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Systematic review: the association between eosinophilic oesophagitis and coeliac disease

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SUMMARY

Background
The relationship between eosinophilic oesophagitis (EoE) and coeliac disease (CD) remains controversial, with studies yielding varied results.

Aim
To systematically review the evidence of a possible association between both diseases.

Methods
Electronic searches were performed with keywords relating to EoE and CD in the MEDLINE, EMBASE and SCOPUS databases. Summary estimates were calculated. A random-effects model was used depending on heterogeneity (I^2). Publication bias was assessed with the aid of funnel plot analysis, along with the Begg–Mazumdar, Harbord and Egger tests.

Results
The search yielded 197 references; 30 were included in the quantitative summary, with most of these presenting methodological inconsistencies. Significant publication bias in favour of short studies reporting positive associations between both diseases was documented. The prevalence of EoE in CD ranged from 0% to 10.7% (I^2 = 78.9%). Prevalence of CD in EoE varied between 0.16% and 57.1% (I^2 = 89%). One high-quality, prospective, randomly selected, population-based study documented a 1.1% prevalence of CD, with no patients presenting EoE. Clinical and methodological heterogeneity hindered the performance of quantitative summaries for prevalence data. A gluten-free diet was effective in achieving histological remission of EoE in 32.1% of coeliac patients (95% confidence interval, 14.9–52.2%; I^2 = 52.2%), which was similar to that expected for wheat elimination in EoE patients.

Conclusions
While a lack of valid studies prevents us from completely ruling out a true association between EoE and CD, currently available evidence does not support this hypothesis. Indeed, the only epidemiological study with sufficient validity points to the independence of both diseases.

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INTRODUCTION

Eosinophilic oesophagitis (EoE) and coeliac disease (CD) are distinct immunological entities affecting the upper gastrointestinal (GI) tract, both of which are triggered and maintained by exposure to food antigens, but with important differences in clinical and histopathological features.

Eosinophilic oesophagitis is an inflammatory disorder characterised by symptoms of oesophageal dysfunction and histological evidence of eosinophil-predominant inflammation in oesophageal mucosal biopsies, but with no involvement of distal GI segments. Diagnosis relies on the persistence of symptoms after the exclusion of other causes of oesophageal eosinophilia, especially gastro-oesophageal reflux disease.[1] EoE is frequently associated with atopic diseases such as bronchial asthma and rhinoconjunctivitis; in all three, a Th2-type immune response seems to be involved.[2] In fact, EoE is now recognised as a particular form of food allergy, after documented disease resolution was achieved through dietary modifications designed to reduce exposure to food antigens.[3, 4]

For its part, CD is a chronic systemic disorder primarily affecting the GI tract, characterised by inflammatory changes in the small bowel that are triggered and maintained by a Th1-type immunological response provoked by exposure to gluten in the diet.[5] CD constitutes the main cause of malabsorption of nutrients in developed countries,[6] manifesting itself in genetically susceptible individuals and frequently leading to various associated disorders.[7] In fact, patients with CD are often susceptible to concomitant autoimmune diseases such as type 1 diabetes mellitus and autoimmune thyroiditis,[8] although their actual risk of developing other atopic diseases remains unclear.[9–12]

Up until 20 years ago, both diseases were considered to be of low prevalence. However, several recent epidemiological studies have clearly shown an increasing number of diagnosed cases in both children and adults. For example, a steady rise in diagnosed cases of CD has been observed over the past few years, with continuous growth in both incidence and prevalence rates over time[5, 13, 14] so that CD now constitutes a highly prevalent disease affecting between 1% and 3% of the European and US populations at some stage in life.[15] In those same populations, EoE is currently estimated to affect 1 of 1800 individuals,[16–18] constituting the second most common cause of oesophageal symptoms after gastro-oesophageal reflux disease (GERD) and being the main cause of dysphagia and food impaction in young patients.[19, 20] It has also become clear that the increased incidence for both diseases cannot be exclusively attributed to better diagnostics or higher detection rates.[14, 21]

In recent years, several case reports and cohort studies have suggested an association between EoE and CD. While this association was initially reported for paediatric patients,[22–26] it has since been reiterated in adult patients,[27] but not universally confirmed in large population-based studies.[28] Even though both diseases are caused by aberrant immune responses to ingested antigens and are potentially responsive to a food elimination diet, differences in the underlying pathophysiological mechanisms leading to each of them,[29, 30] along with the absence of a genetic connection between EoE and CD, have prevented researchers from establishing a direct relationship. As a result, the elucidation of a true association between these disorders remains elusive.

The aim of this study was to evaluate, assess, and quantify the association between EoE and CD by conducting a systematic review of the literature on the relationship of the two disorders in both children and adults, including an evaluation of the efficacy of a gluten-free diet (GFD) in inducing EoE remission among coeliac patients.

METHODS

This systematic review has been registered in the PROSPERO International prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO; register no. CRD42014006981), and was reported in accordance with the PRISMA statements.[31]

Selection of studies

A systematic literature search was performed independently by two researchers (AA and JMT) in three major bibliographical databases (PUBMED, EMBASE and Scopus) for the period up to December 2013. The search was not restricted with regard to date or language of publication. To this end, a predetermined protocol was used in accordance with the quality of reporting meta-analyses of observational studies in epidemiology.[32]

Comprehensive search criteria were used to identify articles dealing with the relationship between EoE and CD. We consulted the thesauri for MEDLINE (MESH) and EMBASE (EMTREE) using the following search strategy: eosinophilic AND ('esophagitis'/exp OR esophagitis) OR eosinophilic AND ('oesophagitis'/exp OR oesophagitis) AND (coeliac) AND ('disease'/exp OR

disease) OR coeliac AND ('disease'/exp OR disease) OR 'gluten'/exp OR gluten AND ('enteropathy'/exp OR enteropathy) OR 'hla'/exp OR hla) AND ('antigens'/exp OR antigens).

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

We also examined the reference lists from retrieved articles and abstracts of conference proceedings (abstract books of the annual Digestive Diseases Week, American College of Gastroenterology Meeting, and the United European Gastroenterology Week for the period between 2004 and 2013) to identify additional relevant studies. Two reviewers (AJL & AA) independently screened the database search for titles and abstracts. If any of the reviewers felt that a title or abstract met the study eligibility criteria, the full text of the study was retrieved.

Inclusion criteria

(i) Studies were included in the systematic review if they provided original data on the concomitant diagnosis of CD in individual patients or patient series with EoE, or, alternatively, if they described a diagnosis of EoE in individuals or series of patients with CD. Such studies were included irrespective of study design (i.e., randomised controlled trials [RCT], observational prospective and retrospective studies, and case series reports).

(ii) Studies evaluating a gluten-free diet-based intervention in EoE patients with CD were also considered if objective quantitative data on efficacy in terms of histological response were provided. EoE remission was considered to be a peak eosinophil count <15 eos/high power field (hpf) in oesophageal biopsies[1] after a GFD-based dietary treatment.

Exclusion criteria

The following were excluded from our analysis:

(i) Reviews on the treatment of EoE that did not provide original data on dietary therapy, along with clinical guidelines and consensus documents.

(ii) Studies not carried out on humans.

(iii) Studies providing duplicated information (i.e., repeated abstracts presented at different congresses or abstracts published later as a full paper).

(iv) Subsets of cases or controls from a previously published article by the same authors.

(v) Studies using a gluten-free diet intervention simultaneously with another therapeutic alternative capable of reducing oesophageal inflammation (topical and systemic steroids and/or immunomodulatory drugs) were not considered in the evaluation of the efficacy of a GFD, but were included in prevalence analyses.

Quality assessment

Cohort studies, case series and case reports were evaluated for quality only if the article described all patients' demographical data, diagnostic criteria for EoE and CD, the proportion of EoE patients among CD patients (or vice versa) and study design. The effects of a gluten-free diet on resolution of EoE were also assessed. Quality assessment was checked with a specific evaluation form for observational studies developed by our group and based on the Strobe statements.[33] A study was considered to be at low risk for bias if each of the bias items could be categorised as low risk. On the contrary, studies were judged to have a high risk of bias if even one of the items was deemed high risk. Two investigators (AJL & AA) independently gave each eligible study an overall rating of high, low or unclear risk of bias; if disagreements arose, a third reviewer (JMT) was consulted.

Data extraction

Two reviewers (AJL, AA) independently extracted relevant information from each eligible study using a standardised data extraction sheet and then proceeded to cross-check the results. The data extracted included the trial study areas, the last name of the first author, year of publication, age and gender of study participants, sample size, methodological design, study period, and, whenever possible, the effectiveness of a GFD on EoE. At the same time, data on the key outcomes, including prevalence of EoE among CD patients and/or prevalence of CD among EoE patients, were extracted from all included studies. Disagreements between reviewers regarding data extraction were resolved through discussion.

Statistical analysis

Response percentages for dietary intervention were summarised with the aid of a fixed- or random-effects meta-analysis weighted for inverse variance following DerSimonian and Laird's method. Summary estimates, including 95% confidence intervals (CI), were calculated for the prevalence of EoE among CD and vice versa, as well as for the efficacy of a GFD on EoE remission.

Heterogeneity between studies was assessed by means of a chi-square test (Cochran Q statistic) and quantified

with the I^2 statistic. Generally, I^2 was used to evaluate the level of heterogeneity, assigning the categories low, moderate and high to I^2 values of 25%, 50% and 75% respectively.[34] Publication bias was evaluated with the aid of a funnel plot, the asymmetry of which was assessed with Begg–Mazumda's rank test[35] along with the Egger[36] and Harbord tests.[37]

For the primary outcome, planned subgroup analyses were performed based on the primary population studied (patients with EoE or patients with CD) and age (adults vs. children).

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

RESULTS

The search strategy yielded 197 references; 153 documents were excluded after examining the title and abstract because they did not fulfil the inclusion criteria. Of the remaining 43 references, four abstracts were excluded either because they were subsequently published as full papers or because they had been presented multiple times at different conferences. For the remaining 39 references considered to be potentially relevant, the full text was retrieved for detailed evaluation. Of these, nine were excluded because they did not include data suitable for calculations. In the end, 30 studies were included in the systematic review (Figure 1).

The main characteristics of each study are summarised in Table 1. Of the 30 documents analysed, 10 were full text articles and 20 were abstracts. Overall, data from

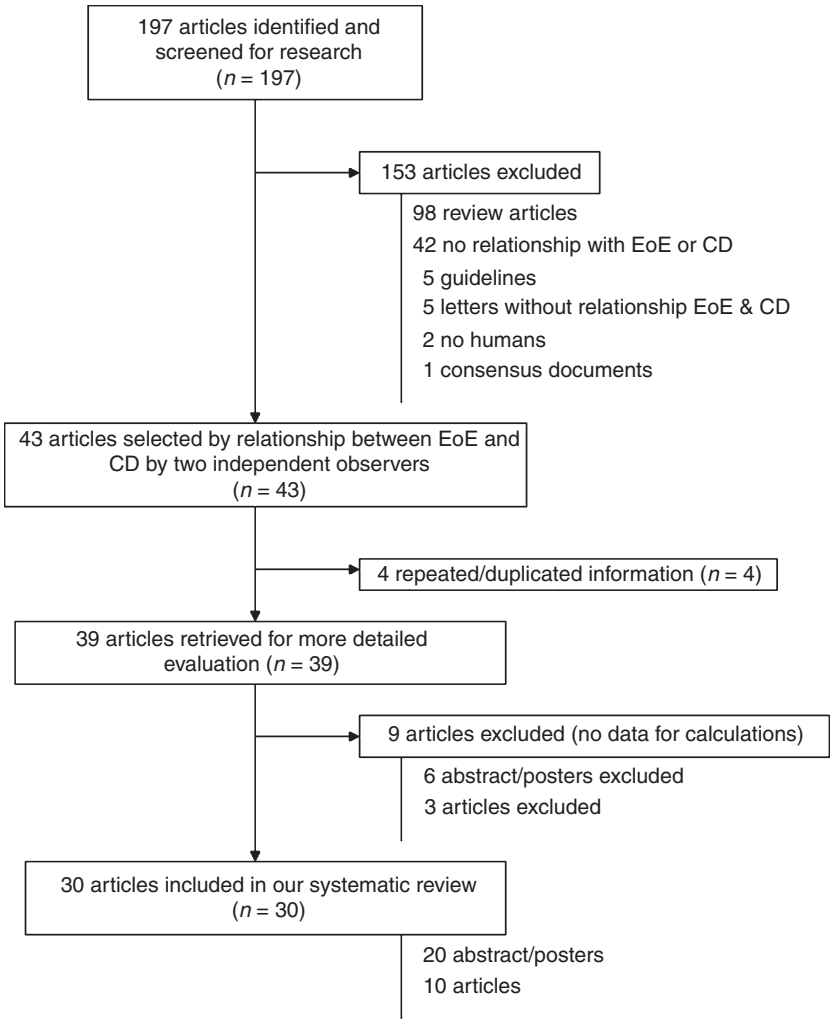

Figure 1 | Flow chart for the process of identifying studies that were included in and excluded from the systematic review.

Table 1 | Demographics and characteristics of studies included in our systematic review on the relationship between eosinophilic oesophagitis (EoE) and coeliac disease (CD)

First author, publication year	Population	Study period	*N*	Design	Outcome indicator
Full papers					
Kagalwalla, 2007[23]	Children	2006	1	Case report	100% (1 patient with EoE and CD)
Quaglietta, 2007[24]	Children	2005–2006	315	Prospective	1.9% (6 EoE / 315 CD)
Verzegnassi, 2007[25]	1 Child / 2 adults	2006	3	Case report	100% (3 patients with EoE and CD)
Ooi, 2008[38]	Children	2000–2007	221	Retrospective	3.2% (7 EoE / 221 CD)
Leslie, 2010[39]	Children	1999–2007	121	Retrospective	8.2% (10 EoE / 121 CD)
Sánchez-García, 2011[40]	Children	2010	1	Case report	100% (1 patient with EoE and CD)
Abraham, 2012[41]	Children	2009–2011	206	Retrospective	4.4 % (9 EoE / 206 CD)
Thompson, 2012[26]	1142 Adult / 297 children	1981–2012	1439	Retrospective	Adults: 0.9% (10 EoE /1142 CD) Children: 1.3 % (4 EoE / 297 CD)
Stewart, 2013[42]	518 Adult / 2 45 children	2004–2008	763	Retrospective	Adults: 0% (0 EoE / 518 CD) Children: 1.2% (3 EoE / 245 CD)
Ludvigsson, 2013[28]	Adult	–	1000	Prospective Randomly selected	0% (0 CD /11 EoE)
Abstract					
Shah AA, 2006[22]	Children	2002–2006	6	Case report	100% (6 patients with EoE and CD)
De la Hoz, 2009[43]	Children	2001–2009	17	Prospective	29.4% (5 CD / 17 EoE)
Francavilla, 2009[44]	Children	2007–2008	176	Retrospective	1.1% (2 EoE / 176 CD)
Johnson, 2010[45]	Adult	2009	29	Retrospective	13.8% (4 CD / 29 EoE)
Rutigliano, 2010[46]	Children	2008–2009	51	Retrospective	4% (2 EoE / 51 CD)
Melton, 2010[47]	–	2004–2008	306	Retrospective	1.96% (6 EoE / 306 CD)
Weinstein, 2010[48]	Children	2006–2010	93	Retrospective	2.1% (2 EoE / 93 CD)
Hiremath, 2010[49]	Children	–	70	Retrospective	5.7% (4 CD / 70 EoE)
Patel, 2010[50]	–	2004–2008	78	Retrospective	5.1% (4 EoE / 78 CD)
Garret, 2010[51]	Children	–	971	Retrospective	2.3% (22 CD / 971 EoE)
Chong, 2010[52]	Children	2004–2009	31	Retrospective	3.2% (1 CD / 31 EoE)
Prasad, 2011[53]	Children	–	7	Retrospective	57.1% (4 CD / 7 EoE)
Fung, 2011[54]	Children	–	617	Retrospective	0.2% (1 CD / 617 EoE)
Ho, 2011[55]	Adult	2001–2008	157	Retrospective	1.3% (2 CD / 157 EoE)
Croaker, 2012[56]	Children	2003–2011	124	Retrospective	3.2% (4 EoE / 124 CD)
Constable, 2012[57]	Adult	2012	1	Case report	100% (1 patient with EoE and CD)
Guandalini, 2013[58]	Children	–	115	Retrospective	0.9% (1 EoE/115 CD)
Convers, 2013[59]	Children	2004–2012	67	Retrospective	8.9% (6 EoE / 67 CD)
Alli-Akintade, 2013[60]	Adult	–	1	Case report	100% (1 patient with EoE and CD)
Dharmaraj, 2013[61]	Children	2010–2012	56	Retrospective	10.7% (6 EoE / 56 CD)

7043 patients (3809 children, 2850 adults and 384 not determined) were retrieved, with the size of the various study populations ranging from 1 to 1439 cases.

Prevalence of EoE among CD patients

Fifteen studies reported on the prevalence of EoE among CD patients; most of these were short, retrospective case reports of paediatric populations (Table 1). Overall, six case reports included 13 patients with both EoE and CD. The remaining documents were predominantly short case series, including a total of 78 EoE patients among 4131 patients with CD.

The prevalence of EoE among CD patients ranged from 0% to 10.71% (I^2 = 78.9%) (Figure 2). Differences were observed when paediatric and adult patients were analysed separately (0–0.87% vs. 0.87–10.71) (Figure 3a, b, respectively), although in both cases a wide variability was found (I^2 = 63.2% and 75.2%, respectively).

Funnel plot analysis revealed a significant publication bias (*P* value for the Egger test <0.0001; *P* value for the Harbord test = 0.0048) (Figure 4a); studies that included small numbers of coeliac patients with an increased prevalence of EoE (thus favouring the existence of an association between both disorders) were predominant.

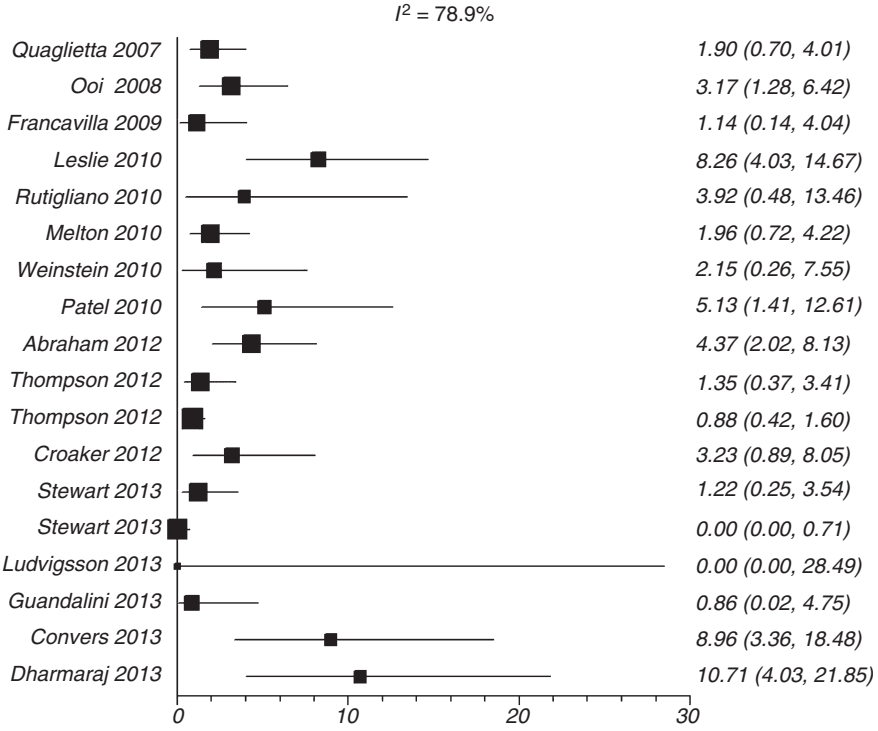

Figure 2 | Studies evaluating the prevalence of EoE among patients with CD, which ranged from 0% to 10.71%. A summary estimate of combined prevalence rates was not performed due to clinical and methodological heterogeneity. The I^2 value of 78.9% indicates that intra-study differences (statistical heterogeneity) account for 78.9% of the variability in the overall effect size.

Prevalence of CD among patients with EoE

Ten studies reported on the prevalence of CD among EoE patients (Table 1), including the aforementioned six documents which described 13 patients sharing both disorders. Most of the remaining studies were retrospective case series reports and included a total of 1905 EoE patients, of whom 49 also presented CD. The vast majority of patients were children. All of these studies were judged as having low methodological quality.

The combined prevalence of CD among EoE patients varied from 0.16% to 57.7% (I^2 = 89%) (Figure 5). However, one high-quality, prospective, randomly selected, population-based study carried out on 1000 adult patients identified 11 coeliac subjects, none of whom presented with EoE.[28]

Once again, funnel plot analysis identified a clear publication bias in favour of studies showing a positive association between EoE and CD (Figure 4b), a finding that was statistically confirmed (*P* value for the Egger test = 0.0101; *P* value for the Harbord test = 0.021).

Efficacy of a gluten-free diet on the EoE remission

The combined efficacy documented in the 15 studies evaluating the efficacy of a GFD in reversing EoE among coeliac patients (11 of which were carried out on paediatric populations and four on adult patients) was 32.1% (95% CI, 14.9–52.2%). Combined results from 61 patients (53 children and eight adults) were highly heterogeneous (I^2 = 64.7%), regardless of the age of the population being assessed (68.3% and 60% for children and adults, respectively) (Table 2 and Figure 6).

A significant publication bias in favour of reporting a positive effect of a GFD in achieving EoE remission was documented with every statistical test performed (*P* value for the Begg–Mazumdar test = 0.0009; *P* value for the Egger test = 0.0143; *P* value for the Harbord test = 0.0147).

Genetic associations between EoE and CD

Two studies have determined the presence of HLA-DQ2 and DQ8 conferring risk for CD in patients with EoE: One Australian case series of 10 correlatively diagnosed EoE patients reported that eight of the 10 expressed the

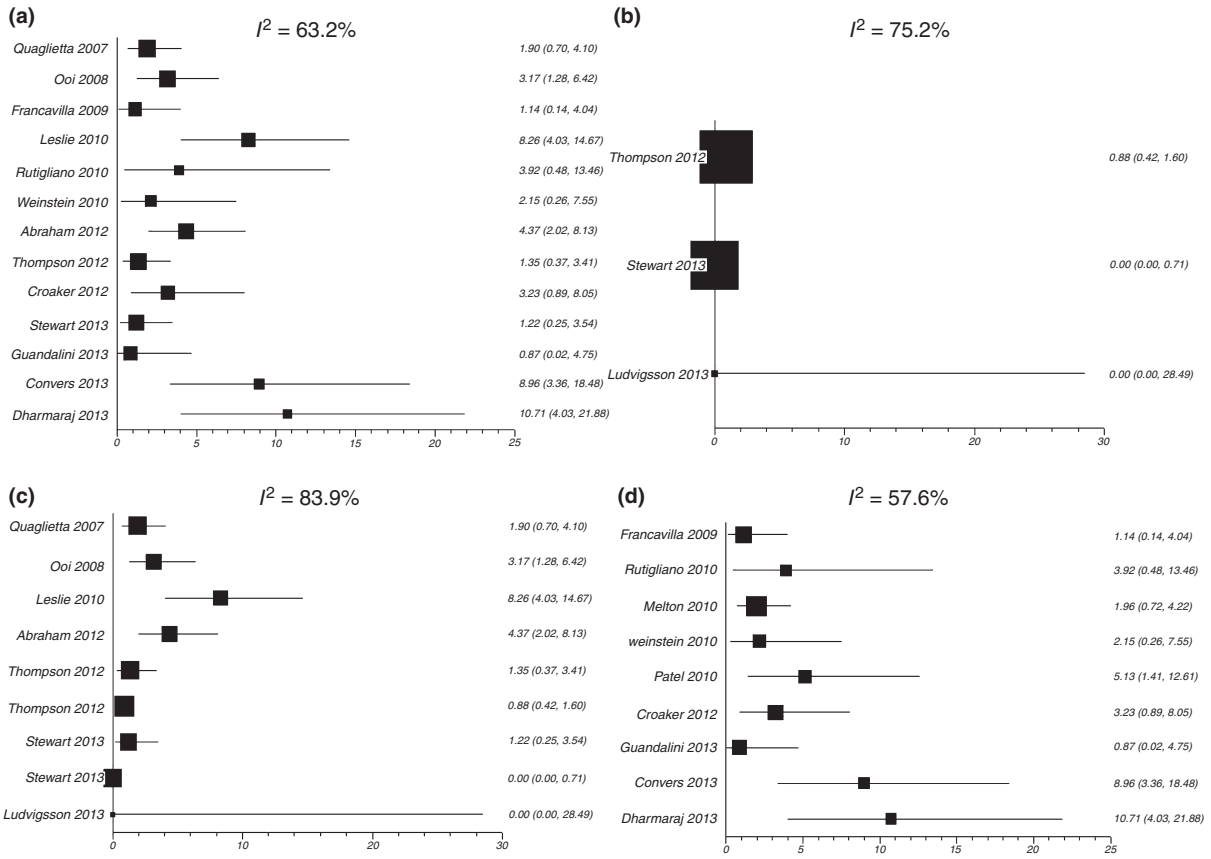

Figure 3 | Subgroup analysis of studies evaluating the prevalence of EoE among patients with CD; (a) prevalence in paediatric coeliac population; (b) prevalence of EoE in adult CD patients; (c) prevalence in studies published as full articles, and (d) prevalence in studies published as abstracts. I^2 denotes intra-study differences in statistical heterogeneity.

HLA-DQ2 haplotype (with a frequency affecting approximately 45% of the local population), with another patient presenting DQ8.[27] This increased frequency of the HLA-DQ2 and DQ8 alleles predisposing for CD was not documented in a multicentre, observational study carried out in Spain on 78 adult EoE patients as compared with the allelic frequency among healthy individuals.[62] Hence, a common genetic basis for EoE and CD cannot be established.

Subgroup analysis

The clinical and methodological variability in the studies examined prevented us from calculating summary estimates; however, a tentative analysis of subgroups categorised according to quality and type of document was carried out (Table 3). In the hypothetical case that the retrieved studies had shown enough consistency to have undergone meta-analysis, subgroup analyses would have indicated a stronger association between EoE and CD in low-quality studies compared with those considered of mild/high quality. Regarding the type of publication, a higher association between CD and EoE would have been observed in research published as an abstract compared to that published as a full paper (Figure 3c, d, respectively). Finally, the coexistence of EoE and CD would have been more common in children than in adult patients.

DISCUSSION

This systematic review of 30 publications on the existence of a possible relationship between EoE and CD has revealed a high heterogeneity in the results provided, both with regard to the actual association as well as concerning the quality of the data. Most of the information available in the literature comes from case reports and short series of patients who share both entities; indeed, this appears to be a compelling reason for publication. Our findings show significant publication bias indepen-

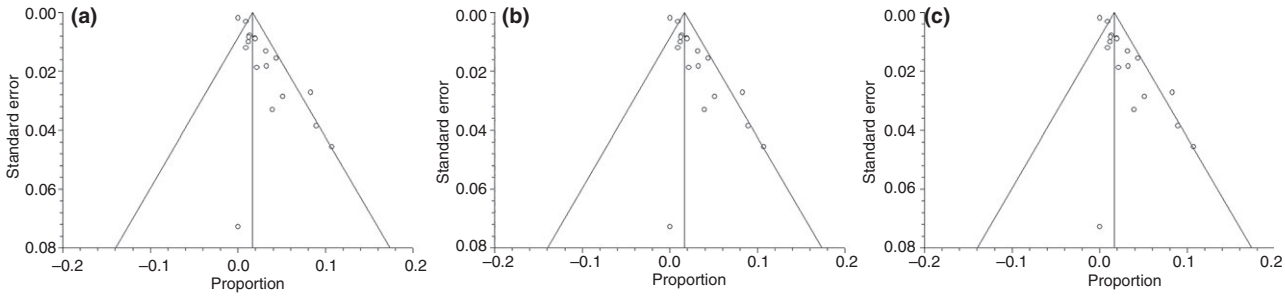

Figure 4 | Begg funnel plot of studies evaluating publication bias of articles on the relationship between EoE and CD. (a) Studies assessing the prevalence of EoE among coeliac patients; (b) studies assessing the prevalence of CD among patients with EoE, and (c) studies evaluating the ability of a gluten-free diet to achieve histological remission of EoE in patients who also presented CD. Statistically significant publication bias was demonstrated by the fact that studies including small numbers of coeliac patients with an increased prevalence of EoE predominated.

dent of the study area, with the inclusion of source information from three major databases supporting our interpretation. This bias severely affected the results of our meta-analysis. In fact, such a significant publication bias in favour of short case series of patients sharing both conditions could well have influenced the undue conclusion that there is a true association between EoE and CD.

The growing recognition of EoE worldwide in recent years has motivated an increasing amount of research on this disorder along with the proactive search for a diagnosis in patients with upper GI symptoms. In a clinical scenario of the increasing prevalence of CD affecting a higher proportion of the population, the availability of serological screening tests may also have contributed to the identification of EoE patients who were referred for endoscopic exams. In this case, the recognition of oesophageal mucosal abnormalities indicative of EoE in patients undergoing an endoscopic exam to obtain duodenal biopsies after a positive serology for CD may favour increased diagnosis of asymptomatic cases of EoE. Inversely, the systematic procurement of duodenal biopsies to exclude eosinophilic gastroenteritis in patients suspected of having EoE, especially in children (as

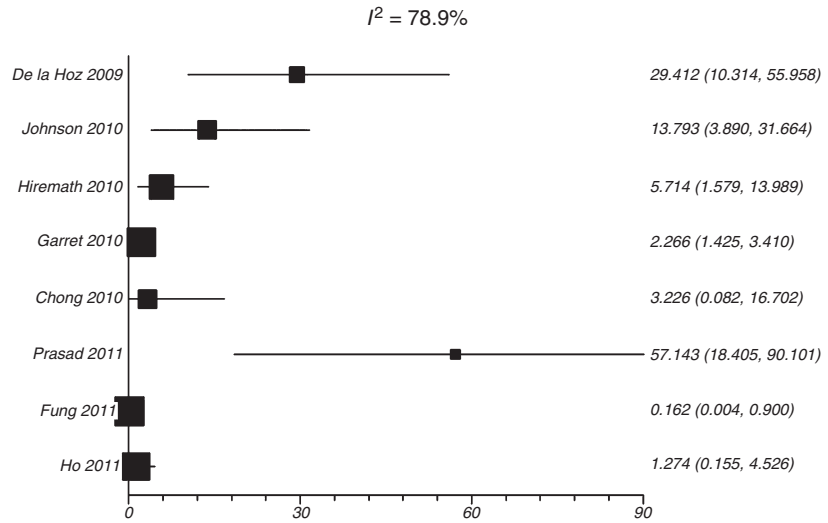

Figure 5 | Studies evaluating the prevalence of EoE among patients with CD, which ranged from 0.16% to 57.7%. A summary estimate of combined prevalence was not calculated because of clinical and methodological heterogeneity among selected studies. The I^2 value of 89% indicates that intra-study differences (statistical heterogeneity) account for 89% of the variability in the overall effect size.

Table 2 | Studies including patients who share both coeliac disease and eosinophilic oesophagitis (EoE), in whom the efficacy of a gluten-free diet (GFD) in achieving histological remission of EoE was assessed

First author, publication year	Population	*N*	Results
Full articles			
Kagalwalla, 2007[23]	Children	1	Resolution after diet without gluten and milk
Quaglietta, 2007[24]	Children	315	100% resolution after a GFD (3/3; biopsies were not taken in other 3 patients)
Verzegnassi, 2007[25]	1 Children / 2 adults	3	50% resolution after a GFD (1/2; an additional patient did not follow the diet correctly)
Ooi, 2008[38]	Children	221	0% resolution after a GFD (0/2)
Leslie, 2010[39]	Children	121	0% resolution after a GFD (0/4)
Sánchez-García, 2011[40]	Children	1	Resolution after a gluten, egg and milk- free diet
Abraham, 2012[41]	Children	206	14.3% resolution after a GFD (1/7)
Thompson, 2012[26]	1142 adults / 297 children	1439	0% resolution after a GFD, which was assessed only in adults (0/3)
Abstracts			
Johnson, 2010[45]	Adult	29	50% resolution after a GFD (2/4)
Rutigliano, 2010[46]	Children	51	0% resolution after a GFD (0/2)
Garret, 2010[51]	Children	971	4.5% resolution after a GFD (1/22)
Fung, 2011[54]	Children	617	100% resolution after a GFD (1/1)
Croaker, 2012[56]	Children	124	0% resolution after a GFD (0/2)
Constable, 2012[57]	Adult	1	100% resolution after a GFD (1/1)
Convers, 2013[59]	Children	67	0% Resolution after a GFD (0/6)

recommended in current guidelines[1]), also favours the diagnosis of CD, even in patients with no symptoms of the disease.

The prevalence of CD has been established as affecting 1% of the population, based on serological screening methods.[63] However, many authors have repeatedly warned that serological tests underestimate the true prevalence of CD[64–66] because seronegative cases are not detected. On the other hand, a population-based epidemiological study defined a prevalence of eosinophilic infiltration compatible with EoE (defined as 15 or more eosinophils/hpf) in 1% of randomly selected subjects undergoing endoscopic sampling from the distal oesophagus.[67] With this high prevalence, the identification of patients sharing both disorders cannot be regarded as unusual, even if both disorders are independent from each other.

The study conducted by Ludvigsson *et al.* had the design with the least risk of bias.[28] It was based on a probabilistic sampling from the general population (external validity), with a high response rate to endoscopic exploration (73%) and carried out independently of patient symptoms. Furthermore, endoscopists were blinded to the ASQ responses and medical history, thus avoiding an important source of information bias. Finally, endoscopic findings were verified by an expert endocopist and a professor of gastrointestinal surgery. In this sample, EoE was diagnosed in 11 (1.1%) patients, whereas coeliac disease was found in none of them (controls: 18/989). These figures show a clear independence between the prevalence of EoE and CD.

Thompson *et al.*[26] analysed a cohort of patients diagnosed with CD along a 10-year period (2000 to 2009). Routinely (in paediatric cases) and at the discretion of the clinician (in adult patients), oesophageal biopsies were performed and EoE was diagnosed according to standard criteria. The observed number of EoE cases was compared to the theoretically expected number of cases obtained from incidence figures reported in the study conducted in Olmsted County (Minnesota) by Prasad *et al.*[68] A standardised incidence ratio (SIR) higher than 10 was estimated in all groups, which were stratified by gender and age. However, this study presents bias and drawbacks that explain, in part, the association observed. Firstly, CD patients with EoE could be diagnosed and detected more easily because of an accumulation of symptoms from both diseases. Secondly, the risk period for the development of both diseases should be calculated from the inception of the cohort and not exclusively between the date of diagnosis of CD and EoE. Finally, the reference used to calculate the expected number of cases was extracted from medical records (cases elicited by a patient's demand of consultation), which could have led to an important underestimation

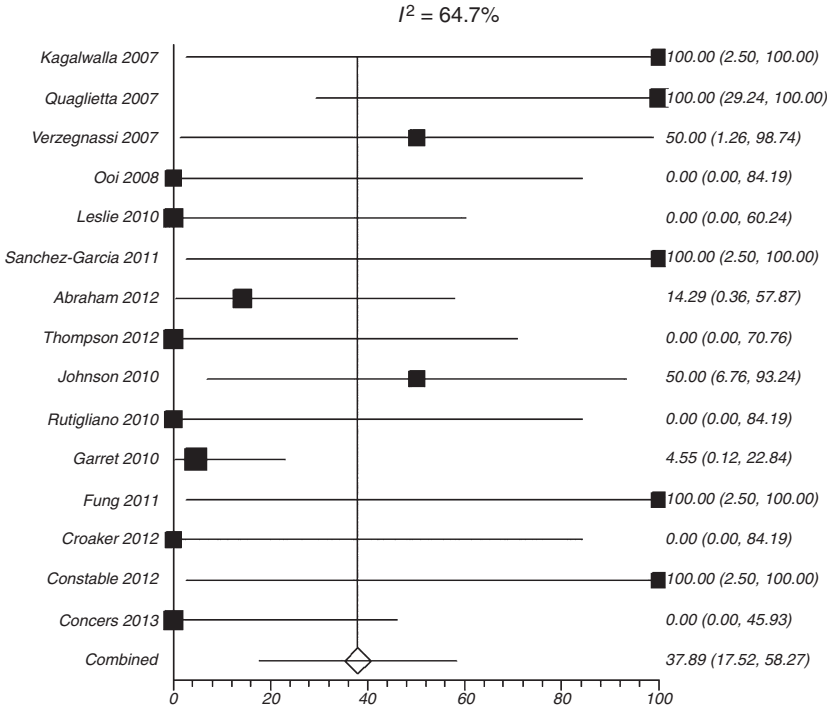

Figure 6 | Overall combined effects of a gluten-free diet (GFD) for inducing remission of oesophageal eosinophilic infiltration in coeliac patients who also suffered from eosinophilic oesophagitis. Percentage of histological improvement after following a GFD was extracted from each article/abstract and 95% confidence intervals were calculated using the exact binomial method. A random-model effect was used to calculate the overall effect size. The I^2 value of 64.7% indicates that intra-study differences (heterogeneity) account for 64.7% of the variability in the overall effect size.

Table 3 | Subgroup analysis results obtained in the hypothetical case that the retrieved studies in our systematic review would had shown enough consistency as to have been meta-analysed. These results can be taken only as an academic exercise and no final conclusions can be obtained from them due to publication biases. *n*, number of studies included in each subgroup analysis

	Overall %	*n*	Children %	*n*	Adults %	*n*
EoE among CD patients	2.77 (1.7–4.1)	18	3.36 (2.16–4.81)	13	0.43 (0.0135–1.72)	3
Subgroups according to quality						
Medium/high	2.15 (1.10–3.54)	11	3.06 (1.79–4.66)	7	0.43 (0.000135–1.72)	3
Low	4.22 (1.93–7.35)	7	4.05 (1.57–7.62)	6	–	–
Subgroups according to type of publication						
Article	2.06 (0.89–3.68)	9	3.02 (1.62–4.83)	6	0.43 (0.000135–1.72)	3
Abstract	3.66 (2.06–5.69)	9	3.90 (1.82–6.72)	7	–	–
CD among EoE patients	6.02 (2.45–11.04)	8	6.51 (2.15–12.99)	6	6.07 (0.026–24.18)	2
Subgroups according to quality						
Medium/high	6.07 (0.026–24.18)	2	–		6.07 (0.026–24.18)	2
Low	6.51 (2.15–12.99)	6	6.51 (2.15–12.99)	6	–	–
Remission of EoE after a GFD	32.1 (14.9–52.2)	15	28.7 (9.9–52.5)	11	41.6 (4.7–85.8)	3
Subgroups according to quality						
Medium/high	27.6 (8.6–52.4)	8	24.8 (2.04–61.2)	5	26.0 (0.05–75.1)	2
Low	41.1 (10.8–75.8)	7	33.8 (6.4–69.4)	6	–	1
Subgroups according to type of publication						
Article	38.9 (12.8–69.2)	8	45.12 (11.30–81.82)	6	–	1
Abstract	24.9 (5.8–51.7)	7	11.65 (1.05–31.32)	5	61.13 (25.31–91.11)	2

of the true incidence of EoE. Thus, if we compare the figures of approximately one case in 10 000 (Prasad) and one in 100 (Ludvigsson), for the latter reference, the SIR in Thompson's study should be approximately one, which is compatible with the hypothesis of no association. Similar objections can be made for the study conducted by Stewart,[42] which also found only three cases of concomitant CD and EoE.

Additional proof of the absence of a relationship between EoE and CD can be found in the limited efficacy of a gluten-free diet in reversing EoE-associated histopathological lesions documented in patients with CD; even when a broad heterogeneity (I^2 = 64.7%) was found, the summarised result was just 32.7%. Wheat has repeatedly been demonstrated as the second most common food trigger for EoE in both children and adults after cow's milk, responsible for symptoms and eosinophilic inflammation in 22–60% of patients.[69–72] In fact, a positive response to a wheat elimination diet in EoE does not necessarily imply that these patients also have CD.

CD is considered to be a genetically determined disease that affects genetically susceptible individuals who carry the HLA-DQ2 or DQ8 molecules.[73] These HLA heterodimers are known to be the major genetic risk factors for CD, with a negative predictive value of almost 100%; however, the positive predictive value is poor, as approximately 40% of the population carries one or both of these alleles.[74] Indeed, one large, multicentre, observational study demonstrated that the prevalence of HLA heterodimers conferring risk for CD in adult EoE patients was not superior to that found in healthy individuals,[62] thus providing additional evidence for the absence of an association between both diseases.

The strength of our research lies in the fact that it compiles the results of an exhaustive literature search from three major databases, that recovered studies were critically appraised according to their methodological aspects, and that different investigators independently extracted the data from the studies included. The possibility of not recovering all the relevant information published on the putative relationship between EoE and CD has thus been minimised by exhaustive searching; indeed, a significant publication bias has been demonstrated by means of funnel plot analysis, which showed a trend to reporting a positive association between both diseases. In addition, most of the documents retrieved were case reports and short case series, with the most solid data coming from observational studies.

One limitation of this systematic review is that there was a certain amount of small study (or publication) bias. Funnel plot asymmetry might be a consequence of small study bias (often referred to as publication bias) which suggests either selective reporting of positive associations between EoE and CD or poor methodological quality.

In conclusion, given the lack of valid studies, we cannot rule out an association between the two diseases, but the evidence currently available does not unequivocally support this hypothesis. Indeed, the only epidemiological study with sufficient validity suggests the independence of both diseases, with other studies providing evidence against the existence of a link between EoE and CD. However, more well-designed studies are needed to confirm the results gleaned from this systematic review.

AUTHORSHIP

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Author contributions: Alfredo J. Lucendo: study conception and design, data extraction, analysis and interpretation of data, quality rating, manuscript writing and final approval of the manuscript. Ángel Arias: study conception and design, article retrieval, data extraction, analysis and interpretation of data, quality rating, statistical analyses and final approval of the manuscript. José M Tenias: article retrieval, analysis and interpretation of data, statistical analyses and final approval of the manuscript. All authors approved the final version of the manuscript, including the authorship list.

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