. The researchers used a predetermined protocol in accordance with the quality standards for reporting meta-analyses of observational studies in epidemiology.[13]

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")

For the Scopus database, only free text searches with truncations were carried out. The search was not restricted with regard to date or language of publication.

We also examined the reference lists from retrieved articles and abstracts of conference proceedings (these were 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 2005 and 2014) to identify additional, relevant studies. Two reviewers (IP-M & AA) 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.

Inclusion criteria

A diagnosis of EoE was based on a combination of symptoms referred to oesophageal dysfunction and a dense eosinophilic infiltration (≥15 eosinophils per high power field) in oesophageal biopsies. 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.

Exclusion criteria

Our analysis 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 (i.e. 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.

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% confidence interval (95% CI).

Risk of bias assessment was checked with a specific evaluation form for observational studies developed by our group and based on the STROBE statements[14] and critical appraisal tools from the Critical Appraisal Skill Program. A study was considered to be at low risk for bias if each of the bias items could be categorised as low risk. On the contrary, studies were judged to have a high risk of bias if even one of the items was deemed high risk. Two investigators (IP-M & AA) independently gave each eligible study an overall risk of bias rating of high, low or unclear; if disagreements arose, a third reviewer (AJL) was consulted.

Data extraction

Three reviewers (IP-M, AA, & AJL) independently extracted relevant information from each eligible study using a standardised data extraction sheet and then proceeded to cross-check the results. The extracted data included the last name of the first author, year of publication, 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 sex 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 risk of bias assessment for all included studies were also extracted. Disagreements between reviewers regarding data extraction were resolved through discussion.

Statistical analysis

Estimations of both prevalence and incidence were carried out with the aid of a fixed or random-effects meta-analysis weighted for inverse variance following DerSimonian and Laird's method. Summary estimates, along with their 95% CIs, were calculated for the prevalence and incidence rates of EoE among children and adults.

Heterogeneity between studies was assessed with 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 of 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 with both the Begg-Mazumda's rank test[16] and the Harbord test.[17]

For the primary outcome, planned subgroup analyses were performed based on the geographic origin of patients (comparisons of figures were made by continent), age (adults vs. children) and study dates (before vs. after 2008). The effect of gender in individual studies was estimated as male/female odds ratios. Estimations were made through random-effects meta-analysis. Comparisons between summary estimates were done by a random-effects meta-regression model of aggregate-level data, specifying the standard error of dependent variables (incidence or prevalence) within each study (STATA 13.0, StataCorp LP, College Station, TX, USA).

A subgroup analysis was performed with regard to risk of bias and type of document (full-length article *vs.* abstract presented at conference proceedings). All calculations were made with StatsDirect statistical software version 2.7.9 (StatsDirect Ltd, Cheshire, UK).

RESULTS

Literature search

The search strategy yielded 1334 references; 1307 were excluded on the basis of the specific article type (editorial, letter, comment, and review and guidelines) or after reviewing the abstract. Of the remaining 27 studies, 13 were excluded for the reasons listed in Figure 1 while four additional documents were retrieved through reference tracking. This left 18 documents: 15 full-text articles[9–11, 18–29] and 3 abstracts,[30–32] one of which has recently been published in full.[33] Five of the 18 selections included subsets of patients who were included in subsequent articles published by the same research group and were thus excluded. Table 1 summarises the characteristics of the 13 studies included in the final meta-analysis. Of the 13 full-text incidence and/or prevalence-related studies, most (69.2%) showed a low risk of bias.

Prevalence rates and changes according to regional distribution

Of the 13 documents mentioned above, eight studies were conducted in North America (six from the US[9, 18, 20, 23, 28, 30, 31] and one from Canada,[25, 26]) while two were conducted in Northern Europe,[21, 22, 24, 32, 33] two in Central Europe,[10, 27, 29] and one in Southern Europe.[11] An additional study was carried out with data from Western Australia.[19]

The overall prevalence of EoE in the 13 retrieved studies was 22.7 cases per 100 000 inhabitants/year (95%

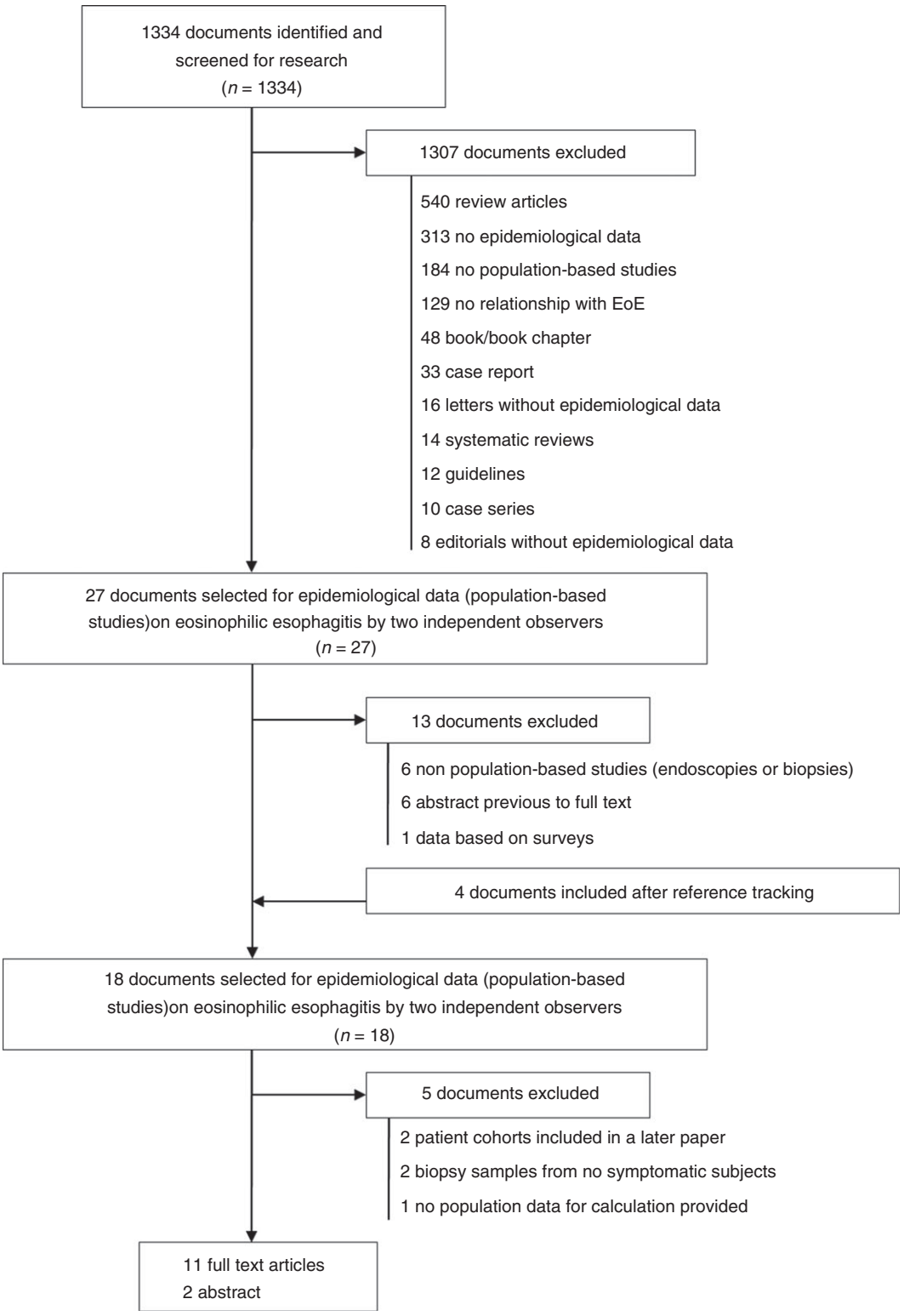

Figure 1 | Flow chart for the process of identifying studies included in and excluded from the systematic review.

CI: 12.4–36; I^2 = 99.9%; Figure 2). Differences in the overall prevalence rates were also documented according to study region, being higher for North America (30.7; 95% CI: 16.2-49.8; I^2 = 99.9%) than for Europe (16.1; 95% CI: 7.9–27.1; I^2 = 99.4%), although these differences were not statistically significant (P = 0.25).

Table 1 | Demographics and characteristics of population-based studies included in our systematic review and meta-analysis

First author, publication year	Country	Reference Population	Cases of ;EoE	Study design	Age of patients	Study period	Incidence/100 000 (95% CI)		Prevalence/ 100 000 (95% CI)	
							Average for the period	Annual rate/ age specific	Annual rate/ age specific	
Noel R *et al.* (2004)[18]	USA	239 758*	103	Retrospective	Children	2000–2003	10.7 (8.8–13)*	2000: 9.1 2001: 9.9 2002: 10.3 2003: 12.8	2000: 9.91 2001: 19.83 2002: 30.16 2003: 42.96	
Cherian S *et al.* (2006)[19]	Australia	3 198 653*	285	Retrospective	Children	1995, 1999, 2004	NA		1995: 0.5 1999: 3.1 2004: 8.9	
Gill R *et al.* (2007)[20]	USA	600 000	44	Retrospective	Children	1995–2004	0.7 (0.5–1)*		7.3	
Prasad G *et al.* (2009)[23]	USA	120 000	78	Retrospective	55 Adult & 23 Children	1976–2005	2.2 (1.7–2.7)*	1991–1995 0.35 (0–0.9) 2001–2005 9.4 (7.1–11.8)	55 (42.7–67.2)	
Dalby K *et al.* (2010)[24]	Denmark	256 164	6	Prospective	Children	2005–2007	1.6 (0.6–3.4)		2.3	
Hruz P *et al.* (2011)[10] [including Straumnan A *et al.* (2005)[29]]	Switzerland	90 000	46	Retrospective	Adult	1989–2009	2.45	1989–1991: 1.2 (0.3–3.5) 1992–1994: 1.6 (0.4–3.98) 1995–1997: 1.1 (0.2–3.4) 1998–2000: 0.7 (0.1–2.7) 2001–2003: 0.7 (0.1–2.7) 2004–2006: 4.4 (2.3–7.8) 2007–2009: 7.4 (4.5–11.3)	1989–1991: 3.6 (0.7–10.6) 1992–1994: 7.9 (3.3–16.8) 1995–1997: 11.5 (5.5–21.1) 1998–2000: 12.5 (7.1–23.8) 2001–2003: 13.4 (8.6–26.4) 2004–2006: 26.6 (18.9–42.4) 2007–2009: 42.8 (37–67.3)	
Syed A *et al.* (2012)[25] & Stewart M *et al.* (2013)[26]	Canada	1 250 000	421	Retrospective	338 Adult & 83 Children	2004–2008	6.7 (6.1–7.4)*	2004: 2.1 2005: 5 2006: 7.2 2007: 9.4 2008: 10.7	33.7*	
Arias A *et al.* (2012)[11]	Spain	89 642	40	Retrospective	Adult	2005–2011	6.37 (6.31–6.44)		44.62 (30–59)	
Van Rhijn B *et al.* (2013)[27]	The Netherlands	16 615 394	674	Retrospective	538 Adult & 136 Children	1996–2010	0.28 (0.26–0.3)	1996 0.01 (0–0.02) 2010 1.3 (1.1–1.5)	4.05*	
Prakash R *et al.* (2013)[31]	USA	14 360 300	4680	Retrospective	Adult & Children	2010–2013	2.3 (2.3–2.4)*	Adult: 2.1 (2–2.1)* Children: 2.9 (2.7–3)*	Adult: 29 Children: 40	
Ally M *et al.* (2014)[28]	USA (Military Population)	10 180 515	987	Retrospective	728 Adult & 259 Children	2008–2009	4.8 (4.5–5.2)*	Adult 4.7 (4.4–5.1)* Children 5.2 (4.6–5.9)*	9.7 (9.1–10.3)	Adult 9.5 (8.8–10.3) Children 10.5 (9.2–10.3)
Dellon E *et al.* (2014)[9]	USA	11 569 217	6513	Retrospective	4700 Adult & 1813 Children	2009–2011	18.8 (18.3–19.2)*	Adult 19.6 (19.1–20.2)* Children 16.8 (16.1–17.6)*	56.7	Adult 58.9 Children 50.5
Dellon E *et al.* (2015)[32, 33]	5 572 463*	769	Retrospective	Adult & Children	1997–2011	0.9 (0.9–1)*	1997: 0.13 2012: 2.6	5 572 463*	769	

95% CI, 95% confidence interval; NA, not available.

Prevalence and incidence rate figures were provided for authors of individual studies, except (*), which denotes figures calculated/estimated from original data provided in the research.

Age-specific EoE prevalence rates

Population-based data on the prevalence of EoE in children could be extracted or calculated from seven studies[9, 18–20, 24, 28, 31] while four additional studies allowed for the extraction of prevalence data in adults.[9, 11, 28, 31]

No statistically significant differences were noted in subgroup analyses by patient age, even though EoE was generally more prevalent in adults (32.5; 95% CI: 12.4–62.2; I^2 = 99.9%) than in children (19.1; 95% CI: 7.9–32.5; I^2 = 99.7%; P = 0.38). However, significant differences by age were observed in studies judged to be of a lower risk of bias (28.1; 95% CI: 13–49; I^2 = 99.9%) compared to figures from studies with higher risk of bias (12.2; 95% CI: 8.6–16.4; I^2 = 98.6%; P = 0.019). Five studies provided overall data from patients of all ages that could not be analysed separately.[9, 10, 23, 25–29, 32] Table 2 summarises prevalence rate calculations and 95% CIs for the retrieved documents and subgroup analysis.

Temporal variations in prevalence rates

An increase in EoE prevalence rates was observed upon comparison of studies carried out before and after 2008. The overall prevalence rates in studies carried out before 2008 was 17.9 cases per 100 000 inhabitants/year (95% CI 7.4–32.9; I^2 = 98.3%), which rose to 26.3 cases per 100 000 (95% CI 12.3–45.5; I^2 = 99.9%) in research carried out in 2008 or later, although these differences were not statistically significant (P = 0.46). Subgroup analyses also confirmed this

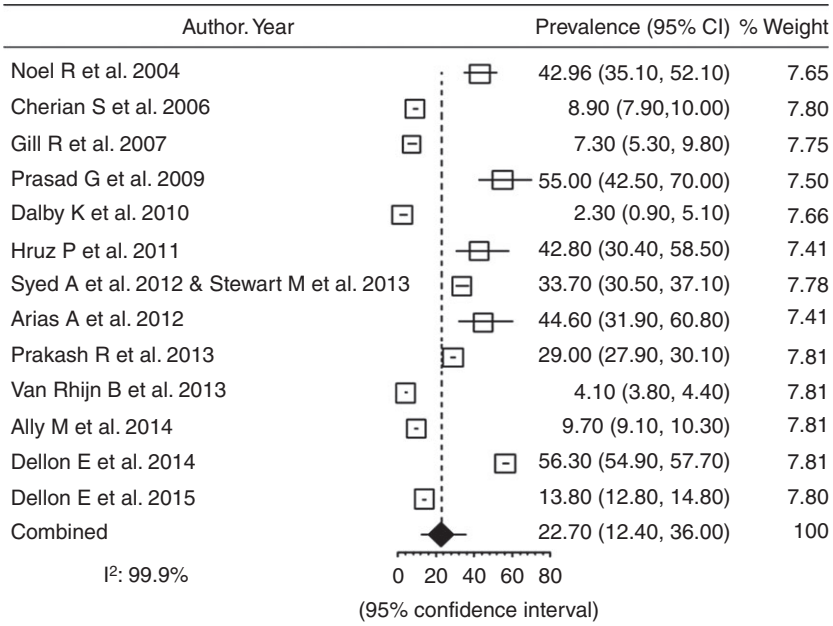

Figure 2 | Summary estimates for population-based prevalence of EoE. Summary estimates are expressed as the number of EoE patients/100 000 inhabitants. An I^2 value (statistical heterogeneity) of 99.9% indicates a high variability in intra-study differences in the overall effect size.

Table 2 | Summary estimates and 95% CIs of population-based prevalence from studies dealing with the epidemiology of eosinophilic oesophagitis in children, adults and studies not distinguishing patients' ages

Prevalence	Overall/100 000	*n*	Children/100 000	*n*	Adults/100 000	*n*	Age not specified/100 000	*n*
Overall	22.7 (12.4–36)	13	19.1 (7.9–35.2)	7	32.5 (12.4–62.2)	4	25.6 (12.4–43.1)	5
Subgroups according to geographical areas								
North America (USA & Canada)	30.7 (16.2–49.8)	7	26.9 (12.3–47.3)	5	28.9 (8.2–62.3)	3	43.1 (24.7–66.7)	2
Europe	16.1 (7.9–27.1)	5	–	1	–	1	15.9 (6.3–30)	3
Subgroups according to year of publication								
Before 2008	17.9 (7.4–32.9)	5	11.9 (4.3–23.5)	4	–	0	–	1
2008 and after	26.3 (12.3–45.5)	8	30.9 (12.1–58.4)	3	32.5 (12.4–62.2)	4	20.1 (8.3–37.2)	4
Subgroups according to study risk of bias								
Low/medium	28.1 (13–49)	9	29.5 (17.5–44.7)	4	43.4 (22.5–71.2)	3	23.3 (11.7–38.9)	4
High	12.2 (8.6–16.4)	4	9.2 (7.7–10.7)	3	–	1	–	1

trend (Table 2). Figure 3 shows individual prevalence rates and summary estimates for paediatric and adult studies carried out after 2008.

Overall incidence rate and temporal variations

In the 12 studies from which the incidence figures for EoE could be extracted or calculated,[9–11, 18, 20, 23–28, 31, 32] the reported annual incidence ranged from 0.28[27] to 19.6[9] cases per 100 000 inhabitants/year. The included studies were pooled to give an overall incidence rate estimate of 3.7 (95% CI: 1.7–6.5) per 100 000 inhabitants/year at risk for EoE based on a random-effects model (I^2 = 99.9%; Table 3; Figure 4).

No significant differences were noted for pooled incidence rates, although they tended to be slightly higher for adults (7; 95% CI: 1–18.3 per 100 000 inhabitants/year) than for children (5.1; 95% CI: 1.5–10.9 per 100 000 inhabitants/year; P = 0.68).

Subgroup analysis demonstrated changes through time in incidence rates when comparing studies carried out before and after 2008, with pooled incidence rates for EoE being higher in studies performed in and after 2008 (7.2/100 000 inhabitants/year, 95% CI: 0.8–20.2) in comparison to research conducted before 2008 (2.8/100 000 inhabitants/year, 95% CI: 1.7–4.1) (P = 0.07).

Incidence rates according to regional distribution

The annual incidence rates of EoE varied by geographic region (Figure 5), with estimates ranging from 5.4 (95%

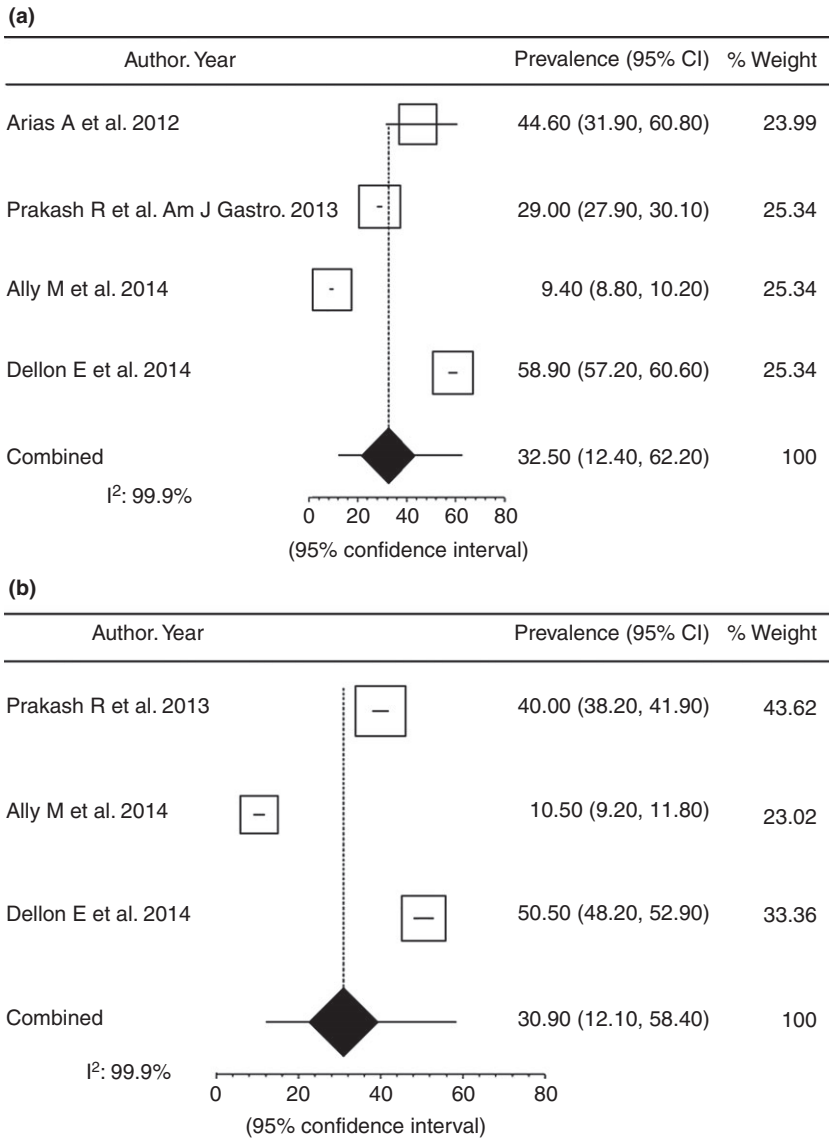

Figure 3 | Subgroup analysis of studies conducted in or after 2008 that evaluated the population-based prevalence of EoE in (a) adult and (b) paediatric patients. Summary estimates are expressed as the number of EoE patients/100 000 inhabitants. An I^2 value (statistical heterogeneity) of 99.8% indicates a high variability in intra-study differences in the overall effect size.

Table 3 | Summary estimates and 95% CIs of incidence rates of eosinophilic oesophagitis in population-based epidemiological studies in children, adults and studies not distinguishing patients' ages

Incidence	Overall/100 000	*n*	Children/100 000	*n*	Adults/100 000	*n*	Age not specified/100 000	*n*
Overall	3.7 (1.7–6.5)	12	5.1 (1.5–10.9)	6	7 (1–18.3)	4	2 (0.9–3.5)	5
Subgroups according to geographical areas								
North America (USA & Canada)	5.4 (1.6–11.5)	7	6 (1.7–12.9)	5	7.2 (0.6–21)	3	4.2 (0.9–9.8)	2
Europe	1.7 (1–2.7)	5	–	1	–	1	1 (0.4–1.9)	3
Subgroups according to year of publication								
Before 2008	2.8 (1.7–4.1)	9	3.3 (0.02–112)	3	–	1	2 (0.9–3.5)	5
2008 and onwards	7.2 (0.8–20.2)	3	7.3 (1.2–18.5)	3	7.2 (0.6–21)	3	–	–
Subgroups according to study risk of bias								
Low/medium	3.8 (1.5–7.2)	9	6.8 (1–17.7)	4	7.9 (0.2–26.8)	3	1.3 (0.6–2.1)	4
High	3.6 (0.1–7.7)	3	2.5 (0.03–8.9)	2	–	1	–	1

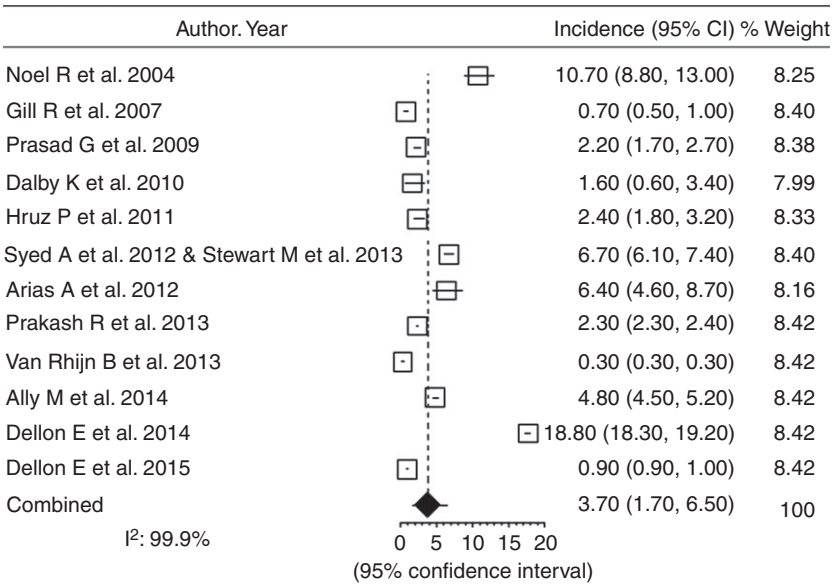

Figure 4 | Summary estimates for population-based incidence of EoE. Summary estimates are expressed as the number of EoE patients/100 000 inhabitants. An I^2 value (statistical heterogeneity) of 99.9% indicates a high variability.

CI: 1.6–11.5; I^2 = 99.9%) per 100 000 inhabitants/year in North America to 1.7 (95% CI: 1.0–2.7; I^2 = 99.3%) per 100 000 inhabitants/year in Europe (P = 0.11).

No significant differences were found between individual studies with different risk of bias.

Prevalence rate ratio for females vs. males

The prevalence rate ratio by sex was reported in five studies.[9, 11, 23, 28, 33] Although a significant heterogeneity in the results was observed, the pooled prevalence of EoE among male patients was 53.8 (95% CI: 14.2–118.9) patients per 100 000 inhabitants, while in females it was 20.1 (95% CI: 3.8–49.1). Males were thus at greater risk for presenting EoE compared to females, with an odds ratio (OR) of 2.01 (95% CI: 1.63–2.48; Figure 6).

Publication bias assessment

Funnel plot analyses of studies assessing the prevalence of EoE revealed no significant publication bias, with the P value for the Begg-Mazumda's rank test being 0.329 while for the Harbord bias test it was 0.795. Likewise, studies reporting on the incidence of EoE exhibited no significant publication bias (Begg-Mazumda's rank test P = 0.654; Harbord test P = 0.1).

DISCUSSION

This review of 13 publications represents the first systematic review and meta-analysis of population-based prevalence and incidence rates for EoE in patients of all ages. In our meta-analysis, the studies included came from several countries in different parts of Europe and North America, along with an additional study from

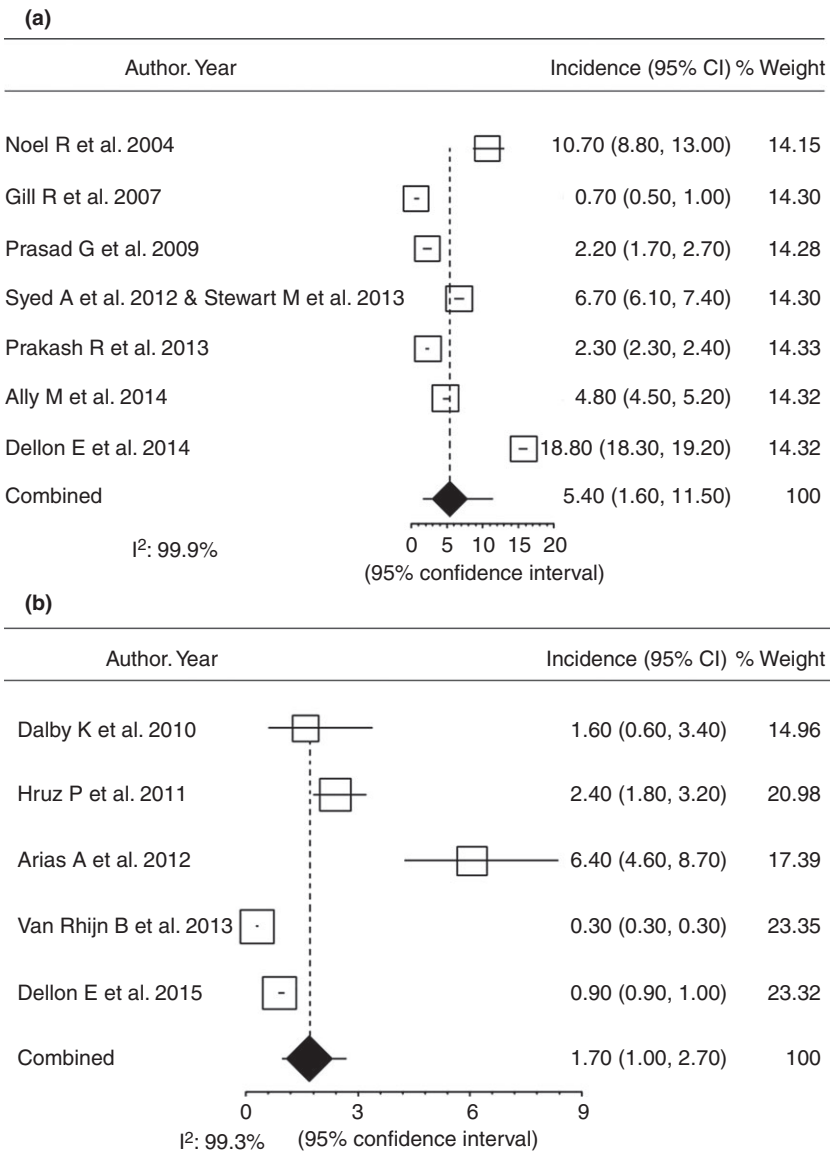

Figure 5 | Subgroup analysis of studies by geographic region, evaluating the population-based incidence of EoE in (a) North American and (b) European patients. Summary estimates are expressed as the number of EoE patients/100 000 inhabitants. An I^2 value (statistical heterogeneity) of 99.3% indicates a high variability in intra-study differences in the overall effect size.

Australia. It should be noted that population-based data on the epidemiology of EoE is scarce to non-existent from regions, where EoE has only recently started to be diagnosed, including Central and South America,[34–37] Asia,[38–40] and Northern Africa.[41, 42]

Analysis of 13 studies revealed a pooled incidence rate for EoE of 3.7 (95% CI: 1.7–6.5) new cases per 100 000 inhabitants/year, a figure that rose to 7.2 (95% CI: 0.8–20.2) in research carried out after 2008. These rates are similar to those described for the incidence of inflammatory bowel disease in Europe,[43–45] thus underscoring the burden of EoE on health systems in our region. In studies deemed to be of lower risk of bias, pooled incidence rates of EoE were higher in adults than in children, with values of 7.9 (95% CI: 0.2–26.8) and 6.8 (95% CI: 1–17.7), respectively. This finding is consistent with the chronic nature of the disorder[46] and its persistence in children as they progress into adulthood.[47]

In parallel with an increasing incidence rate, our results also show that the population-based prevalence of EoE varies widely among the Westernised countries, with an overall summarised estimation of 22.7 (95% CI 12.4–36) cases per 100 000 inhabitants, which rose to 28.1 (95% CI: 13–49) when the data from the 12 studies with the lowest risk of methodological bias were analysed. Subgroup analyses also allowed us to shed light on regional and age-related differences, as well as the current trends of this disorder. Indeed, our results indicate that estimations of the overall prevalence for EoE are higher in adults than in children, and that they increased significantly in studies carried out in 2008 and later. As ours is the first meta-analysis to evaluate the prevalence of EoE in population-based

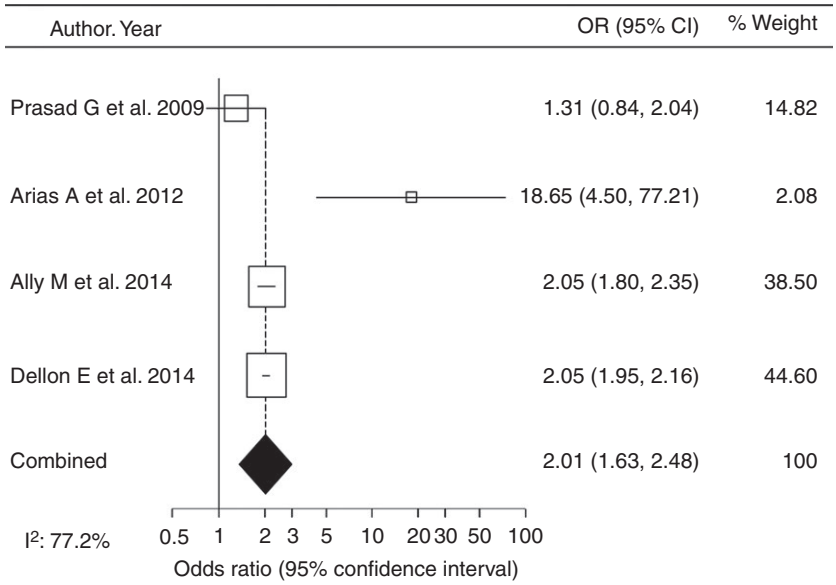

Figure 6 | Summary estimates for population-based prevalence of EoE in male and female patients, expresses as Odds ratio (OR). Summary estimates are expressed as the number of EoE patients/ 100 000 inhabitants. An I^2 value (statistical heterogeneity) of 99.9% indicates a high variability.

research, our results are not directly comparable with previous summary estimations.[48–50] However, our figures for the prevalence of EoE reflect the increasing frequency of this disorder as reported in single-center research conducted in recent years. For example, the cumulative prevalence of EoE in Olten County, Switzerland, increased from 23[29] to 42.8[10]/100 000 inhabitants between 2003 and 2009, while in Olmsted County, Minnesota, the reported prevalence of EoE has increased over the last three decades to 56.1/100 000 inhabitants.[23]

Unlike prior studies that investigated the prevalence of EoE in patients either undergoing oesophagogastroduodenoscopy for any indication or those presenting histological oesophageal disease upon endoscopy for abdominal pain,[48, 49] our study focuses exclusively on epidemiological data from population-based studies, an approach that has not been employed in previous research. The well-described predominance of EoE among male patients has also been documented in our results, which indicated a two- to threefold prevalence of the disorder in males compared to females.

In this systematic review, we have tried to overcome the limitations of previous reviews on the epidemiology of EoE, which were not based on population data, but rather on the registry of cases submitted for endoscopic evaluation due to upper gastrointestinal symptoms. Although a wide heterogeneity was found in both the prevalence and incidence rates provided by the studies we retrieved, referral bias is less likely to significantly affect our results than those from previous studies. The wide variability in the results of previous research is probably due to variations in accessibility to endoscopic resources in different settings, which varies widely between countries and regions, along with physician awareness and/or willingness to perform an upper endoscopy in patients who present with symptoms suggestive of EoE, especially children. Another factor in the heterogeneity of the results is whether oesophageal biopsies are obtained at the time of EGD, regardless of macroscopic appearance of the oesophagus.[48, 49] Although these same factors could have had an impact on the results of the various population-based studies included in our meta-analysis, which would partially explain the heterogeneity observed for most of our summary estimates, the exclusive selection of population-based studies allowed us to achieve a more accurate set of pooled results.

The strength of our research lies in the fact that it compiles the results of an exhaustive literature search from three major databases, that the studies recovered were critically appraised according to their methodology, and that different investigators independently extracted the data from the studies included. The possibility of not recovering all the relevant information published on population-based epidemiological data concerning EoE has thus been minimised; moreover, no significant publication bias was found when the results were subjected to funnel plot analysis.

Still, the possibility of not having retrieved all the relevant information published on the prevalence and/or incidence rates of EoE should be considered one of the limitations of our study, along with the risk of bias that remains despite our attempts to exclude publication bias by means of funnel plot analysis. In addition, risk of bias in the studies included in our systematic review was

assessed with a nonvalidated evaluation tool, because commonly accepted criteria that have proven validity for this purpose are not currently available. Our tool is based on the application of some items of the STROBE Statement and forms for critical appraisal of observational studies, in the same way that new pilot checklist recently proposed.[51, 52] The utilisation of our tool can be justified because, at least, it was useful in the assessment of designing and conducting observational studies. Furthermore, most of the information retrieved comes from retrospective, single-center, observational research. Unfortunately, the only studies based on a random sample from the general population had to be excluded due to the fact that the diagnosis of EoE was based exclusively on histopathological evaluation of endoscopic biopsy samples with no consideration of the presence of symptoms of oesophageal dysfunction required for a diagnosis of EoE.[21, 22]

In conclusion, our results confirm that EoE now constitutes a highly prevalent disorder, with rising incidence and prevalence rates in recent years. Currently available population-based studies, which are mainly restricted to North America and Europe, have consistently demonstrated the predominance of EoE among adults compared to children. This, along with the fact that, according to our research, EoE may now affect up to 0.281% of the population in Europe and the US, should prompt healthcare professionals to consider the costs associated with the diagnosis and treatment of EoE, its chronic nature, and the impact of the disease on patients' health-related quality of life and social activities[53–56] to design sustainable health policies with regard to the disease. Further epidemiological studies should validate our results and assess both the impact of current disease management alternatives in improving patient quality of life and the impact of EoE on healthcare systems in general.

AUTHORSHIP

Guarantor of the article: Alfredo J Lucendo.

Author contributions: Ángel Arias: study conception and design; article retrieval; data extraction; analysis and interpretation of data; risk of bias rating; statistical analyses. Isabel Pérez-Martínez: data extraction; analysis and interpretation of data; risk of bias rating. José M Tenías: article retrieval; statistical analyses. Alfredo J. Lucendo: study conception and design; data extraction; analysis and interpretation of data; risk of bias rating; manuscript writing.

All authors approved the final version of the manuscript, including the authorship list.

ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

REFERENCES

1. 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.
2. Attwood SE, Smyrk TC, Demeester TR, *et al.* Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* 1993; **38**: 109–16.
3. Straumann A, Spichtin HP, Bernoulli R, *et al.* Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings. *Schweiz Med Wochenschr* 1994; **124**: 1419–29.
4. Lucendo AJ, Arias A. Eosinophilic gastroenteritis: an update. *Expert Rev Gastroenterol Hepatol* 2012; **6**: 591–601.
5. Lucendo AJ, Sánchez-Cazalilla M. Adult versus pediatric eosinophilic esophagitis: important differences and similarities for the clinician to understand. *Expert Rev Clin Immunol* 2012; **8**: 733–45.
6. Dellon ES. Epidemiology of eosinophilic esophagitis. *Gastroenterol Clin North Am* 2014; **43**: 201–18.
7. Prasad GA, Talley NJ, Romero Y, *et al.* Prevalence and predictive factors of eosinophilic esophagitis in patients presenting with dysphagia: a prospective study. *Am J Gastroenterol* 2007; **102**: 2627–32.
8. Mackenzie SH, Go M, Chadwick B, *et al.* Eosinophilic oesophagitis in patients presenting with dysphagia–a prospective analysis. *Aliment Pharmacol Ther* 2008; **28**: 1140–6.
9. Dellon ES, Jensen ET, Martin CF, *et al.* Prevalence of eosinophilic esophagitis in the United States. *Clin Gastroenterol Hepatol* 2014; **12**: 589–96.
10. 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**: 1349–50.
11. Arias A, Lucendo AJ. Prevalence of eosinophilic oesophagitis in adult patients in a central region of Spain. *Eur J Gastroenterol Hepatol* 2013; **25**: 208–12.
12. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *BMJ* 2009; **339**: b2535.
13. 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**: 2008–12.
14. von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology* 2007; **18**: 800–4.
15. Higgins JP, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–60.
16. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test

for publication bias. *Biometrics* 1994; **50**: 1088–101.
17. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006; **25**: 3443–57.
18. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004; **351**: 940–1.
19. Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. *Arch Dis Child* 2006; **91**: 1000–4.
20. 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**: 2281–5.
21. Ronkainen J, Talley NJ, Aro P, *et al.* Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: the population-based Kalixanda study. *Gut* 2007; **56**: 615–20.
22. Ludvigsson JF, Aro P, Walker MM, *et al.* Celiac disease, eosinophilic esophagitis and gastroesophageal reflux disease, an adult population-based study. *Scand J Gastroenterol* 2013; **48**: 808–14.
23. Prasad GA, Alexander JA, Schleck CD, *et al.* Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol* 2009; **7**: 1055–61.
24. 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**: 280–2.
25. Syed AA, Andrews CN, Shaffer E, *et al.* The rising incidence of eosinophilic oesophagitis is associated with increasing biopsy rates: a population-based study. *Aliment Pharmacol Ther* 2012; **36**: 950–8.
26. 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.
27. van Rhijn BD, Verheij J, Smout AJ, *et al.* Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol Motil* 2013; **25**: 47–52.
28. Ally MR, Maydonovitch CL, Betteridge JD, *et al.* Prevalence of eosinophilic esophagitis in a United States military health-care population. *Dis Esophagus* 2015; **28**: 505–11.
29. Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005; **115**: 418–9.
30. Buckmeier BK, Rothenberg ME, Collins MH. The incidence and prevalence of eosinophilic esophagitis. *J Allergy Clin Immunol* 2008; **121**(Suppl. 1): S–71.
31. Prakash R, Maradey C, Fass R. Eosinophilic esophagitis is much less common than previously thought: a large nationwide database study. *Am J Gastroenterol* 2013; **108**(Suppl. 1): S33.
32. Dellon ES, Erichen R, Baron JA, *et al.* The increasing incidence and prevalence of eosinophilic esophagitis outpaces changes in endoscopic and biopsy practice: national population-based estimates from Denmark. *Gastroenterology* 2014; **146**(Suppl. 1): S664.
33. 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**: 662–70.
34. Rezende ER, Barros CP, Ynoue LH, *et al.* Clinical characteristics and sensitivity to food and inhalants among children with eosinophilic esophagitis. *BMC Res Notes* 2014; **7**: 47.
35. Pinheiro MI, de Goes Cavalcanti LP, Honorio RS, *et al.* Eosinophilic esophagitis in brazilian pediatric patients. *Clin Med Insights Pediatr* 2013; **7**: 41–8.
36. De la Cruz-Patino E, Ruíz Juárez I, Meixueiro Daza A, *et al.* Eosinophilic esophagitis prevalence in an adult population undergoing upper endoscopy in southeastern Mexico. *Dis Esophagus* 2015; **28**: 524–9.
37. Rodríguez H, Cuestas G, Sasson L. Eosinophilic esophagitis associated with laryngeal papillomatosis in a child. *Acta Otorrinolaringol Esp* 2014; **65**: 383–4.
38. Tomomatsu Y, Yoshino J, Inui K, *et al.* Clinical features of eosinophilic esophagitis: ten Japanese cases. *Dig Endosc* 2013; **25**: 117–24.
39. Shimura S, Ishimura N, Tanimura T, *et al.* Reliability of symptoms and endoscopic findings for diagnosis of esophageal eosinophilia in a Japanese population. *Digestion* 2014; **90**: 49–57.
40. Ma X, Xu Q, Zheng Y, *et al.* Prevalence of esophageal eosinophilia and eosinophilic esophagitis in adults: a population-based endoscopic study in Shanghai, China. *Dig Dis Sci* 2015; **60**: 1716–23.
41. Saadah OI, Aburiziza AJ, Abu Shakra RI. Eosinophilic esophagitis in children from Western saudi arabia: relative frequency, clinical, pathological, endoscopic, and immunological study. *Gastroenterol Res Pract* 2012; **2012**: 328253.
42. Hunter SS, Helmy DO, Zayedl NA, *et al.* Eosinophilic esophagitis in Egyptian adult patients presenting with upper gastrointestinal symptoms. *Open J Gastroenterol* 2014; **4**: 88–95.
43. Sjöberg D, Holmström T, Larsson M, *et al.* Incidence and clinical course of Crohn's disease during the first year - results from the IBD Cohort of the Uppsala Region (ICURE) of Sweden 2005-2009. *J Crohns Colitis* 2014; **8**: 215–22.
44. Burisch J, Pedersen N, Èukoviæ-Èavka S, *et al.* East-West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. *Gut* 2014; **63**: 588–97.
45. Lucendo AJ, Hervías D, Roncero Ó, *et al.* Epidemiology and temporal trends (2000-2012) of inflammatory bowel disease in adult patients in a central region of Spain. *Eur J Gastroenterol Hepatol* 2014; **26**: 1399–407.
46. Straumann A, Spichtin HP, Grize L, *et al.* Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003; **125**: 1660–9.
47. DeBrosse CW, Franciosi JP, King EC, *et al.* Long-term outcomes in pediatric-onset esophageal eosinophilia. *J Allergy Clin Immunol* 2011; **128**: 132–8.
48. Soon IS, Butzner JD, Kaplan GG, *et al.* Incidence and prevalence of eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr* 2013; **57**: 72–80.
49. Sealock RJ, Rendon G, El-Serag HB. Systematic review: the epidemiology of eosinophilic oesophagitis in adults. *Aliment Pharmacol Ther* 2010; **32**: 712–9.
50. Sealock RJ, Kramer JR, Verstovsek G, *et al.* The prevalence of oesophageal eosinophilia and eosinophilic oesophagitis: a prospective study in unselected patients presenting to endoscopy. *Aliment Pharmacol Ther* 2013; **37**: 825–32.
51. Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. *Int J Health Policy Manag* 2014; **3**: 123–8.
52. Shamliyan TA, Kane TL, Ansari MT, *et al.* Development quality criteria to evaluate nontherapeutic studies of incidence, prevalence, or risk factors of chronic diseases: pilot study of new checklists. *J Clin Epidemiol* 2011; **64**: 637–57.

53. Taft TH, Kern E, Kwiatek MA, *et al.* The adult eosinophilic oesophagitis quality of life questionnaire: a new measure of health-related quality of life. *Aliment Pharmacol Ther* 2011; **34**: 790–8.
54. Klinnert MD. Psychological impact of eosinophilic esophagitis on children and families. *Immunol Allergy Clin North Am* 2009; **29**: 99–107.
55. Klinnert MD, Silveira L, Harris R, *et al.* Health Related Quality of Life Over Time in Children with Eosinophilic Esophagitis (EoE) and their Families. *J Pediatr Gastroenterol Nutr* 2014; **59**: 308–16.
56. Lucendo AJ, Sánchez-Cazalilla M, Molina-Infante J, *et al.* Transcultural adaptation and validation of the "Adult Eosinophilic Esophagitis Quality of Life Questionnaire" into Spanish. *Rev Esp Enferm Dig* 2014; **6**: 386–94.