

# Incidence and Prevalence of Eosinophilic Esophagitis in Children

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## ABSTRACT

**Objectives:** The aim of the present study was to conduct a systematic review with meta-analysis on the epidemiology of eosinophilic esophagitis (EoE) in children.

**Methods:** Studies investigating incidence and prevalence of EoE in children ( $\leq 18$  years) were identified in a systematic review of MEDLINE (1950–2011) and Embase (1980–2011). Meta-analyses were performed for incidence and subgroups with  $\geq 5$  studies: esophagogastroduodenoscopy (EGD) for any indication, histologic esophageal disease, and celiac disease, and EGD for abdominal pain. We used a random effects model, *Q* statistic to assess heterogeneity, and joinpoint analysis to assess time trends.

**Results:** We included 25 studies. The incidence of EoE varied from 0.7 to 10/100,000 per person-year and the prevalence ranged from 0.2 to 43/100,000. The incidence and prevalence increased over time. Prevalence was highest in children with food impaction or dysphagia (63%–88%). The pooled prevalence was 3.7% (95% confidence interval [CI] 2.4–5.1) in EGD for any indication, 24% (95% CI 19–28) in histologic esophageal disease, 2.3% (95% CI 1.0–3.6) in celiac disease, and 2.6% (95% CI 1.2–4.1) in EGD for abdominal pain.

**Conclusions:** During the last 2 decades, the incidence and prevalence of EoE in children have increased significantly; however, the population-based incidence and prevalence of EoE vary widely across geographic variations, potentially because of variations in case of ascertainment between centers. Because EoE is common among children with food impaction and dysphagia, children with this presenting complaint should be rapidly identified at triage for timely endoscopic assessment.

**Key Words:** eosinophilic esophagitis, epidemiology, pediatrics

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Eosinophilic esophagitis (EoE) was first described in a child in 1983 (1). During the last 15 years, EoE has become recognized as an important clinicopathologic entity by primary care providers, gastroenterologists, and allergists. The number of publications that focused on EoE have markedly increased from 2 in 1993 to  $>110$  in 2011. In 2007, the first consensus guidelines on the diagnosis and

treatment of EoE were published and then updated in 2011 (2,3). The present guidelines define EoE as an esophageal disease characterized by clinical symptoms caused by esophageal dysfunction and histologic evidence of eosinophil-predominant inflammation ( $\geq 15$  eosinophils per high-power field [hpf]) upon exclusion of other causes of esophageal eosinophilia (3).

Mounting data from animals and humans support the pathogenesis of EoE as a chronic antigen-driven immune response occurring in a genetically susceptible individual (3). The clinical manifestations of EoE in children vary by age. They may include feeding difficulties, failure to thrive, gastroesophageal reflux, nausea, vomiting, chest or epigastric pain, food impaction, and dysphagia (4–6). Atopy is frequent, with up to 60% of children with EoE having a concurrent atopic disease such as allergic rhinitis, asthma, eczema, and IgE-mediated food allergies (6–8). EoE occurs with greater frequency in non-Hispanic white males in childhood and early adulthood; however, EoE has been reported at any age, in both sexes, and in most racial and ethnic groups (3,9). The management of EoE is centered primarily on medical (corticosteroid) or dietary therapy (3). EoE poses a large burden to the health care system because of the chronic nature of the disease; requirement of endoscopy for diagnosis, monitoring of disease activity, and management of complications; and involvement of multidisciplinary services including dietitians and allergists.

Despite the growing interest and publications on EoE, few studies have evaluated the population-based incidence and prevalence of EoE. A recent systematic review of the epidemiology of EoE in adults found that the prevalence of EoE varied widely based on the study population, with estimates highest in patients with acute food bolus obstruction (48%) (10) and lowest in population-based studies (0.23/1000) (11,12). In children, the incidence and prevalence of EoE have not yet been systematically reviewed. The objectives of our study were to conduct a systematic review and meta-analysis on the incidence and prevalence of EoE in children and to evaluate the variation in incidence and prevalence across different geographic regions, time periods, and disease states. Improved knowledge of the incidence and prevalence of EoE enhances our understanding of the burden of disease.

## METHODS

### Search Strategy

We conducted a systematic literature search using a predetermined protocol in accordance with the quality of reporting meta-analyses of observational studies in epidemiology (13). We searched 2 computer-stored databases, MEDLINE (1950–May 2011) and Embase (Excerpta Medica Database; 1980–May 2011), for studies describing the epidemiology of EoE in children. The search strategy for MEDLINE and Embase was based on 2 themes. The first theme combined the exploded version of medical subject headings “eosinophilic esophagitis” or “esophagitis.” The second theme combined the exploded version of medical subject

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headings terms “incidence” or “prevalence” or “demography” or “epidemiology.” All key words were used to search titles and abstracts. The 2 themes were then combined using the Boolean operator “AND.” The search was not limited by language or human subjects to ensure the capture of all appropriate studies. The reference lists of relevant articles were also reviewed and appropriate studies were included.

## Selection Criteria

Two reviewers (J.D. and I.S.) conducted an initial search of identified abstracts and titles independently. Abstracts were eliminated if they were not EoE-related, nonhuman, or did not report original data (eg, review articles). The remaining abstracts were eligible for further review. We included articles or abstracts that described their study design, defined a source population, and reported an incidence rate and/or prevalence of EoE or provided adequate information to calculate these estimates. Studies describing the incidence or prevalence of EoE only in adults (ie, age at diagnosis >18 years) were excluded as a recent systematic review on the epidemiology of EoE in adults was published (12). Disagreement between reviewers was resolved by consensus with a third-party expert (G.K.).

## Data Extraction

Patient characteristics at diagnosis including age, sex, ethnicity, and personal and family history of atopy were documented. Secondary variables extracted included study design (ie, retrospective or prospective); country of origin; publication year; time of study; source of subjects; and information on key indicators of study quality, using meta-analyses of observational studies in epidemiology (13). Two reviewers independently completed data extraction forms for each study. Prevalence and incidence rates with 95% confidence intervals (CIs) for the overall study period were collected. Incidence rates and prevalence for the different time periods were documented. The prevalent studies were categorized by population-based studies (8,14,15), all of the children undergoing an esophagogastroduodenoscopy (EGD) for any indication (7,15–18), children with histologic esophageal disease detected on EGD (7,14,17–20), and specific subgroups including children with celiac disease (21–25), children post–liver transplantation (26,27), children with ulcerative colitis (UC) (28), children with abdominal pain (29–31), and children who underwent EGD for esophageal food impaction or dysphagia (32,33).

## Summary of Data

The incidence of EoE in children was summarized using incidence rates, defined as the number of cases per 100,000 children per year. When incidence rates were adjusted for confounding factors, these estimates were reported. Prevalence of EoE in children was defined as the number of prevalent cases in a defined region per 100,000 children.

In studies that reported at least 4 time points, we conducted time–trend analyses using joinpoint regression analysis whereby a series of permutations were used to assess whether the addition of joinpoints resulted in statistically significant linear changes in the direction of magnitude of the rates in comparison with the linear line (34). Two joinpoints at most were considered. The parameter estimate used to summarize the trend during the fixed interval was the average annual percentage change according to a generalized log-linear model that assumed a Poisson distribution.

A meta-analysis of incidence and prevalence of EoE of all of the studies was not conducted because of the diversity in population subgroups and limited number of studies. We limited our meta-analyses to subgroups with  $\geq 5$  studies that reported the prevalence of EoE. These subgroups for children who had an esophageal biopsy included all children undergoing an EGD for any indication (7,15–18) and children with histologic esophageal disease detected on EGD (7,14,17–20). A sensitivity analysis was performed in subgroups with  $\geq 5$  full-text studies to minimize heterogeneity. Only studies that reported diagnostic criteria of EoE were included in any meta-analysis; studies that did not report EoE diagnostic criteria were still described in the systematic review but not included in any meta-analysis. Heterogeneity was assessed with the  $Q$  statistic (5% level). Random effects models were used because of heterogeneity between studies. The possibility of publication bias was assessed using the Begg tests.

## RESULTS

The search strategy retrieved 384 unique citations: 157 from MEDLINE and 365 from Embase. Of these, 304 citations were excluded after the first screening based on titles and abstracts, leaving 80 articles for possible inclusion (Fig. 1). For the first review of titles and abstracts, the observed agreement between reviewers was 96%, corresponding to a  $\kappa$  statistic of 0.87. The second review of 80 full-text articles and abstracts excluded 56 studies (reasons listed in Fig. 1), leaving 24 studies. One additional study was found from reference review of relevant articles. Hence, a total of 25 studies (16 full-text studies and 9 abstracts from conference proceedings) were included in the systematic review. The first study appeared in 2003 (33). The agreement between reviewers for eligibility of articles was 100%, corresponding to a  $\kappa$  of 1. Characteristics of the 25 included studies are shown in Table 1.

The annual incidence rates varied by geographic region, with an incidence rate of 1.6 in Denmark (35), 8.0 in United Kingdom (16), and ranging from 0.7 to 10/100,000 children in the United States (8,19,36,37). Heterogeneity across studies was observed ( $Q$  statistic 165;  $P < 0.001$ ). Two studies reported temporal trends of incidence rates, with both demonstrating a significant increase during the study period (Fig. 2) (8,19). The average annual percentage increase in incidence of EoE was 17% (95% CI 9.7–25) in a retrospective study that reexamined esophageal biopsy specimens obtained between 1983 and 1992 (19). Similarly, an average annual percentage increase in incidence of EoE of 12% (95% CI 0–25) was shown in a retrospective population-based cohort study identifying cases of EoE from a pathology database between 2000 and 2003 (Table 1) (8).

The population-based prevalence also varied by geographic region, with most present reported rates ranging between 0.2 in United Kingdom (15), 8.9 in Australia (14) and 43/100,000 children in the United States (8). Two studies reported temporal trends of prevalence of EoE (Fig. 3). One study demonstrated a significant increase in prevalence between 2000 and 2003, with an average annual percentage increase of 56% (95% CI 25–96) (8).

For children who underwent an EGD for any indication, the prevalence of EoE ranged from 2.3% to 6.8%, with a pooled prevalence of 3.7% (95% CI 2.4–5.1; Fig. 4) (5,7,15–18). There was significant heterogeneity across studies ( $Q$  statistic 33;  $P < 0.001$ ). The prevalence rates of EoE among EGDs with histologic esophageal disease ranged from 18% to 32%, with a pooled prevalence of 24% (95% CI 19–28; Fig. 5) (5,7,14,17–20). Heterogeneity across studies was observed ( $Q$  statistic 31;  $P < 0.001$ ). A sensitivity analysis including only full-text studies resulted in a similar pooled prevalence of 24% (95% CI 18–29). The prevalence

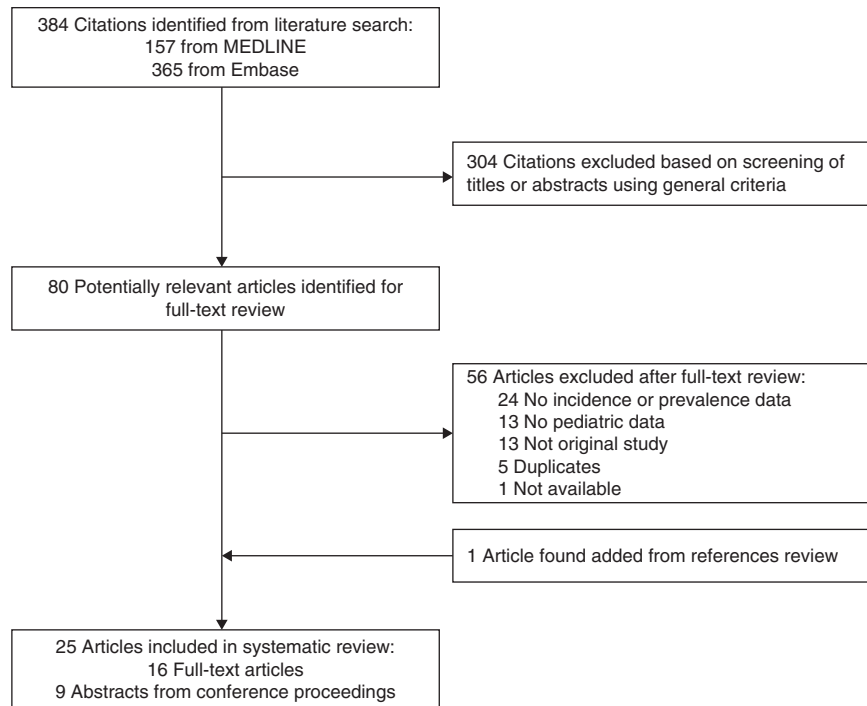


FIGURE 1. Literature search results.

of EoE among children with EGD done for esophageal food impaction was 63% (32), and among children with dysphagia and/or food impaction, the prevalence of EoE was 88% (33).

Among children who underwent EGD for abdominal pain, the prevalence of EoE ranged from 2.1% to 4.9% (29–31), whereas the prevalence of EoE among children with celiac disease ranged from 1.1% to 5.1% (21–25). The prevalence of EoE among children post–liver transplantation were 2.4% and 3.0% (26,27). The only study evaluating the prevalence of EoE among children with UC reported a prevalence of 8.0% (28).

All population-based studies reported a male predominance (range 54%–83%) (8,14,16,19,35–37). The mean/median ages at diagnosis ranged from 6.0 to 10.5 years for population-based studies (8,16). In contrast, the mean age at diagnosis from a single study evaluating the prevalence of EoE among children with esophageal food impaction was 10.1 years (33). Personal history of atopy was found in 14% to 100% (8,16,20,25–27,32,33,35–37) and family history of atopy was present in 7% to 38% of children (8,20,32,35). No publication bias was observed among all subgroups using the Begg test:  $P=0.19$  (EGD for any indication) and  $P=0.88$  (EGD with histologic esophageal disease).

## DISCUSSION

We present the first systematic review and meta-analysis of the incidence and prevalence of EoE in children. The population-based incidence rates of EoE in children varied by geographic region, ranging from 1.6 in Denmark (35) to 10 per 100,000 children per year in the United States (8). Likewise, the population-based prevalence varied by geographic region, with the most present reported rates ranging between 0.2 in United Kingdom (15), 8.9 in Australia (14) and 43 per 100,000 children in the United States (8). Similar to our findings, a recent systematic review of the epidemiology of EoE in adults demonstrated a wide variation in population-based prevalence ranging from 20 to 700/100,000 with a

pooled prevalence of 30/100,000 individuals (11,12,38). In our systematic review, given that both studies in Australia and the United States were conducted in sole referral centers for the region from which the denominator population was determined, referral bias is less likely to contribute to variations in population-based prevalence; however, the variations may be because of differing distributions of ethnicity, sex, age groups, diagnostic criteria for EoE, and threshold to perform endoscopy and biopsy between study centers. In particular, because EoE is diagnosed endoscopically, detection of disease is largely driven by accessibility to endoscopy services, which may vary widely between regions depending on the presence and number of pediatric gastroenterologists along with wait times to assessment by gastroenterologists and to endoscopy. In addition, detection of EoE is affected by physician awareness and/or willingness to perform an EGD in a patient who presents with symptoms suggestive of EoE and whether a physician routinely obtains esophageal biopsies at the time of EGD regardless of macroscopic appearance of the esophagus.

During the last few decades, both incidence and prevalence increased significantly, with average annual percentage increases of 12% to 17% and 56%, respectively (8,19). The increased incidence of EoE over time in children may be because of a genuine increase in incidence, greater recognition of EoE, or higher use of diagnostic EGDs in children, with the wide variety of symptoms suggestive of EoE. In the study by DeBrosse et al (19), the authors reexamined esophageal biopsy specimens obtained between 1982 and 1999 and found that the proportion of biopsy specimens with  $\geq 15$  eosinophils/hpf remained stable in spite of a 40-fold increase in the number of biopsy specimens collected, suggesting that the rise in incidence of EoE is because of enhanced disease recognition rather than higher detection from increased EGD use.

Although EoE accounts for only a minority of children who underwent EGD for any indication (pooled prevalence 3.7%) (7,15–18), the prevalence of EoE among EGDs performed in children with esophageal food impaction and/or dysphagia was

TABLE 1. Study characteristics

Study author (reference)	Study design	Region	Years of study	Source of population	Prevalence/AAPC (if applicable)	Incidence per 100,000 person-years/AAPC (if applicable)	Diagnostic criteria	Personal or family history of atopy, n/N (%)	Sex and race n/N (%)	Age, y
Population-based Noel et al (8)	Retrospective population-based cohort study	Hamilton County, OH	2000–2003	Population-based institutional pathology database of EoE patients	9.9/100,000 (2000); 19.8/100,000 (2001); 30.2/100,000 (2002); 43.0/100,000 (2003); AAPC 56% (95% CI 25–96)	9.1 (2000); 9.9 (2001); 10.3 (2002); 12.8 (2003); AAPC 12% (95% CI 0–25)	≥24 eos/hpf, epithelial proliferative changes, absence of eosinophilia in any other intestinal segment	Personal 59/103 (57%); family history of atopy 76/103 (74%); family history of EoE 7/103 (6.8%)	Male 73/103 (71%)	Mean 10.5 (SD 5.4)
Cherian et al (14)	Retrospective population-based cohort study	Perth, Australia	1995, 1999, 2004	Population based with case ascertainment from histologic review of all children with esophageal inflammation	0.5/100,000 (1995); 3.1/100,000 (1999); 8.9/100,000 (2004)	NA	>24 eos/hpf	NA	Male 35/54 (65%)	Median 6.6
Gill et al (36)	Retrospective population-based cohort study	Huntington, WV	1995–2004	All children with histologic esophageal inflammation	54/285 (19%)	NA	>15 eos/hpf	Personal 14/44 (32%)	Male 32/44 (73%)	Mean 9.0 (range 0.8–18.0)
Dannluri et al (15)	Retrospective population-based cohort study	Bristol, UK	2007–2008	Population based review of random selection of 25% of all initial EGDs	0.2/100,000	NA	≥15 eos/hpf	NA	NA	NA
Prasad et al (37)	Retrospective population-based cohort study	Olmsted County, MN	1976–2005	All children undergoing EGD	3/132 (2.3%)	0.69 (95% CI 0.42–0.96)	≥15 eos/hpf	Personal 7/11 (64%); family history of EoE 6/16 (38%)	Male 15/23 (65%)	Mean 10.0 (SD 6.0)
Rao et al 2009* (16)	Retrospective population-based cohort study	Northern England	2007–2008	Population based with case ascertainment from all children undergoing EGD	NA	8.0	≥15 eos/hpf	Personal 8/24 (33%)	Male 13/24 (54%)	Median age 6 (range 0.5–15.0)
Dalby et al (35)	Prospective population-based study	Southern Denmark	2005–2007	Population based with case ascertainment from all children referred for evaluation of GERD after failure with PPI	24/1046 (2.3%)	NA	≥15 eos/hpf	Personal 3/6 (50%); family 2/6 (33%)	Male 5/6 (83%)	Median 9.6
DeBrosse et al (19)	Retrospective population-based cohort study	Hamilton County, OH	1982–1999	Population based with case ascertainment from histologic review of all children with esophageal inflammation	198/666 (30%)	0 (1982); 0.38 (1983); 0 (1984); 0 (1985); 0.39 (1986); 0.78 (1987); 0 (1988); 1.19 (1989); 1.61 (1990); 1.61 (1991); 2.42 (1992); 2.02 (1993); 4.86 (1994); 4.49 (1995); 4.93 (1996); 3.29 (1997); 4.56 (1998); 2.09 (1999); AAPC 17% (95% CI 9.7–25)	≥15 eos/hpf	NA	Male 143/198 (72%)	Mean 8.1

TABLE 1. (Continued)

Study author (reference)	Study design	Region	Years of study	Source of population	Prevalence/AAPC (if applicable)	Incidence per 100,000 person-years/AAPC (if applicable)	Diagnostic criteria	Personal or family history of atopy, n/N (%)	Sex and race n/N (%)	Age, y
Children undergoing esophagogastroduodenoscopy for any indication										
Aceves et al (7)	Retrospective cohort study	San Diego, CA	1998–2002	All children undergoing EGD	102/1998 (5.1%)	NA	>20 eos/hpf	Personal 40/67 (60%)	Male 76/102 (75%)	Median 9.5 (range 2.0–17.0)
Lee et al (18)	Retrospective cohort study	Buffalo, NY	1980–1988	Children with histologic esophageal eosinophilic inflammation All children undergoing EGD	102/556 (18.3%) 12/188 (6.4%)	NA	>15 eos/hpf	NA	NA	NA
Pulcini et al* (17)	Retrospective cohort study	MS	2000–2007	Children with histologic esophageal disease All children undergoing EGD	12/62 (19%) 30/132 (23%) 30/322 (9.3%)	NA	>20 eos/hpf	NA	Male 39/51 (76%); white 44/51 (86%)	Mean 8.5 (SD 4.0)
Children with esophagogastroduodenoscopy for abdominal pain										
Thakkar et al (29)	Retrospective cross-sectional cohort study	TX and VA	2002–2005	Children undergoing EGD for abdominal pain	51/2013 (2.5%) 51/216 (24%)	NA	NA	NA	NA	NA
Thakkar et al 2009* (30)	Prospective cross-sectional study	USA	2007–2008	Children undergoing first EGD for chronic abdominal pain	25/1191 (2.1%) 7/142 (4.9%)	NA	NA	NA	NA	NA
Thakkar et al (31)	Prospective cross-sectional study	Houston, TX	2008–2009	Children undergoing EGD for chronic abdominal pain	3/92 (3.3%)	NA	NA	NA	NA	NA
Children with histological esophageal disease										
Lai et al (20)	Retrospective study	Edmonton, Canada	2000–2004	Children with histologic diagnosis of esophagitis	64/202 (31.7%)	NA	>20 eos/hpf	Personal 43/64 (67%); family history of atopy 35/64 (55%)	Male 49/64 (77%)	Mean 10.0
Children with celiac disease										
Francavilla et al* (21)	Prospective cohort study	Italy	2007–2008	Children with suspected celiac disease undergoing endoscopy	2/176 (1.1%)	NA	NA	NA	Male 2/2 (100%)	NA
Thompson et al (22)	Retrospective cohort study	New York City, NY	2000–2010	Histologic review of children as having celiac disease with increased esophageal eosinophils	4/297 (1.3%)	NA	≥15 eos/hpf with eos clustering and/or microabscess formation and eos degranulation and esophageal symptoms	NA	Male 2/4 (50%)	Mean 8.0 (SD 3.3)
Patel et al* (23)	Retrospective cohort study	Kansas City, MO	2004–2008	Children diagnosed as having celiac disease	4/78 (5.1%)	NA	NA	NA	NA	NA
Leslie et al (24)	Retrospective cohort study	Western Australia	2000–2007	Children diagnosed as having celiac disease	10/250 (4.0%)	NA	>15 eos/hpf	NA	Male 6/10 (60%)	Median 9.0 (range 2.0–14.0)
Ooi et al (25)	Retrospective cohort study	Sydney, Australia	1999–2007	Children diagnosed as having celiac disease	7/221 (3.2%)	NA	≥20 eos/hpf with epithelial proliferation	Personal 1/7 (14%); family history 0/7 (0%)	Male 3/7 (43%)	Median 5.4 (range 4.2–10.0)
Children with liver transplantation										
Noble et al (26)	Retrospective cohort study	Queensland, Australia	1992–2007	Children after liver transplantation	4/130 (3.1%)	NA	≥20 eos/hpf	Personal 4/4 (100%)	NA	NA
Miloh et al* (27)	Retrospective cohort study	VA	1995–2010	Children after liver transplantation	7/288 (2.4%)	NA	NA	Personal 7/7 (100%)	NA	NA

Children with ulcerative colitis Gersten et al (28) Retrospective cohort study	NY	NA	Children newly diagnosed as having ulcerative colitis	2/24 (8.3%)	NA	NA	NA	NA	NA	NA
Children with esophageal food impaction Hurtado et al (32) Retrospective cohort study	Denver, CO	2005–2009	Children with esophageal food impaction with undergoing EGD with biopsies	15/24 (62.5%)	NA	>20 eos/hpf	NA	NA	NA	NA
Cheung et al (33) Retrospective cohort study	Melbourne, Australia	1989–2000	Children with dysphagia and/or acute food bolus impaction	21/42 (46.7%)	NA	>20 eos/hpf	Personal 14/21 (67%)	NA	NA	Mean 10.1 (SD 4.0)

AAPC = average annual percentage change; CI = confidence interval; EGD = esophagogastroduodenoscopy; eos/hpf = eosinophils per high-power field; EoE = eosinophilic esophagitis; GERD = gastroesophageal reflux disease; NA = not available; PPI = proton pump inhibitor; SD = standard deviation; \* Published in abstract form only.

high (63%–88%) (32,33). Similarly, the prevalence of EoE in unselected adults undergoing an EGD ranged from 1.0% to 6.5% (39,40). In comparison to children, adults with food bolus impaction or dysphagia had lower prevalence of EoE (12%–48%) (10,41,42). The lower prevalence of EoE in adults with food bolus impaction or dysphagia compared with children may be accounted for by the wider differential diagnosis for food bolus impaction or dysphagia in adults such as esophageal malignancy, peptic stricture, and connective tissue disorders. Because the highest diagnostic yield of endoscopy for EoE occurred among children with dysphagia or food impaction, children with such presenting complaints should be identified at triage and undergo rapid and timely evaluation with EGD to facilitate the diagnosis of EoE. Limited studies have investigated the prevalence of EoE among specific immune-mediated conditions. The pooled prevalence of EoE was 2.3% for children with celiac disease (21–25). Detection bias from frequent biopsy sampling is unlikely to fully explain the elevated prevalence of EoE in celiac disease. A gluten-free diet in patients with celiac disease reduced esophageal eosinophilia in some studies (43,44), whereas others demonstrated persistent esophageal eosinophilia (24,25). Although EoE is thought to be a T<sub>H</sub>2-mediated atopic disease and celiac disease is a T<sub>H</sub>1-mediated autoimmune disease, an association between these 2 diseases may be biologically plausible because recent studies suggest the coexistence of T<sub>H</sub>1- and T<sub>H</sub>2-mediated diseases is the result of generalized immune dysregulation (22,43,44).

The prevalence of EoE ranged from 2.4% to 3.0% for children post–liver transplantation (26,27). In liver transplant recipients, de novo development of food allergy and gastrointestinal eosinophilic inflammation may be attributed to the potential effect of tacrolimus suppression of T<sub>H</sub>1 response and promotion of T<sub>H</sub>2 signal pathways (26,45–47). The prevalence of EoE was 8% among children with UC (28). Like EoE, UC is thought to be T<sub>H</sub>2 mediated (48).

In our systematic review, EoE primarily was more commonly diagnosed among male children of white ethnicity who had a personal and/or family history of atopy. The male predominance was also seen in adults (12). The median age at diagnosis reported in the studies ranged from 5.4 to 9.6 years. The presenting symptoms of EoE vary by age. Younger children are more likely to present with a wider variety of symptoms compared with older children, who often present with dysphagia or food bolus impaction (6). The predominant symptom of EoE in young adults is dysphagia, similar to that of older children (12). Therefore, the index of suspicion for EoE and rapidity of evaluation with EGD should be guided by the clinical presentation.

In the meta-analyses performed for population-based incidence, children who underwent EGD, and children with histologic esophageal disease, significant heterogeneity was found. Heterogeneity may be explained by differences in geographic region, study period, and intrinsic biases associated with observational studies. Given the small number of studies, stratified or sensitivity analyses were not possible to explore reasons for heterogeneity. To account for heterogeneity, a random effects model was used in all of the meta-analyses. Using the Begg test, we did not find any evidence of publication bias in these subgroups.

The limitations of our systematic review should be considered. First, the quality of the studies was not always optimal. An ideal quality study would be a prospective population-based study with well-described methods of case ascertainment and diagnostic criteria. For optimal accuracy of estimates, this ideal study would take place in a region with a well-defined source population, readily available endoscopy services, and appropriate physician awareness and willingness to conduct EGD and collect esophageal biopsies in patients presenting with symptoms suggestive of EoE. Our

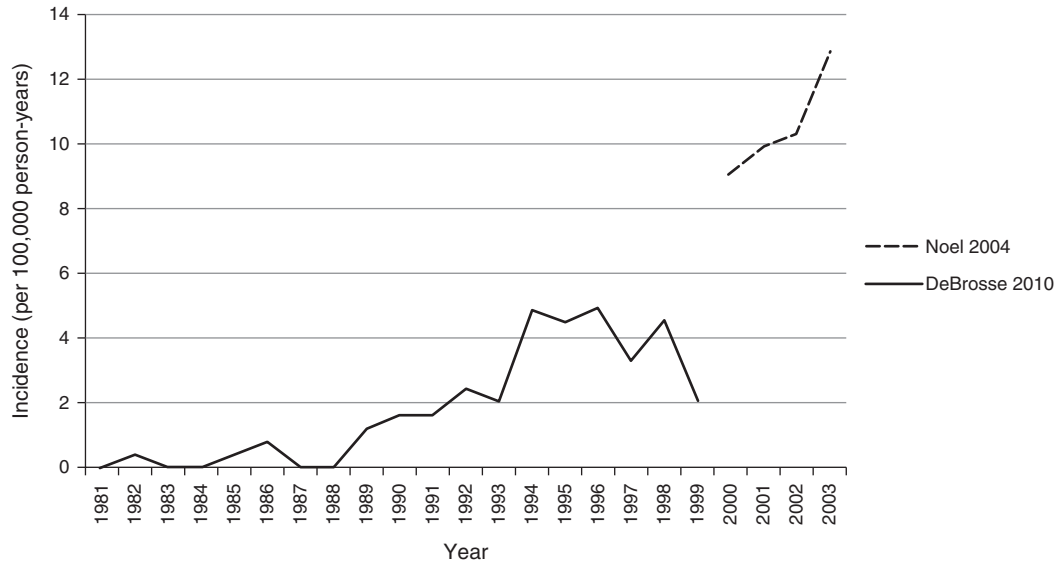


FIGURE 2. Temporal trends of incidence rates of eosinophilic esophagitis.

systematic review yielded variable methods of case ascertainment and minimal prospective studies. We limited the meta-analyses to subgroups containing  $\geq 5$  studies, and studies in which the diagnostic criteria were not reported were excluded from the meta-analyses. Quality characteristics of each study (study design, source of population, and diagnostic criteria for EoE) are shown in Table 1. Second, in the studies identified through the systematic review, the case definition of EoE focused primarily on histologic findings, whereas the present definition of EoE encompasses both clinical and histologic manifestations. Also, the histologic criteria of EoE varied between studies, ranging from 15 to 24 eosinophils/hpf. Acknowledging that the 2011 consensus guidelines recommend a minimum threshold of 15 eosinophils/hpf for the diagnosis of EoE, the incidence and prevalence of EoE in previous studies were likely underestimated

(2,3). Third, our search strategy revealed only a small number of studies, all from developed countries. Thus, we cannot comment on the incidence and prevalence of EoE in developing countries. Despite these limitations, we used a comprehensive search strategy and included studies published in all languages and in both abstract and full-article format. Therefore, this review provides a comprehensive summary of the present literature on the epidemiology of EoE in children.

EoE is a chronic disease that has major implications for the consequential burden of disease. Children with EoE will use health care resources in procedures such as EGD, hospital admissions, and clinic visits for diagnosis, monitoring response to therapy, and management of complications (3). In addition, children with EoE often require multidisciplinary services including gastroenterologist, allergist, and dietician.

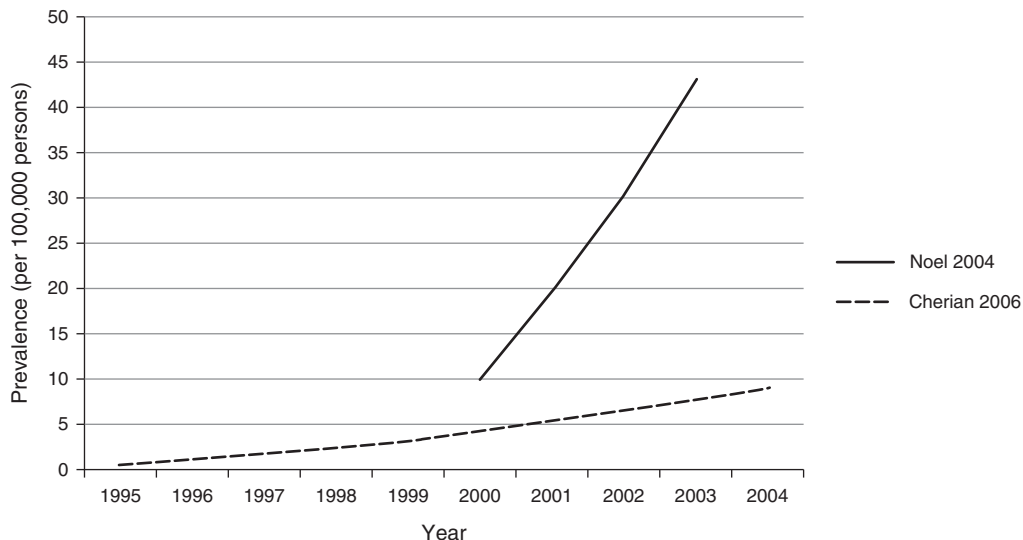


FIGURE 3. Temporal trends of prevalence of eosinophilic esophagitis.

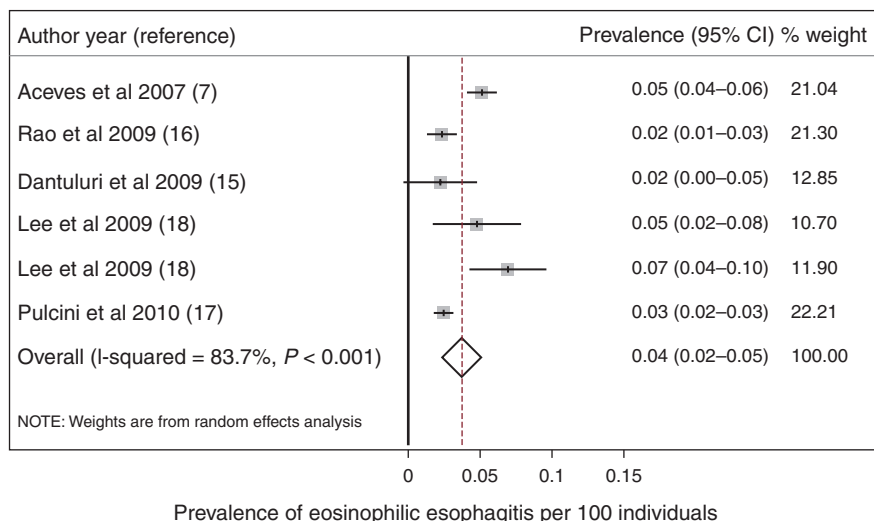


FIGURE 4. Pooled prevalence of eosinophilic esophagitis per 100 children who underwent esophagogastroduodenoscopy for any indication.

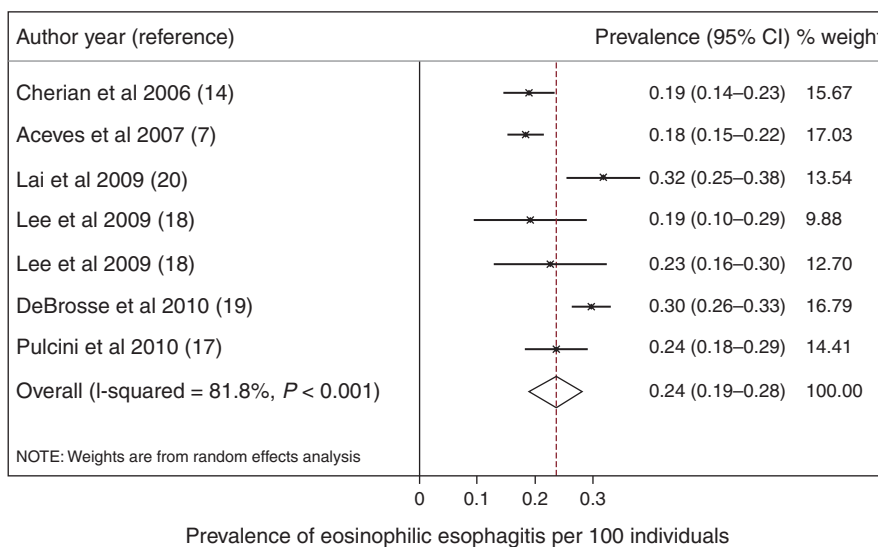


FIGURE 5. Pooled prevalence of eosinophilic esophagitis per 100 children who underwent esophagogastroduodenoscopy with histologic esophageal disease.

In conclusion, the incidence rates and prevalence of EoE in children vary by geographic regions in developed countries, with significant increases in these rates with time. Although the prevalence of EoE is low among children who undergo EGD or children with abdominal pain, the prevalence of EoE is high among children who present with food impaction or dysphagia. In younger children with chronic unexplained upper gastrointestinal symptoms unresponsive to present management strategies, the diagnosis of EoE should be considered. To improve our understanding of the worldwide epidemiology of EoE in children, future studies using recently accepted diagnostic criteria for EoE in defined geographic regions should be conducted, especially in developing countries.

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