Coeliac disease is a strong risk factor for Gastro-oesophageal reflux disease while a gluten free diet is protective: a systematic review and meta-analysis

Mudar Zand Irani,[a,b] Guy D. Eslick,[a,b] Grace L. Burns,[a,b] Michael Potter,[a,b] Magnus Halland,[a,b] Simon Keely,[a,b] Marjorie M. Walker,[a,b] and Nicholas J. Talley[a,b,*]

[a]College of Health, Medicine and Wellbeing, University of Newcastle, Newcastle, Australia
[b]NHMRC Centre of Research Excellence in Digestive Health, University of Newcastle, Newcastle, Australia

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Summary

Background Gastro-oesophageal reflux disease (GORD) mechanisms are well described, but the aetiology is uncertain. Coeliac disease (CD), a gluten enteropathy with increased duodenal eosinophils overlaps with GORD. Functional dyspepsia is a condition where duodenal eosinophilia is featured, and a 6-fold increased risk of incident GORD has been observed. Perturbations of the duodenum can alter proximal gastric and oesophageal motor function. We performed a systematic review and meta-analysis assessing the association between CD and GORD.

Methods A systematic search of studies reporting the association of GORD and CD was conducted. CD was defined by combined serological and histological parameters. GORD was defined based on classical symptoms, oesophagitis (endoscopic or histologic) or abnormal 24-h pH monitoring; studies reporting oesophageal motility abnormalities linked with GORD were also included. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using a random-effects model.

Findings 31 papers were included. Individuals with CD on a gluten containing diet were 3 times more likely to have GORD than controls (OR: 3.37, 95% CI: 2.09–5.44), and over 10 times more likely when compared to those on a gluten free diet (GFD) (OR: 10.20, 95% CI: 6.49–16.04). Endoscopic oesophagitis was significantly associated with CD (OR: 4.96; 95% CI: 2.22–11.06). One year of a GFD in CD and GORD was more efficacious in preventing GORD symptom relapse than treatment with 8 weeks of PPI in non-CD GORD patients (OR: 0.18, 95% CI: 0.08–0.36). Paediatric CD patients were more likely to develop GORD (OR: 3.29, 95% CI: 1.46–7.43), compared to adult CD patients (OR: 2.55, 95% CI: 1.65–3.93).

Interpretation CD is strongly associated with GORD but there was high heterogeneity. More convincingly, a GFD substantially improves GORD symptoms, suggesting a role for duodenal inflammation and dietary antigens in the aetiology of a subset with GORD. Ruling out CD in patients with GORD may be beneficial.

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Keywords: Gastroesophageal reflux disease; Coeliac disease; Oesophagitis; Gluten; Gluten-free diet

Introduction

Gastroesophageal reflux disease (GORD) is highly prevalent and defined by the reflux of gastric contents into the oesophagus causing troublesome symptoms, quality of life impairment, and/or leading to mucosal damage.[1] GORD presents a significant disease burden and treatment is suboptimal in a major subset of patients.[2,3] The causes of GORD are uncertain, although pathophysiological mechanisms including lower gastro-esophageal sphincter incompetence have been traditionally linked to the disease.[4] In most cases, reflux events occur during increased transient lower oesophageal sphincter relaxations (TLOSRs) of an otherwise competent sphincter,[5,6] where dyssynchronous gastro-esophageal contractions lead to the escape of gastric contents into the lower oesophagus.[7,8] While the

*Corresponding author. Faculty of Health and Medicine, University of Newcastle, HMRI building, Lot 1, Kookaburra Circuit, New Lambton Heights, NSW, 2305, Australia.
E-mail address: nicholas.talley@newcastle.edu.au (N.J. Talley).

Research in context

Evidence before this study

A systematic search of databases (pubmed and embase) yielded no previous systematic reviews or meta-analyses on the association of Coeliac disease and gastro-esophageal reflux disease (GORD). Following prospero registration, the electronic databases Medline (Ovid), EMBASE (Ovid), Web of Science (Thomson Reuters), SCOPUS (Elsevier) and Cochrane Library (Wiley Online) were systematically searched from inception through March 7th 2024.

Added value of this study

The strong association between CD and GORD implicates duodenal inflammation in CD as one pathway leading to GORD through mechanisms such as eosinophilic neural induced damage in the duodenum. There may be a benefit in screening for CD in those with GORD.

Implications of all the available evidence

The aetiology of GORD is unknown, it is plausible that in a subset of GORD (not limited to coeliac disease), intestinal inflammation may be causal. Prospective data suggests that gluten free diet without proton pump inhibitors is sufficient in resolving symptoms of GORD in coeliac disease.

aetiology of increased TLOSRs remains unclear, duodenal perturbations leading to impaired modulation of gastro-oesophageal function is one plausible mechanism.[9]

The duodenal villous mucosa is the first site of detailed chyme antigen sampling. A primary role of the duodenum is controlling the transit of gastric contents from the proximal (acidification compartment) to the antropyloric (grinding gastric compartment) and through the pylorus, a process tightly regulated by duodenal assessment of chyme characteristics,[9,10] including nutritional composition,[11] caloric content,[12] pH[11] and osmolarity.[13] In patients with GORD, duodenal fat infusion provokes reflux during transient lower oesophageal relaxations to a higher extent than healthy controls,[14] and in animal models experimental duodenal irritation impairs the lower oesophageal pressure.[15] Functional dyspepsia, characterised by a constellation of postprandial symptoms including early satiety,[16] significantly overlaps with GORD in population studies suggesting a shared aetiopathogenesis,[17] and features similar patterns of gastric dysmotility such as impaired fundic accommodation,[7,18–20] which is physiologically controlled by duodenal sensing of nutrients.[9] Histological duodenal microinflammation featuring eosinophil and mast cell infiltration is strongly linked to functional dyspepsia,[21] and duodenal eosinophilia is independently associated with a 6-fold increase in GORD upon prospective follow up,[22] but the role of duodenal inflammation in the aetiopathogenesis of GORD remains little studied.

Coeliac disease (CD) is a gluten sensitive enteropathy that is characterised by villous atrophy and duodenal inflammation including eosinophils and mast cells.[23] There are robust data linking antigen driven mucosal inflammation to motility abnormalities in CD throughout the gastrointestinal tract, and to symptom generation.[24] CD has been associated with an increased risk of GORD which may improve on a gluten free diet.[25] However, this association is under-appreciated in clinical practice and there have been no prior systematic reviews. Therefore, we aimed to conduct a systematic review and meta-analysis to determine the relationship between CD and GORD.

Methods

Search strategy

A systematic search was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[26] The electronic databases Medline (Ovid), EMBASE (Ovid), Web of Science (Thomson Reuters), SCOPUS (Elsevier) and Cochrane Library (Wiley Online) were systematically searched from inception through March 7th 2024. No search for unpublished literature was performed. The search strategy included terms capturing surrogates of GORD (Supplementary Table S1). Following the literature search and duplicate removal, two reviewers (MZI, GLB) independently screened titles and abstracts of all articles, a third reviewer (MP) reviewed conflicting search outcomes, and any remaining conflicts were resolved by all three reviewers. The study was registered with Prospero (ID: CRD42021267818).

Study selection, quality assessment and definitions

All studies reporting the association of CD and GORD were included with no exclusions apart from non-English studies. Standardized data extraction was independently performed capturing diagnostic characteristics of GORD and CD. The Newcastle–Ottawa scale (NOS) was applied for quality assessment for both case–control and cross-sectional studies. Cases were defined as CD on a gluten containing diet (GCD) based on histology and/or serology (or both), or based on reflective clinical codes. Controls were defined as either healthy volunteers, non-CD patients presenting for endoscopic assessment for a variety of GI symptoms and/or iron deficiency, or those with CD on a gluten free diet (GFD). GORD was defined based on

symptoms, endoscopic oesophagitis, histological oesophagitis, or abnormal pH monitoring. Studies reporting oesophageal motility abnormalities associated with GORD were also included. Paediatric studies used an age cut-off of less than 18 years.

Statistical analysis

Pooled prevalence of GORD in CD was calculated for cross-sectional studies. Meta-analysis was performed on case–control studies, and a subgroup analysis according to various control and GORD definitions. Multiple comparisons were not allowed for the same study when different control groups were available, in order to avoid overinflating type 1 error.

Pooled analysis was reported as odds ratios (OR) and 95% confidence intervals (95% CI).[27] Heterogeneity was assessed using the I^2 statistic.[28] The alpha level of significance was set at $p < 0.05$. All analyses used Comprehensive Meta-Analysis (CMA), Version 4. Borenstein, 2022.[29]

Role of funding source

The study was supported by an Investigator Grant from the NHMRC to Dr. Talley. The funding source played no role in the study design or analysis. Contact the first author (MZI) for access to the dataset. The decision to submit made by NJT.

Results

Study characteristics

In total, 31 out of 3083 studies met the inclusion criteria (Fig. 1). 17 were case-control studies (12 included adults only and 5 included children only), with collectively 3467 cases and 8472 controls, and additionally, a large medical record based study[30] included 433 cases and 4330 controls (Table 1). The mean Newcastle–Ottawa Scale (NOS) quality score was 5.18 out of 9 (range 3–7, standard deviation (SD) = 1.72). Common exclusions included studies reporting various indications for endoscopies in centres, hence capturing CD and GORD terms without reporting the association between the two.

14 cross-sectional studies with 4438 cases were included (9 included adults only, 3 included children only and 1 included both) with a mean NOS of 5.38 (range 2–8, SD = 1.66) (Table 2). Two studies by Collin et al. included an overlapping population derived from a hospital database and therefore the earlier study was excluded.[47,48] Various criteria were used to define CD (Tables 1 and 2), this included; histology and symptoms (2 studies), duodenal histology and serology (16 studies), histology alone (7 studies), jejunal histology plus serology (1 study) and clinical codes (5 study). All but one (Barratt et al.[41]) of the case–control studies included in the meta-analysis and prevalence estimation, used consecutive newly diagnosed individuals with CD with various symptoms, who were being clinically assessed (Table 1).

Prevalence data

Prevalence of GORD in CD was 19.2% (95% CI: 18.3–20.1%; n = 7659, 23 studies). This consisted of 3753 CD cases from 10 cross sectional studies, with a GORD prevalence of 10.0% (95% CI: 8.0%–13.0%), and 3906 CD in 14 case–control studies with a prevalence 26.0% (95% CI: 21.0%–33.0%) (Fig. 2). The prevalence of GORD was higher among paediatric CD patients compared to adult CD patients (27.0%, 95% CI: 17.0%–40.0%) versus (19.0%, 95% CI: 14.0%–24.0%).

Prevalence of identifying CD by obtaining duodenal biopsies in patients presenting for endoscopic assessment of GORD was 0.92% (95% CI: 0.64–1.2%; n = 3799, 3 studies[48,55,57]). However, some of those individuals may have already been screened with CD serology, and the prevalence of CD in all-comers with GORD undergoing coeliac serology was not reported.

Association of CD and GORD

In the pooled analysis of 12 case–control studies (n = 105,051), CD was strongly associated with GORD compared to non-CD controls (OR: 3.37, 95% CI: 2.09–5.44; $I^2 = 92.58$, $p < 0.0001$). Subgroup analysis was performed based on the 3 different control group definitions (a) healthy volunteers (OR: 3.54, 95% CI: 2.17–5.77; $I^2 = 41.73$, $p = 0.16$), (b) non-CD patients presenting for endoscopic assessment for a variety of GI symptoms or iron deficiency (OR: 1.68, 95% CI: 0.84–3.37; $I^2 = 94.14$, $p < 0.0001$), and (c) those with CD on a GFD (OR: 10.20, 95% CI: 6.49–16.04; $I^2 = 0.00$, $p = 0.84$) (Fig. 3). Paediatric CD patients were more likely to develop GORD (OR = 3.29, 95% CI: 1.46–7.43), compared to adult CD patients (OR = 2.55, 95% CI: 1.65–3.93).

Analysis based GORD definition

GORD symptoms

The pooled OR of 7 studies (n = 7561) revealed that GORD symptoms are strongly associated with CD (OR: 3.19; 95% CI: 2.06–4.96; $I^2 = 75.83$, $p < 0.0001$). Six studies reported quantitative questionnaires (Table 1), and one relied on diagnostic codes (Fig. 4).[30]

Endoscopic oesophagitis

The pooled OR of 3 studies (n = 5598) showed that endoscopic oesophagitis is strongly associated with CD (OR = 4.96; 95% CI: 2.22–11.06; $I^2 = 79.34$, $p = 0.00080$). Only one study used LA grading, where oesophagitis cases were all either LA grade A or B.[37] Oderda et al.[31] used their own classification and reported the majority of cases as mild (101 children with oesophagitis and CD; erythema (n = 73), erosions (n = 16) and ulcerations (n = 5)). Prinzbach et al.[30] relied on a clinical code which could have included cases of eosinophilic and non-specific oesophagitis. Bagci et al.[39] reported the rate of coeliac antibodies in 68 reflux oesophagitis patients to be 8.8% for antigliadin IgA and 10.3% for antigliadin

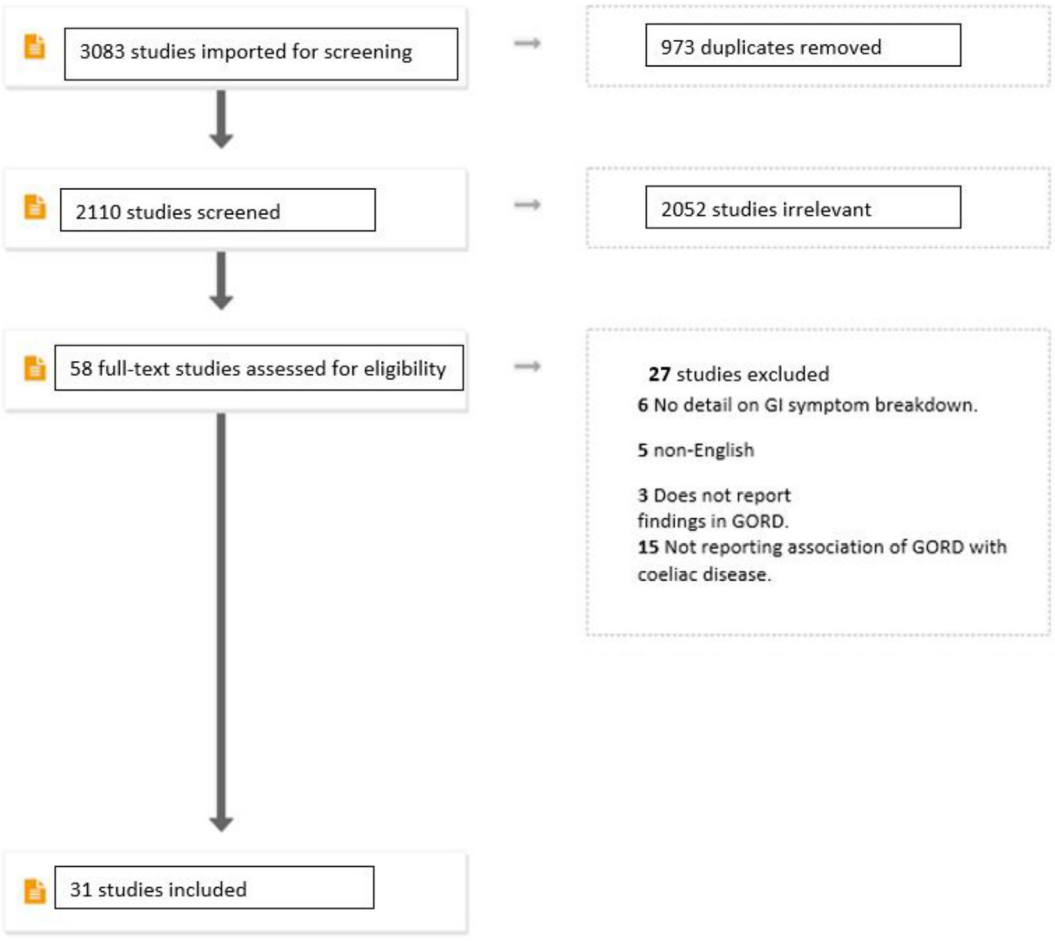

Fig. 1: Flow diagram of the search criteria.

IgG, however, the proportion with confirmed CD or tissue transglutaminase was not reported.

Histological oesophagitis

The pooled OR of 4 studies (n = 91,892) was 0.93 (95% CI: 0.71–1.22; I^2 = 43.81, p = 0.15, Fig. 4). None of the controls were healthy asymptomatic subjects (all had GI symptoms). The pooled prevalence of histological oesophagitis was 18% (10–32%) (6 studies, 2196 CD subjects). The biopsy location was variable, and parameters used were not standardized (Tables 1 and 2). Severity grading was only reported by one study,[31] where 27 out of 29 were classified as mild. The prevalence of high oesophageal intraepithelial lymphocytic count (>50/HPF) was found to be significantly greater in untreated CD compared to irritable bowel syndrome, and to CD on a GFD for 6 months (4/41 versus 0/45 and 0/13, respectively), however, the prevalence of histological oesophagitis was not reported,[46] and the mean oesophageal intraepithelial lymphocyte count between CD and controls was not different in this study[46] and in another smaller study of 10 subjects.[32]

24-H pH-monitoring

Pooled prevalence of abnormal 24-h pH-monitoring in untreated CD was 35% ((95% CI: 8–76%), n = 65, 4 studies),[35,37,45,52] none of which included controls.

Oesophageal motility abnormalities

The lower oesophageal sphincter pressure was more likely to be reduced in CD compared to healthy volunteers based on 2 studies (n = 36)[36,37]; (OR = 0.31; 95% CI: (0.12–0.86). Moreover, the pooled mean LES was lower in CD patients compared to controls (−3.3 mmHg (95% CI: −5.46 to −1.11), p = 0.0050; I^2 = 0.00, p = 0.87).[36,37] A 50% prevalence of either hyper and hypocontractile oesophageal motility abnormalities were reported in 30 CD patients.[35]

Author, year	Design, year, and country	Sample size, mean age and gender	Diagnosis of coeliac disease	Control definition	Diagnosis of GORD	Newcastle–Ottawa score	Predictors of GORD
Paediatric studies							
Oderda 1993[31]	Retrospective, Italy, 1983–1993. Consecutive.	**Size**: 230 CD, 113 on GCD and 51 GFD. 230 non-CD. **Age:** 8 (1–16) years. **Gender:** not reported.	Espagan criteria 1973 (abnormal duodenal histology with improvement on gluten restriction)	1. Various indications for gastroscopy. 2. CD after GFD.	Reflux oesophagitis on endoscopy and histology; 2 cm above the Z-line	7/9	no
Alsaigh 1996[32]	Prospective, USA 1996. Non-consecutive (not specified)	Cases **Size:** 5. **Age:** 4.9; 1.1–11.6 years Controls **Size: 5**, **Age**: 7.5 range, 2–14 years. **Gender:** not reported.	Serology and villous atrophy.	Various GI complaints	Oesophageal intraepithelial lymphocyte count	3/9	no
Sayej 2011[33]	Retrospective, USA, 2003–2007. Consecutive.	Cases: **Size:** 49 CD. **Age**: mean: 9.7 years, range 1–18 years. **Gender**: 26 females. Controls **Size:** 2169 **Age:** mean. 10.77 years, range 0.25–24 year. **Gender:** 1072 (49%) females.	Diagnostic code	Various symptoms and no CD: Abdominal pain, bloating, diarrhoea, weight loss, poor-weight gain, failure to thrive, positive serology for tissue transglutaminase (TTG) or anti-endomysial antibody, reflux symptoms, and failed treatment with acid suppression therapy	Histological oesophagitis. Upper, mid and lower oesophageal biopsies.	4/9	yes
Prinzbach 2018[30]	Retrospective, USA, 2012–2016. Unclear if consecutive.	**Size:** 433 cases, 4330 controls. **Age:** mean 9.53 ± 4.71 years. **Gender:** females 61% (per group breakdown not given)	Diagnostic codes: Anti-tissue transglutaminase **and** abnormal duodenal biopsy.	Age and gender matched non-CD based on diagnostic code.	Diagnostic code "Phenome wide association"	5/9	no
Smolander 2020[34]	Retrospective, Finland, 2007–14. Consecutive.	Cases and controls: **Size:** 316 CD and 378 controls. **Age** (mean) and gender (provided based on outcome): Oesophagitis. 8.9 years (5.8–12.3) 68% females. No oesophagitis: 7.5 years (4.4–11.7) 66% females.	Histology: villous atrophy and crypt hyperplasia in well-orientated duodenal biopsy samples	Anaemia, abdominal pain, GORD.	Histological oesophagitis: mid and lower oesophageal biopsies	4/9	yes
Adult studies							
Usai 1997[35]	Prospective, Italy 1997. Consecutive.	Cases**: Size:** 30. **Age:** 37 ± 16 years. **Gender:** 7 Males. Controls: **Size:** 30. **Age** and **gender** matched.	Histological intestinal assessment	HV	1. Symptom questionnaire. 2. pH monitoring. 3. Oesophageal manometry	7/9	No
Iovino 1998[36]	Prospective, Italy, 1998. Consecutive.	Cases: **Size:** 22. **Age:** mean: 31, range 17–63 years. **Gender:** 19 females. (Cases as baseline and self-controls as 1 year post GFD) Controls for symptom questionnaires: **Size**: 44. **Age** mean: 33.3 range 23–47 years.). **Gender:** 37 females. Control group for the manometric evaluation: **Size:** 11. **Age**: mean 35.6, range (22–46). **Gender:** 9 females.	Antibodies against gliadin and endomysium and jejunal biopsy (total or subtotal atrophy of intestinal villi, crypt hyperplasia, and lymphoplasmacellular infiltration) and measurement of fecal fat excretion	1. HV 2. CD after GFD	1. Symptom frequency questionnaire. 2. Oesophageal Manometry	6/9	yes
Cuomo 2003[37]	Retrospective, Italy, 1996–2001. Consecutive.	Cases: **Size:** 205. **Age:** mean: 32, range (18–66 years). **Gender:** 153 females. Controls: **Size**: 400. **Age** mean: 37, range (20–68). **Gender:** 244 females.	Serology (EMA) and histology (total or subtotal villus atrophy, crypt hyperplasia, and lymphoplasmacellular infiltration)	1. Dyspeptic non-coeliac patients. 2. Reflux oesophagitis.	1. Symptom frequency questionnaire 2. Endoscopic oesophagitis. 3. pH monitoring	6/9	no
Midhagen 2003[38]	Retrospective, Sweden, 1984–1988. Consecutive.	Cases: **Size:** 51 CD in remission on GFD. **Age:** mean 45–64 years. **Gender:** 30 females. Controls: **Size:** 182. **Age:** 45–64 years. **Gender:** 104 females.	CD on GFD for 8–12 years	Respondents to a mailed survey	Gastrointestinal Symptoms Rating Scale	4/9	no

(Table 1 continues on next page)

Author, year	Design, year, and country	Sample size, mean age and gender	Diagnosis of coeliac disease	Control definition	Diagnosis of GORD	Newcastle–Ottawa score	Predictors of GORD
(Continued from previous page)							
Bagci 2006[39]	Prospective, Turkey, 2003–2004. Non- consecutive.	Cases: **Size:** 68 reflux oesophagitis assessed with coeliac serology. **Age**: median: 41 (range: 20–77) years. **Gender**: 48 females. Controls: **Size**: 40. **Age**: median 38 range: (20–68) years. **Gender**: 28 females.	Prevalence of CD not mentioned. Outcomes based on serum antibodies (antigliadin and anti-endomysium) in patients with reflux oesophagitis, no data on confirmed CD diagnosis.	Controls with dyspepsia and no GORD	Endoscopic reflux oesophagitis	3/9	No
Usai 2008[40]	Unclear temporal direction, Italy, 2008. Consecutive.	Cases: **Size**: 105 **Age**: mean: 40.5, range 17–68 years. **Gender:** 95 females. Controls: **Size** 30. **Age**: mean 42, range 18–65. **Gender**: 27 females.	IgA anti-endomysial antibodies or IgA antigliadin antibodies, and small intestine biopsy	1. Non-erosive reflux disease. 2. CD after GFD.	Symptom questionnaire	7/9	no
Barratt 2011[41]	Prospective, UK, 2005–2008. Non-consecutive.	Cases: **Size**: 225 CD. **Age:** >18 years. Controls: **Size**: 458 Inflammatory bowel disease. 348 HV. **Age:** >18 years **Gender:** breakdown not reported.	Confirmed clinical records attending outpatient follow up.	Non healthcare seeking adults. Inflammatory bowel disease (228 ulcerative colitis, 230 Crohn's)	Symptoms severity scale.	7/9	yes
Nachman 2011[42]	Prospective, Argentina, 2004–2005. Consecutive.	Cases: CD: **Size** 133 cases. **Age:** mean 38.1 (range: 16–72) years. **Gender:** 114 females. Controls: healthy volunteers: **Size:** 70. **Age:** mean 39.5 range (19–71) years. **Gender:** 55 females.	Histological (duodenal biopsies), serological and clinical features.	1. Healthy volunteers. 2. CD after GFD.	Gastrointestinal Symptoms Rating Scale (GSRS)	7/9	no
Jensen 2015[43]	Retrospective, USA, 2009–2012. Consecutive.	Cases: CD: **Size:** 1203. **Age**: CD: mean49.6 ± 18.7 years. **Gender**: 732 females (61%) Controls: **Size:** 87,314. **Age**: 51.1 ± 18.2 years. **Gender** 53,999 (62%) females.	Duodenal histology: Villous atrophy (3a 3b, 3c with >40 intraepithelial lymphocytes/100 enterocytes.	Not meeting CD histological criteria. (Various indications for endoscopy which may have included GORD)	1-Symptoms from clinical records. 2-Histological oesophagitis, did not specify location of oesophageal biopsies.	3/9	no
Laurikka 2016[44]	Prospective, Finland, 2016. Consecutive.	Cases: CD: **Size:** 856 Short-term GFD: (1–2 yrs), **Size:** 93. **Age** mean 51 (16–80) years, **Gender:** 72% females. Long-term GFD (≥3): **Size:** 635. **Age** mean 55 (17–85) years, **Gender:** 75% females. Untreated: **Size:** 128. **Age:** mean 47 (15–72) years. **Gender:** 76% females. Controls: **Size:** 160 HV. **Age** mean 55 (23–87) years. **Gender:** 72% females.	Histology and IgA EmA.	1. HV 2. CD after GFD	Gastrointestinal Symptom Rating Scale (GSRS) questionnaire.	7/9	no
Pinto-Sanchez 2016[45]	Prospective, Canada, 2016. Consecutive.	Cases: CD: **Size:** 25. **Age** 28 (18–73) years. **Gender:** 68% females Controls: GORD: **Size** 19. **Age:** mean 44 (24–68) years. **Gender:** 45% females Plus 11 asymptomatic adults. **Age:** 36. **Gender:** 60% females.	Marsh III or greater + serology	GORD and HV.	1. Symptoms: Gastrointestinal Symptoms Rating Scale (GSRS). 2. 24-pH monitoring 3. Oesophageal manometry. 4. Electron microscopy: Dilated intercellular spaces of oesophageal epithelium.	3/9	no
Chauhan, 2021[46]	Prospective, India, 2021. Consecutive.	Cases: **Size:** 42. **Age:** mean = 27.98 ± 10.37 years. **Gender:** females 52.4%. Controls: **Size:** 45. **Age** mean 34.29 ± 10.09. **Gender:** 31.1% females.	Modified European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) criteria: Clinical symptoms, positive serology, villous atrophy and unequivocal response to GFD.	1. Irritable bowel syndrome (ROME IV). 2. CD after 6 months of GFD.	Oesophageal lymphocyte count	4/9	no

Abbreviations: CD, Coeliac disease; GCD, Gluten containing diet; GFD, Gluten free diet; GORD, Gastro-oesophageal reflux disease; HV, Healthy volunteers.

Table 1: **The characteristics and quality assessment of case–control studies.**

Author, year	Design, year and country	Sample size, age and gender	Diagnosis of CD	Diagnosis of GORD	Newcastle–Ottawa score	Predictors
Paediatric studies						
Kho 2015[49]	Cross-sectional, New Zealand, 2000–2011	**Size:** 263. **Age** mean 7.88 (0.8–16.9) years. **Gender:** not reported.	Marsh criteria, unspecified threshold	Oesophageal biopsies	6/9	no
Boschee 2017[50]	Retrospective case-series, Canada 2017	**Size:** 140. **Age** mean = 9.1 ± 4.3 years. **Gender:** 86 females	Marsh grade 2 and 3 on gluten containing diet.	Endoscopic and histologic oesophagitis.	4/9	no
Dehbozorgi 2020[51]	Cross-sectional, Iran, 2018–2019	**Size:** 130. **Age** mean = 9.9 (range: 2.5–18 years) **Gender:** not reported. 130	Marsh ≥2	Symptoms	6/9	yes
Adult studies						
Usai 1995[52]	Prospective case-series, Italy, 1994	**Size:** 36. **Age** mean = 39.71 ± 2.6 years. **Gender:** not reported.	Intestinal histology and clinical improvement with gluten free diet.	1. 24 pH monitoring 2. Oesophageal manometry	2/9	no
Collin 2004[48]	Retrospective, Finland 1990–2002.	**Size, age and gender** (mean, range): CD + Gluten containing diet: 382, 46, (15–81) females 72%. CD + Gluten free diet: 232, 47 (16–89), females 71% GORD: 2525, 56 (15–87), females 61% Dyspepsia: 5404, 56 (11–93), females 61%	Histology: Villous atrophy and crypt hyperplasia	1. Symptoms 2. Endoscopic oesophagitis	7/9	no
Carrocio 2008[53]	Case-series, Italy, 2008	**Size:** 69. **Age** mean = 42.5 (17–71) years. **Gender:** 57 females	Previous diagnosis of CD at the same institute with 12 months of GFD	Symptoms	3/9	no
Taavela, 2013[54]	Case-series, Finland, 2013	**Size:** 638. **Age** mean = 52 (16–81) years. **Gender:** 68% females.	Small-bowel mucosal villous atrophy and crypt hyperplasia.	Gastrointestinal Symptoms Rating Scale (GSRS)	6/9	yes
Ludvigsson 2013[55]	Prospective, cross-sectional, Sweden 2000	**Size**: 1000*, **Age** mean = 50.4, **Gender:** 51%. Females * 1000 non-healthcare seeking survey respondents. Case-control design with 400 with GORD symptoms and 600 with no GORD symptoms). 18 cases of CD.	Positive serology AND mucosal abnormalities of the small intestine (≥25 intraepithelial lymphocytes/100 enterocytes and/or villous atrophy).	Symptom questionnaire (Abdominal symptom questionnaire)	8/10	no
Volta 2014[56]	Cross-sectional, Italy, 1998–2012	**Size:** 770. **Age:** mean = 36 (18–78) year. **Gender:** not reported.	Duodenal biopsy (Marsh criteria, unspecified threshold) AND serology AND HLA typing when indicated.	Symptoms	5/9	no
Mooney 2015[57]	Prospective, cross-sectional, UK, 2004–2014	**Size:** 11 CD and 839 GORD derived from 3368 individuals with duodenal biopsies. **Age** mean = 53.4 years. **Gender:** 59% females	Serology and histopathology: - Endomysial antibody and IgA tissue transglutaminase antibody and total IgA level - Villous atrophy (Marsh 3a–3c).	Self-reported reflux symptoms Endoscopic oesophagitis	7/9	yes
Spijkerman, 2016[58]	Cross-sectional, Netherlands, 2003–2013	**Size:** 412. **Age** mean: 39.45 (21.4–57.6) years **Gender:** not reported.	Villous atrophy (Marsh ≥2) AND compatible HLA	Clinical code	6/9	no
Maimaris 2020[59]	Cross-sectional, Italy, 1999–2017	**Size:** 278. **Age** mean = 38 ± 13 years. **Gender:** not reported.	Marsh ≥3a **AND** IgA endomysial antibodies	Symptoms	5/9	no
Majeed 2021[60]	Cross-sectional, Iraq, 2017–2020	**Size:** 161. **Age** mean = 24.2 ± 14.8 years. **Gender:** not reported.	Anti-tissue transglutaminase **AND** histopathology	Symptoms	5/9	no
Stefanolo 2022[61]	Retrospective, cross-sectional, multiple countries. Included a control group which was not analysed due to unclear definition.	**Size:** 1328. **Age** mean = 35 (27–43) years. **Gender:** 80% females	Positive serology and confirmed by biopsy.	Reflux oesophagitis on endoscopy	7/9	Yes

Abbreviations: CD, Coeliac disease; GCD, Gluten containing diet; GFD, Gluten free diet; GORD, Gastro-oesophageal reflux disease; HV, Healthy volunteers.

***Table 2*: The characteristics and quality assessment of cross-sectional studies.**

Longitudinal effect of GFD on GORD in CD

The effect of a GFD on GORD in CD had been reported based on symptoms, changes in oesophageal manometry, and in oesophageal histology. Symptom data are available from 4 studies (n = 139) (Fig. 5).[36,37,40,42] Based on 3 studies,[36,37,40] GORD symptom relapse at 1 year was less likely in CD treated with a GFD compared to controls (OR 0.18; 95% CI: 0.08–0.36, $p < 0.0001$; $I^2 = 0.00$, $p = 0.64$), with a prevalence of symptoms after 1 year of intervention of 20.9% (18 out of 86) in CD, and 47.9%

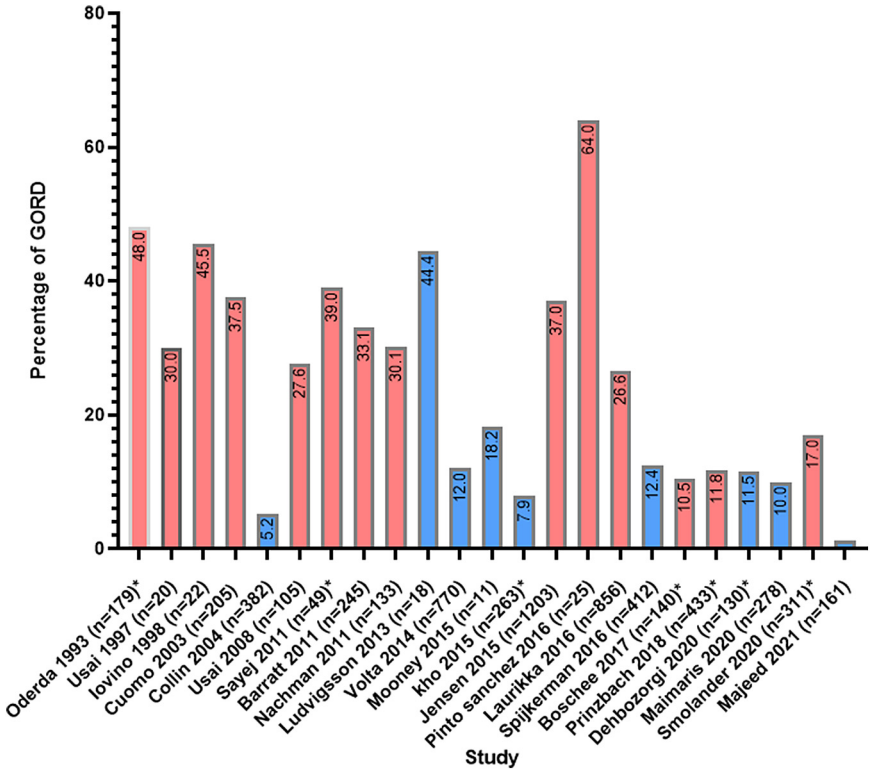

Fig. 2: The prevalence of Gastro-oesophageal reflux disease (GORD) in Coeliac disease based on cross-sectional (blue) and case–control (pink) studies. All case–control studies except Barratt et al. included consecutively recruited subjects with CD amongst whom the prevalence of GORD was reported. (n; number of subjects with both CD and GORD) (*) denotes paediatric studies.

(46 out 96) in controls. Two of those studies had a similar design,[37,40] where non-CD individuals with GORD treated with standard dose proton pump inhibitors for 8 weeks were assigned as controls (Fig. 5), the third study used community-based healthy volunteers with or without GORD symptoms.[36]

Considering oesophageal manometry, one year of a GFD significantly improved the mean LES pressure in 22 CD patients compared to controls (mean LES pressure rose from 17.5 to 19 mmHg, $p < 0.0001$).[36] Two studies reported on oesophageal histology; a statistically significant histological improvement occurred with gluten restriction alone in terms of oesophageal dilated interepithelial space diameter in 25 CD, from a level comparable to GORD to healthy control levels.[45] A 6-month follow-up of 17 CD patients undergoing gluten restriction showed no change in oesophageal intraepithelial lymphocyte counts but a reduction of oesophageal IgA anti-tTG2 deposits (from 46.2% of the cohort, to 23.1%, $p = 0.17$).[46]

Predictors of GORD in CD

Pooled data from 4 studies showed that within CD, males were slighlty more likely to have GORD symptoms (OR: 1.40, 95% CI: 0.45–4.37, $I^2 = 83.59$, $p < 0.0001$), which was not statistically significant ($p = 0.56$).[33,34,37,40] Our analysis of data from Stefanolo et al.[61] showed no significant difference of the prevalence of GORD in CD in those less than 50 years of age (6.1% of 1140) compared to those older (8.5% of 188, $p = 0.20$), and age appeared to have no influence on the prevalence of GORD in CD based on 3 studies,[33,34,57] but a pooled statistical analysis was not possible. Two studies[53,54] yielded conflicting results regarding duodenal histology predicting GORD symptoms, with a larger study of 549 CD cases reporting mucosal integrity, denoted by villous height/crypt depth ratio, negatively correlating with GORD symptoms ($r = -0.115$, $p = 0.0070$). One study assessed the role of serial levels of tissue transglutaminase and found concurrent improvement in GORD symptoms parallels reduction of serum tissue transglutaminase over 4 years of follow up (no statistical analysis reported).[42]

Other predictors of CD and GORD compared to CD without GORD include reduced quality of life,[41] steatorrhea[36] and histological gastritis.[34]

Publication bias

There was evidence of publication bias using Egger's regression analysis ($p = 0.00040$). The Fail-Safe method

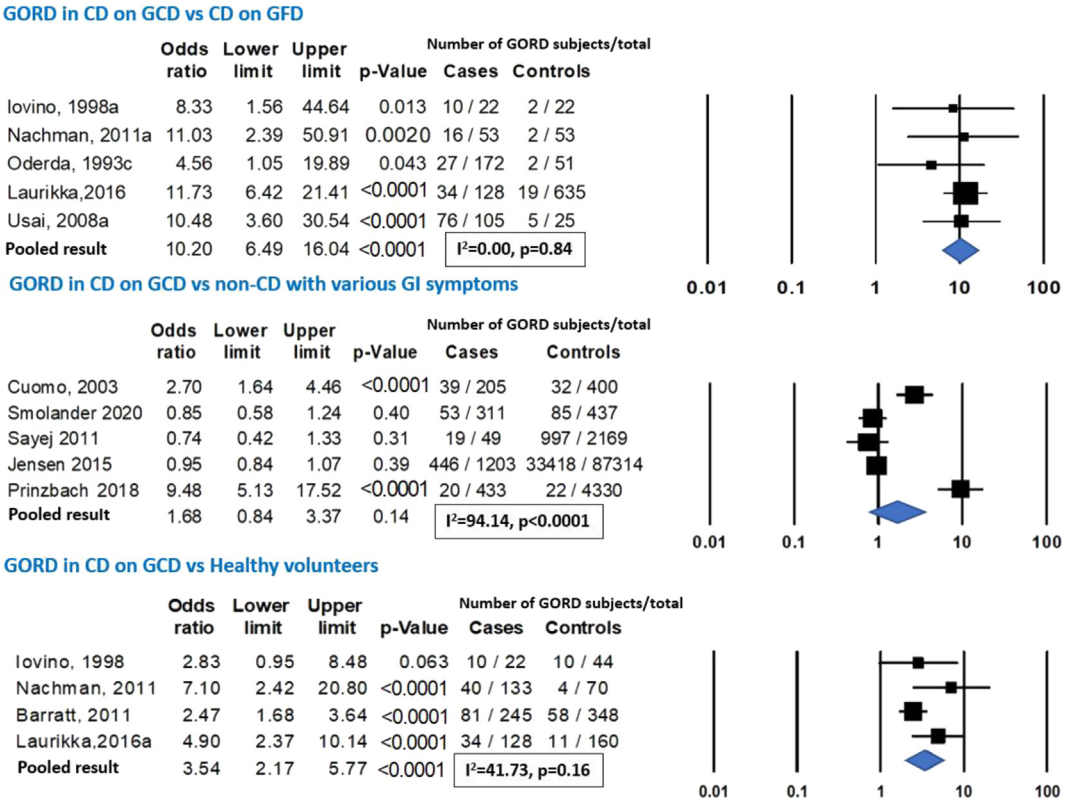

Fig. 3: **Analysis based on control type.** Meta-analysis results: Prevalence of gastro-oesophageal reflux disease (GORD) in individuals with Coeliac disease (CD) on a gluten containing diet (GCD) in comparison to different control groups. GFD, Coeliac disease on gluten free diet; HV, Healthy volunteers.

was used,[62] and indicated that 753 publications with no significant association between GORD and CD would be required to nullify the effect found.

Discussion

This systematic review and meta-analysis identified a relationship between GORD and CD. While the association between CD and GORD varied with applying different definitions, overall there was a three to four-fold increase, which was statistically significant, yet there was high heterogeneity. Subgroup analyses demonstrated an independent relationship between CD and GORD in reflux oesophagitis, GORD symptoms and manometric abnormalities. The most convincing evidence of an association between GORD and CD was GORD symptom relapse at 1 year was over five times less likely in CD treated with GFD compared to controls with no heterogeneity.

Several possible mechanisms may explain the link we have observed between CD and GORD pooling the available studies. Untreated CD is associated with malabsorption of dietary osmotically active compounds,[63] and fermentation products in the colon may exacerbate reflux by increasing TLOSRs and lowering the lower oesophageal pressure though neurohormonal disturbances.[64,65] Among patients with CD and GORD, the association of lower oesophageal dysfunction was strongest in individuals with malabsorption characterised by steatorrhea.[36] Duodenal mucosal damage may impair duodenal regulatory function on upper gastrointestinal motility; perturbations of the duodenum in animal models (e.g. acid infusion) can alter proximal gastric motor dysfunction and increase transient lower oesophageal sphincter relaxations in these models.[15] When induced in animal models, intestinal eosinophilic inflammation impairs gastric motility.[66] In functional dyspepsia, duodenal eosinophilia is associated with structural and functional alterations of duodenal nerves,[67] and is linked to impaired enteric hormonal levels.[68] Increased duodenal eosinophils is a histologic feature of CD but does not predict worse symptoms.[23] Similarly, CD features abnormal levels of enteric hormones such as secretin and cholecystokinin,[69] which are directly implicated in the duodenal feedback on the lower oesophagus.[70] Therefore, it is possible that in CD, duodenal dysfunction may be mediated by activated duodenal eosinophils altering pathways that promote increased TLOSRs.

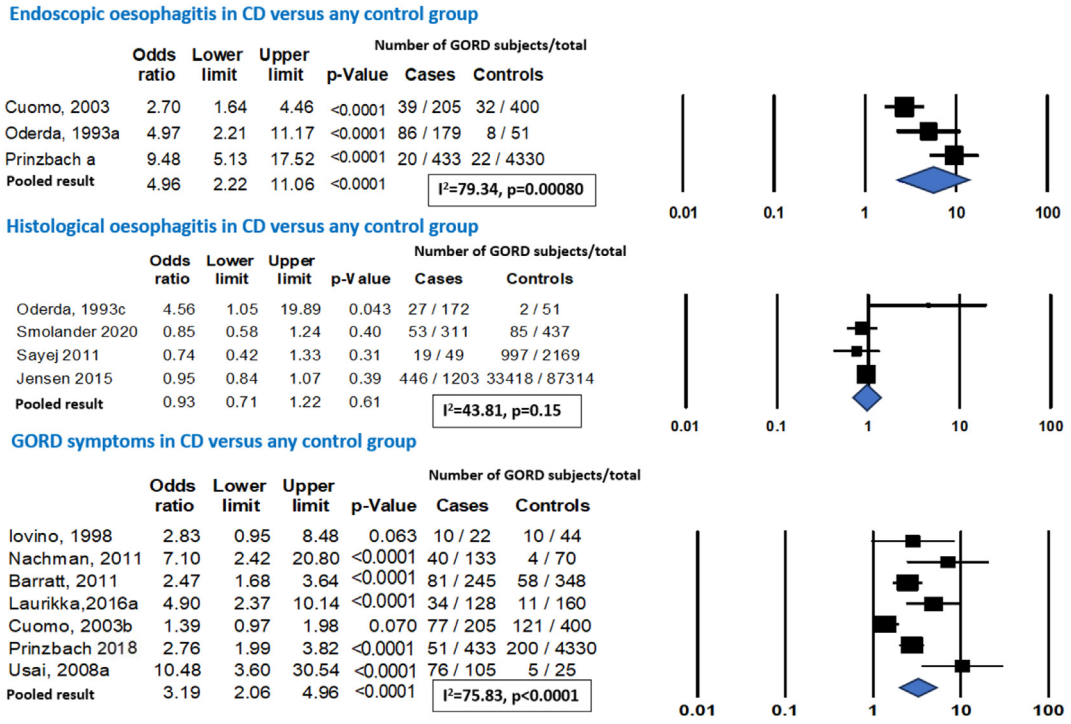

Fig. 4: **Analysis based on disease type.** Meta-analysis results: Prevalence of gastro-oesophageal reflux disease (GORD) in individuals with Coeliac disease (CD) on a gluten containing diet (GCD) in comparison to controls of any type, using 3 different definitions of GORD: Endoscopic oesophagitis, histological oesophagitis and GORD symptoms.

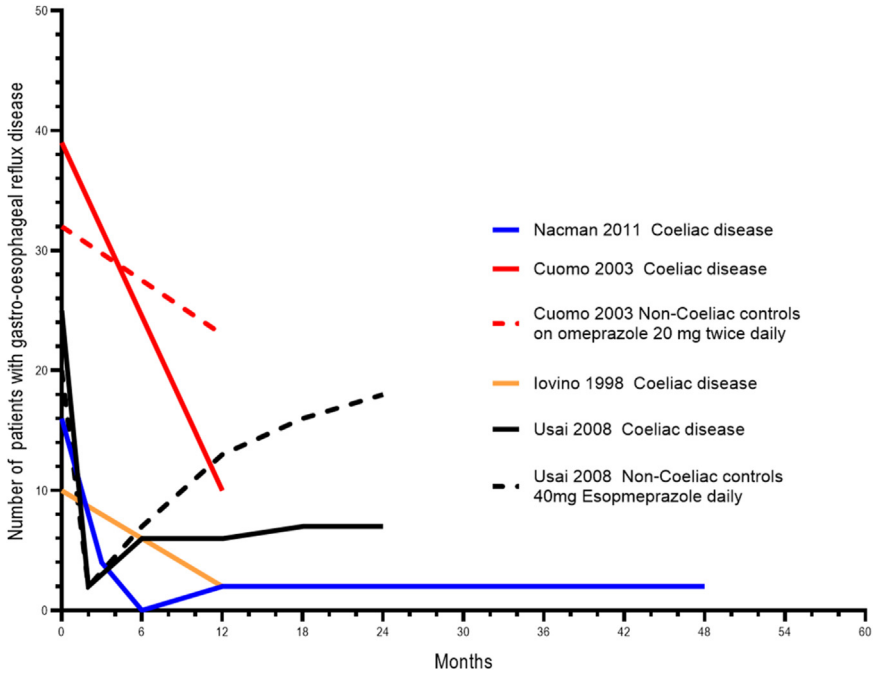

Fig. 5: The proportion of individuals with GORD symptoms after commencing gluten free diet in coeliac disease. Two studies had comparative control arms (denoted by interrupted lines) of non-coeliac patients with GORD, treated with proton pump inhibitors commenced at time zero. The follow-up period for Iovino et al. was 12 months.

We found individuals with untreated CD to be almost five times more likely to have reflux oesophagitis albeit with high heterogeneity. A direct immune mediated effect of gluten on the oesophageal mucosa is a plausible underlying mechanism, supported by subepithelial transglutaminase antibody deposition alongside oesophageal epithelial damage found in CD.[45,46] Oesophageal epithelial dilated intercellular spaces (spongiosis) in CD resolves with a GFD based upon serial assessments.[45] Similar findings were reported in the oral squamous mucosa of CD,[71] suggesting that the epithelial damage could occur independent of reflux of gastric juice exposure, but may rather predispose to reflux induced damage. The subsequent inflammatory cascade and deep cytokine release may impair peristalsis, such as through altering thresholds to initiate contractions to clear the refluxate,[72,73] akin to other disorders of oesophageal inflammation such as eosinophilic oesophagitis, another immune oesophageal disorder linked to dietary antigens including wheat.[74]

The predictors of GORD in CD remain poorly defined. In one study, GORD symptoms were weakly but significantly correlated with histological duodenal severity (correlation factor (r) = –0.115, p = 0.0070),[54] while another study found the opposite association.[53] A large study not confined to GORD in 500 CD patients showed a poor correlation of histological damage to various gastrointestinal symptoms reported.[75] Hence the data suggest that additional factors to histological damage alone are likely implicated. It has been reported that small intestinal microbiome alterations and mast cell expansion influence symptom generation in CD more so than histological damage,[75–78] but their specific role in provoking GORD in CD has not been reported in any of the reviewed studies.

It is not considered part of the routine assessment to assess for CD in patients with GORD.[79] Three large studies reviewed here examined the value of obtaining duodenal biopsies to rule out CD in those presenting with GORD symptoms and concluded this rarely alters management,[48,55,57] however, the prevalence of coeliac serology in all comers with GORD is unclear from these studies. The strong association between CD and GORD suggests the need for screening for CD in those with GORD. On the other hand, we have shown a GFD is of benefit for GORD associated with CD, and in these cases, may improve management.

The strengths of this meta-analysis include the application of different definitions of GORD based on various diagnostic procedures, and the inclusion of different control groups. It is possible that cases selected for case–control studies might have an enriched population with reflux disease although we suspect this is less likely as clinicians would not be aware of the strong relationship between CD and reflux disease. Publication bias is an important factor in any meta-analysis, Egger's regression analysis showed that publication bias was present. We used the fail-safe method to estimate the number of potential missing studies needed to significantly change the conclusion of our findings. This analysis showed that, to nullify our estimated effect size, more than 700 studies with non-significant findings would be needed. Based on the fact that there have been no more than 35 studies published over the past 25 years, it is highly improbable that such a large number of similar studies would have gone unpublished or have been missed by our extensive search strategy. Furthermore, the missing studies are likely to be small, the effect of which is probably very negligible. In addition, a Duval and Tweedie's trim and fill analysis showed no significant difference in the observed and adjusted point estimates. New techniques for assessing publication bias have been developed[80] but they have not been adequately validated at this time.[81] Another potential weakness is the high heterogeneity found in the analyses of the association of CD with GORD, although this can be expected to some extent given the variable control groups and various disease definitions applied. Moreover, the heterogeneity was not significant when CD on a GCD was compared to CD on a GFD, where the association was strongest. The association found is also limited to cases of CD that are formally diagnosed, while a proportion of individuals remain undiagnosed in the community. Additionally, potential bias relating to different biopsy protocols influenced by the clinician assessment of symptoms, although the majority of studies reported on consecutive patients diagnosed with coeliac and were therefore inclusive. In addition, the possibility that small trials reporting an effect had a poor-quality score, this may be true in some instances, but we feel that this sample of studies represents the true evidence on this topic and reflect what happens in clinical practice.

In conclusion, there is evidence supporting a strong association between GORD and CD. This may implicate duodenal inflammation in CD as one pathway leading to GORD through mechanisms such as eosinophilic neural induced damage in the duodenum altering entero-gastric reflex responses, impairing fundic accommodation and promoting reflux events.[9,23,36,67] Another possible pathway may be the presence of a common mucosal immunogenic response to gluten affecting both the duodenum and oesophagus.[45] As CD and GORD are linked, the benefits of a GFD should be assessed in CD and coexistent GORD, and the need for PPI therapy should regularly be reviewed after a GFD is commenced.

Contributors

Conceptualization: MZI, NJT. Data curation: MZI, MDP, NJT, GE. Formal analysis: MZI, GE. Methodology: MZI, GE. Software: MZI, GE. Supervision: GE, NJT, MMW. Writing: MZI, NJT, GE. Editing: MZI, NJT, MMW, GLB, SK, MH.

Data sharing statement

A spreadsheet containing data on all included studies in the meta-analysis, and the results of the meta-analysis are available upon request from the corresponding author via email.

Declaration of interests
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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102577.

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