

# Incidence and prevalence of eosinophilic oesophagitis across Europe: A systematic review and meta-analysis

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## Abstract

**Background:** Several studies have reported large increases in the incidence of eosinophilic oesophagitis (EoE) in the last 20 years. We aimed to systematically review the incidence and prevalence of EoE, focused on all European countries.

**Methods:** Systematic review and meta-analysis up to 31 December 2022, based on PubMed, CINAHL and extensive hand searching of reference lists. Twenty-five eligible studies were identified and included.

**Results:** For both adults and children, the highest EoE incidence and prevalence have been reported from regional studies in Spain. EoE incidence for both adults and children was significantly lower ( $p < 0.001$ ) in nationwide studies (meta-analysis = 3.64 per 100,000 person-years overall) compared with regional or centre-based studies (7.16). EoE incidence and prevalence were significantly higher ( $p < 0.001$ ) in adults than children. All studies that reported on longitudinal trends in EoE incidence showed increases over time, more markedly during more recent years. Larger increases in incidence tend to refer to regional rather than nationwide studies; from Spain, Switzerland and Denmark, both for paediatric and adult age groups. Increases in EoE incidence 100,000 person-years were larger than for incidence per number of diagnostic endoscopies. The most frequently reported co-morbidities in adults were rhinitis, followed by asthma, food allergy and gastroesophageal reflux disease, and in children, erosive oesophagitis, asthma, food allergy and rhinitis.

**Conclusions:** The incidence of EoE has increased in Europe over the last 30 years, exceeding increases in the volume of oesophago-gastro-duodenoscopies performed. The patchy and low incidence and prevalence of EoE generally in Europe and compared with North America, may reflect a lack of clinical awareness and research focus rather than a genuinely low incidence of EoE. A co-ordinated Europe-wide study that uses standardised methodology is urgently needed to provide a comprehensive picture of EoE incidence and prevalence across Europe.

## KEYWORDS

eosinophilic oesophagitis, Europe, incidence, prevalence, trends

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## INTRODUCTION

Eosinophilic oesophagitis (EoE) was first reported in 1978,<sup>1</sup> and was subsequently described in the first reports of patient case series with EoE from Olten, Switzerland,<sup>2</sup> and Omaha, Nebraska,<sup>3</sup> during the early-mid 1990s. There have been several subsequent systematic reviews of the incidence and prevalence of EoE.<sup>4-9</sup> These have all been global in scope rather than focused specifically on Europe, all are from North America or East Asia and all do not cover much of the European literature on the incidence of EoE.

In 2012, United European Gastroenterology commissioned the authors to review the burden of disease and the organisation and delivery of services for gastrointestinal and liver disorders across 35 European countries.<sup>10</sup> This paper provides a more detailed systematic review and meta-analysis of the incidence and prevalence of EoE, focused on all European states, up to 31 December 2022.

The main objectives of the review were, first, to systematically review the incidence and prevalence of EoE across Europe in both adults and children; second to assess trends in incidence per 100,000 person-years and per volume of oesophago-gastro-duodenoscopies (OGDs) performed; and finally, to provide a meta-analysis of the prevalence of EoE across Europe. The main review hypothesis was that there would be large increases in the incidence of EoE in some studies, typically from specialist centres, but less evidence of large increases from nationwide studies.

## METHODS

### Inclusion and exclusion criteria

This systematic review covered all European states. We included reports of population-based incidence or prevalence of EoE, based on cohort studies and other population-based studies published up to 31 December 2022. Some studies also reported incidence per volume of OGDs, which we also assessed in this review. We included studies of paediatric and adolescent age groups, studies confined to adults and those that covered all age groups. We included published reports written in all languages and included published conference abstracts and other short reports.

We excluded studies that did not report the incidence and/or prevalence of EoE per population at risk. These include several types of study design, such as case control studies, cross sectional surveys and case reports. Studies that reported less than three cases of EoE were also excluded. Where two publications reported exactly the same incidence or prevalence from the same location during the same time period, only the first study identified was included.

### Search criteria and data extraction

The search terms used are provided in Table 1. The information sources searched were PubMed and CINAHL. Additional studies

### Key summary

#### Summarise the established knowledge on this subject

- Eosinophilic oesophagitis (EoE) was first reported in 1978.
- Previous systematic reviews on the incidence of EoE have all been global rather than focused on Europe.
- All of these global reviews are from North America or East Asia and do not cover much of the European literature.

#### What are the significant and/or new findings of this study?

- This European review shows that the incidence of EoE has increased across Europe over the last 30 years, which has exceeded increases in the volume of oesophago-gastro-duodenoscopies performed.
- Incidence is significantly lower in nationwide than regional or centre-based studies and increases in incidence tend to be more moderate.
- This suggests widespread lack of condition awareness and focused case finding approaches focused case finding outside specialist centres across Europe.
- A co-ordinated Europe-wide study based on standardised methodology is urgently needed to provide a comprehensive picture of EoE across Europe.

**TABLE 1** Search terms.

(Eosinophilic oesophagitis OR "EoE" OR "Eosinophilic Esophagitis"[MESH])

AND

(Incidence OR prevalence OR "Incidence"[MESH] OR "Prevalence"[MESH])

AND

(Albania OR Andorra OR Armenia OR Austria OR Azerbaijan OR Belarus OR Belgium OR Bosnia\* OR Bulgaria OR Croatia OR Czech\* OR Cyprus OR Denmark OR Estonia OR France OR Germany OR Georgia OR Hungary OR Iceland OR Ireland OR Italy OR Kazakhstan OR Kosovo OR Latvia OR Lithuania OR Luxembourg OR Liechtenstein OR Malta OR Moldova OR Monaco OR Macedonia OR Montenegro OR Netherlands OR Holland OR Norway OR Poland OR Portugal OR Russia OR Romania OR San Marino OR Serbia OR Slovakia OR Slovenia OR Soviet OR Spain OR Sweden OR Switzerland OR Turkey OR Ukraine OR Vatican OR Yugoslavia OR England OR Wales OR Scotland OR Britain OR United Kingdom OR UK OR Europe\*)

were identified through extensive hand searching of reference lists of published studies included in this review as well as those in previous systematic reviews. Eligible studies were reviewed for inclusion against the stated inclusion and exclusion criteria and STROBE guidelines.<sup>11</sup> The review included literature published or in the public

domain as of 31 December 2022. The PRISMA flow diagram provides the number of studies included at each stage of the systematic review screening process (Figure 1).

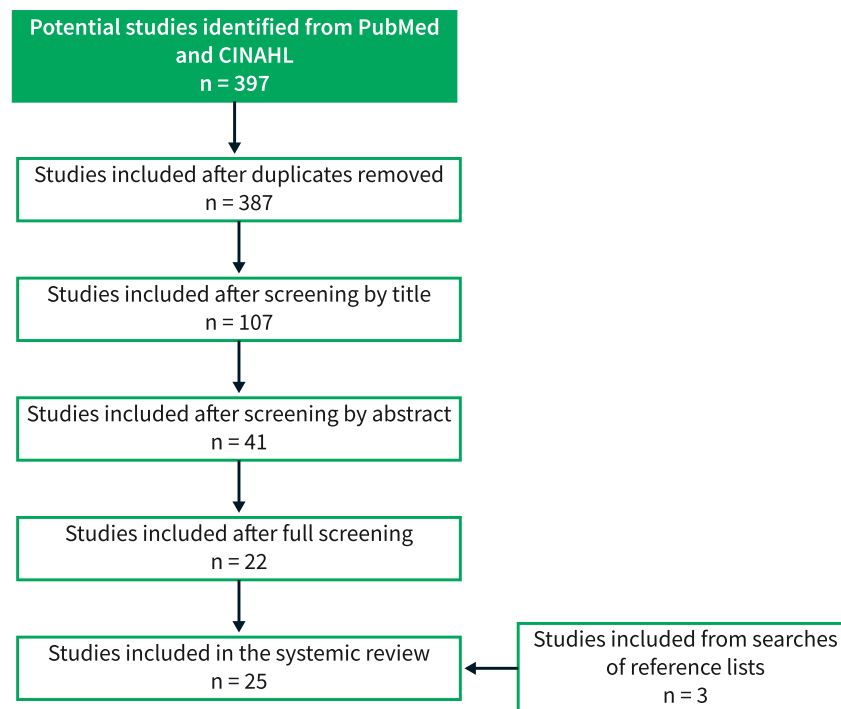
The following data items were extracted using a designed data extraction sheet: the country and region of the study, the definition of EoE used (including the number of eosinophils), study setting, population size, information sources used, study time period, age group of the study subjects, number of cases, percentage female, mean or median age in years, incidence and prevalence per 100,000 person-years and population respectively, and—where reported—incidence per 1000 OGDs, along with the number of OGDs carried out. SER selected the papers, SER and SMR extracted the data from the studies independently and compared findings. Where consensus was not reached, another investigator was consulted to resolve discrepancies. The investigators have published many previous systematic reviews and took advice on systematic review search terms and methodology from a specialist medical school librarian. There is no review protocol.

## Methods of analysis

The main systematic review outcome measures were the incidence and prevalence rates of EoE, reported separately for adults or all age groups and children. They were calculated using the numbers of cases as numerators and the study populations as denominators and were expressed per 100,000 person-years and population, respectively. Where possible, from the studies included in the systematic

review, incidence was also assessed based on the number of diagnostic endoscopies (OGDs) performed as denominators and were expressed per 1000 OGDs performed. To assess changes over time in EoE incidence, time trend analyses and mean annual changes were used. Time trends were presented graphically with mid points that were spaced, where possible, at approximately 4 years apart. Sub-group analyses were conducted on studies of paediatric, adult and all age groups.

Geographical mapping was used to illustrate EoE incidence across Europe, with rates ordered by size and grouped into quintiles, based on equal numbers of studies in each quintile. For longitudinal studies, incidence rates used were taken from the most recent time periods. Meta-analyses were used to establish pooled incidence and prevalence rates of EoE per 100,000 person-years and population across Europe, respectively, and to provide pooled demographic (mean age and percentage of female cases) summaries. For incidence and prevalence, in longitudinal studies, the meta-analyses were based on the most recent study time periods, as presented in Tables 3 and 4. These were calculated based on weighting according to the number of cases in each study or—for incidence and prevalence—the most recent time period in each study. In the meta-analysis, using Meta Essentials software,<sup>12</sup> heterogeneity was assessed using the  $I^2$  statistic, based on random effects models and quantitative assessment of publication bias was based on Egger's test. Fisher's exact test was used to assess the significance of comparisons regionally across Europe for studies that reported 'high' or 'low' incidence. The leading patient co-morbidities and presenting symptoms that were documented in at least three reports were averaged over study sources. A



**FIGURE 1** PRISMA flow diagram.

threshold of 4 per 100,000 person-years was used to distinguish high from low incidence, based on similar numbers of cases in the two categories. Significance was measured at the conventional 5% level.

## RESULTS

The PRISMA flow diagram is provided in Figure 1. Three hundred and eighty-seven studies were assessed for inclusion, 107 after screening by title, 41 after screening by Abstract and 24 after screening full-text versions of papers. Twenty-five studies ultimately fulfilled the inclusion and exclusion criteria and were included in the systematic review. These include three further papers that were obtained through extensive hand searching of reference lists. Each of the 25 studies included was appropriate for assessing the study hypothesis. Of the 25 studies, 16 reported on EoE in adults or all age groups and 16 reported on EoE in children.

### Regional coverage of studies across Europe

Table 2 summarises the numbers of studies and countries covered for the main study outcome measures for EoE. Overall, most evidence has come from northern Europe (10 studies), followed by southern (8), western (6) and eastern (1) Europe. The reporting came from 10 countries: Spain (6 studies), Denmark (5), Switzerland and The Netherlands (3 each), England and Ireland (2 each), Poland, Serbia, Slovenia and Sweden (one each). Sixteen studies reported specifically on paediatric age groups, from 9 different countries (Table 2).

### EoE patient demographics across Europe

Of the studies that reported on demographics (Table 3), all reported a minority of cases among females rather than males, ranging from 5% in a study from Castilla-La Mancha, Spain,<sup>17</sup> to 46% in a study from Sheffield, England,<sup>28</sup> (meta-analysis = 27.9% female; 95% confidence interval [CI] = 27.1%–28.4%). The meta-analysis percentage of female cases was similar in studies of adults (28.9%; 27.4%–30.5%) and children (25.7%; 22.9%–28.6%). The mean age at diagnosis ranged from 6.0 to 13.1 years (meta-analysis = 10.3 years) for children and from 29 to 47 years (meta-analysis = 40.4 years) for adults or all age groups.

### Incidence and prevalence of EoE for adults across Europe

Figure 2a and Table 3 show highest incidence of EoE for adult or all age groups from small regional studies in Castilla-La-Mancha, Spain (11.9 per 100,000 person-years during 2015–2017),<sup>16</sup> and Cáceres, Spain (10.5 in 2014–2016),<sup>18</sup> followed by a nationwide study across Denmark (7.8 in 2016–2018),<sup>14</sup> and two regional studies from Olten County, Switzerland (7.4 in 2007–2009),<sup>24</sup> and north Denmark (7.1 in 2015–2017).<sup>15</sup> Lowest EoE incidence refers to nationwide studies in Denmark (1.9 in 2009–2012),<sup>23</sup> and The Netherlands (1.9 in 2012–2015),<sup>20</sup> a regional study from Navarra, Spain (2.1 in 2002–2008),<sup>26</sup> and two nationwide studies from The Netherlands (2.6 in 2015–2019),<sup>13</sup> and Sweden (2.8 in 2013–2015).<sup>19</sup> The meta-analysis-incidence of EoE was 4.11 per 100,000 (95% CI = 4.03–4.19; Figure 3a).

**TABLE 2** A summary of the numbers of countries and studies regionally across Europe that reported on the study outcome measures.

Outcome measure	Number of countries (and number of studies covered)			
	Western Europe	Southern Europe	Eastern Europe	Northern Europe
All studies				
Incidence of EoE per 100,000 person-years	2 (6)	3 (8)	1 (1)	5 (10)
Prevalence of EoE per 100,000 population	2 (3)	2 (4)	-	2 (3)
Trends in the incidence of EoE per 100,000 person-years	2 (6)	3 (6)	1 (1)	5 (7)
Incidence of EoE per 1000 OGDs	1 (1)	2 (3)	-	3 (6)
Studies of paediatric age groups				
Incidence of EoE per 100,000 person-years	2 (4)	3 (5)	1 (1)	3 (6)
Prevalence of EoE per 100,000 population	1 (2)	1 (3)	-	1 (1)
Trends in the incidence of EoE per 100,000 person-years	1 (2)	2 (4)	1 (1)	3 (3)
Incidence of EoE per 1000 OGDs	-	2 (3)	-	3 (6)

Note: The European countries were searched individually and grouped into four regions of Europe: Northern Europe (Denmark, Finland, Iceland, Ireland, Norway, Sweden and England, Wales, Scotland and Northern Ireland–UK). Western Europe (Austria, Belgium, France, Germany, Liechtenstein, Luxembourg, Monaco, The Netherlands and Switzerland). Eastern Europe (Armenia, Azerbaijan, Belarus, Bulgaria, the Czech Republic, Estonia, Georgia, Hungary, Kazakhstan, Latvia, Lithuania, Moldova, Poland, Romania, Russia, Slovakia and Ukraine). Southern Europe (Albania, Andorra, Bosnia and Herzegovina, Croatia, Cyprus, Greece, Italy, Kosovo, Macedonia, Montenegro, Malta, Portugal, San Marino, Serbia, Slovenia, Spain, Turkey and the Vatican City).

Abbreviations: EoE, eosinophilic oesophagitis; OGDs, oesophago-gastro-duodenoscopies.

**TABLE 3** Incidence and prevalence of EoE (per 100,000 person-years and population) among adults or all age groups across Europe (studies are ordered chronologically).

Country	Region	EoE definition	Study setting	Study sources	Study time period	Age group (years)	Number of EoE cases (% female; mean age) <sup>a</sup>	Incidence per 100,000 person-years	Prevalence per 100,000 population	The first author (s) and reference
The Netherlands	Nationwide	≥15 eos	National pathology registry	Pathology data	2015–2019	18+	Total 3422 (29% f; 42.9 years)	2.6	23.5 (in 2019)	De Rooij et al. <sup>13</sup>
					2010–2014			1.4		
					2005–2009			0.6		
					1995–2004			0.0 <sup>b</sup>		
Denmark	Nationwide	≥15 eos	Nationwide pathology registry	Pathology data	2016–2018	All ages	2749 total (30% f; overall)	7.8	45 (in 2018)	Allin et al. <sup>14</sup>
					2012–2015			4.3	6 (in 2008)	
					2008–2011			2.3 <sup>b</sup>		
					2015–2017	18+	236 total (25% f; 47 years)	7.1	-	Melgaard et al. <sup>15</sup>
			2012–2014				6.7			
			2008–2011				1.2 <sup>b</sup>			
Spain	Castilla-La Mancha, Central Spain	≥15 eos	Two hospitals	Pathology and OGD records	2014–2017	16+	42	11.9	112 (in 2017)	Arias and Lucendo <sup>16</sup>
					2010–2013		29	7.9		
					2006–2009		27 (11% f; 33.8 years)	7.5		
					2005–2011		40 (5% f; 29.4 years)	6.4	45 (in 2011)	Arias and Lucendo <sup>17</sup>
Spain	Cáceres, west Spain	≥15 eos	Patients were referred to one hospital clinic	Registry with pathology and OGD data	2014–2016	16+	137 total (27% f; 36 years)	10.5	81.7 (in 2016)	Molina-Infante et al. <sup>18</sup>
					2011–2013			9.6		
					2007–2010			5.2		
					2013–2015	All ages	1412 total (25% f; 35.3 years)	2.8		Garber et al. <sup>19</sup>
Sweden	Nationwide	≥15 eos	All (28) pathology departments	Pathology data	2010–2012			1.5		
					2007–2009			0.5		
					2004–2006			0.0 <sup>b</sup>		
					2012–2015	18+	1796 total (27% f overall; 38 years)	1.9	-	Warners et al. <sup>20</sup>
The Netherlands	Nationwide	≥15 eos	Nationwide pathology registry	Pathology data	2008–2011			1.2		Van Rhijn et al. <sup>21</sup>
					2003–2007			0.2		
					1996–2002			0.0 <sup>b</sup>		
					2011–2013	All ages	179 total (27% f; 41 years)	4.9	24 (in 2013)	Giriens et al. <sup>22</sup>
Switzerland	Canton of Vaud, west Switzerland	≥15 eos	Survey of pathology institutes	Pathology reports	2008–2010			2.6	10 (in 2010)	
					2004–2007			0.7	2.7 (in 2007)	
					1993–2003			0.0	0 (in 2003)	
					2009–2012	All ages	844 total (29% f; 48 years)	1.9	13.8 (in 2012)	Dellon et al. <sup>23</sup>
Denmark	Nationwide	≥15 eos	Nationwide pathology registry	Pathology registry	2005–2008			1.2		
					2001–2004			0.6		
					1997–2000			0.2 <sup>b</sup>		
					2009–2012	All ages	844 total (29% f; 48 years)	1.9	13.8 (in 2012)	Dellon et al. <sup>23</sup>

(Continues)

TABLE 3 (Continued)

Country	Region	EoE definition	Study setting	Study sources	Study time period	Age group (years)	Number of EoE cases (% female; mean age) <sup>a</sup>	Incidence per 100,000 person-years	Prevalence per 100,000 population	The first author (s) and reference
Switzerland	Olten County	≥24 eos	The county database	Pathology and OGD data	2007–2009 2004–2006	All ages	69 total (25% f; 41 years) Total 46 (24% f; 41 years)	7.4 4.4	43 (in 2009) 27 (in 2006) <sup>a</sup>	Hruz et al. <sup>24</sup> Straumann and Simon <sup>25</sup>
Spain	Navarra	≥15 eos	One hospital	Pathology and OGD records	2002–2008	15+	25 (40% f; 31 years) <sup>c</sup>	2.1	-	Nantes Castillejo et al. <sup>26</sup>
Ireland	South west Dublin	≥15 eos	One tertiary referral hospital	Pathology and OGD records	2000–2008	All ages	13 (15% f; 23 years) <sup>c</sup>	5.7	-	O'Donnell <sup>27</sup>

Abbreviations: -, not specified; EoE, eosinophilic oesophagitis; OGD, oesophago-gastro-duodenoscopy.

<sup>a</sup>'Overall' refers to both adult and paediatric cases.

<sup>b</sup>Estimated from a published graph.

<sup>c</sup>Median age reported rather than mean age.

Of 11 longitudinal studies that reported on trends in incidence, all show increases (Figure 4a), with larger increases evident during more recent years and in regional studies from Spain,<sup>16,18</sup> Switzerland,<sup>22,24</sup> and from regional,<sup>15</sup> and nationwide studies from Denmark.<sup>14</sup> Nationwide studies from The Netherlands,<sup>13,20,21</sup> Sweden,<sup>19</sup> and Denmark,<sup>23</sup> show more moderate increases. After excluding studies that reported incidence of zero or close to zero ( $\leq 0.2$  per 100,000), mean annual increases in incidence were calculated for the remaining reports. These ranged from 7.1% in Castilla-La-Mancha, Spain,<sup>16</sup> to 75.6% in North Denmark.<sup>15</sup>

Nine studies reported on the prevalence of adult EoE per 100,000 population (Table 3), which ranged from 13.5 per 100,000 in a nationwide study from Denmark to 112 in Castilla-La Mancha, Spain,<sup>16</sup> with an overall meta-analysis-prevalence of 32.7 per 100,000 (95% CI = 31.9–33.4; Figure 5a). The  $I^2$  heterogeneity statistic was 99.5% and there was no significant evidence of publication bias ( $p = 0.183$ ).

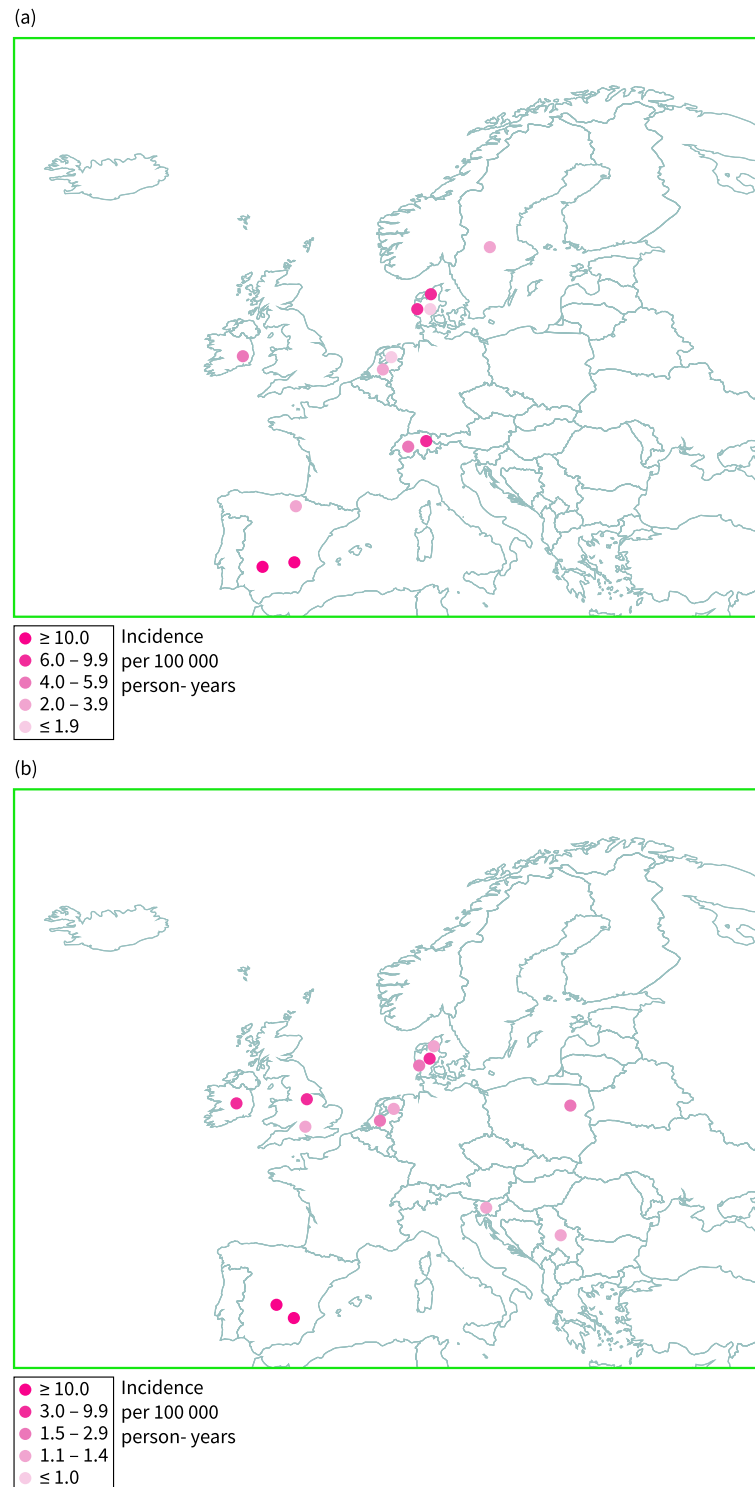
Three studies reported on the age-specific incidence of EoE across detailed (adult) age groups. The highest incidence was reported among people aged 30–39 years across The Netherlands,<sup>21</sup> in those aged 15–19 and 35–44 across Sweden,<sup>19</sup> and among 40–64 year olds across Denmark.<sup>14</sup> Of the patient co-morbidities that were documented in at least three studies, the most frequent in adults was rhinitis (average = 44.6% of cases), followed by asthma (26.3%), food allergy (19.1%), and gastroesophageal reflux disease (7.3%). The most frequently reported presenting symptoms were dysphagia (64.0%), food impaction (27.9%), heartburn (21.7%) and chest pain (15.2%).

### Incidence and prevalence of EoE for children across Europe

Figure 2b and Table 4 show highest incidence of paediatric EoE from regional studies in Castilla-La-Mancha, Spain (15.4 per 100,000 person-years during 2015–2017),<sup>16</sup> and south-west-Madrid, Spain (15.2 in 2014–2016).<sup>32</sup> Lowest paediatric EoE incidence of  $< 1.5$  per 100,000 was from nationwide studies in Slovenia (in 2011–2012),<sup>35</sup> and The Netherlands (2012–2015),<sup>20</sup> a regional study from Denmark (2015–2017),<sup>30</sup> and from 2 regional studies from Bristol, England (2007–2008),<sup>36</sup> and Belgrade, Serbia (2014–2017).<sup>31</sup> The meta-analysis-incidence of paediatric EoE was 3.49 per 100,000 (95% CI = 3.33–3.65; Figure 3b), which is significantly lower than that for adults (4.11).

Of 10 longitudinal studies (Figure 4b), all show increases in paediatric EoE incidence, with larger increases in more recent years and from regional studies. After excluding studies with paediatric EoE incidence  $\leq 0.2$  per 100,000 during earliest years, mean annual increases ranged from 7.2% in Dublin and Limerick, Ireland,<sup>34</sup> to 129% in South West Madrid,<sup>33</sup> and were similar in studies of children (38%) and adults (34%).

Four studies reported on paediatric EoE prevalence (Table 4; Figure 5b), ranging from 0.2 per 100,000 in a study from Bristol, England,<sup>36</sup> to 112 in Castilla-La Mancha, Spain.<sup>16</sup> The meta-



**FIGURE 2** The incidence of EoE (per 100,000 person-years) across Europe, grouped into quintiles, for (a) adults or all age groups and (b) paediatric age groups. Circles denote the approximate locations of the studies. Where studies report incidence for both paediatric age groups and for adults/all ages, both are included in this map. Further details of the studies are provided in Figure 1 and Table 2. EoE, eosinophilic oesophagitis.

analysis-prevalence for EoE for children (18.1 per 100,000; 95% CI = 16.0–20.3; Figure 5a) was significantly lower than for adults (32.7). The meta-analysis-prevalence for all age groups was 32.2 (95% CI = 31.5–32.9). The  $I^2$  heterogeneity statistic was 95.8% with an

indication of publication bias ( $p = 0.014$ ). Of paediatric co-morbidities reported in 3+ studies, the most frequent was erosive oesophagitis (average = 41.8% of all cases), then asthma (31.3%), food allergy (25.6%), rhinitis (24.6%) and dermatitis (11.9%). The most frequent



**FIGURE 3** Meta-analysis of the incidence of EoE (per 100,000 person-years) across Europe for (a) adults or all age groups and (b) paediatric age groups. Horizontal bars represent 95% confidence intervals. EoE, eosinophilic oesophagitis.

presenting symptoms were abdominal pain (40.2%), dysphagia (37.0%), food impaction (32.5%), vomiting (24.1%), weight loss (16.0%) and heartburn (15.5%).

### EoE per volume of endoscopies performed

Nine studies reported on trends in the number of diagnostic endoscopies performed and/or trends in the incidence of EoE in terms of the number of diagnostic endoscopies.<sup>13,16,20-24,30,31</sup> One study, from Castilla-La-Mancha in Spain, reported no increase in the incidence of EoE per 1000 endoscopies.<sup>16</sup> The other eight showed increases in incidence per endoscopies, which were all lower than the corresponding increases in incidence per 100,000 person-years.

### Nationwide versus regional studies

Overall, EoE incidence was significantly lower by half in nationwide studies (3.64 per 100,000; 95% CI = 3.57-3.71) compared with regional or centre-based studies (7.16; 95% CI = 6.76-7.57). This

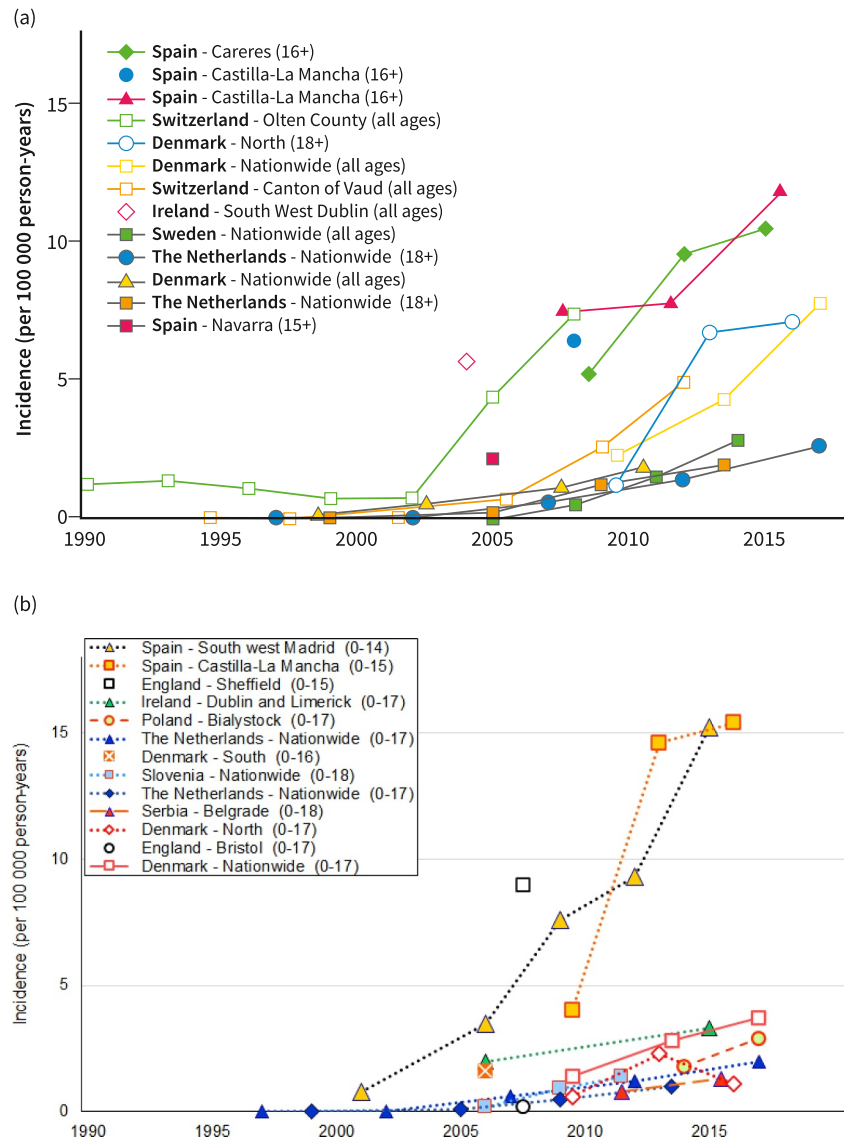
significant reduction for EoE incidence in nationwide studies was evident in both adults (3.85% vs. 7.86%) and children (1.98% vs. 6.52%). Figure 4a,b show that the larger increases in EoE incidence tend to refer to regional rather than nationwide studies.

### DISCUSSION

In the published literature to December 2022, the incidence and prevalence of EoE across Europe vary widely. EoE incidence was significantly lower in nationwide studies, compared with regional studies. All studies that reported on population-based trends in incidence showed increases over time, which were greater than increases in incidence per 1000 OGDs performed. The meta-analysis-incidence-and-prevalence of EoE across Europe was higher in adults than in children.

A major strength is that this systematic review of EoE with meta-analyses is focused on all European countries. Previous systematic reviews on EoE incidence and/or prevalence are from North America or East Asia, have been global in scope, not focused on Europe and have not covered much of the evidence from Europe. A





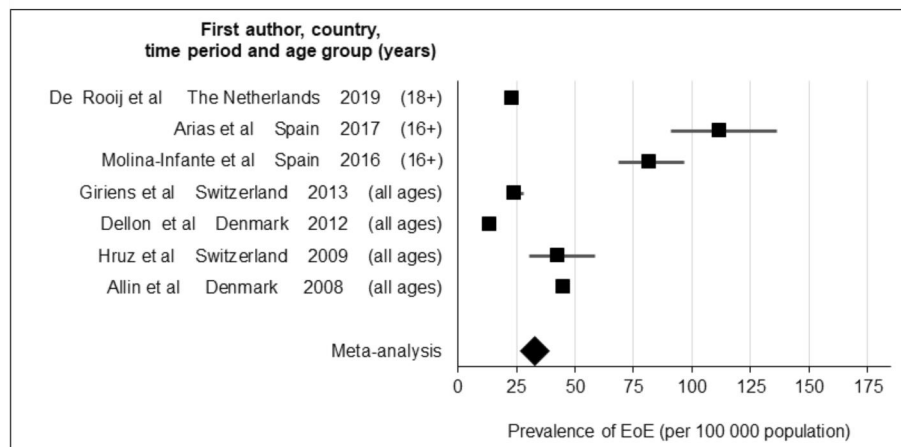
**FIGURE 4** Trends in the incidence of EoE (per 100,000 person-years) across Europe for (a) adults or all age groups and (b) paediatric age groups. EoE, eosinophilic oesophagitis.

limitation is the lack of studies that have reported on EoE incidence and prevalence to date. The evidence base is restricted to 25 published papers from 10 different countries, with only one study from eastern Europe, and nationwide studies confined to four countries—The Netherlands,<sup>13,20,21</sup> Denmark,<sup>14,23</sup> Slovenia,<sup>35</sup> and Sweden.<sup>19</sup> The diagnostic criteria for EoE have changed over time, with a consensus-based definition published in 2011,<sup>38</sup> which means that there has been considerable heterogeneity of studies in this regard. We have not applied a rigorous definition as a criterion for inclusion in this review, and we acknowledge this as a potential weakness. However, the paucity of studies indicates an urgent need to raise awareness and interest in the condition, and we hope our review will contribute to this. All studies included provided clear reporting of methodology and the main review outcome measures, EoE incidence and prevalence. Further limitations are that some studies did not

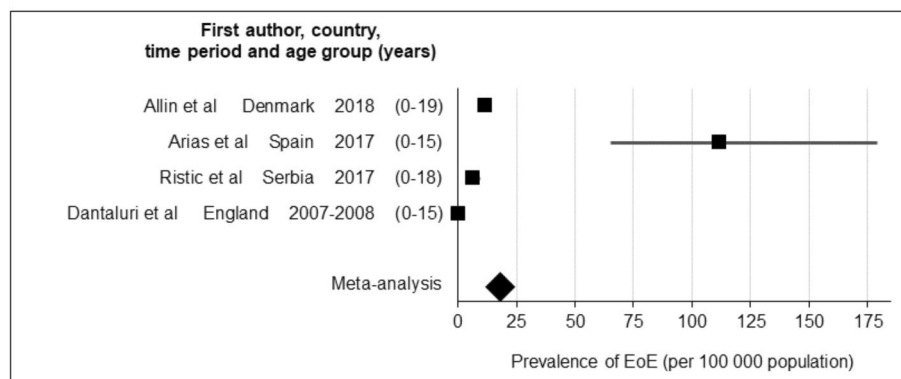
distinguish EoE in children from adults and only three studies reported on detailed age-specific incidence. Most studies reported crude rather than standardised incidence and prevalence rates, which can be affected by variation in the demographic profiles of patients and in the incidence and prevalence rates of EoE across age-groups.

In both adults and children, the highest incidence of EoE has been documented from regional studies in Spain, while nationwide studies have reported significantly reduced incidence, both in adults and children. Incidence rates increased more rapidly than the volume of OGDs performed, which suggests that the increases in incidence are mostly genuine rather than artefactual of increases in diagnostic activity. However, the increases were largest in regional or single centre studies rather than nationwide studies. The lowest incidence rates—and more modest increases over time—tended to be reported from

## a). Adults or all age groups:



## b). Paediatric age groups



**FIGURE 5** Meta-analysis of the prevalence of EoE (per 100,000 population) across Europe for (a) adults or all age groups and (b) paediatric age groups. Horizontal bars represent 95% confidence intervals. EoE, eosinophilic oesophagitis.

nationwide rather than regional, centre-based studies. This may suggest that the low incidence and prevalence of EoE generally is due to a lack of condition awareness and unfocused case finding in most hospitals.

Apart from the high incidence of EoE reported from regional studies from Spain and Switzerland and low levels in nationwide studies from The Netherlands and Denmark, there was little evidence of any geographical patterns in incidence. This partly reflects the limited number of studies that have reported population-based incidence rates. The systematic review shows that EoE occurs more frequently in men than women (27% female through meta-analysis) and in younger adult age groups (40.4 years mean age through meta-analysis), which is broadly consistent with previous global reviews.<sup>4-9,39</sup>

Our overall meta-analysis-prevalence for all age groups (32.2 per 100,000 population) across Europe compares with a global prevalence of 34.4 per 100,000 up to September 2018.<sup>8</sup> This global review reported a higher EoE prevalence for North America (41 per 100,000) than for Europe (29). Our European systematic review, with greater study coverage, includes 9 (36%) studies that were published after

2018, typically with major increases in incidence and prevalence in their most recent time periods. Another subsequent global review has also reported higher prevalence in North America (51.0) than in Europe (42.5).<sup>9</sup> This all suggests that the reported prevalence of EoE is considerably lower in Europe than in North America and may reflect greater awareness of the condition, interest and improved case-finding across North America, compared with much of Europe generally.

We found that the incidence and prevalence of EoE were significantly and considerably higher in adults than in children, which is consistent with previous global reviews of EoE.<sup>6-8,39</sup> There was no significant evidence of publication bias in studies of EoE prevalence for adults, but a significant indication for children, although the latter reflects the very small number of reports (four) and extreme variation reported. The high heterogeneity in EoE prevalence also reflects wide variation and large increases in EoE reported over time.

The wide variation in both prevalence and incidence reported across countries, and even within countries, is likely to reflect variation in clinical awareness, case finding approaches and study methodologies. There were no multinational studies that reported across different countries and there were nationwide studies only

**TABLE 4** Incidence and prevalence of EoE (per 100,000 person-years and population) among paediatric age groups across Europe (studies are ordered chronologically).

Country	Region	EoE definition	Study setting	Study sources	Study time period	Age group (years)	Number of EoE cases (% female; mean age) <sup>a</sup>	Incidence per 100,000 person-years	Prevalence per 100,000 population	The first author (s) and reference
The Netherlands	Nationwide	≥15 eos	National pathology registry	Pathology data	2015–2019 2010–2014 2005–2009 1995–2004	0–17	639 total (-; 10.9 years)	2.0 1.2 0.6 0.0 <sup>b</sup>	-	De Rooij et al. <sup>13</sup>
Poland	Białystok	>15 eos	One hospital	Pathology and OGD records	2016–2018 2013–2015	0–17	36 total (22% f; 10 years) <sup>c</sup>	2.9 1.8 <sup>b</sup>	-	Zdanowicz et al. <sup>29</sup>
Denmark	Nationwide	>15 eos	Nationwide pathology registry	Pathology data	2016–2018 2012–2015 2008–2011	0–17	218 total (30% f overall; -)	3.7 2.8 1.4 <sup>b</sup>	12 (in 2018) 5 (in 2008)	Allin et al. <sup>14</sup>
Denmark	North	≥15 eos	Regional pathology registry	Pathology data	2015–2017 2011–2014 2007–2010	0–17	18 total (6% f; 12 years)	1.1 2.3 0.6 <sup>b</sup>	-	Hollaender et al. <sup>30</sup>
Serbia	Belgrade	≥15 eos	One children's hospital	Pathology and OGD records	2014–2017 2010–2013	0–18	35 total (26% f; 12.5 years)	1.3 0.8 <sup>b</sup>	6.8 (in 2017)	Ristic et al. <sup>31</sup>
Spain	Castilla-La Mancha, central Spain	≥15 eos	Two public hospitals with specialist services	OGD and pathology records	2015–2017 2012–2014 2008–2011	0–15	8 8 3 (21% f; 9.6 years)	15.4 14.6 4.0	112 (in 2017)	Arias and Lucendo <sup>16</sup>
Spain	South-west Madrid	≥15 eos	12 public hospitals	Pathology and OGD records	2014–2016	0–17	148 (34% f; 9.7 years)	15.2	-	La Orden Izquierdo et al. <sup>32</sup>
			11 public hospitals		2011–2013 2008–2010 2005–2007 2002–2004	0–14	134 83 31 6 (24% f; 9.2 years)	9.3 7.5 3.5 0.8	-	La Orden Izquierdo et al. <sup>33</sup>
The Netherlands	Nationwide	≥15 eos	Nationwide pathology registry	Pathology data	2012–2015 2008–2011 2003–2007 1996–2002	0–17	365 total (-; 10 years)	1.0 0.5 0.1 0.0 <sup>b</sup>	-	Warners et al. <sup>20</sup> Van Rhijn et al. <sup>21</sup>
Ireland	Dublin and Limerick	ns	Three hospitals	OGD and pathology records	2006–2015	0–17	358 total (25 f; ns)	3.3 (2015) 2.0 (2006)	-	O'Malley et al. <sup>34</sup>
Slovenia	Nationwide	≥15 eos	Referrals to one national paediatric hospital	Pathology records	2011–2012 2008–2010 2005–2007	0–18	25 total (8% f; 9.5 years)	1.4 0.9 0.2	-	Homan et al. <sup>35</sup>

(Continues)

TABLE 4 (Continued)

Country	Region	EoE definition	Study setting	Study sources	Study time period	Age group (years)	Number of EoE cases (% female; mean age) <sup>a</sup>	Incidence per 100,000 person-years	Prevalence per 100,000 population	The first author (s) and reference
England	Sheffield	≥15 eos	One paediatric gastroenterology hospital department	Pathology and OGD records	2007–2008	0–15	24 (46% f; 6 years)	9.0	-	Cohen et al. <sup>28</sup>
England	Bristol	≥15 eos	One children's hospital	Pathology and OGD records	2007–2008	0–17	3 (-; -)	0.2	0.2 (in 2007/2008)	Dantuluri et al. <sup>36</sup>
Denmark	Esbjerg, Kolding, Sønderborg & Odense –South Denmark	≥15 eos	3 secondary hospitals, and one tertiary paediatric centre	Pathology records	2005–2007	0–16	6 (17% f; 9.6 years)	1.6	-	Dalby et al. <sup>37</sup>

Abbreviations: -, not specified; EoE, eosinophilic oesophagitis; OGD, oesophago-gastro-duodenoscopy.

<sup>a</sup>'Overall' refers to both adult and paediatric cases.

<sup>b</sup>Estimated from a published graph.

<sup>c</sup>Median age reported rather than mean age.

from four countries. A co-ordinated Europe-wide study that uses standardised methodology is urgently required.

The patchy and low prevalence of EoE generally in Europe, when compared with North America, may reflect a lack of clinical awareness, interest and/or research focus in some countries rather than a genuinely lower incidence of the disorder. This can only be proven by a concerted, pan-European approach to case finding and reporting, based on consistent case-definition. We hope this review will stimulate such a development, under the leadership of United European Gastroenterology.

#### AUTHOR CONTRIBUTIONS

Stephen E. Roberts and John G. Williams designed the study; Stephen E. Roberts and Sian Morrison-Rees conducted the review and the analyses; Stephen E. Roberts wrote the first drafts; Stephen E. Roberts, Sian Morrison-Rees, Nikhil Thapar and John G. Williams interpreted the study findings and edited subsequent drafts.

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#### CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

#### DATA AVAILABILITY STATEMENT

Data are available on reasonable request.

#### ETHICS APPROVAL

Not applicable.

#### INFORMED CONSENT

Not applicable.

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#### SUPPORTING INFORMATION

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

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