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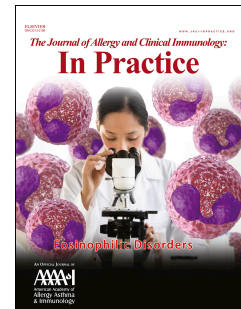
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Epidemiology of non-esophageal eosinophilic gastrointestinal diseases in symptomatic patients: a systematic review and meta-analysis

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Conflicts of interest

The authors declare no conflict of interest, financial or otherwise.

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Abstract

Background: Primary eosinophilic gastrointestinal diseases (EGIDs) are increasingly described disorders that include eosinophilic esophagitis (EoE), eosinophilic gastritis (EoG), gastroenteritis (EoGE) and colitis (EoC). The exact epidemiology of non-EoE EGIDs is still unclear.

Objective: To evaluate the epidemiology of non-esophageal EGIDs (non-EoE EGIDs) in adults and children referred to outpatient clinics for gastrointestinal symptoms.

Methods: We conducted a systematic review and meta-analysis using a protocol registered and published with the international prospective register of systematic reviews (PROSPERO CRD42018111437). We searched PubMed, EMBASE, Web of Science, Scopus, and CINAHL for cohort or cross-sectional studies published since 1990, evaluating incidence and prevalence of non-EoE EGIDs. We assessed study quality and risk of bias using items derived from the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.

Results: A total of 576 articles were identified. Ten studies with 13,377 participants were included in the analysis, with the results showing high heterogeneity. No significant publication bias was found. The overall prevalence of non-EoE EGIDs in patients with gastrointestinal symptoms was 1.9% (95% CI: 0.575 – 3.894; $I^2 = 92.72\%$; $p < 0.001$). Because none of the examined studies were prospectively designed, incidence rates could not be determined.

Conclusion: More prospective, large-scale, multicenter studies are needed to evaluate reported data and to further investigate the epidemiology of non-EoE EGIDs and their possible risk factors and comorbidities.

What is already known about this topic? Non-EoE EGIDs are rare but they are emerging gastrointestinal diseases that might affect adults and children. The exact epidemiology is still unclear.

What does this article add to our knowledge? We found a higher prevalence of non-EoE EGIDs than what is estimated in existing populations-based studies.

How does this study impact current management guidelines? Management guidelines of non-EGIDs in adults and children are still lacking.

Key words:

Primary eosinophilic gastrointestinal diseases

Epidemiology

Prevalence

Incidence

Gastrointestinal symptoms

List of Abbreviations:

EGIDs: eosinophilic gastrointestinal diseases

Non-EoE EGIDs: non-esophageal eosinophilic gastrointestinal diseases

EoE: eosinophilic esophagitis

EoG: eosinophilic gastritis

EoGE: eosinophilic gastroenteritis

EoC: eosinophilic colitis

HPF: high power field

IBD: inflammatory bowel diseases

GI: gastrointestinal

Introduction

Primary eosinophilic gastrointestinal diseases (EGIDs) represent a heterogeneous group of rare but increasingly described disorders, characterized by a prevalent eosinophilic inflammation in specific gastrointestinal tracts.¹⁻³ The exact pathogenesis is still unknown; however, T helper 2 (Th2) immune response may play a central role in dysfunctional eosinophilic inflammation against allergens or with autoimmune etiopathology.^{4,5} EGIDs include eosinophilic esophagitis (EoE), gastritis (EoG), gastroenteritis (EoGE), and colitis (EoC). Non-esophageal eosinophilic gastrointestinal diseases (non-EoE EGIDs) are defined by the abnormal eosinophilic infiltration in the gastrointestinal (GI) tract not limited to the esophagus, and in the absence of secondary causes of GI eosinophilia (food hypersensitivity, drug reactions, parasite infections, malignancies, and inflammatory bowel diseases).^{1-4,6,7} Since their first description in 1937⁸, few case reports, case series and retrospective studies have been reported on non-EoE EGIDs⁹⁻¹⁵, with rare studies often limited to specific geographical areas in the discussion of incidence and prevalence of the disease.¹⁶ Therefore, the exact epidemiology of non-EoE EGIDs remains still unknown. There are no systematic reviews or meta-analyses on the global epidemiology of EGIDs at any age. We performed a systematic review and meta-analysis to estimate the incidence and prevalence rates of non-EoE EGIDs in adults and children referred to outpatient clinics for gastrointestinal symptoms.

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108 Methods

109 The protocol of our systematic review and meta-analysis was registered and published with the
110 international prospective register of systematic reviews
111 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=111437; register number
112 CRD42018111437) prior to starting the study. We followed the Preferred Reporting Items for
113 Systematic Reviews and Meta-Analyses (PRISMA) guidelines to report our results.¹⁷

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116 Outcomes

117 Primary outcomes (Table I) for the systematic review were incidence and prevalence of non-EoE
118 EGIDs in adult and pediatric patients referred to outpatient clinics for gastrointestinal symptoms.
119 The main analysis focused on overall prevalence, whereas secondary analyses included prevalence
120 estimates based on demographic data, symptoms, allergic comorbidities and diagnostic criteria.

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123 Search strategy

124 A highly sensitive and extensive search strategy was designed to retrieve all articles combining the
125 terms of eosinophilic gastritis, gastroenteritis and colitis, and epidemiology from the major
126 electronic bibliographic databases (PubMed, EMBASE, Web of Science, Scopus, and CINAHL).
127 Conference proceedings were acquired from abstract books and the annual Digestive Diseases
128 Week, American College of Gastroenterology Meetings, United European Gastroenterology Week,
129 and from the European Society for Pediatric Gastroenterology Hepatology and
130 Nutrition Congresses. We included all articles and conference proceedings published in all
131 languages from 1990 to 2018. The search strategy used generic terms to avoid excluding possible

eligible articles (Table E1 in the Online Repository). Search results were compiled using the citation management software Refworks[®]. According to the quality standards for reporting meta-analysis of observational studies¹⁸, two researchers independently screened the reference lists of eligible articles. Full texts of records deemed eligible were retrieved and independently assessed for inclusion by the same investigators. Any discrepancies were resolved by discussion and consensus. Authors of publications reporting unclear data, subjected to multiple interpretations, were contacted by email for clarification or to request supplemental information. Figure 1 illustrates the search strategy process.

Study selection (inclusion/exclusion criteria)

We included cohort and cross-sectional studies about the epidemiology of primary non-EoE EGIDs, reporting prevalence/incidence with a 95% confidence interval (95% CI). Our analysis excluded clinical guidelines, case reports, consensus documents, clinical trials, and reviews that did not provide epidemiological data and studies about the secondary causes of intestinal hypereosinophilia. We also excluded electronic surveys and epidemiological studies based on health plan claims databases to obtain a more reliable estimate of the epidemiology of non-EoE EGIDs in patients referred to clinics for gastrointestinal symptoms. The inclusion criteria are described in Table I.

Risk of bias assessment

Eligible articles were assessed for risk of bias, according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.¹⁹ Moreover, for cohort and cross-sectional studies, risk of bias was assessed through a question tool developed specifically for this review and derived from the STROBE statement: 1) Were more than 90% of patients followed-up

until the end of the study? 2) Were all patients free of the outcome of interest at baseline included?
3) Were the diagnoses/exclusions free from outcome misclassification? The last two items were
used to assess the included cross-sectional studies (Table E2 in the Online Repository).
Two investigators independently assigned an overall risk of bias to each eligible study, and if they
disagreed, a third reviewer was consulted. All studies with one or more risks of bias were excluded.

Data extraction

Two reviewers independently extracted information from each eligible study using a standardized
data extraction sheet and then proceeded to cross-check the results. We extracted the following
information: first author name; year of publication; type of study (cross-sectional or cohort study);
country and language; type of patients (children or adults); age and gender of participants; sample
size; prevalence and/or incidence with 95% CI; localization of eosinophilic inflammation; number
of eosinophils per high power field (Eo/HPF); peripheral eosinophilia; allergy and imaging tests;
therapies; symptoms (abdominal pain, nausea, vomiting and diarrhea, gastrointestinal bleeding,
anemia, protein-losing enteropathy, malabsorption, failure to thrive, amenorrhea, delayed puberty);
clinical complications (ascites, pancreatitis, bowel obstruction, bowel perforation, intestinal ulcer,
cystitis, hepatitis); and atopic comorbidities (asthma, allergic rhinitis, atopic dermatitis, food and
drug allergy). If not directly reported, the prevalence rate was calculated. Risk of bias assessment
for all included studies was also evaluated. Disagreements between reviewers regarding data
extraction were resolved through discussion and consensus.

Data synthesis and statistical analysis

We estimated prevalence or incidence and their corresponding 95% confidence interval (CI), as calculated as an exact binomial proportion (from affected and the total of enrolled patients). Prevalence was estimated by pooling results of cross-sectional studies or cohort studies at baseline. Incidence was estimated by pooling results of cohort studies that were free of non-EoE EGIDs at baseline. Estimations of prevalence and incidence were calculated with the aid of a fixed or random-effects meta-analysis weighted for inverse variance following the DerSimonian and Laird's method. Heterogeneity between studies was evaluated with a chi-square test and quantified with the I^2 statistic. I^2 is a measure of the level of heterogeneity, expressed in three categories on the basis of low, moderate and high I^2 values (25%, 50% and 75%, respectively)²⁰. Publication bias was evaluated by means of a funnel plot. For the secondary outcomes, planned subgroup analyses were based on the geographic origin of studies (developed vs. developing countries) and age (adults vs. children). We used the statistical software package MedCalc (Statistical Software 19.1, Belgium).

Results

A total of 576 articles were found. After removing 370 duplicates, 206 were reviewed on title and abstract, and of this group, 78 articles were excluded because they focused on secondary causes of non-EoE EGIDs. One hundred and twenty-eight (128) full texts were screened, and 92 were excluded on the basis of the specific article type (reviews, systematic reviews, case-control studies, case reports, oral communication, survey). Thirty-six articles (36) were assessed for eligibility (cross-sectional and cohort studies). Only 10 articles met the inclusion criteria and were included in the final meta-analysis (Figure 1).

Quality assessment

The 10 included cross-sectional studies showed low risks of bias (Table II). Publication bias was not detected (Figure 2), but common methodological flaws included the method of data collection and the definition of the study period.

Study characteristics

None of the articles included for the analysis were published before 2000. Two studies were conducted in United States^{21, 22}, two in Europe (one in Denmark²³ and one in Italy²⁴), five in Asia (two in India^{25,26}, one in China²⁷, in Malaysia²⁸, and in Japan²⁹) and one in Saudi Arabia.³⁰ A total of 13,377 patients (adults and children) were enrolled, and all of them were affected by primary

non-EoE EGIDs diagnosed by endoscopy and histology. Three studies reported the diagnostic cut-off value of tissue eosinophils for HPF.^{21,23,28} While two studies were based only on pediatric patients^{23,29} and five on adult patients with non-EoE EGIDs^{22,24,25,27,28}, three studies were characterized by mixed population.^{21,26,30} The distribution of the population by sex was reported only in four articles, and male sex ranges from 38% to 100% of affected patients. Male sex is prevalent in children with non-EoE EGIDs (64% vs. 36%).²³ Study characteristics are summarized in Table III.

Prevalence and incidence of non-EoE EGIDs and analysis of subgroups

In the 10 retrieved studies, the overall prevalence of non-EoE EGIDs among patients referred to clinics for GI symptoms was 1.9% (95% CI: 1.035–2.992; $I^2 = 92.70\%$; $p < 0.0001$) (Figure 3). Data on the prevalence of non-EoE EGIDs in adults were obtained from five studies. In adults with GI symptoms prevalence of non-EGIDs was 1.9% (95% CI: 0.575 – 3.894; $I^2 = 92.72\%$; $p < 0.0001$ for heterogeneity) (Table IV). The limited number of available studies did not allow us to analyze the prevalence of non-EoE EGIDs in children. Pooling results by patient country indicates that prevalence of non-EoE EGIDs in developed countries was 2.4%, (95% CI: 0.723 – 5.515; $I^2 = 92.7\%$; $p < 0.001$ for heterogeneity) in and 1.5% (95% CI: 0.703 – 2.886; $I^2 = 94.16\%$; $p < 0.0001$ for heterogeneity) in developing countries (Table V).

Because none of the included articles were prospectively designed, we were unable to assess the incidence rate.

Description of clinical features, endoscopic findings and therapies in included studies

The limited number of available studies and the lack of details in reports did not allow us to analyze the prevalence of non-EoE EGIDs according to the planned subgroups (gender, age at diagnosis and

symptoms onset, clinical symptoms, therapies, allergic comorbidities, localization of eosinophilic inflammation and diagnostic tests).

Symptoms reported in the 10 studies included in our analysis are summarized in Table VI. Abdominal pain is the main gastrointestinal symptom in children with non-EoE EGIDs (94%)²³, while diarrhea is the most prevalent symptom (100%) in adults.²⁵ Only one study, conducted by Alhmoud et al in pediatric patients and one in adult patients, reported this information.²¹ In their retrospective cohort study of 13 non-EoE EGIDs cases, they noted the following clinical presentations: nausea (31%), vomiting (31%), gastrointestinal bleeding (8%), anemia (15%), weight loss (15%), and failure to thrive (15%) reported in adults and children.

Constipation is described in 3% of patients with non-EoE EGIDs.²⁸ Ascites and bowel obstruction are also reported as clinical complications.²¹ Atopic comorbidities (Table VII) range from 25% to 54% of patients with non-EoE EGIDs.^{21,23,28} Asthma, allergic rhinitis and eczema are reported in 54% of patients and food allergy in 38% of patients with non-EoE EGIDs.²¹

Regarding the diagnostic management, four studies reported endoscopic findings.^{21,23,26,28} A normal mucosa is the prevalent endoscopic finding reported in the included studies (35%-100%), as described in Table E3 in the Online Repository. None of the included studies reported other diagnostic tests, such as specific serum IgE levels, skin prick test, imaging, or blood tests.

Therapies are described in only three studies^{21,23,28} (Table VIII). Steroid therapy was reported with 100% efficacy in children with non-EoE EGIDs.²³ Effective response to first line-therapy (steroids, diet, montelukast and ketotifen) was reported in 89% to 100% of all patients with non-EoE EGIDs.^{21,23,28}

Discussion

Our study represents the first systematic review and meta-analysis of prevalence for non-EoE EGIDs in patients referred to outpatient clinics for gastrointestinal symptoms. The included studies were conducted in Europe, North America, and Asia. Epidemiological data from Central and South America, Australia, and Africa are still lacking.

We found a higher overall prevalence of non-EoE EGIDs (1.9%) in symptomatic patients than that estimates from population-based studies that were mainly realized in the US using survey or health plan claims databases. Spergel et al. reported an overall prevalence of 28/100,000 people for non-EoE EGIDs by administering an electronic survey to allergists and gastroenterologists.³¹ Additionally, in a retrospective analysis of a large population-based database of more than 35 million US people, Mansoor et al. reported a prevalence rate for EoGE and EoC of 5.1/100,000 and 2.1/100,000 people respectively.³² Finally, using diagnostic (ICD-9) codes through a health plan claims database, Gupta et al. and Alhmoud et al. reported an overall prevalence of 6/100,000 and 1.7/100,000 patients respectively^{33,34}, while Jensen et al. estimated the prevalence of EoGE and EoC as 8.4/100,00 and 3.3/100,000 respectively.¹⁶ An older study estimated that the prevalence of EoGE in US was 2.5/100,000 people, using an electronic survey.³⁵ The differences in the prevalence between these large studies can be attributed to the discrepancy in the study design (retrospective studies on the prevalence of non-EoE EGIDs in US people), methods of data collection (electronic surveys and databases), data analyses, and sample size. In addition, as described in a retrospective study of Consortium of Eosinophilic Gastrointestinal Researchers (CEGIR), non-EoE EGIDs have increased in frequency over the past decade.³⁶ Despite the

heterogeneity of the studies, our findings add to the literature by more accurately depicting the prevalence rates in real life situations of patients with gastrointestinal symptoms accessing health care, rather than what is seen in the general population. They offer insight to alert clinicians to suspect and diagnose early these emerging disorders.

Our analysis revealed that the prevalence of non-EoE EGIDs varies widely among studies and by locale. The prevalence of non-EoE EGIDs reported in developing countries is lower (1.5%) than what is described in developed countries (2.4%). In a single large Asian retrospective cross-sectional study, Yphoon et al.³⁷ reported an overall prevalence for non-EoE EGIDS of 0.6/100,000, lower than what has been described in earlier US studies. Environmental (diet, lifestyle, intestinal microbiome, allergen exposition) and genetic factors might explain the different prevalence of non-EoE EGIDs in Caucasians than in African-Americans and Asians.^{31,32}

Our results indicated that the prevalence of non-EoE EGIDs in adults is 1.9%. Mansoor et al. reported the prevalence of EoGE in children as slightly higher than in adults (5.3/100,000 and 5.1/100,000 respectively) while the prevalence of EoC was higher in adults than in children³² (1.6/100,000 and 2.3/100,000 respectively). However, a high prevalence (10.7/100,000 people) of non-EoE EGIDs in the US has been described in people < 20 years of age.¹⁶ Finally, the age at onset of EGIDs varies widely, and large epidemiological studies in children are needed.

Unfortunately, none of the selected studies were prospectively designed to evaluate the incidence rate.

Surprisingly, our results showed that the prevalence of non-EoE EGIDs among symptomatic patients is higher than the prevalence rates estimated for inflammatory bowel disease (IBD) in all ages. The highest reported prevalence rates of IBD were in Western Countries (especially in Europe and North America) and corresponded to 505/100,000 people for ulcerative colitis (UC) and 322/100,000 for Crohn's disease (CD).³⁸ This highlights the clinical relevance of these emerging conditions.

337 The low number of selected studies with complete epidemiological data did not allow us to analyze
338 the stratified prevalence or meta-regression, according to all planned secondary analyses.

339 We could therefore only describe data on symptoms, allergic comorbidities, endoscopic features
340 and therapies in the included studies. The main reported symptoms were unspecific.^{1-4,6,36} The
341 prevalence of allergic comorbidities (asthma, allergic rhinitis, eczema, and food allergy) was similar
342 to those reported by Mansoor et al.³² and Pesek et al.³⁶, and confirms the strong association between
343 EGIDs and atopic diseases.

344 A normal mucosa is the prevalent endoscopic finding reported, particularly in patients with EoGE
345 and EoC, who might present non-specific endoscopic patterns.^{1,6,39}

346 First-line therapy (diet, oral steroids, montelukast and ketotifen) was considered effective in most
347 included studies. Diet and steroids were the first-line therapies in patients with EoE-EGIDs.^{1,4,6,39}

348 Food-elimination diet and elemental diet improved clinical symptoms and reduced mucosal
349 eosinophils in more than 75% of children with non-EoE EGIDs.^{40,41} Retrospective studies have
350 reported clinical remission in 50% to 90% of patients with EGIDs treated with oral corticosteroids
351 (prednisone and budesonide).^{1,39,42-44} In the CEGIR study, the therapeutic approach varied widely
352 across centers and disease localization (EoG, EoGE and EoC); however, the response to therapies
353 was achieved in most enrolled patients.³⁶ The efficacy of montelukast and ketotifen in EGIDs
354 remains controversial and is limited to a few case series.³⁹

355 We found extensive heterogeneity among the included studies and the few subgroups that we could
356 assess, without significant publication bias. Heterogeneity is probably due to several factors: first,
357 the sample size varied from 105 to 5,100 patients. Second, only two studies included just pediatric
358 patients^{23,29}, while the others included adult only and mixed population.^{21,22,24-28,30} Finally, different
359 diagnostic histological criteria might have been used. In fact, management guidelines for non-EoE
360 EGIDs in all ages are still lacking, and different cut-offs of intestinal eosinophils for the histological
361 diagnosis are reported in literature.^{1,4,45} Unfortunately, the cut-off of intestinal eosinophils per HPF
362 is specified in only three included studies (in all three, > 20 Eo/HPF).^{21,23,28}

Conclusion

This is the first systematic review and meta-analysis focusing on the epidemiology of non-esophageal gastrointestinal diseases in adults and children referred to outpatient clinics for gastrointestinal symptoms. Our research showed that non-EoE EGIDs seems to be highly prevalent disorders, with rising prevalence rates in recent years.³⁶ Non-EoE EGIDs affect about 1.9% of patients referred to the hospitals for gastrointestinal symptoms, so physicians may recognize these disorders and consider their prevalent chronic nature⁴⁶, and the impact on patients' quality of life.⁴⁷ Finally, our results may lead researchers to develop shared management guidelines in adults and children. More prospective, large-scale, multicenter studies are needed to evaluate reported data and to further investigate the epidemiology of non-EoE EGIDs and their possible risk factors and comorbidities.

Acknowledgments

MV and AL equally contributed to study conception, data extraction, risk of bias rating and manuscript writing. LS and ADS contributed to study conception and design, analysis and interpretation of data and statistical analyses. CR conducted the article retrieval. AC and GLM revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript, including the authorship list. The guarantor of the article was AL.

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515 **Figure 1.** Study flow chart from identification to inclusion of final articles.

516 **Figure 2.** Funnel plot for publication bias.

517 **Figure 3.** The overall prevalence estimates of non-EoE EGIDs. Summary estimates are expressed
518 as a percentage of patients with non-EoE EGIDs.

Table I. Inclusion criteria

Criteria	Specifics
Population	Adult/pediatric patients referred to outpatient clinics for gastrointestinal symptoms
Study design	Cross-sectional and cohort studies
Outcome	Prevalence or incidence of eosinophilic gastroenteritis and eosinophilic colitis
	Description of diagnostic criteria in studies
	Description of therapy in studies (dietary treatment, corticosteroids, other drugs)
	Explore variation of prevalence estimates according to: - Age (adult vs pediatrics) - Gender (males vs females) - Country (developing vs developed countries; US vs European countries) - Symptoms (GI symptoms: abdominal pain, nausea, vomiting and diarrhea, gastrointestinal bleeding, anemia, protein-losing enteropathy, malabsorption; pediatric symptoms: failure to thrive, amenorrhea, delayed puberty; complications: ascites, pancreatitis, bowel obstruction, bowel perforation, intestinal ulcer, cystitis, hepatitis) - Allergic diseases (asthma, allergic rhinitis or atopic dermatitis, and food or drug allergy) - Age at symptom onset - Age at diagnosis - Localization of eosinophilic inflammation (stomach, duodenum, jejunum, ileum, large intestine; mucosal or muscular or serosa involvement) - Diagnostic criteria (endoscopy, number of eosinophils/HPF, peripheral eosinophilia, allergy tests (skin prick test, total IgE level, allergen specific IgE), capsule endoscopy, magnetic resonance, computed axial tomography) - Years (1990-2000-2010-2018)

GI, gastrointestinal; HPF, high power field.

Table II. Quality assessment of included studies

Authors, year	Risk of bias for cross-sectional studies	
	1	2
J. Tilma <i>et al</i> , 2018	Yes	Yes
Chee K Hui <i>et al</i> , 2018	Yes	Yes
G. A. Bonagura <i>et al</i> , 2017	Yes	Yes
T. Alhmoud <i>et al</i> , 2016	Yes	Yes
A.A. Al Quorain <i>et al</i> , 2000	Yes	Yes
D. Channaiah <i>et al</i> , 2017	Yes	Yes
Y. Guo <i>et al</i> , 2016	Yes	Yes
M. Kusakari <i>et al</i> , 2012	Yes	Yes
C. Panackel <i>et al</i> , 2010	Yes	Yes
T. Kerdsirichairat <i>et al</i> , 2010	Yes	Yes

1: Were all patients free of the outcome of interest at the time of the study included? 2: Were diagnosis/exclusion of non-EoE EGIDs free from outcome misclassification?

Table III. Characteristics of included studies

First author and publication year	Study design	Study period	Country	Language	Reference population	Age of patients	Sex (%)		Prevalence of non-EoE EGIDs (%) (95% CI)
							Male	Female	
J. Tilma <i>et al</i> (2018)	Cross-sectional	2011 - 2016	Denmark	English	381	Children	64%	36%	2.90 (1.450 - 5.107)
Chee K Hui <i>et al</i> (2018)	Cross-sectional*	2009 - 2015	Malaysia	English	2,469	Adult	62.5%	37.5%	2.592 (2.002 - 3.298)
G. A. Bonagura <i>et al</i> (2017)	Cross-sectional	2003 - 2013	Italy	English	105	Adult	n.a.	n.a.	1.905 (0.232 - 6.712)
T. Alhmoud <i>et al</i> (2016)	Cross-sectional	2004 - 2014	USA	English	361	Adult and Children	38%	62%	3.601 (1.931 - 6.079)
A.A. Al Quorain <i>et al</i> (2000)	Cross-sectional	1983 - 1996	Saudi Arabia	English	1,590	Adult and Children	100%	0%	0.126 (0.0152 - 0.454)
D. Channaiah <i>et al</i> (2017)	Cross-sectional	n.a.	India	English	309	Adult	n.a.	n.a.	0.647 (0.0785 - 2.318)
Y. Guo <i>et al</i> (2016)	Cross-sectional*	n.a.	China	English	122	Adult	n.a.	n.a.	5.738 (2.338 - 11.465)
M. Kusakari <i>et al</i> (2012)	Cross-sectional	2001 - 2011	Japan	English	552	Children	n.a.	n.a.	3.986 (2.514 - 5.972)
C. Panackel <i>et al</i> (2010)	Cross-sectional	2009 - 2010	India	English	5,100	Adult and Children	n.a.	n.a.	1.196 (0.916 - 1.534)
T. Kerdsirichairat <i>et al</i> (2010)	Cross-sectional	2003 - 2010	USA	English	2,388	Adult	n.a.	n.a.	0.419 (0.201 - 0.769)

*People with non-EoE EGIDs were enrolled as a cohort-study; measures of prevalence were evaluated as a cross-sectional study.

n.a., not available.

Table IV. Prevalence of non-EoE EGIDs in adults referred to outpatient clinics for gastrointestinal symptoms

Study	Sample size	Proportion (%)	95% CI*
Chee K Hui <i>et al</i>	2,469	2.592	2.002 to 3.298
G. A. Bonagura <i>et al</i>	105	1.905	0.232 to 6.712
D. Channaiah <i>et al</i>	309	0.647	0.0785 to 2.318
Y. Guo <i>et al</i>	122	5.738	2.338 to 11.465
T. Kersirichairat <i>et al</i>	2,388	0.419	0.201 to 0.769
Total (fixed effects)	5,393	1.373	1.080 to 1.721
Total (random effects)	5,393	1.872	0.575 to 3.894

*CI was calculated as an exact binomial proportion.

Table V. Prevalence of non-EoE EGIDs in developing and developed countries

Developing countries				Developed countries			
Study	Sample size	Proportion (%)	95% CI	Study	Sample size	Proportion (%)	95% CI
Chee K Hui <i>et al</i>	2,469	2.592	2.002 to 3.298	J. Tilma <i>et al</i>	381	2.887	1.450 to 5.107
A.A. Al Quorain <i>et al</i>	1,590	0.126	0.0152 to 0.454	G. A. Bonagura <i>et al</i>	105	1.905	0.232 to 6.712
D. Channaiah <i>et al</i>	309	0.647	0.0785 to 2.318	T. Alhmoud <i>et al</i>	361	3.601	1.931 to 6.079
Y. Guo <i>et al</i>	122	5.738	2.338 to 11.465	M. Kusakari <i>et al</i>	552	3.986	2.514 to 5.972
C. Panackel <i>et al</i>	5,100	1.196	0.916 to 1.534	T. Kerdsirichairat <i>et al</i>	2,388	0.419	0.201 to 0.769
Total (fixed effects)	9,590	1.269	1.055 to 1.514	Total (fixed effects)	3,787	1.245	0.917 to 1.651
Total (random effects)	9,590	1.462	0.513 to 2.886	Total (random effects)	3,787	2.446	0.723 to 5.151

Table VI: Summary of clinical symptoms reported in included articles

Authors, year	Abdominal pain	Nausea	Vomiting	Dysphagia	Diarrhea	Gastrointestinal bleeding	Constipation	Anemia	Protein-losing enteropathy	Malabsorption	Weight loss	Failure to thrive	Delayed puberty and amenorrhea	Ascites	Bowel obstruction	Other clinical complication*
J. Tilma <i>et al</i> , 2018	94%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Chee K Hui <i>et al</i> , 2018	36%	n.a.	n.a.	n.a.	47%	0	3%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
G. A. Bonagura <i>et al</i> , 2017	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
T. Alhmoud <i>et al</i> , 2016	62%	31%	31%	n.a.	31%	8%	n.a.	15%	n.a.	n.a.	15%	15%	n.a.	23%	8%	n.a.
A.A. Al Quorain <i>et al</i> , 2000	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
D. Channaiah <i>et al</i> , 2017	n.a.	n.a.	n.a.	n.a.	100%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Y. Guo <i>et al</i> , 2016	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
M. Kusakari <i>et al</i> , 2012	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
C. Panackel <i>et al</i> , 2010	63%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
T. Kerdichairat <i>et al</i> , 2010	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

*Other clinical complications: bowel perforation, pancreatitis, intussusception, intestinal ulcer, eosinophilic cystitis and hepatitis

n.a., not available

Table VII: Summary of comorbidities described in included articles.

Authors, year	Atopy	Asthma	Sinusitis	Allergic rhinitis	Eczema	Urticaria	Food allergy	Drug allergy
J. Tilma <i>et al</i> , 2018	25%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0%
Chee K Hui <i>et al</i> , 2018	33%	17%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
G. A. Bonagura <i>et al</i> , 2017	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
T. Alhmoud <i>et al</i> , 2016	54%	54%	n.a.	54%	54%	n.a.	38%	n.a.
A.A. Al Quorain <i>et al</i> , 2000	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
D. Channaiah <i>et al</i> , 2017	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Y. Guo <i>et al</i> , 2016	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
M. Kusakari <i>et al</i> , 2012	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
C. Panackel <i>et al</i> , 2010	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
T. Kerssirichairat <i>et al</i> , 2010	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

n.a., not available

Table VIII: Therapeutic management and its efficacy in included articles

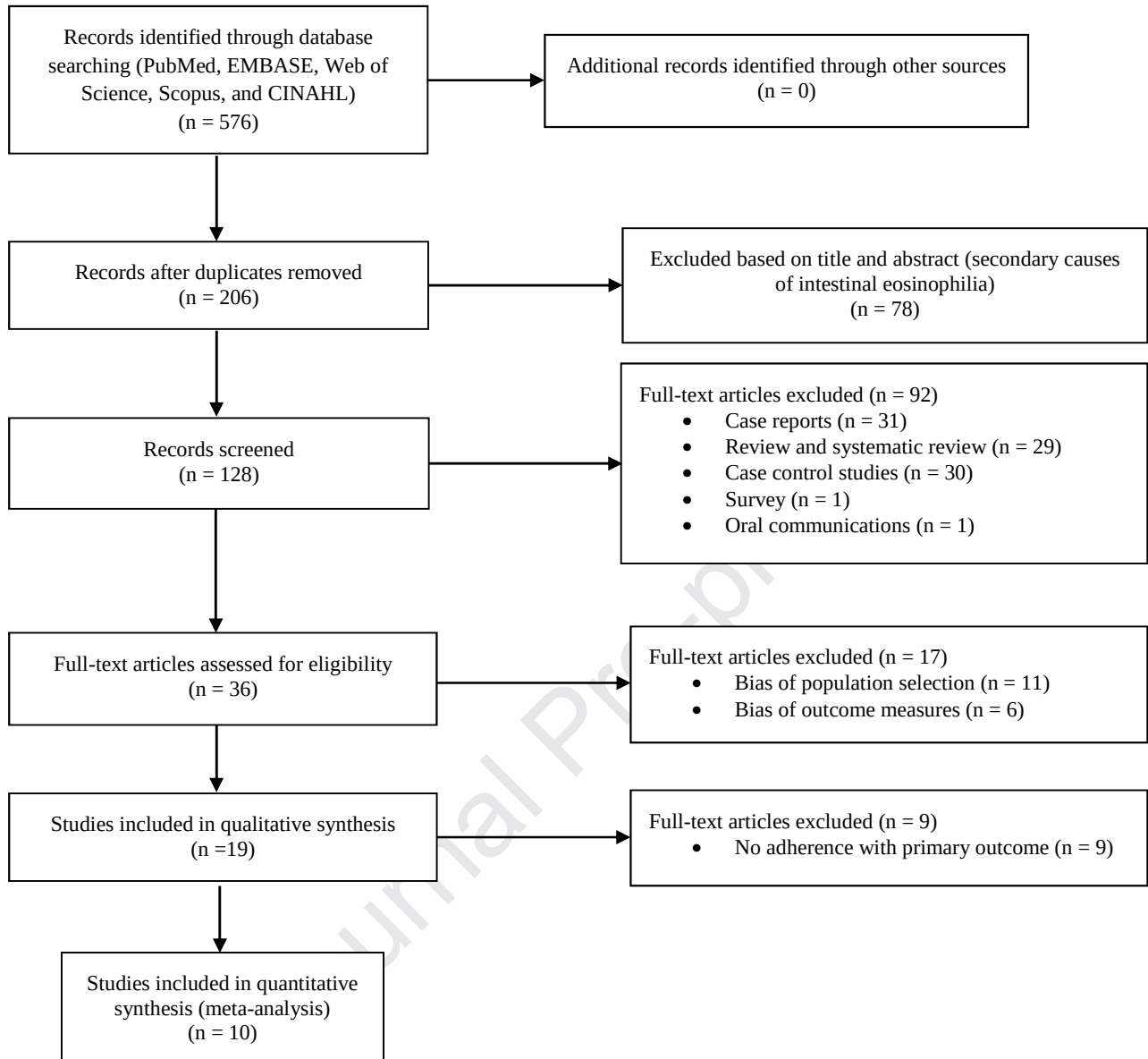
Authors, year	First-line therapy			Response to first-line therapy		Second-line therapy			Response to second-line therapy	
	Steroids	Diet	Other therapies	Yes	No	Steroids	Diet	Other therapies	Yes	No
J. Tilma <i>et al</i> , 2018	100%	n.a.	n.a.	100%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Chee K Hui <i>et al</i> , 2018	n.a.	n.a.	100%*	89%	11%	100%	n.a.	n.a.	100%	n.a.
G. A. Bonagura <i>et al</i> , 2017	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
T. Alhmoud <i>et al</i> , 2016	46%	23%	11%#	90%	10%	100%	n.a.	n.a.	100%	n.a.
A.A. Al Quorain <i>et al</i> , 2000	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
D. Channaiah <i>et al</i> , 2017	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Y. Guo <i>et al</i> , 2016	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
M. Kusakari <i>et al</i> , 2012	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
C. Panackel <i>et al</i> , 2010	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
T. Kerdsirichairat <i>et al</i> , 2010	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

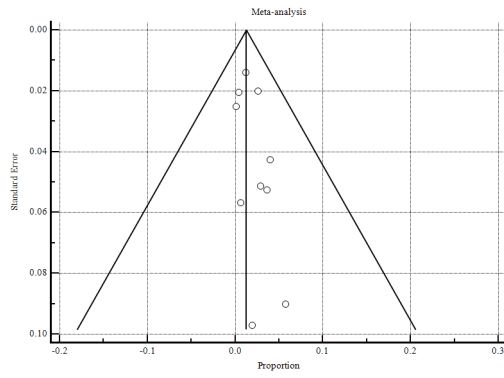
* montelukast and ketotifen

montelukast

n.a., not available

Journal Pre-proof





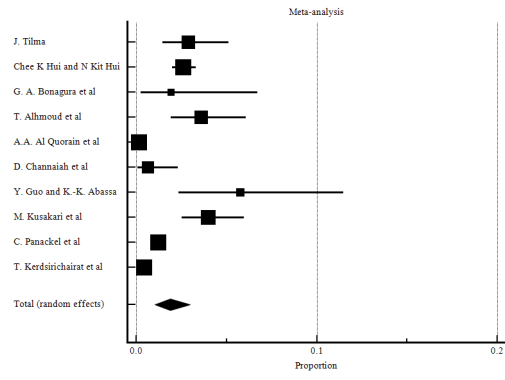


Table E1 Search strategy.

Search Strategy
<i>PubMed</i>: ("Eosinophilic gastrointestinal disorders" OR "Eosinophilic gastrointestinal disorder" OR "Eosinophilic gastroenteritis" OR "Eosinophilic colitis") AND ("prevalence"[mesh] OR "incidence"[mesh] OR prevalence OR incidence). Filters: Publication date from 1990/01/01 to 2018/05/28. <i>Web of Science Core Collection</i>: TS= ("Eosinophilic gastrointestinal disorder*" OR "Eosinophilic gastroenteritis" OR "Eosinophilic colitis") AND (prevalence OR incidence). Filters: Publication date from 1990/01/01 to 2018/05/28. <i>Scopus</i>: TIABKW ("Eosinophilic gastrointestinal disorder*" OR "Eosinophilic gastroenteritis" OR "Eosinophilic colitis") AND (prevalence OR incidence). Filters: Publication date from 1990/01/01 to 2018/05/28; publication type: article, review, conference paper, editorial, note, letter, short survey. <i>CINAHL</i>: ("Eosinophilic gastrointestinal disorder*" OR "Eosinophilic gastroenteritis" OR "Eosinophilic colitis") AND ("prevalence"MH OR "incidence"MH OR prevalence OR incidence). Filters: Publication date from 1990/01/01 to 2018/05/28; academic journals. <i>Embase</i>: ('eosinophilic gastroenteritis'/exp OR 'eosinophilic colitis'/exp OR 'eosinophilic gastrointestinal disorder*' OR 'eosinophilic gastroenteritis' OR 'eosinophilic colitis') AND ('prevalence'/exp OR 'incidence'/exp OR prevalence OR incidence). Filters: [1990-2018]/py.

Table E2 Risk of bias assessment of included studies.

Cohort studies	Cross-sectional studies
Selection bias of the cohort: were all patients free of the outcome of interest at baseline included?	Selection bias: were all patients free of the outcome of interest at the time of the study included?
Losses to follow-up: were all patients (or a relevant proportion >90%) followed up until the end of the study?	Outcome ascertainment: were diagnosis/exclusion of non-EoE EGIDs free from outcome misclassification?
Outcome ascertainment: were diagnosis/exclusion of non-EoE EGIDs free from outcome misclassification?	

Table E3: Endoscopic findings.

Authors, year	Macroscopic findings	
	Normal	Abnormal
J. Tilma <i>et al</i> , 2018	100%	0%
Chee K Hui <i>et al</i> , 2018	92%	8%
G. A. Bonagura <i>et al</i> , 2017	n.a.	n.a.
T. Alhmoud <i>et al</i> , 2016	54%	46%
A.A. Al Quorain <i>et al</i> , 2000	n.a.	n.a.
D. Channaiah <i>et al</i> , 2017	n.a.	n.a.
Y. Guo <i>et al</i> , 2016	n.a.	n.a.
M. Kusakari <i>et al</i> , 2012	n.a.	n.a.
C. Panackel <i>et al</i> , 2010	35%	65%
T. Kerdsirichairat <i>et al</i> , 2010	n.a.	n.a.

n.a., not available