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Association Between Inflammatory Bowel Diseases and Celiac Disease: A Systematic Review and Meta-Analysis

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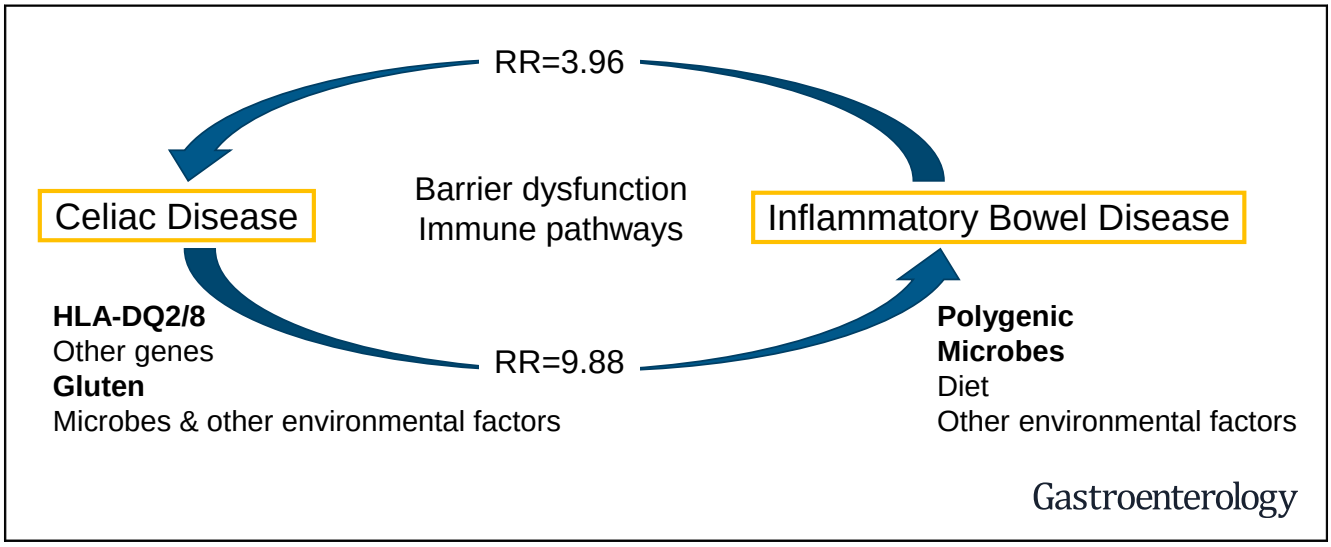

BACKGROUND & AIMS: There is controversy over the association between celiac disease (CeD) and inflammatory bowel diseases (IBD). We performed a systematic review and meta-analysis to assess evidence for an association between CeD and IBD. **METHODS:** We searched databases including MEDLINE, EMBASE, CENTRAL, Web of Science, CINAHL, DARE, and SIGLE through June 25, 2019 for studies assessing the risk of CeD in patients with IBD, and IBD in patients with CeD, compared with controls of any type. We used the Newcastle-Ottawa Scale to evaluate the risk of bias and GRADE to assess the certainty of the evidence. **RESULTS:** We identified 9791 studies and included 65 studies in our analysis. Moderate certainty evidence found an increased risk of CeD in patients with IBD vs controls (risk ratio [RR] 3.96; 95% confidence interval [CI] 2.23–7.02) and increased risk of IBD in patients with CeD vs controls (RR 9.88; 95% CI 4.03–24.21). There was low-certainty evidence for the risk of anti-*Saccharomyces* antibodies, a serologic marker of IBD, in patients with CeD vs controls (RR 6.22; 95% CI 2.44–15.84). There was low-certainty evidence for no difference in risk of HLA-DQ2 or DQ8 in patients with IBD vs controls (RR 1.04; 95% CI 0.42–2.56), and very low-certainty evidence for an increased risk of anti-tissue transglutaminase in patients with IBD vs controls (RR 1.52; 95% CI 0.52–4.40). Patients with IBD had a slight decrease in risk of anti-endomysial antibodies vs controls (RR 0.70; 95% CI 0.18–2.74), but these results are uncertain. **CONCLUSIONS:** In a systematic review and meta-analysis, we found an increased risk of IBD in patients with CeD and increased risk of CeD in patients with IBD, compared with other patient populations. High-quality prospective cohort studies are needed to assess the risk of CeD-specific and IBD-specific biomarkers in patients with IBD and CeD.

Keywords: Gluten; Crohn's Disease; Ulcerative Colitis; Autoimmune and Immune-Mediated Comorbidities.

Celiac disease (CeD) is an immune-mediated condition affecting the proximal small intestine in 1% of

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Abbreviations used in this paper: **AGA, anti-gliadin antibodies; ASCA, anti-*Saccharomyces cerevisiae* antibody; CeD, celiac disease; CI, confidence interval; DGP, deamidated gliadin peptide; EMA, anti-endomysial antibodies; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IBD, inflammatory bowel disease; IC, indeterminate colitis; ICD codes, International Statistical Classification of Diseases and Related Health Problems codes; Ig, immunoglobulin; IL, interleukin; pANCA, perinuclear antineutrophil cytoplasmic antibodies; RR, risk ratio; tTG, tissue transglutaminase; UC, ulcerative colitis.**

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the global population.[1] Its prevalence has increased 4-fold in the past 50 years as suggested by studies from the United States and Europe.[2] The disease requires genetic susceptibility given by either the HLA-DQ2 or HLA-DQ8 genotype and is triggered by dietary gluten and related prolamins.[3] CeD primarily affects the small intestine, where gluten causes an immune response that progressively leads to villous atrophy.[4] It is typically diagnosed through a combination of serological testing and histological evidence of villous atrophy.[4] Common serological markers include immunoglobulin (Ig)A anti-tissue transglutaminase (tTG) antibodies, IgA anti-endomysial antibodies (EMA), anti-gliadin antibodies (AGAs), and anti-deamidated gliadin peptide antibodies (DGP).[4] Patients with CeD are more likely to suffer from autoimmune diseases than the general population, with confirmed associations to type 1 diabetes, thyroid conditions, and autoimmune hepatitis.[5] The association with chronic inflammatory conditions such as inflammatory bowel disease (IBD) is more controversial. Understanding this relationship is important, as it may affect clinical management and screening strategies in CeD.

The prevalence of IBD has recently increased in North America, with up to 0.55% of the population being affected.[6] The prevailing hypothesis is that IBD is caused by a dysregulated immune response to unknown environmental factors in genetically predisposed individuals.[6] IBD is diagnosed through a combination of serological, endoscopic, and histological evidence of inflammation, and by serological markers including anti-*Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), which may be present in a subset of patients with IBD.[7] IBD has also been associated with several immune-mediated comorbidities, including primary sclerosing cholangitis, autoimmune hepatitis, and CeD.[8]

Common genetic, immunological, and environmental factors play a role in IBD and CeD. Genome-wide association studies have shown that CeD and Crohn's disease share genetic risk loci, including PTPN2, IL18RAP, TAGAP, and PUS10.[9] In both diseases, increased intestinal permeability,[10] impaired T regulatory cell function,[11,12] and proinflammatory cytokines, such as interleukin (IL)-15,[13,14] IL-17, IL-21, and interferon-gamma[15] have been involved. Finally, a role for microbial factors has been reported in both diseases.[16,17]

An association between villous atrophy and ulcerative colitis (UC), 1 of the 2 forms of IBD, was demonstrated by Salem and colleagues[18] as early as 1964 and a recent review by Shah et al[19] investigated the association between CeD and IBD in adults up to March 2016. This review found that patients with CeD are at higher risk of IBD and that patients with IBD, to a lesser degree, have an increased risk of CeD. As several studies have since been published,[20–28] we performed a systematic review and meta-analysis to update and evaluate the bidirectional association between CeD and IBD.

Methods

We included 2 types of studies: (1) prognosis studies, which evaluate the risk of future events in populations with a given characteristic or disease compared with controls; and (2) prevalence studies, which assess the proportion of the population with a given characteristic or disease.[29] We included studies that assessed the prevalence and/or risk of CeD (or related serological markers) in IBD and/or IBD (or related serological markers) in CeD. Studies included adult and/or pediatric populations. Risk factors included the number of people with CeD or IBD. Outcomes included (1) IBD or CeD; (2) CeD serology (tTG/EMA/DGP/AGA) in IBD; (3) false positive rate of CeD serology (tTG/EMA/DGP/AGA) in IBD; (4) IBD serology (ASCA/pANCA) in CeD; (5) false positive rate of IBD serology (ASCA/pANCA) in CeD; and (6) HLA-DQ2/8 genotype in IBD. Controls of any type were included. Diagnosis of CeD was based on duodenal biopsy showing enteropathy and/or CeD-specific serology (tTG/EMA/DGP). Genetic risk of CeD was determined by a positive HLA-DQ2/8 genotype. IBD diagnoses were based on clinical parameters (disease activity scores), imaging techniques, colonoscopy, inflammatory markers (C-reactive protein and/or fecal calprotectin), and histology. Diagnoses were confirmed by the investigator or through secured medical records, including verified International Statistical Classification of Diseases and Related Health Problems (ICD) codes. Specific diagnostic criteria for each study are provided in Appendix 1. The protocol for this review was not registered.

Types of Studies

We included any study that identified as cohort, case-control, cross-sectional, or randomized controlled trial. We considered any study that assessed the risk of developing CeD in IBD or IBD in CeD, compared with controls, to be a prognostic study. We excluded case reports. We considered studies regardless of language and publication status. We included abstracts if the authors provided additional information.

We searched EMBASE (OvidSP), MEDLINE (OvidSP), CINAHL, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), OpenSIGLE, and the Database of Abstracts of Reviews of Effectiveness (DARE) from inception up to June 25, 2019. The references of the included studies were screened for other eligible studies. The search strategy is outlined in Appendix 2.

Selection of Studies

Once a list of publications was produced, duplicates were removed. Subsequently, 2 reviewers (MIPS and CLS) independently screened the titles and abstracts and selected potentially relevant studies. Next, the full texts for the studies and their translations were obtained, when needed. Both reviewers independently performed the full-text screening and selected the eligible studies. In all cases of disagreement, the 2 reviewers were able to decide which study was eligible or not. The 2 reviewers independently extracted the data and collected information regarding study design, population, and outcomes.

The database included information on authors, setting (primary/secondary/tertiary care), funding source (industry-sponsored/grant-sponsored/investigator-funded), country of publication, age category (children/adults), number of males/females per group, IBD diagnosis criteria (biopsy-proven, endoscopy, etc.), CeD diagnosis criteria (serology and/or biopsy), total number patients with CeD, total number patients with IBD (Crohn's/UC/indeterminate colitis [IC]), total number

of concurrent IBD and patients with CeD, tTG/EMA/AGA/DGP positivity in IBD, HLA-DQ2/8 positivity in IBD, and ASCA/pANCA positivity in CeD. We also recorded the number of patients with concurrent IBD and CeD who were first diagnosed with CeD, first diagnosed with IBD, or diagnosed with both concurrently, the number taking different types of medications, who were hospitalized, had surgery, or had concurrent osteoporosis and/or osteopenia.

Patient demographics and outcomes were recorded using the mean and standard deviation for continuous data or proportions (n/N or %) when applicable. Information to identify possible risk of bias, or systematic error, in the individual studies was also collected in this form using modified Newcastle-Ottawa Scales[30] for prognosis and prevalence studies (Appendices 3 and 4). We modified these quality assessment scales to account for all relevant sources of bias in prognostic and prevalence studies. If any information was missing at the end of the data extraction, authors were contacted to recover the necessary data. The overall certainty of the evidence was assessed according to study design, inconsistency, indirectness, imprecision, publication bias, large effects, dose response, and opposing confounding using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation).[31] When assessing prognosis, evidence from observational studies starts as high certainty and is rated down based on the GRADE domains.[29]

Measures of Treatment Effect

The total number of participants who did and did not develop CeD in IBD or IBD in CeD was collected and reported as number over the total sample population (n/N) and compared with the number of controls who developed IBD or CeD, respectively (n/N).

Observational studies with controls were summarized using the ratio of the risk of an event in the 2 groups, or risk ratio (RR), and 95% confidence interval (CI) and pooled in meta-analysis using Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). Prevalence data were pooled with the *metaprop* function in R version 3.5.0 using the Freeman-Tukey double arcsine transformation. All data were pooled using a random effects model. Heterogeneity, the variability between studies in a systematic review, was assessed through both the I^2 statistic and χ^2 test. Significant heterogeneity was considered when I^2 was greater than 25% or when the χ^2 test had $P < .10$. To address possible sources of heterogeneity, we performed the following prespecified subgroup analyses: (1) IBD subtype (Crohn's/UC/IC); (2) children vs adults; and (3) study location (North America vs other countries). A large effect was considered when RR >2.00. If subgroup analyses did not resolve heterogeneity, the following prespecified sensitivity analyses were performed to determine other sources of heterogeneity: (1) risk of bias (high vs low); and (2) publication type (full-text vs abstract). The following sensitivity analyses were conducted post hoc: (1) type of controls (healthy vs diseased); (2) data source (population-based vs hospital-based); and (3) diagnosis method (ICD codes vs other diagnosis method).

To analyze the risk of publication bias, funnel plots were created for outcomes with more than 10 studies.[32] A world map showing the RR in different countries was also generated using the *rworldmap* package in R version 3.5.0.

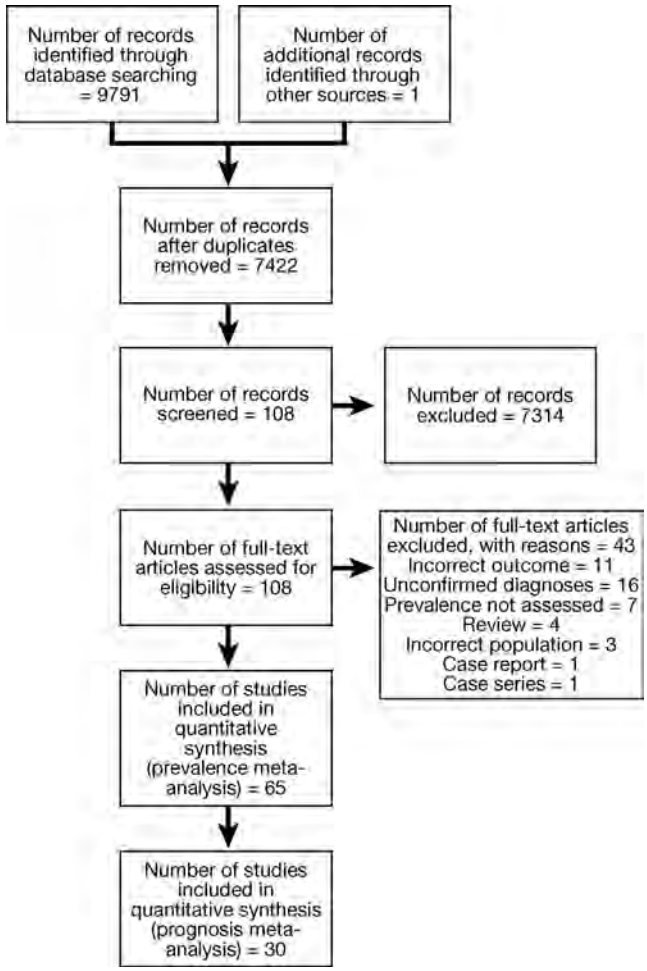


Figure 1. Flowchart of study selection (PRISMA).

Results

We identified 9791 studies through the database search and 1 additional study from the review by Shah et al.[19] A total of 7422 citations remained after removing duplicates. From these, 7314 were excluded at the title and abstract screening stage and 108 were eligible for full-text screening (Figure 1). After full-text review, 43 articles were excluded (Appendix 5) and therefore 65 studies were included for meta-analysis.

Characteristics of Included Studies

Sixty-five studies were eligible for quantitative analysis (see Appendix 6 for references of the included studies). From them, 30 studies included control groups and were pooled by RR with 13,679,013 participants: 43,026 patients with CeD, 165,637 patients with IBD (38,606 Crohn's disease, 55,515 patients with UC, and 3276 patients with IC), and 13,470,350 controls. The studies were published between 1978 and 2019. Forty-three studies were conducted in adults, 12 studies in children, and 9 studies in all ages. There were 39 studies in Europe, 12 in North America, 11 in Asia, 3 in South America, and 1 in Africa; 58 articles were published in English, 2 in Hungarian, 1 in Italian, 1 in Persian, 1 in Polish, 1 in Spanish, and 1 in Turkish. The risk of

bias for the individual studies is shown in Table 1 and Appendix 7. The included studies are summarized in Table 2 and Appendices 8 and 9. The summary of findings is shown in Table 3. World maps showing the RR of CeD in IBD and vice versa are shown in Appendices 10 and 11.

Risk of CeD in IBD vs Controls

We pooled 15 studies (n = 254,093) and found an increased risk of CeD in IBD (RR 2.90; 95% CI 1.88–4.48; I^2 = 72%, P < .00001) (Appendix 12). Overall, the pooled prevalence of CeD in IBD was 0.75% (95% CI 0.51%–1.04%, n = 36 studies, n = 116,096 participants), whereas the pooled prevalence of CeD in controls was 0.3% (95% CI 0.11%–0.55%, n = 15 studies, n = 147,661 participants). We found differences between population-based, hospital-based, and mixed studies and by diagnosis method (Appendices 13 and 14), with high risk of bias in the hospital-based studies. Sensitivity analyses by risk of bias found that low risk of bias studies had a greater risk of CeD in IBD (RR 3.96; 95% CI 2.23–7.02; n = 189,344 participants; n = 5 studies; I^2 = 81%; P < .00001) but not high risk of bias studies (RR 1.30; 95% CI 0.50–3.42; n = 64,749 participants; I^2 = 67%; P = .59) (Figure 2*A*; Appendix 15).

The certainty of the evidence on the risk of CeD in IBD (RR 3.96) was moderate. Only low risk of bias studies were included; therefore, the quality of the evidence was not downgraded for risk of bias. The quality of evidence was downgraded for heterogeneity due to variation in the point estimates. Despite the asymmetric funnel plot, publication bias was not suspected because the potentially missing studies would increase the risk (Appendix 16).

Risk of CeD in Crohn's Disease vs Controls

We pooled 10 studies (n = 96,455) and found an increased risk of CeD in Crohn's disease vs controls (RR 3.15; 95% CI 1.77–5.62; I^2 = 74%; P = .0001) (Appendix 17). Overall, the pooled prevalence of CeD in Crohn's disease was 0.64% (95% CI 0.34%–1.00%, n = 26 studies, n = 40,853 participants). We found differences by data source and diagnostic method (Appendices 18 and 19). Low risk of bias studies had a greater risk of CeD in Crohn's disease (RR 4.43; 95% CI 2.15–9.14; n = 60,443 participants; n = 4 studies; I^2 = 78%; P < .0001) but this was not seen in high risk of bias studies (RR 0.58; 95% CI 0.07–4.62; n = 36,012 participants; I^2 = 76%; P = 0.60) (Figure 2*B*; Appendix 20).

The certainty of the evidence on the risk of CeD in Crohn's disease was moderate. Only low risk of bias studies were included; therefore, the quality of evidence was not downgraded for risk of bias. However, the quality of evidence was downgraded for heterogeneity. Despite the asymmetric funnel plot, publication bias was not suspected because the potentially missing studies would increase the risk (Appendix 21).

Risk of CeD in UC vs Controls

Pooled analyses of 10 studies (n = 148,890) found an increased risk of CeD in UC (RR 2.81; 95% CI 1.82–4.36; I^2 = 63%; P < .00001) (Figure 2*C*). Overall, the pooled prevalence of CeD in UC was 0.71% (95% CI 0.39%–1.09%, n = 24 studies, n = 58,212 participants). There were differences in risk when subgrouped by region: North American studies showed a greater risk of CeD in UC vs controls (RR 3.92; 95% CI 2.57–5.96; n = 126,750 participants; I^2 = 48%; P < .00001) with a lower effect in non-North American studies (RR 1.96; 95% CI 1.38–2.79; n = 22,140 participants; I^2 = 0%; P = .0002) (Appendix 22).

The certainty of the evidence on the risk of CeD in UC was moderate. There was no difference between high and low risk of bias studies (Appendix 23); therefore, the evidence was not downgraded for risk of bias. However, the certainty was downgraded due to heterogeneity between regions. Despite the asymmetric funnel plot, publication bias was not suspected because the potentially missing studies would increase the risk (Appendix 24).

Risk of CeD in IC vs Controls

We pooled 2 studies (n = 9251) and found an increased risk of CeD in IC vs controls (RR 6.51; 95% CI 2.33–18.21; I^2 = 0%; P = .0004) (Appendix 25). The certainty of the evidence was low. Both studies were at low risk of bias, but we detected very serious imprecision (n = 24 events).

Risk of IBD in CeD vs Controls

Data from 12 studies (n = 1,854,479) found a higher risk of IBD in CeD vs controls (RR 5.32; 95% CI 3.79–7.46; I^2 = 78%; P < .00001) (Appendix 26). Overall, the pooled prevalence of IBD in CeD was 1.59% (95% CI 0.90%–2.45%, n = 30 studies, n = 37,753 participants), whereas the pooled prevalence of IBD in controls was 0.34% (95% CI 0.08%–0.72%, n = 12 studies, n = 1,821,555 participants). Sensitivity analysis removing the only study with diseased controls showed similar results on the risk of IBD in CeD (RR 5.68; 95% CI 4.16–7.77; n = 1,853,809 participants; I^2 = 74%; P < .00001; Appendix 27). We found differences between population-based, hospital-based, and mixed studies (Appendix 28); however, this was likely due to high risk of bias in the hospital-based studies. We also found differences between studies that used ICD codes vs other diagnosis methods (Appendix 29). Low risk of bias studies showed a greater risk of IBD in CeD (RR 9.88; 95% CI 4.03–24.21; n = 148,646 participants; n = 5 studies; I^2 = 87%; P < .00001), whereas the effect was smaller for high risk of bias studies (RR 3.55; 95% CI 2.28–5.53; n = 1,705,833 participants; I^2 = 67%; P < .00001) (Figure 3*A*; Appendix 30). Therefore, we included the results from the low risk of bias studies.

The overall certainty of the evidence on the risk of IBD in CeD (RR 9.88) was moderate. The evidence was not downgraded for risk of bias because only high-quality studies were included. However, the evidence was downgraded for heterogeneity because there was variation in the point estimates of the included studies. The funnel plot was symmetric and did not indicate publication bias (Appendix 31).

Table 1. Quality Assessment of Studies Using a Modified Newcastle-Ottawa Scale for Prognostic Studies

	Selection	Comparability	Outcome	Total
Study ID	Max. 3	Max. 3	Max. 2	Max. 8
Aletaha 2019	⊕⊕⊕	⊕⊕⊕	⊕⊕	⊕⊕⊕ ⊕⊕⊕ ⊕⊕
Alper 2018	⊕⊕⊕	⊖⊖⊖	⊕⊕	⊕⊕⊕ ⊖⊖⊖ ⊕⊕
Assa 2017	⊕⊕⊕	⊕⊖⊖	⊕⊕	⊕⊕⊕ ⊕⊖⊖ ⊕⊕
Bibbò 2017	⊖⊕⊕	⊕⊕⊕	⊕⊕	⊖⊕⊕ ⊕⊕⊕ ⊕⊕
Bizzaro 2003	⊖⊕⊕	⊕⊖⊖	⊕⊕	⊖⊕⊕ ⊕⊖⊖ ⊕⊕
Bosca-Watts 2018	⊕⊕⊕	⊕⊖⊖	⊕⊕	⊕⊕⊕ ⊕⊖⊖ ⊕⊕
Canova 2017	⊕⊕⊕	⊕⊕⊕	⊕⊕	⊕⊕⊕ ⊕⊕⊕ ⊕⊕
Casellas 2016	⊕⊕⊕	⊕⊖⊖	⊕⊕	⊕⊕⊕ ⊕⊖⊖ ⊕⊕
Collin 1994	⊕⊕⊕	⊕⊕⊖	⊕⊕	⊕⊕⊕ ⊕⊕⊖ ⊕⊕
Damoiseaux 2002	⊕⊕⊕	⊕⊖⊖	⊕⊕	⊕⊕⊕ ⊕⊖⊖ ⊕⊕
Delcò 1999	⊕⊕⊕	⊖⊖⊖	⊕⊕	⊕⊕⊕ ⊖⊖⊖ ⊕⊕
El-Matary 2012	⊕⊕⊕	⊕⊕⊖	⊕⊕	⊕⊕⊕ ⊕⊕⊖ ⊕⊕
Grode 2018	⊕⊕⊕	⊕⊕⊕	⊕⊕	⊕⊕⊕ ⊕⊕⊕ ⊕⊕
Halling 2017	⊕⊕⊕	⊕⊕⊕	⊕⊕	⊕⊕⊕ ⊕⊕⊕ ⊕⊕
Inserra 2011	⊕⊕⊕	⊖⊖⊖	⊕⊕	⊕⊕⊕ ⊖⊖⊖ ⊕⊕
Jandaghi 2015	⊕⊕⊕	⊕⊖⊖	⊕⊕	⊕⊕⊕ ⊕⊖⊖ ⊕⊕
Korponay-Szabó 1993	⊖⊕⊕	⊖⊖⊖	⊕⊕	⊖⊕⊕ ⊖⊖⊖ ⊕⊕
Kull 1999	⊕⊕⊕	⊕⊕⊖	⊕⊕	⊕⊕⊕ ⊕⊕⊖ ⊕⊕
Leeds 2007	⊕⊕⊕	⊕⊕⊕	⊕⊕	⊕⊕⊕ ⊕⊕⊕ ⊕⊕

Table 1. Continued

Study ID	Selection Max. 3	Comparability Max. 3	Outcome Max. 2	Total Max. 8
Oxford 2013	+ + +	− − −	+ +	+ + + − − − + +
Paolella 2014	− − −	+ + −	+ +	− − − + + − + +
Prinzbach 2018	+ + +	+ + +	+ +	+ + + + + + + +
Ribeiro-Cabral 2011	+ + +	− − −	+ +	+ + + − − − + +
Sjöberg 2002	− − −	+ − −	+ +	− − − + − − + +
Toumi 2007	− + +	+ − −	+ +	− + + + − − + +
Ventura 1999	+ + +	− − −	+ +	+ + + − − − + +
Virta 2013	+ + +	+ + +	+ +	+ + + + + + + +
Watanabe 2014	− + +	+ − −	+ +	− + + + − − + +
Yang 2005	+ + +	− − −	+ +	+ + + − − − + +
Yehuda 2019	+ + +	+ + +	+ +	+ + + + + + + +

NOTE. The plus and minus signs are used to display whether points were awarded for the Newcastle-Ottawa Scale for prognostic studies (Appendix 3). If a study received full points on the Newcastle-Ottawa Scale, it would be awarded 8 plus signs (or stars). If a study did not receive full points on a question, the corresponding entry in Table 1 would have a minus sign.

Risk of Crohn's Disease in CeD vs Controls

We pooled 7 studies (n = 232,323) and found an increased risk of Crohn's disease in CeD (RR 7.73; 95% CI 5.09–11.73; I^2 = 32%; P < .00001; Figure 3*B*). Overall, the pooled prevalence of Crohn's disease in CeD was 0.53% (95% CI 0.20%–0.97%, n = 24 studies, n = 18,222 participants). The certainty of the evidence was rated as high. The quality of the evidence was not downgraded for risk of bias because there was no significant difference between high and low risk of bias studies (Appendix 32). Publication bias could not be assessed due to the small number of studies.

Risk of UC in CeD vs Controls

We pooled 8 studies (n = 234,500) and found an increased risk of UC in CeD (RR 4.08; 95% CI 2.40–6.95; I^2 = 43%; P < .00001; Figure 3*C*). Overall, the pooled prevalence of UC in CeD was 0.68% (95% CI 0.19%–1.37%, n = 24 studies, n = 18,222 participants). The certainty of the evidence was rated as moderate and was not downgraded for risk of bias (Appendix 33) or inconsistency. Publication bias could not be assessed because of the small number of studies.

Risk of IC in CeD vs Controls

Four studies with n = 125,226 participants reported only n = 9 events. Therefore, the studies were not pooled. The certainty of the evidence was rated very low due to the very serious imprecision (n = 9 events). Further, the only study that reported events[33] had an unclear definition of IC. Therefore, this outcome was downgraded for indirectness.

Risk of HLA-DQ2/8 in IBD vs Controls

We pooled 2 studies (n = 1396) and found no increased risk of HLA-DQ2/8 genotype in IBD (RR 1.04; 95% CI 0.42–2.56; I^2 = 26%; P = .93) (Figure 4*A*). The certainty of the evidence on the risk of HLA-DQ2/8 in IBD vs controls is low

Table 2. Characteristics of Included Studies

Author (ref)	Country of origin/ study design	Population	Controls	Outcomes assessed
Akin 2012	Turkey Single center Cohort	22 adult biopsy-confirmed CeD patients	-	Number of patients with IBD
Akkelle 2019 *Abstract*	Turkey Single center Cross-sectional	125 pediatric IBD (57 Crohn's, 66 UC, 2 IC) patients, diagnosis methods unspecified	-	Number of patients with CeD Number of patients with HLA-DQ2/8 genotypes
Aletaha 2019	US Population-based Cohort	68,535 adult IBD and 19,217 adult CeD patients, based on ICD-9 codes	42,371,769 IBD-matched and 11,520,448 CeD-matched controls matched by age, sex, insurance plan type, and state of residence	Number of patients with CeD or with IBD
Alper 2018	US Single center Cohort Chart review	130 pediatric IBD (75 Crohn's, 55 UC) patients, diagnosed by clinical, lab, & histology from medical records	257 children presenting with gastrointestinal symptoms	Number of patients with CeD
Assa 2017	Israel Population-based Cross-sectional	7145 adolescent CeD patients, diagnosed by histology & serology	1,580,896 Jewish Israeli adolescents attending obligatory medical board examinations at army recruitment centers	Number of patients with IBD
Basaranoglu 2015 *Abstract*	Turkey Single center Cohort	198 CeD patients, diagnosis not described	-	Number of patients with IBD
Bibbò 2017	Italy Single center Case-control	255 adult CeD patients, diagnosed by clinical, serological, & histological evidence	250 age and sex-matched patients with functional dyspepsia and/or functional GI symptoms; IBD patients were excluded	Number of patients with IBD
Biedermann 2018 *Abstract*	Switzerland Multicenter Cohort	2019 adult IBD (1150 Crohn's, 812 UC, 45 IC) patients, diagnosis methods unspecified	-	Number of patients with CeD
Bizzaro 2003	Italy Single center Case-control	170 adult IBD (70 Crohn's, 100 UC) patients, diagnosed by Lennard-Jones criteria	120 healthy adults	Number of patients with CeD
Bosca-Watts 2018	Spain Single center Case-control	457 adult IBD (250 Crohn's, 207 UC) patients, from hospital records	577 organ donors	Number of patients with HLA-DQ2/8 genotypes
Breen 1987	Ireland Single center Cohort	42 adult CeD patients, diagnosed by histology & response to GFD	30 patients with diarrhea of unknown etiology; IBD patients were excluded	Number of patients with UC
Canova 2017	Italy Population-based Cohort	1294 pediatric CeD patients, identified by ICD-9 codes and/or pathology reports	6470 age and sex-matched members of the general population	Number of patients with IBD
Casella 2010	Italy Multicenter Cohort	1711 adult IBD (860 Crohn's, 791 UC, 60 IC) patients, based on endoscopic, radiological, & histological criteria	-	Number of patients with CeD
Casellas 2016 *Abstract*	Spain Single center Cross-sectional	407 adult IBD (236 Crohn's, 171 UC) patients, based on clinical, endoscopic, & histologic criteria	Epidemiological study of CeD in general population (0.47%); not cited in abstract	Number of tTG+ patients Number of patients with CeD

Table 2. Continued

Author (ref)	Country of origin/ study design	Population	Controls	Outcomes assessed
Collin 1994	Finland Single center Cohort	335 adult biopsy-proven CeD patients	335 age and sex-matched upper GI endoscopy outpatients	Number of patients with IBD
Conti 2018	Italy Single center Case-control	341 adult biopsy-proven CeD patients	-	Number of patients with IBD
Cooper 1978	UK Single center Cohort	314 adult biopsy-proven CeD patients	-	Number of patients with IBD
Cuoco 2014** *Abstract*	Italy Cohort	Bilateral 744 adult CeD and 179 adult IBD (71 Crohn's, 108 UC) patients, diagnosis methods unspecified	-	Number of patients with CeD and with IBD
Damoiseaux 2002	Netherlands Multicenter Cohort	37 adult and pediatric biopsy-confirmed CeD patients	35 healthy controls	Number of patients with IBD Number of ASCA+ and pANCA+ patients
De Carvalho 2018	Brazil Single center Cross-sectional	83 adult IBD (36 Crohn's, 47 UC) patients, based on endoscopic and histologic findings	-	Number of patients with CeD
Delcò 1999	US Population-based Case-control	458 adult CeD patients, based on ICD-9 codes	2692 US military veterans	Number of patients with IBD
Dhaliwal 2009** *Abstract*	Canada Single center Cohort	150 adult Crohn's patients, diagnosis methods unspecified	-	Number of patients with CeD
Dominguez Castro 2017	Ireland Multicenter Cohort	749 adult CeD patients, diagnosed by serology & histology	-	Number of patients with IBD
El-Matary 2012** *Thesis*	Canada Single center Cohort	164 pediatric IBD (85 Crohn's, 79 UC) patients, based on clinical, radiological, & endoscopic evidence	164 age-matched controls with functional gastrointestinal problems	Number of patients with CeD
Giorgetti 2006	Italy Single center Cohort	48 adult Crohn's patients, based on radiological, endoscopic, & histological evidence	-	Number of patients with CeD
Grode 2018	Denmark Population-based Cohort	10,285 adult and pediatric CeD patients, identified by ICD-8 codes	104,928 age and sex-matched Danish citizens	Number of patients with IBD
Halling 2017	Denmark Population-based Cross-sectional	47,325 adult IBD (13,343 Crohn's, 31 066 UC, 2916 both) patients, identified by ICD-10 codes	92,839 IBD-matched, 26,172 Crohn's-matched, 60,951 UC-matched, and 5716 Crohn's & UC-matched controls; matched by age, sex, & location	Number of patients with CeD

Table 2. Continued

Author (ref)	Country of origin/ study design	Population	Controls	Outcomes assessed
Hernandez Camba 2013** *Abstract*	Spain Single center Cross-sectional	91 adult biopsy-proven CeD patients	-	Number of patients with IBD
Inserra 2011	Italy Single center Cross-sectional	1268 adult CeD patients, diagnosed by serology & jejunal biopsy	Epidemiological study of IBD in general population of Florence, Italy[41]	Number of patients with IBD
Jandaghi 2015	Iran Single center Cohort	406 adult biopsy-proven IBD patients (206 Crohn's, 200 UC)	Epidemiological study of CeD in general Iranian population[42]	Number of patients with CeD
Jansson-Knodell 2018	US Population-based Cohort	282 adult CeD patients, identified by medical records, ICD-9 codes, serology, and/or histology	-	Number of patients with HLA-DQ2/8 genotypes
Juhász 2012	Hungary Single center Cohort	132 adult CeD patients, diagnosed by serology & biopsy	-	Number of patients with IBD
Klincewicz 2007	Poland Single center Cohort	136 pediatric IBD (49 Crohn's, 87 UC) patients, based on clinical, endoscopic, & histologic evidence	-	Number of patients with CeD
Kocsis 2015	Hungary Single center Cohort	245 adult CeD patients, diagnosed by serology & biopsy	-	Number of patients with IBD
Korponay-Szabó 1993	Hungary Single center Cross-sectional	38 pediatric IBD patients, based on histological & radiological evidence	718 children with nonspecific gastrointestinal complaints	Number of patients with CeD Number of EMA+ patients
Kull 1999	Estonia Single center Case-control	50 adult UC patients diagnosed by Lennard-Jones criteria	53 age and sex-matched healthy controls	Number of patients with CeD Number of AGA+ and EMA+ patients
Lakatos 2003	Hungary Single center Cohort	873 adult and pediatric IBD (254 Crohn's, 619 UC) patients, based on clinical, endoscopic, & histological evidence	-	Number of patients with CeD
Leeds 2007	UK Multicenter Case-control	Bilateral 305 adult CeD and 354 adult IBD (173 Crohn's, 154 UC, 18 IC) patients, histologically confirmed	601 healthy controls	Number of patients with IBD and with CeD
Limketkai 2018	US Single Center Cross-sectional	102 adult IBD patients, based on specialist diagnoses	-	Number of patients with CeD
Lu 2015** *Abstract*	Canada Multicenter Chart reviews Cross-sectional	780 IBD patients, based on chart reviews	-	Number of patients with CeD Phenotype of patients with concurrent CeD and IBD

Table 2. Continued

Author (ref)	Country of origin/ study design	Population	Controls	Outcomes assessed
Malmborg 2017	Sweden Single center Cohort	256 pediatric IBD (190 Crohn's, 60 UC, 6 IC) patients, by ESPGHAN diagnostic recommendations	-	Number of patients with CeD
Mantzaris 2005	Greece Single center Cohort	53 adult CeD and 639 IBD (281 Crohn's, 358 UC) patients	-	Number of patients with CeD and with IBD
Merrick 2015** *Abstract*	Scotland, UK, Canada Population-based Cohort	809 pediatric IBD (533 Crohn's, 204 UC, 72 IC) patients, based on Lennard-Jones/Porto criteria	-	Number of patients with CeD
Motta 2018	Argentina Single center Cross-sectional	59 adult biopsy-proven CeD patients	-	Number of ASCA+ patients
Nijhawan 2013	India Single center Cohort	363 adult and pediatric CeD patients, diagnosed by serology & biopsy	-	Number of patients with IBD
Oxford 2013	US Multicenter Cross-sectional	33,963 adult IBD (17,288 Crohn's, 16,675 UC) patients, based on ICD-9 codes	17,503 multiple sclerosis patients from the Partners Healthcare database	Phenotype of patients with concurrent CeD and IBD Number of patients with CeD
Paolella 2014** *Abstract*	Italy Single center Case-control	350 pediatric CeD patients, diagnosis not described	350 matched controls	Number of patients with IBD
Perez 2017	UK Single center Retrospective Cohort	578 pediatric IBD patients, based on lab & endoscopic findings	-	Number of patients with CeD
Prinzbach 2018	US Population-based Cross-sectional	433 pediatric CeD patients, diagnosed by serology & biopsy	4330 age, sex, and race-matched healthy controls	Number of patients with IBD
Ribeiro-Cabral 2011	Brazil Single center Case-control	33 adult Crohn's patients, diagnosed by clinical, radiological, endoscopic, & morphological evidence	45 type 1 diabetes patients	Number of patients with CeD
Rönnblom 2015	Sweden Population-based Cohort	790 adult and pediatric IBD patients (264 Crohn's & 526 UC), diagnosed by Montreal criteria recorded in medical charts	-	Number of patients with CeD Phenotype of patients with concurrent CeD and IBD
Sjöberg 2002	Sweden Single center Cross-sectional	57 adult IBD patients (34 Crohn's, 23 UC)	44 healthy plasma donors	Number of tTG+ and EMA+ patients
Sood 2003	India Single center Cohort	96 adult CeD patients, diagnosed by ESPGHAN criteria	-	Number of patients with IBD

Table 2. Continued

Author (ref)	Country of origin/ study design	Population	Controls	Outcomes assessed
Spijkerman 2016	Netherlands Single center Cohort	412 adult biopsy-proven CeD patients	-	Number of patients with IBD
Szaflarska-Poplawska 2016	Poland Multicenter Cohort	71 adult and pediatric Crohn's patients, diagnosed by clinical, radiological, endoscopic, & histopathologic evidence	-	Number of tTG+ and DGP+ patients
Taghvaii 2014	Iran Single center Cross-sectional	84 adult UC patients, diagnosed by clinical, histological, & endoscopic evidence	-	Number of patients with CeD
Tavakkoli 2012	Iran Single center Cross-sectional	100 adult IBD (30 Crohn's, 70 UC) patients, assessed by Lennard-Jones criteria	-	Number of patients with serologic CeD
Toumi 2007	Tunisia Multicenter Cohort	238 adult and pediatric biopsy-confirmed CeD patients	80 healthy blood donors	Number of ASCA+ patients
Tursi 2005	Italy Single center Cohort	27 adult Crohn's patients, based on radiologic, endoscopic, & histologic evidence	-	Number of patients with CeD
Ventura 1999	Italy Multicenter Cohort	909 adult and pediatric CeD patients, diagnosed by biopsy & clinical improvement on GFD	1268 healthy university students	Number of patients with IBD
Virta 2013	Finland Population-based Cohort	595 pediatric IBD (233 Crohn's, 362 UC) patients, based on ICD-10 codes	2380 age, sex, & location-matched healthy controls (932 matched to Crohn's; 1448 matched to UC)	Number of patients with IBD
Watanabe 2014	Japan Single center Cohort	172 adult IBD (62 Crohn's, 110 UC) patients, diagnosed by clinical, histological, & endoscopic evidence	190 asymptomatic patients scheduled for colonoscopy	Number of patients with CeD
Yang 2005	US Single center Cohort	455 adult biopsy-proven CeD patients	Epidemiological studies of Crohn's and UC in general population of Olmsted county, Minnesota[43,44]	Number of patients with IBD
Yehuda 2019	Israel Population-based Cohort	12,625 adult IBD (6364 Crohn's, 6261 UC, 342 IC) patients, based on ICD-9 codes	12,625 age, sex, & socioeconomic status-matched controls	Number of patients with CeD
Zwolinska-Wcislo 2009	Poland Single center Cohort	80 adult UC patients, endoscopically confirmed	-	Number of patients with CeD

Table 3. Summary of Findings Table

Patient or population: CeD or IBD
Risk factor: IBD or CeD
Comparison: Controls of any type

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with controls	Risk with IBD or CeD				
Risk of CeD in IBD vs controls	1 per 1000	**5 per 1000** (3 to 10)	**RR 3.96** (2.23 to 7.02)	189,344 (5 RCTs)	⊕⊕⊕◯ MODERATE[b,c,d]	The risk of CeD is likely much higher in IBD than in controls.
Risk of CeD in Crohn's vs controls	2 per 1000	**10 per 1000** (5 to 20)	**RR 4.43** (2.15 to 9.14)	60,443 (4 RCTs)	⊕⊕⊕◯ MODERATE[b,c,d]	The risk of CeD is likely much higher in Crohn's than in controls.
Risk of CeD in UC vs controls	2 per 1000	**5 per 1000** (3 to 8)	**RR 2.81** (1.82 to 4.36)	148,890 (10 RCTs)	⊕⊕⊕◯ MODERATE[c,d,e]	The risk of CeD is likely much higher in UC than in controls.
Risk of CeD in IC vs controls	1 per 1000	**9 per 1000** (3 to 26)	**RR 6.51** (2.33 to 18.21)	9251 (2 RCTs)	⊕⊕◯◯ LOW[f]	The risk of CeD may be much higher in IC than in controls.
Risk of IBD in CeD vs controls	9 per 1000	**88 per 1000** (36 to 216)	**RR 9.88** (4.03 to 24.21)	148,646 (5 RCTs)	⊕⊕⊕◯ MODERATE[b,c]	The risk of IBD is likely much higher in CeD than in controls.
Risk of Crohn's in CeD vs controls	2 per 1000	**14 per 1000** (9 to 21)	**RR 7.73** (5.09 to 11.73)	232,323 (7 RCTs)	⊕⊕⊕⊕ HIGH[e,g]	The risk of Crohn's disease is much higher in CeD than in controls.
Risk of UC in CeD vs controls	5 per 1000	**21 per 1000** (12 to 35)	**RR 4.08** (2.40 to 6.95)	234,500 (8 RCTs)	⊕⊕⊕◯ MODERATE[c,e]	The risk of UC is likely much higher in CeD than in controls.
Risk of IC in CeD vs controls	0 per 1000	**0 per 1000** (0 to 3)	**RR 40.00** (5.01 to 319.54)	125,226 (4 RCTs)	⊕◯◯◯ VERY LOW[f,h]	The evidence is very uncertain about the risk of IC in CeD compared to controls.
Risk of HLA-DQ2/8 in IBD vs controls	297 per 1000	**309 per 1000** (125 to 761)	**RR 1.04** (0.42 to 2.56)	1396 (2 RCTs)	⊕⊕◯◯ LOW[i,j]	There may be little to no difference in the risk of the HLA-DQ2/8 genotype in IBD compared to controls.
Risk of tTG in IBD vs controls	33 per 1000	**50 per 1000** (17 to 145)	**RR 1.52** (0.52 to 4.40)	2017 (6 RCTs)	⊕◯◯◯ VERY LOW[c,i,j]	The risk of tTG positive serology may be higher in IBD compared to controls but the evidence is very uncertain.

Table 3. Continued

Patient or population: CeD or IBD Risk factor: IBD or CeD Comparison: Controls of any type						
	Anticipated absolute effects[a] (95% CI)					
Outcomes	Risk with controls	Risk with IBD or CeD	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
Risk of tTG false positives in IBD vs controls	14 per 1000	**41 per 1000** (9 to 180)	**RR 2.97** (0.68 to 13.04)	2017 (6 RCTs)	⊕◯◯◯ VERY LOW[c,i,j]	The risk of tTG false positives may be higher in IBD compared to controls but the evidence is very uncertain.
Risk of EMA in IBD vs controls	32 per 1000	**23 per 1000** (6 to 88)	**RR 0.70** (0.18 to 2.74)	963 (5 RCTs)	⊕◯◯◯ VERY LOW[f,i]	The evidence is very uncertain about risk of EMA-positive serology in IBD compared to controls.
Risk of ASCA in CeD vs controls	11 per 1000	**67 per 1000** (26 to 170)	**RR 6.22** (2.44 to 15.84)	1090 (3 RCTs)	⊕⊕◯◯ LOW[i,j]	The risk of ASCA-positive serology may be much greater in CeD compared to controls.

NOTE. GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
RCT, randomized controlled trial.
[a]**The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
[b]Used only low risk of bias studies.
[c]Downgraded 1 level for inconsistency.
[d]Despite asymmetric funnel plot, publication bias was not suspected because missing studies would only strengthen the findings.
[e]High and low risk of bias studies had similar results.
[f]Downgraded 2 levels for imprecision.
[g]Not downgraded for inconsistency.
[h]Downgraded 1 level for indirectness.
[i]Downgraded 1 level for risk of bias.
[j]Downgraded 1 level for imprecision.

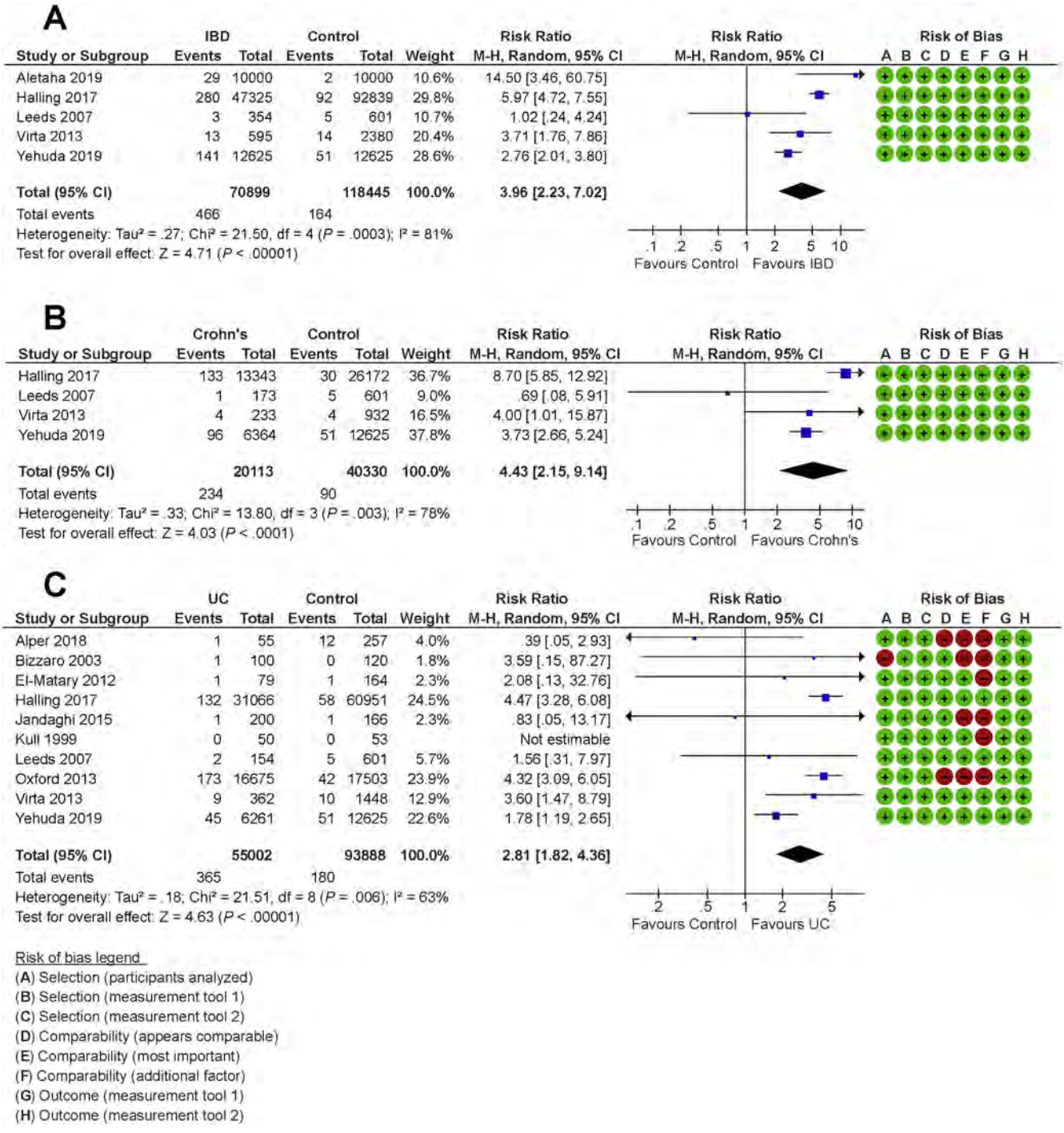


Figure 2. Forest plots of comparisons of observational studies: (*A*) risk of CeD in patients with IBD, vs controls, in low risk of bias studies; (*B*) risk of CeD in patients with Crohn's disease, vs controls, in low risk of bias studies; (*C*) risk of CeD in patients with UC, vs controls.

and was downgraded because of high risk of bias[34,35] and serious imprecision.

Risk of Elevated Anti-tTG Antibodies in IBD vs Controls

We pooled 6 studies (n = 2017) to assess the risk of elevated anti-tTG antibodies, without any biopsy confirmation of CeD, in IBD vs controls. One was based on a retrospective chart review, and the others prospectively screened patients. There was an increased risk of elevated tTG antibodies in IBD vs controls (RR 1.52; 95% CI 0.52–4.40; $I^2 = 65\%$; $P = .045$) (Figure 4*B*). The certainty of the evidence on the risk of tTG in IBD vs controls is very low. The quality of evidence was downgraded due to high risk of bias, serious inconsistency ($I^2 = 65\%$), and serious imprecision.

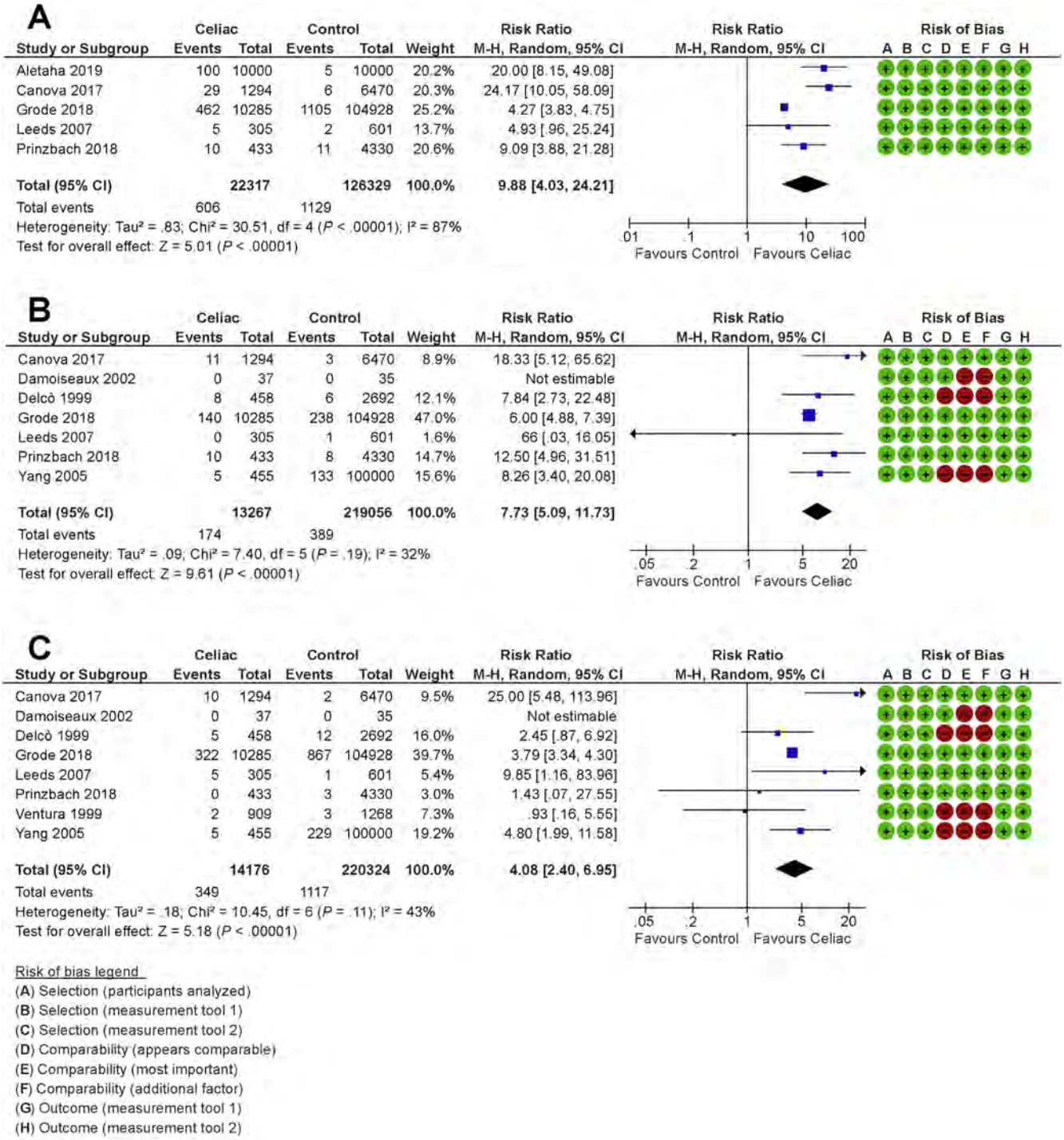
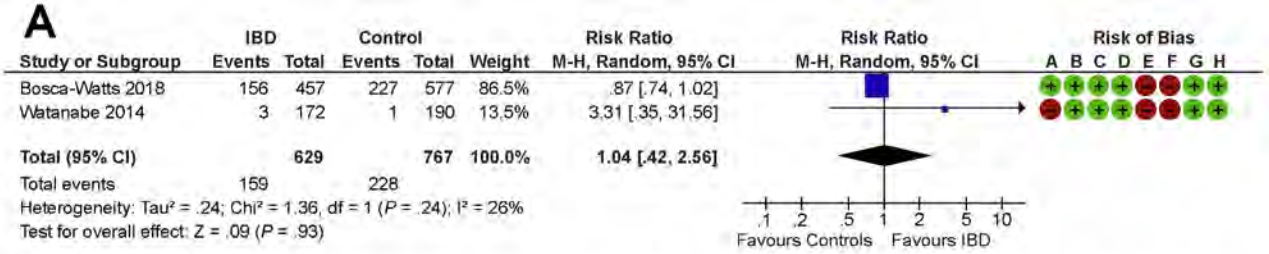


Figure 3. Forest plots of comparisons of observational studies: (*A*) risk of IBD in patients with CeD, vs controls, subgrouped by risk of bias; (*B*) risk of Crohn's in patients with CeD, vs controls; (*C*) risk of UC in patients with CeD, vs controls.

Figure 4. Forest plots of comparisons of observational studies: (A) risk of HLA-DQ2/8 genotype in patients with IBD, vs controls; (B) risk of tTG in patients with IBD, vs controls; (C) risk of tTG false positives in patients with IBD, vs controls; (D) risk of EMA in patients with IBD, vs controls; (E) risk of ASCA in patients with CeD, vs controls.

A



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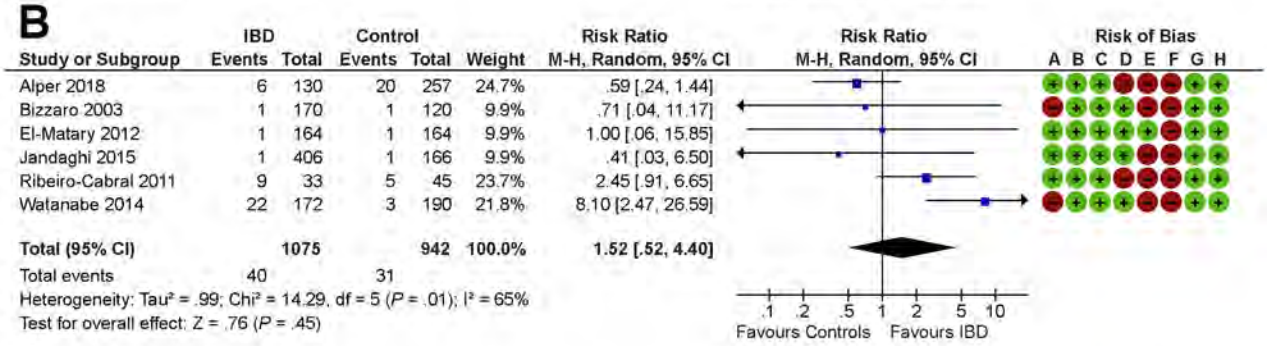

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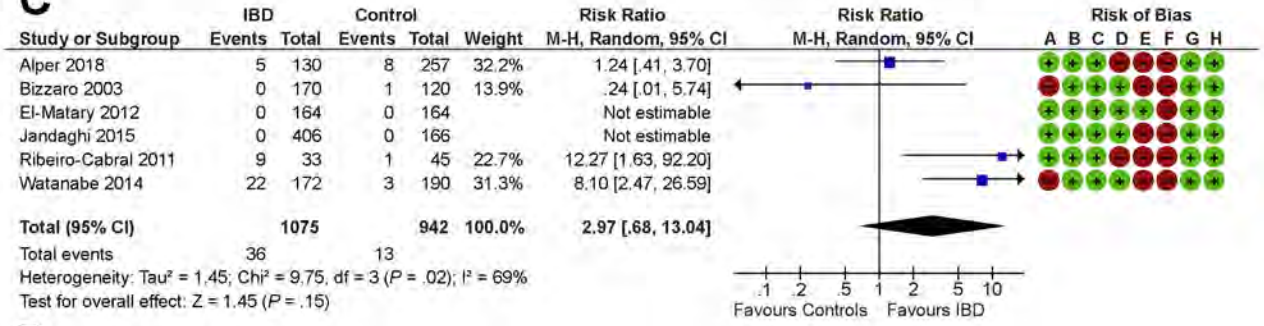

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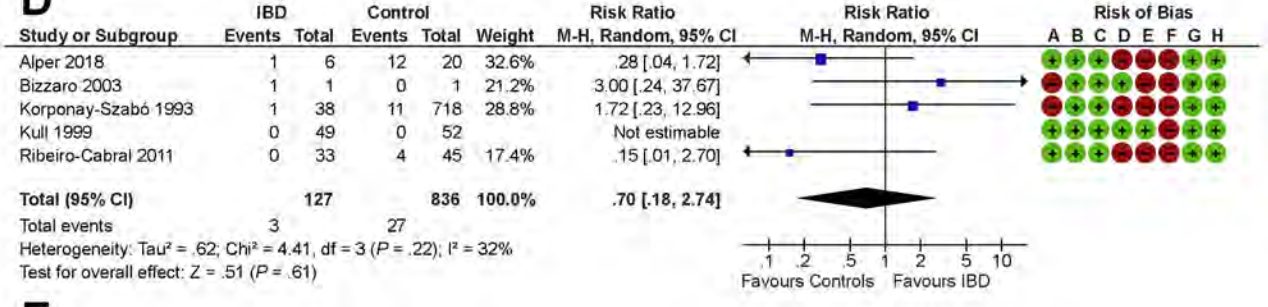
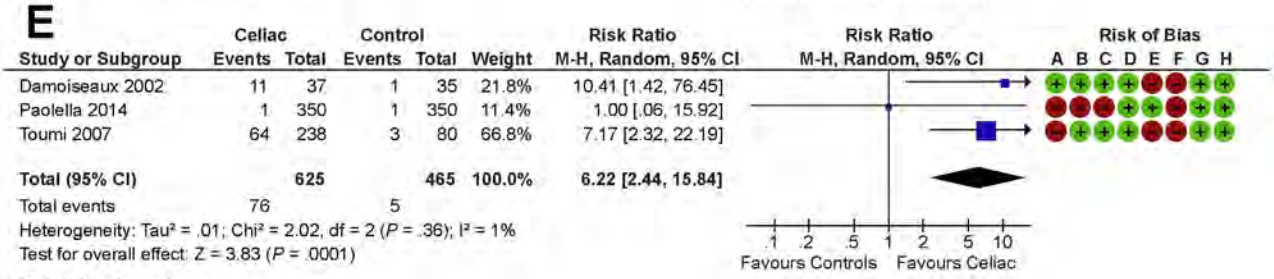


E



Risk of bias legend

(A) Selection (participants analyzed)
(B) Selection (measurement tool 1)
(C) Selection (measurement tool 2)
(D) Comparability (appears comparable)
(E) Comparability (most important)
(F) Comparability (additional factor)
(G) Outcome (measurement tool 1)
(H) Outcome (measurement tool 2)

There was an increased risk of false positive anti-tTG antibodies in IBD vs controls (RR 2.97; 95% CI 0.68–13.04; $I^2 = 69\%$; $P = .015$) (Figure 4*C*). The certainty of the evidence on the risk of false positive tTG in IBD vs controls is very low based on high risk of bias, serious inconsistency ($I^2 = 69\%$), and very serious imprecision.

Risk of Anti-EMA Antibodies in IBD vs Controls

We pooled 5 studies (n = 963) and found a slightly lower risk of presenting positive EMA in IBD vs controls (RR 0.70; 95% CI 0.18–2.74; $I^2 = 32\%$; $P = .61$). The certainty of the evidence was very low based on the high risk of bias and very serious imprecision (n = 30 events) (Figure 4*D*).

Risk of AGA in IBD vs Controls

One study assessed the risk of increased AGA levels in IBD vs controls and no difference in risk was found. The certainty of the evidence was very low. The study was at high risk of bias and there was very serious imprecision (n = 19 events).

Risk of DGP in IBD vs Controls

One study assessed the risk of DGP IgA in IBD vs controls and found increased risk of DGP in IBD vs controls (13.4% of patients with IBD and 0.5% of controls; n = 362; $P < .01$). The certainty of the evidence for the risk of DGP in IBD was very low because of high risk of bias and very serious imprecision (n = 24 events).

Risk of ASCA in CeD vs Controls

We pooled 3 studies (n = 1090) and found an increased risk of elevated ASCA in CeD vs controls (RR 6.22; 95% CI 2.44–15.84; $I^2 = 1\%$; $P = .0001$). The certainty of the evidence was low. All studies were at serious risk of bias and we detected serious imprecision (n = 81 events) (Figure 4*E*).

Risk of pANCA in CeD vs Controls

Two studies assessed the risk of elevated pANCA in CeD vs controls, but only 1 reported events. This study found a greater risk of pANCA in CeD than in controls (21.6% of patients with CeD and 2.9% of controls; n = 72; $P = .02$). The certainty of the evidence for this outcome is very low. The study had high risk of bias and very serious imprecision (n = 9 events).

Discussion

This review found that there is likely a bidirectional association between CeD and IBD. This updated analysis, involving both pediatric and adult populations from a range of geographical locations, confirms and expands the previous findings,[19] showing consistent results over time.

Our review found a 9-fold increased risk of IBD in CeD compared with controls, with a higher risk in Crohn's disease than UC. We found significant heterogeneity in most of the analyses and that the types of controls used for comparison influenced the results. When the only study including controls with various gastrointestinal symptoms was removed from analysis, the risk of IBD in CeD increased. This is the first analysis on the influence of different control groups on the risk of IBD in patients with CeD.

Similarly, we found the risk for CeD is likely increased in patients with IBD, although to a smaller extent. Specifically, we found that the effect was limited to population-based and low risk of bias studies. We found that population-based studies had age- and sex-matched controls representative of the general population, whereas the hospital-based studies typically had less comparable controls, leading to higher risk of bias in these studies. However, it must be noted that most of the population-based studies identified CeD and IBD through ICD codes, which may not correctly identify CeD and patients with IBD. IBD has generally typical symptoms and is easier to diagnose than CeD, which has a protean clinical presentation and is often asymptomatic, leading it to be underrepresented in population-based studies.[36] Further, CeD diagnosis may be more difficult to perform in patients with gastrointestinal symptoms due to IBD. The effect of the association could be underestimated due to immunosuppressant/immunomodulatory therapies for IBD that also "treat" CeD and result in the disease not being detected. In addition, the pooled prevalence of CeD among patients with IBD was 0.75%, whereas it was 0.3% among controls. Considering that CeD has a prevalence of approximately 1% worldwide,[1] it is likely that the prevalence of CeD was underestimated in these studies. Similarly, the widespread use of the gluten-free diet, even in patients with IBD, may "treat" undiagnosed CeD.[37] Conversely, the effect of the association may be overestimated because of the extensive evaluations that CeD and patients with IBD undergo. Persistent symptoms and ongoing testing of these patients may reveal asymptomatic disease that otherwise would not have been found. Once again, our confidence in these results was limited due to significant heterogeneity. We explored different sources of heterogeneity through subgroup analyses; however, we were not able to identify the source.

We assessed whether isolated CeD serology was increased in IBD and vice versa. False positive CeD serology has been reported in other autoimmune conditions, such as type 1 diabetes.[38] Further, it is possible that positive CeD serology predicts the future development of CeD. Very low-certainty evidence showed a trend of lower risk of EMA and a higher risk of tTG false positives in IBD vs controls. Of the 5 studies that assessed tTG-positive and EMA-negative participants, duodenal biopsies were negative. The only study assessing tTG false positives that did not perform EMA was confirmed by positive duodenal biopsy. IBD medications were reported only in 2 studies. Since EMA has higher specificity than tTG,[39] this suggests that many CeD diagnoses in IBD may be performed on the basis of potentially false positive tTG. Therefore, the current evidence is very uncertain to determine whether the risk of CeD-specific markers is elevated in IBD. More studies investigating the risk of CeD-specific serology in

IBD compared with controls are needed to increase the certainty of this evidence.

Low-certainty evidence suggests that patients with CeD are at higher risk of presenting increased ASCA compared with controls. However, the evidence is limited because of the small number of events. In addition, the evidence is very uncertain regarding the risk of pANCA in CeD compared with controls. Therefore, future studies assessing the risk of ASCA and pANCA in patients with CeD should be conducted to clarify whether they have any prognostic value in CeD or if they are instead nonspecific markers of intestinal inflammation. Finally, the evidence suggests there is no increased risk of HLA-DQ2/8 for CeD in IBD; however, the quality of evidence is low and therefore there is uncertainty on the estimation.

Although these results indicate a bidirectional association between CeD and IBD, it is unclear at this point whether screening of IBD should be performed in CeD and vice versa. It is unlikely that screening for IBD in patients with CeD will be cost-effective given that colonoscopy, the gold standard approach, is invasive and expensive. Screening for CeD in patients with IBD may be reasonable considering the high burden of concurrent IBD and CeD. Health economic modeling in irritable bowel syndrome suggests screening is cost-effective if the prevalence of CeD exceeds 1%[40]; however, the prevalence of CeD in IBD seems slightly lower. Further research and health economic modeling should be done to determine whether screening for CeD in IBD is cost-effective. Another underinvestigated area pertains to whether specific subgroups of CeD and patients with IBD are at higher risk for developing the associated condition, as well as which condition precedes the other. Future studies should investigate whether time of diagnosis (ie, pediatric-onset vs adult-onset disease), disease severity, the presence of another autoimmune disease (eg, type 1 diabetes), sex, or any other factor increases the risk of concurrent IBD and CeD, rather than looking at the entire population of CeD or patients with IBD.

We consider our systematic review and meta-analysis rigorous in terms of the methodology used for the search strategy, data extraction, and the analysis of the results. We attempted to reduce the risk of bias at all stages while conducting this systematic review. We modified Newcastle-Ottawa Quality Assessment Scales (Appendices 3 and 4) to account for the risk of bias in all types of studies. This allowed for rigorous sensitivity analyses by risk of bias that accounted for biases, regardless of study design. We conducted a rigorous search of the literature, explored the bias in the included studies, performed sensitivity analyses to understand the effects of the high risk of bias studies, and performed subgroup analyses to determine the effects of age and location on risk of concurrent disease.

In conclusion, the results of our systematic review evaluating the prevalence of IBD in CeD and of CeD in IBD in adults and children indicate an association is likely between the 2 diseases independently of geographical variation. However, our confidence in these results is limited by the heterogeneity, which highlights the need of more prospective cohort studies ideally including controls from the general population. Data obtained in longitudinal cohort studies of at-risk patients, which have been performed in both CeD and IBD, would constitute unique and invaluable cohorts to investigate this association. Based on the evidence we presently have, clinicians could consider IBD or CeD as additional diagnoses in the situation of a patient poorly responsive to an appropriate therapy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.05.016.

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Conflict of interest
These authors disclose the following: DAL is supported by Takeda Pharmaceuticals. CPK has been a scientific advisor/consultant for Cour Pharma, Glutenostics, Immunogenx, Innovate, Takeda Pharmaceuticals; investigator for Allergan, Innovate, Takeda; and has stock options in Cour Pharma, Glutenostics. EFV is member of the advisory board of Biocodex Foundation and received a grant by Gilead unrelated to this paper. MIPS received in kind support from Nestle, unrelated to this paper. PB was a consultant and received grant support from Nestec Switzerland, unrelated to this paper. AA is a Working Group Member of the National Advisory Neurological Disorders and Stroke Council.

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Supplementary Material

Appendix to 'The association between inflammatory bowel disease and celiac disease: a systematic review and meta-analysis'.

This appendix provides supplemental information on this systematic review. It is divided into thirty-three appendices (Appendix 1 – 33).

Table of Contents

Appendix 1. Diagnostic Criteria for Individual Studies

Study	CeD diagnosis criteria	IBD diagnosis criteria
Akin 2012	Endoscopy & duodenal biopsy	Biopsy & colonoscopy
Akkelle 2019	tTG, EMA, HLA genotype	Not specified; pediatric IBD cohort
Aletaha 2019	ICD-9 code (579)	ICD-9 code (Crohn's: 555.x; UC: 556.x)
Alper 2018	Biopsy & serology	Medical records of clinical, laboratory & histology data
Assa 2017	Biopsy, serology & confirmation with specialist	Medical record & verification from family doctor
Basaranoglu 2015	Clinic records	Colonoscopy, rectoscopy and/or double balloon enteroscopy (DBE)
Bibbò 2017	Biopsy & serology	Confirmation from specialist
Biedermann 2018	Serology (tTG IgA, DGP IgG, & total serum IgA)	Lennard-Jones criteria
Bizzaro 2003	Biopsy & serology (tTG & EMA)	Lennard-Jones criteria
Bosca-Watts 2018	HLA DQ2/8 genotype	Clinical, radiological, histologic & endoscopic evidence
Breen 1987	Biopsy & clinical response to gluten-free diet	Histopathologic, clinical & radiologic evidence
Canova 2017	Histological evidence, ICD-9 codes (579.0) or exemption from Italian national health care copayment (I0060)	ICD-9 code (Crohn's: 555.xx; UC: 556.xx [except 556.0, 556.1, 556.4, & 556.8]) or Italian national health care copayment exemption (Crohn's & UC: 900.555)
Casella 2010	Biopsy & serology	Endoscopic, radiological & histologic evidence
Casellas 2016	Biopsy & serology	Clinical, endoscopic & histologic evidence
Collin 1994	Biopsy (subtotal or total villous atrophy)	Medical records from general practitioners and hospitals
Conti 2018	Biopsy & serology	Clinical history, chart review and/or specialist reports
Cooper 1978	Jejunal biopsy	Rectal biopsy, review of medical records, confirmation with patients
Cuoco 2014	Biopsy & serology	Medical history, clinical parameters, small bowel imaging and/or colonoscopy
Damoiseaux 2002	Biopsy, serology & improvement on gluten-free diet	ASCA & pANCA
De Carvalho 2018	Biopsy & serology (EMA)	Endoscopic & histopathologic evidence
Delcò 1999	ICD-9 code 579.0	ICD-9 code (Crohn's: 555.9; UC: not specified)
Dhaliwal 2009	Biopsy & serology	Unspecified; recruited Crohn's patients from an academic GI referral center
Dominguez Castro 2017	Biopsy & serology	Medical records
El-Matary 2012	Biopsy & serology	Clinical, radiological & endoscopic evidence
Giorgetti 2006	Biopsy & serology	Radiological, endoscopic & histologic evidence
Grode 2018	ICD-8 (269.00+269.98) & ICD-10 (K90.0)	ICD-8 (Crohn's: 563.01; UC: 563.19) & ICD-10 (Crohn's: K500; UC: K51)
Halling 2017	ICD-10 code (DK90.0)	ICD-10 codes (Crohn's: K50.0-K50.9; UC: K51.0-K51.9), except codes including "other" or "unspecified"
Hernandez Camba 2013	Biopsy & serology	Medical records, including endoscopic & pathologic evidence
Inserra 2011	Biopsy & serology	Clinical, endoscopic & pathologic evidence
Jandaghi 2015	Biopsy & serology	Biopsy-proven
Jansson-Knodell 2018	ICD-9 (579.0, 694.0)	Medical records
Juhász 2012	Biopsy & serology	Medical records
Klincewicz 2007	Biopsy & serology	Clinical, radiological, histologic & endoscopic evidence
Kocsis 2015	Biopsy & serology	Clinical parameters, imaging, colonoscopy, video capsule endoscopy & histology
Korponay-Szabó 1993	Biopsy & serology	Clinical, radiological, histologic & endoscopic evidence
Kull 1999	Serology (EMA)	Lennard-Jones criteria

Appendix 1. Continued

Study	CeD diagnosis criteria	IBD diagnosis criteria
Lakatos 2003	Medical records	Clinical, radiological, histologic & endoscopic evidence
Leeds 2007	Biopsy & serology	Clinical, radiological, histologic & endoscopic evidence
Limketkai 2018	Biopsy & serology	Specialist diagnoses
Lu 2015	Medical records	Medical records
Malmborg 2017	Biopsy & serology (ESPGHAN)	Clinical, radiological, histologic & endoscopic evidence
Mantzaris 2005	Biopsy & serology	Clinical, radiological, histologic & endoscopic evidence
Merrick 2015	Medical records	ESPGHAN "Porto"-criteria for IBD diagnosis; Lennard-Jones criteria
Motta 2018	Biopsy & serology	ASCA
Nijhawan 2013	Biopsy & serology (modified ESPGHAN)	Colonoscopy & biopsy, medical history
Oxford 2013	ICD-9 code (579.0)	ICD-9 code (Crohn's: 555.x; UC: 556.x)
Paolella 2014	Unclear; authors describe routine lab follow-up of celiac patients on gluten-free diet	Clinical, radiological, histologic & endoscopic evidence & ASCA/ANCA
Perez 2017	Biopsy & serology	Biopsy immunostaining, small bowel imaging & video capsule endoscopy
Prinzbach 2018	Biopsy & serology	ICD-10 codes (Crohn's: K50; UC: K51)
Ribeiro-Cabral 2011	Biopsy & serology	Clinical, radiological, endoscopic & morphological evidence
Rönnblom 2015	Biopsy & serology	Montreal classification
Sjöberg 2002	Serology & biopsy	Unspecified; likely hospital records
Sood 2003	ESPGHAN	Case records from GI unit
Spijkerman 2016	Biopsy	Medical records
Szaflarska-Poplawska 2016	Serology	Clinical, radiological, histologic, endoscopic & pathologic evidence
Taghvaii 2014	Biopsy & serology	Clinical, radiological, histologic & endoscopic evidence
Tavakkoli 2012	Biopsy & serology	Lennard-Jones criteria
Toumi 2007	Biopsy & serology	ASCA/ANCA
Tursi 2005	Biopsy & serology	Clinical, radiological, histologic & endoscopic evidence
Ventura 1999	Biopsy & serology	Medical records of clinical, radiological, histologic & endoscopic evidence
Virta 2013	ICD-10 code (K90) & biopsy	ICD-10 codes (Crohn's: K50; UC: K51)
Watanabe 2014	Biopsy & serology	Clinical, radiological, histologic & endoscopic evidence
Yang 2005	Biopsy & serology	Endoscopic & pathologic evidence
Yehuda 2019	ICD-9 code (579)	ICD-9 (Crohn's: 555.x, except 555.1; UC: 556.x) & validated algorithm
Zwolinska-Wcislo 2009	Biopsy & serology	Clinical, radiological, histologic & endoscopic evidence

Appendix 2. MEDLINE Search Strategy for Article Selection (1 Jan 1970 to 25 June 2019)

SEARCH OVID-MEDLINE (MESH Terms)

1. Inflammatory Bowel Diseases/
2. Crohn Disease/
3. Colitis, Ulcerative/
4. Colitis/
5. Proctocolitis/
6. Celiac Disease/
7. Diet, Gluten-Free/
8. Glutens/
9. Gliadin/
10. HLA-DQ Antigens/

SEARCH OVID-MEDLINE (Keywords)

1. Inflammatory bowel disease?.mp
2. Ibd.mp
3. Inflammatory bowel*.mp
4. Crohn*.mp
5. Coliti*.mp
6. Proctocolitis*.mp
7. C?elia*.mp
8. C?eliac disease?.mp
9. Sprue nontropical.mp
10. Sprue*.mp
11. Gluten*.mp
12. Gliadin*.mp

Appendix 3. Modified Newcastle Ottawa Scale for Prognostic Studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

(adapted for prognostic studies)

Selection: (Maximum 3 stars)

1) Participants analyzed:
   a) All possible subjects or a random sample were obtained. All of these participants were included in the analysis and none were excluded based on outcome. *
   b) Participants were excluded from analysis based on criteria related to the outcome.
   c) No description of participants analyzed.

2) Ascertainment of the exposure (risk factor):
   a) Validated measurement tool. **
   b) Non-validated measurement tool, but the tool is available or described and appropriate. *
   c) No description of the measurement tool.

Comparability: (Maximum 3 stars)

   a) The subjects in different outcome groups do not appear comparable.
   b) The subjects in different outcome groups *appear* comparable. *
   c) Confounding factors are controlled by the most important factor (select one). **
   d) The study controls for any additional factor. ***

Outcome: (Maximum 2 stars)

3) Assessment of the outcome:
   a) Independent blind assessment. **
   b) Record linkage. **
   c) Self report. *
   d) No description.

Total out of 8: _____

Appendix 4. Modified Newcastle Ottawa Scale for Prevalence Studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

(adapted for prevalence studies)
Selection: (Maximum 4 stars)

1) Representativeness of the sample:
   a. Truly representative of the average in the target population. ** (all subjects or random sampling or consecutive subjects)
   b. Somewhat representative of the average in the target population. * (non-random sampling or non-consecutive subjects)
   c. Selected group of users.
   d. No description of the sampling strategy.

2) Ascertainment of the exposure (risk factor):
   a. Validated measurement tool. **
   b. Non-validated measurement tool, but the tool is available or described and appropriate. *
   c. No description of the measurement tool.

Outcome: (Maximum 2 stars)
3) Assessment of the outcome:
   a. Independent blind assessment. **
   b. Record linkage. **
   c. Self report. *
   d. No description.

Total out of 6: _____

Appendix 5. Studies Excluded From This Systematic Review

Author, year	Reason for exclusion
Andreoletti 2015[1]	Not confirmed diagnoses
Aziz 2015[2]	Not intended outcome
Bardella 2009[3]	Did not assess prevalence
Biskou 2016[4]	Did not assess prevalence
Bolgiani 1981[5]	Case series
Bonura 2010[6]	Did not assess prevalence
Bosca 2009[7]	Not intended outcome
Bykova 2016[8]	Not confirmed diagnoses
Conway 2017[9]	Did not assess prevalence
Cottone 2003[10]	Not intended population
D'Argenio 1995[11]	Not confirmed diagnoses
Dahele 2002[12]	Not confirmed diagnoses
Das 2018[13]	Not intended outcome
Ertekin 2010[14]	Not intended outcome
Ferfoglia 1989[15]	Not intended outcome
Freeman 2004[16]	Case report
Glas 2009[17]	Not intended outcome
Ghersin 2018[18]	Not confirmed diagnoses
Grzybowska-Chlebowczyk 2009[19]	Review
Gustafsson 2019[20]	Not confirmed diagnoses
Gutierrez-Achury 2011[21]	Review
Hacsek 1995[22]	Not confirmed diagnoses
Iqbal 2013[23]	Not confirmed diagnoses
Karb 2017[24]	Not confirmed diagnoses
Kotha 2015[25]	Did not assess prevalence
Maglio 2017[26]	Not intended outcome
Mansoor 2018[27]	Not confirmed diagnoses and not intended outcome
Masachs 2007[28]	Not confirmed diagnoses
Mayberry 1986[29]	Not intended population
McGovern 2011[30]	Not confirmed diagnoses
Montalto 2007[31]	Not intended outcome
Parmar 2012[32]	Not intended outcome
Peters 2003[33]	Not intended outcome
Potter 2018[34]	Not confirmed diagnoses
Ricart 2004[35]	Not intended population
Richard-Miceli 2012[36]	Review
Sardu 2012[37]	Not intended outcome
Snook 1989[38]	Did not assess prevalence
Tavakkoli 2013[39]	Not confirmed diagnoses
Therrien 2017[40]	Not confirmed diagnoses
Troncone 2004[41]	Review
Tse 2018[42]	Did not assess prevalence
Volta 1990[43]	Not confirmed diagnoses

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Appendix 7. Quality Assessment of Studies Using a Modified Newcastle-Ottawa Scale for Prevalence Studies

	Selection	Outcome	Total
Study ID	Max. 4	Max. 2	Max. 6
Akin 2012	+ − + +	+ +	+ − + + + +
Akkelle 2019	− − − −	+ +	− − − − + +
Aletaha 2019	+ + + +	+ +	+ + + + + +
Alper 2018	+ + + +	+ +	+ + + + + +
Assa 2017	+ − + +	+ +	+ − + + + +
Basaranoglu 2015	− − + +	+ +	− − + + + +
Bibbò 2017	+ + + +	+ +	+ + + + + +
Biedermann 2018	+ + + +	+ +	+ + + + + +
Bizzaro 2003	− − + +	+ +	− − + + + +
Bosca-Watts 2018	+ + + +	+ +	+ + + + + +
Breen 1987	+ + + +	+ +	+ + + + + +
Canova 2017	+ + + +	+ +	+ + + + + +
Casella 2010	+ + + +	+ +	+ + + + + +
Casellas 2016	− − + +	+ +	− − + + + +
Collin 1994	+ + + +	+ +	+ + + + + +
Conti 2018	+ + + +	+ +	+ + + + + +
Cooper 1978	+ + + +	+ +	+ + + + + +
Cuoco 2014	+ + + +	+ +	+ + + + + +
Damoiseaux 2002	+ + + +	+ +	+ + + + + +

Appendix 7. Continued

Study ID	Selection Max. 4	Outcome Max. 2	Total Max. 6
De Carvalho 2018	+ − + +	+ +	+ − + + + +
Delcò 1999	+ + + +	+ +	+ + + + + +
Dhaliwal 2009	+ − − −	+ +	+ − − − + +
Dominguez Castro 2017	+ + + +	+ +	+ + + + + +
El-Matary 2012	+ + + +	+ +	+ + + + + +
Giorgetti 2006	+ + + +	+ +	+ + + + + +
Grode 2018	+ + + +	+ +	+ + + + + +
Halling 2017	+ + + +	+ +	+ + + + + +
Hernandez Camba 2013	+ + + +	+ +	+ + + + + +
Inserra 2011	+ + + +	+ +	+ + + + + +
Jandaghi 2015	+ − + +	+ +	+ − + + + +
Jansson-Knodell 2018	+ − + +	− −	+ − + + − −
Juhász 2012	+ − + +	− −	+ − + + − −
Klincewicz 2007	− − + +	+ +	− − + + + +
Kocsis 2015	+ − + +	+ +	+ − + + + +
Korponay-Szabó 1993	− − + +	+ +	− − + + + +
Kull 1999	+ + + +	+ +	+ + + + + +
Lakatos 2003	+ − + +	+ +	+ − + + + +
Leeds 2007	+ + + +	+ +	+ + + + + +

Appendix 7. Continued

Study ID	Selection Max. 4	Outcome Max. 2	Total Max. 6
Limketkai 2018	+ − + +	+ +	+ − + + + +
Lu 2015	+ + + −	+ +	+ + + − + +
Malmborg 2017	+ + + +	+ +	+ + + + + +
Mantzaris 2005	+ + + +	+ +	+ + + + + +
Merrick 2015	+ + + +	+ +	+ + + + + +
Motta 2018	− − + +	+ +	− − + + + +
Nijhawan 2013	+ + + +	+ +	+ + + + + +
Oxford 2013	+ + + +	+ +	+ + + + + +
Paolella 2014	− − − −	+ +	− − − − + +
Perez 2017	+ + + +	+ +	+ + + + + +
Prinzbach 2018	+ + + +	+ +	+ + + + + +
Ribeiro-Cabral 2011	+ + + +	+ +	+ + + + + +
Rönnblom 2015	+ + + +	+ +	+ + + + + +
Sjöberg 2002	− − − −	+ +	− − − − + +
Sood 2003	+ + + +	− −	+ + + + + +
Spijkerman 2016	+ + + +	+ +	+ + + + + +
Szaflarska-Poplawska 2016	+ + + +	+ +	+ + + + + +
Taghvaii 2014	+ + + +	+ +	+ + + + + +
Tavakkoli 2012	+ − + +	+ +	+ − + + + +

Appendix 7. Continued

Study ID	Selection Max. 4	Outcome Max. 2	Total Max. 6
Toumi 2007	++++	++	++++ ++
Tursi 2005	+−++	++	+−++ ++
Ventura 1999	−−++	++	−−++ ++
Virta 2013	++++	++	++++ ++
Watanabe 2014	−−++	++	−−++ ++
Yang 2005	++++	++	++++ ++
Yehuda 2019	++++	++	++++ ++
Zwolinska-Wcislo 2009	−−++	++	−−++ ++

NOTE. The plus and minus signs are used to display whether points were awarded for the Newcastle-Ottawa Scale for Prevalence studies (Appendix 4). If a study received full points on the Newcastle-Ottawa Scale, it would be awarded 6 plus signs (or stars). If a study did not receive full points on a question, the corresponding entry in Appendix 7 would have a minus sign.

Appendix 8. Summary of All Studies Evaluating the Prevalence of CeD in IBD

Study, year	Country	Age category	No. celiac per group				
			IBD	Crohn's	UC	IC	Controls
Cohort studies							
Aletaha 2019	US	Adults	2.9/1000[a]	-	-	-	0.2/1000[a]
Alper 2018	US	Children	1/130	0/75	1/55	-	12/257
Bierdermann 2018	Switzerland	Adults	9/2019	-	-	-	-
Casella 2010	Italy	Adults	9/1711	3/860	6/791	0/60	-
Cuoco 2014	Italy	Adults	0/179	0/71	0/108	-	-
Dhaliwal 2009	Canada	Adults	0/150	0/150	-	-	-
El-Matary 2012	Canada	Children	1/164	0/85	1/79	-	1/164
Giorgetti 2006	Italy	Adults	8/48	8/48	-	-	-
Jandaghi 2015	Iran	Adults	1/406	0/206	1/200	-	1/166
Klincewicz 2007	Poland	Children	6/136	4/49	2/87	-	-
Lakatos 2003	Hungary	Both	2/873	1/254	1/619	-	-
Malmborg 2017	Sweden	Children	12/256	9/190	3/60	0/6	-
Mantzaris 2005	Greece	Adults	6/639	1/281	5/358	-	-
Merrick 2015	UK, Scotland, Canada	Children	4/809	4/533	0/204	0/72	-
Perez 2017	UK	Children	8/578	-	-	-	-
Rönnblom 2015	Sweden	Both	17/790	4/264	13/526	-	-
Szaflarska-Poplawska 2016	Poland	Both	0/71	0/71	-	-	-
Tursi 2005	Italy	Adults	5/27	5/27	-	-	-
Virta 2013	Finland	Children	13/595	4/233	9/362	-	14/2380
Watanabe 2014	Japan	Adults	0/172	0/62	0/110	-	0/190
Yehuda 2019	Israel	Adults	141/12625	96/6364	45/6261	0/342	51/12625
Zwolinska-Wcislo 2009	Poland	Adults	4/80	-	4/80	-	-
Case-control studies							
Bizzaro 2003	Italy	Adults	1/170	0/70	1/100	-	0/120
Kull 1999	Estonia	Adults	0/50	-	0/50	-	0/53
Leeds 2007	UK	Adults	3/354	1/173	2/154	0/18	5/601
Ribeiro-Cabral 2014	Brazil	Adults	0/33	0/33	-	-	4/45
Cross-sectional studies							
Akkelle 2019	Turkey	Children	0/125	0/57	0/66	0/2	-
Casellas 2016	Spain	Adults	5/407	-	-	-	0.47%[b]
de Carvalho 2018	Brazil	Adults	0/83	0/36	0/47	-	-
Halling 2017	Denmark	Adults	280/47325	133/13343	132/31066	15/2916	92/92839
Korponay-Szabó 1993	Hungary	Children	1/38	-	-	-	11/718
Limketkai 2018	US	Adults	5/102	-	-	-	-
Lu 2015	Canada	-	10/780	-	-	-	-
Oxford 2013	US	Adults	393/33963	220/17288	173/16675	-	42/17503
Sjöberg 2002	Sweden	Adults	0/57	0/34	0/23	-	0/44
Taghvaii 2014	Iran	Adults	0/84	-	0/84	-	-
Tavakkoli 2012	Iran	Adults	9/100	3/30	6/70	-	-

NOTE. According to the study findings, red means that the study concluded that there was higher prevalence of celiac disease in IBD OR prevalence >1.5%; green means the study concluded that there was a lower prevalence of celiac disease in IBD OR prevalence <0.2%. - means no data available.

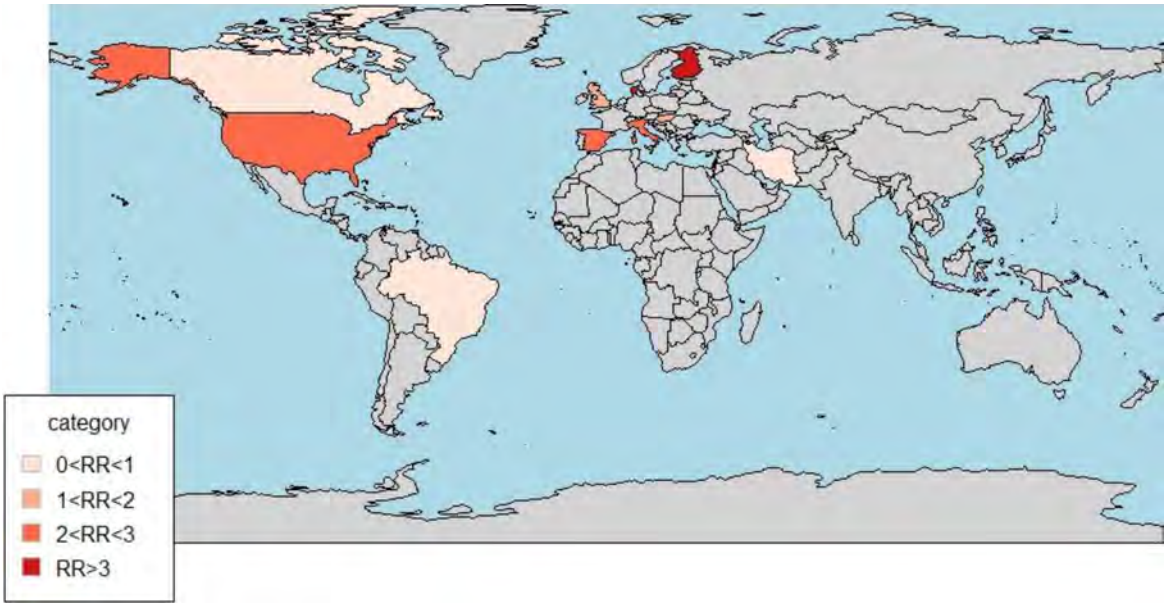
[a]This number represents the incidence rate per 1000.

[b]The control used in this study was based on previously published findings on the prevalence from the same region.

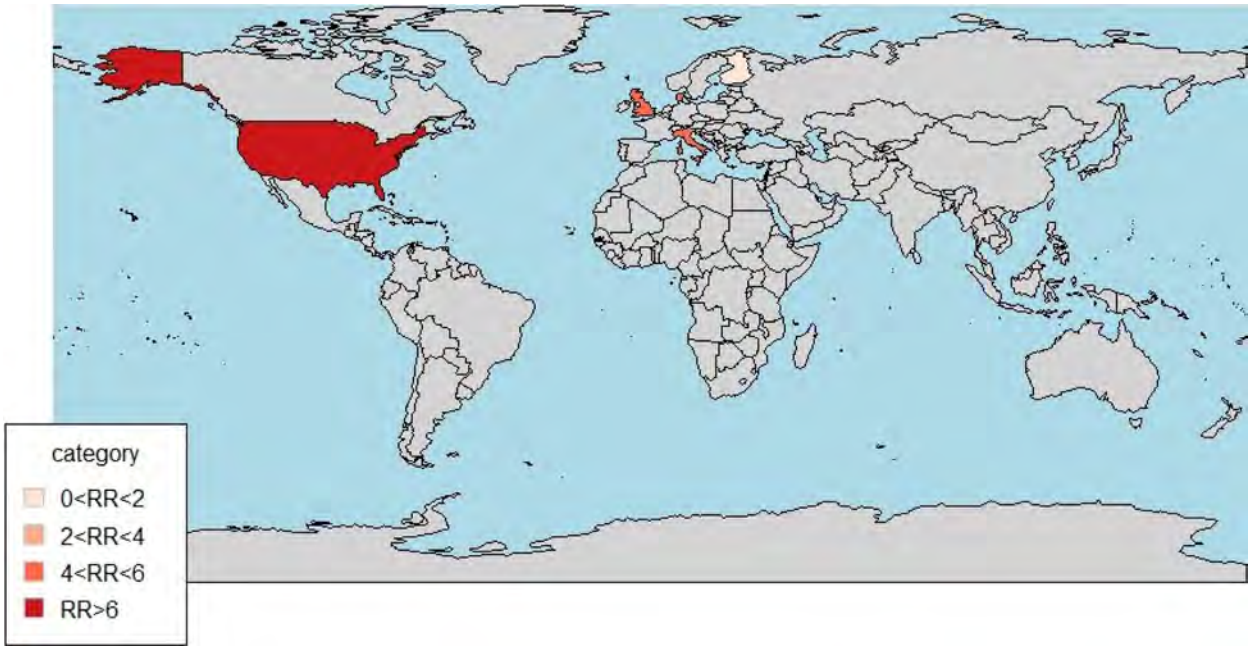
Appendix 9. Summary of All Studies Evaluating the Prevalence of IBD in CeD

			# IBD		# Crohn's		# UC	
Study, year	Country	Age	Celiac	Control	Celiac	Control	Celiac	Control
Cohort Studies								
Akin 2012	Turkey	Adults	1/22	-	1/22	-	0/22	-
Aletaha 2019	Turkey	Adults	10/1000[a]	0.5/1000*	-	-	-	-
Basaranoglu 2015	Turkey	-	5/198	-	1/198	-	4/198	-
Breen 1987	Ireland	Adults	3/42	-	0/42	-	3/42	-
Canova 2017	Italy	Children	29/1294	6/6470	11/1294	3/6470	10/1294	2/6470
Collin 1994	Finland	Adults	1/335	7/335	-	-	-	-
Cooper 1978	UK	Adults	4/314	-	1/314	-	3/314	-
Cuoco 2014	Italy	Adults	0/744	-	0/744	-	0/744	-
Damoiseaux 2002	Netherlands	Both	0/37	0/35	0/37	0/35	0/37	0/35
Dominguez Castro 2017	Ireland	Adults	14/749	-	6/749	-	8/749	-
Jansson-Knodell 2018	US	Adults	4/282	-	4/282	-	0/282	-
Juhász 2012	Hungary	Adults	6/132	-	6/132	-	0/132	-
Kocsis 2015	Hungary	Adults	8/245	-	6/245	-	2/245	-
Mantzaris 2005	Greece	Adults	6/53	-	1/53	-	5/53	-
Nijhawan 2013	India	Both	2/363	-	0/363	-	2/363	-
Sood 2003	India	Adults	3/96	-	0/96	-	3/96	-
Spijkerman 2016	Netherlands	Adults	6/412	-	-	-	-	-
Ventura 1999	Italy	Both	2/909	3/1268	0/909	0/1268	2/909	3/1268
Yang 2005	US	Adults	10/455	362/ 100,000	5/455	133/ 100,000	5/455	229/100,000
Case-control studies								
Bibbò 2017	Italy	Adults	6/255	-	3/255	-	3/255	-
Delcò 1999	US	Adults	13/458	18/2692	8/458	6/2692	5/458	12/2692
Leeds 2007	UK	Adults	5/305	2/601	0/305	1/601	5/305	1/601
Paolella 2014	Italy	Children	0/350	0/350	0/350	0/350	0/350	0/350
Cross-sectional studies								
Assa 2017	Israel	Teens	27/7145	1483/ 1580896	-	-	-	-
Conti 2018	Italy	Adults	1/341	-	-	-	-	-
Grode 2018	Denmark	Both	462/ 10285	1105/ 104928	140/ 10285	238/ 104928	322/ 10285	867/ 104928
Hernandez Camba 2013	Spain	Adults	4/91	-	3/91	-	1/91	-
Inserra 2011	Italy	Adults	80/1268	1.61%[b]	-	-	-	-
Prinzbach 2018	US	Children	10/433	11/4330	10/433	8/4330	0/433	3/4330

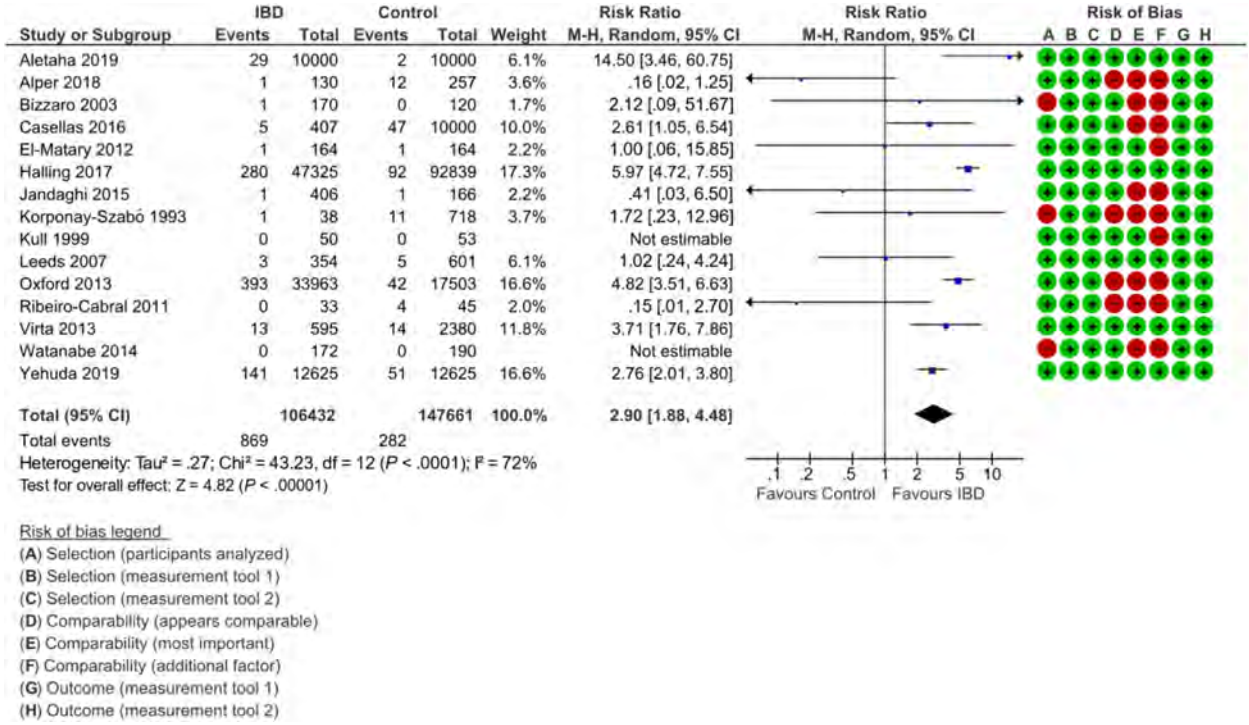
NOTE. According to the study findings, red means that the study concluded that there was higher prevalence of IBD in celiac disease OR prevalence >1.0%; green means the study concluded that there was a lower prevalence of celiac disease in IBD OR prevalence <0.2%.
[a]This number represents the incidence rate per 1000.
[b]Rate given by abstract.



Appendix 10. Global Risk of CeD in IBD vs Controls

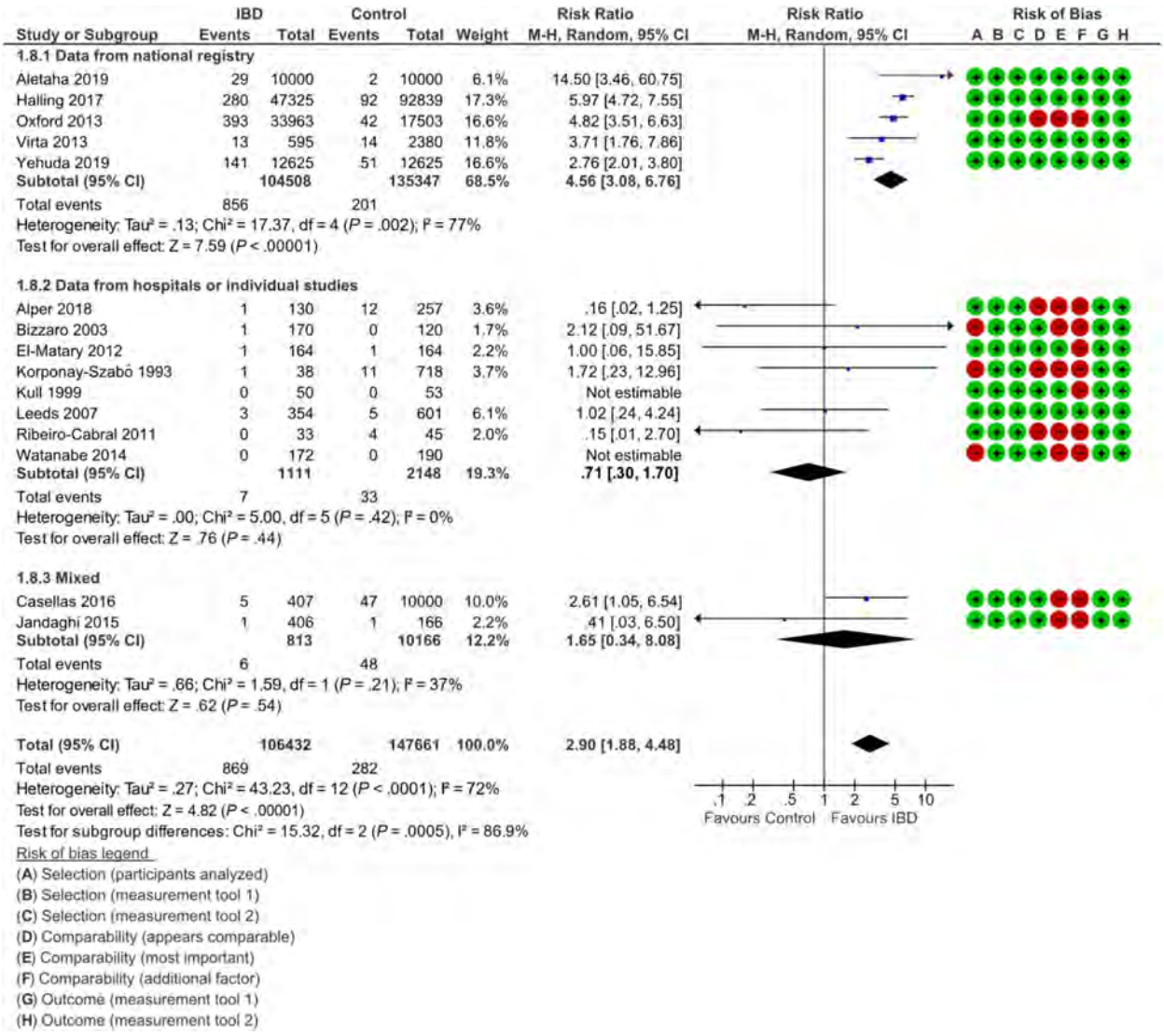


Appendix 11. Global Risk of IBD in CeD vs Controls

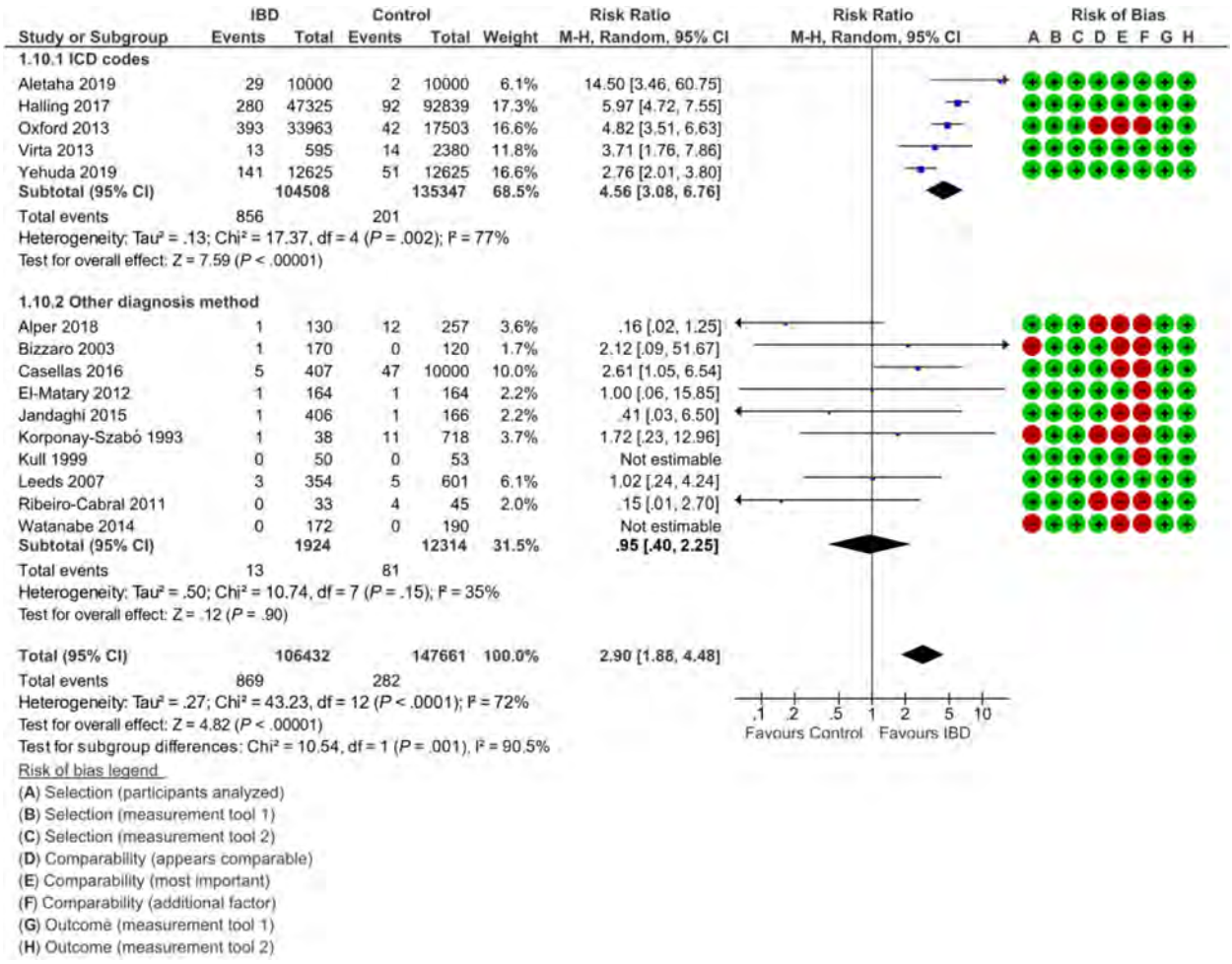


Risk of bias legend
(A) Selection (participants analyzed)
(B) Selection (measurement tool 1)
(C) Selection (measurement tool 2)
(D) Comparability (appears comparable)
(E) Comparability (most important)
(F) Comparability (additional factor)
(G) Outcome (measurement tool 1)
(H) Outcome (measurement tool 2)

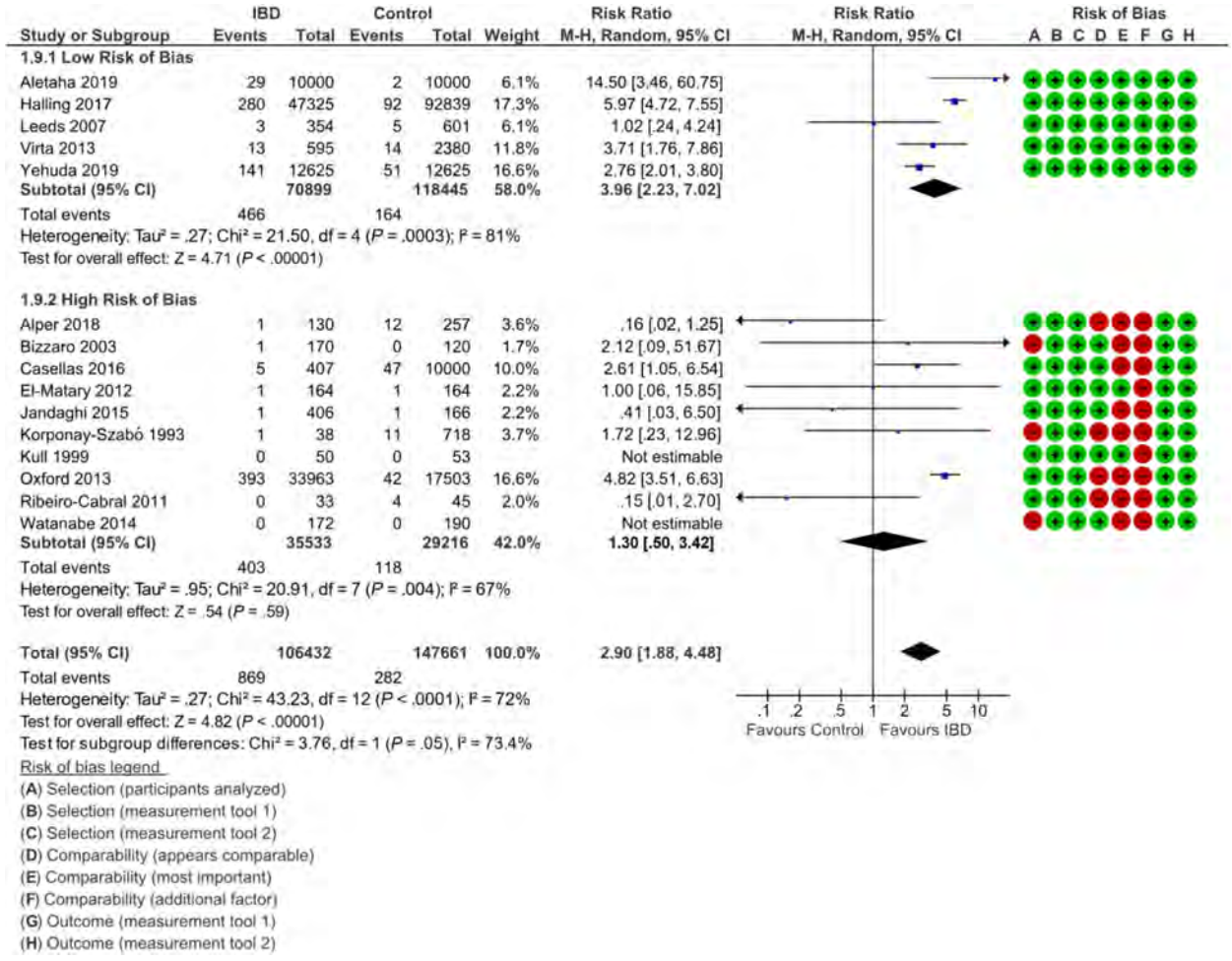
Appendix 12. CeD in IBD vs Controls



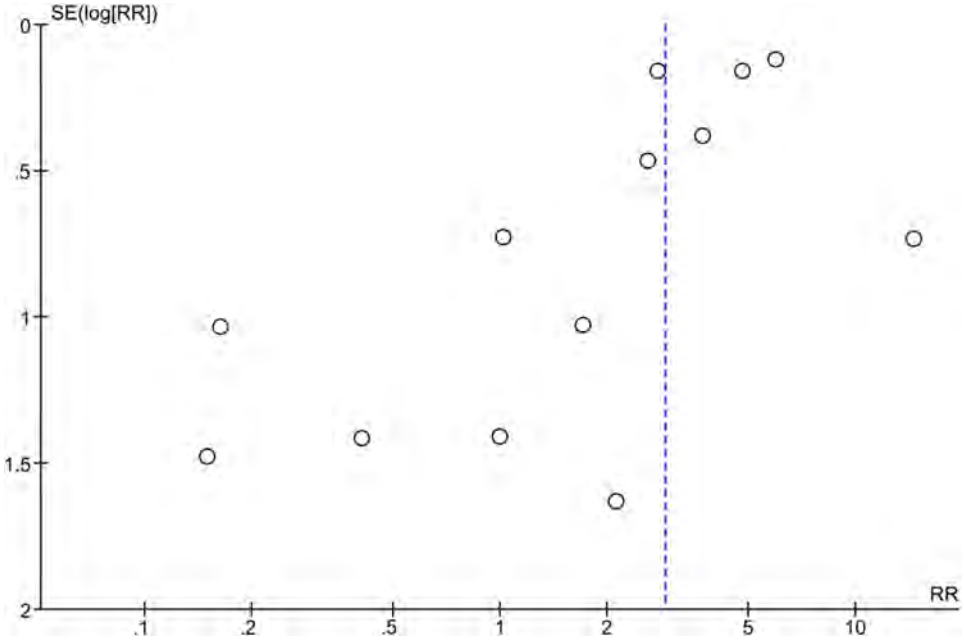
Appendix 13. CeD in IBD vs Controls Subgrouped by Data Source



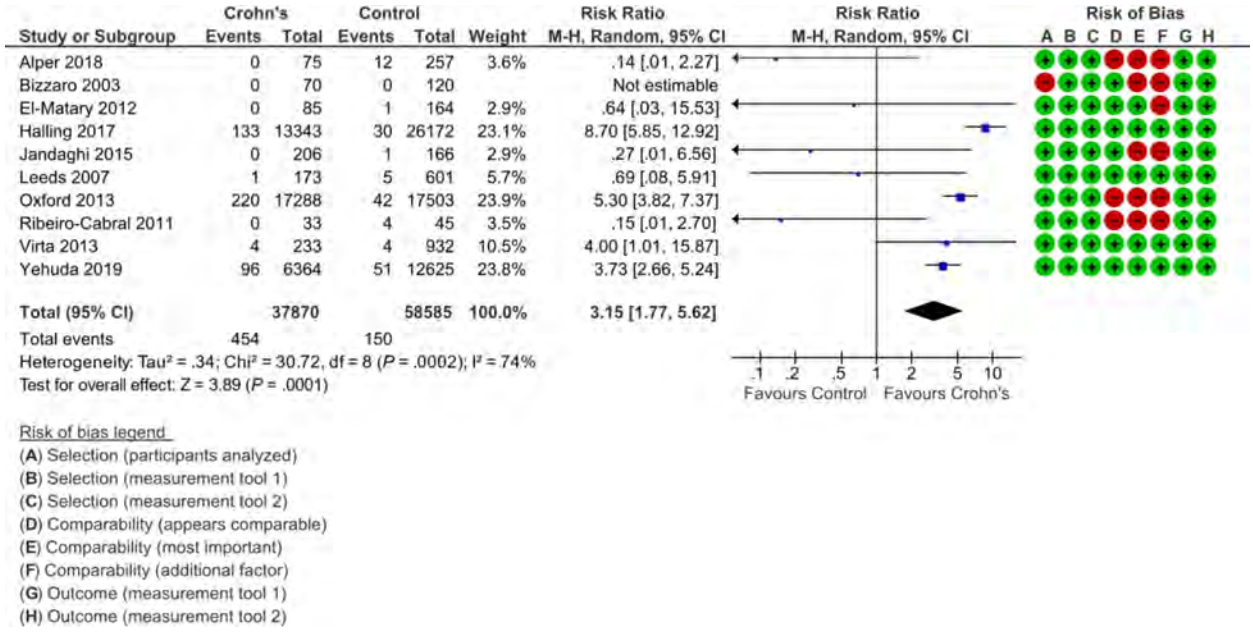
Appendix 14. CeD in IBD vs Controls Subgrouped by Diagnosis Method



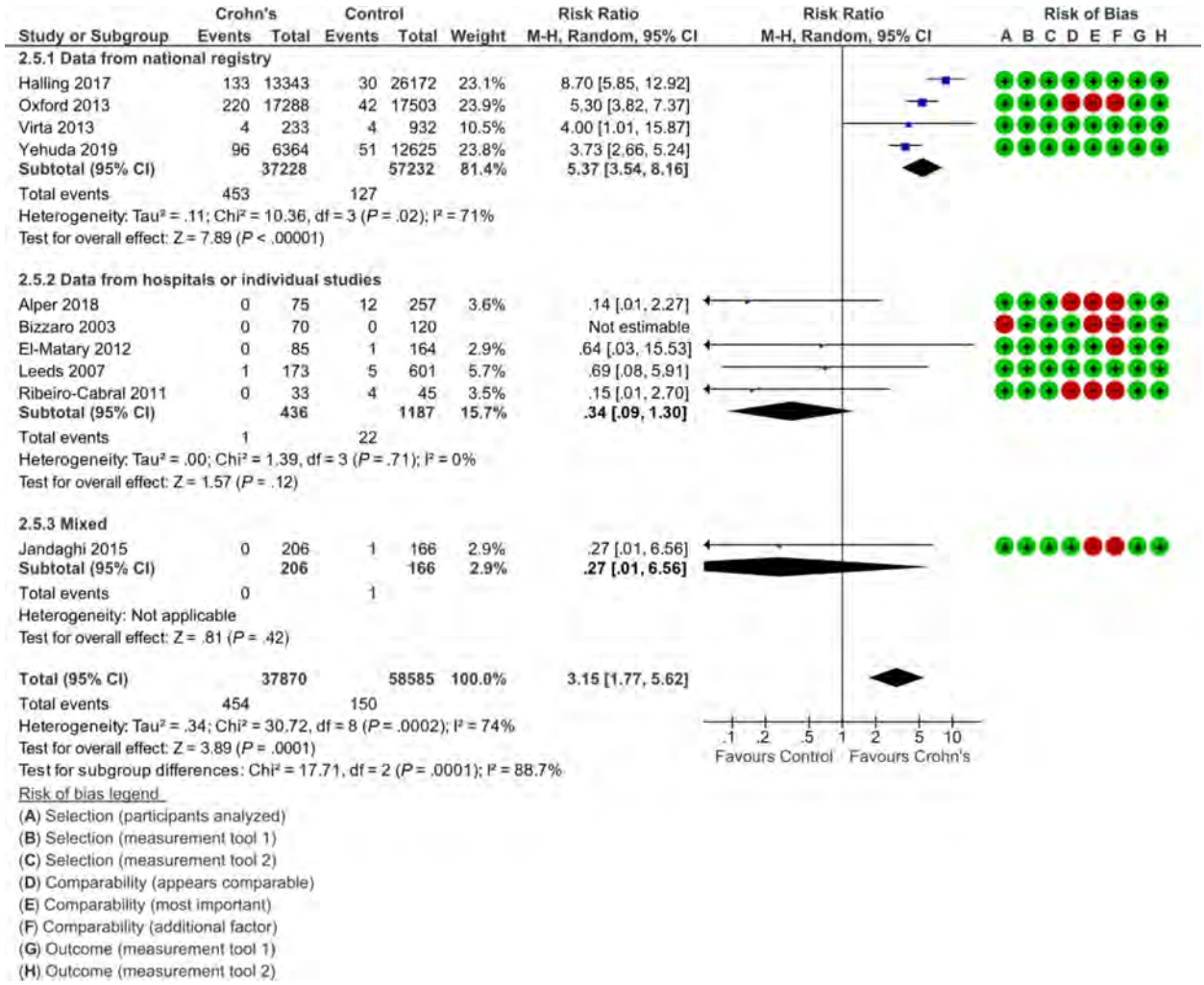
Appendix 15. CeD in IBD vs Controls Subgrouped by Risk of Bias



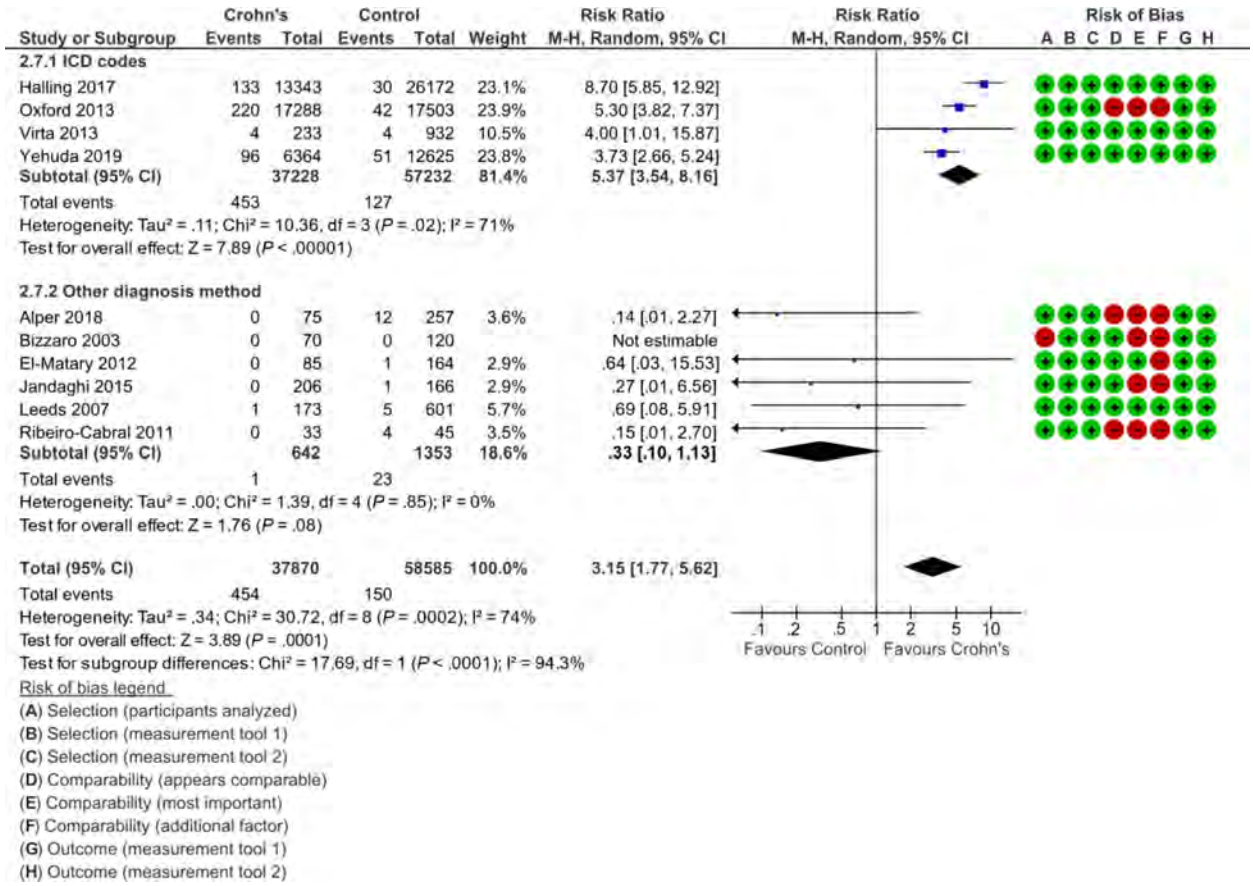
Appendix 16. CeD in IBD vs Controls Funnel Plot



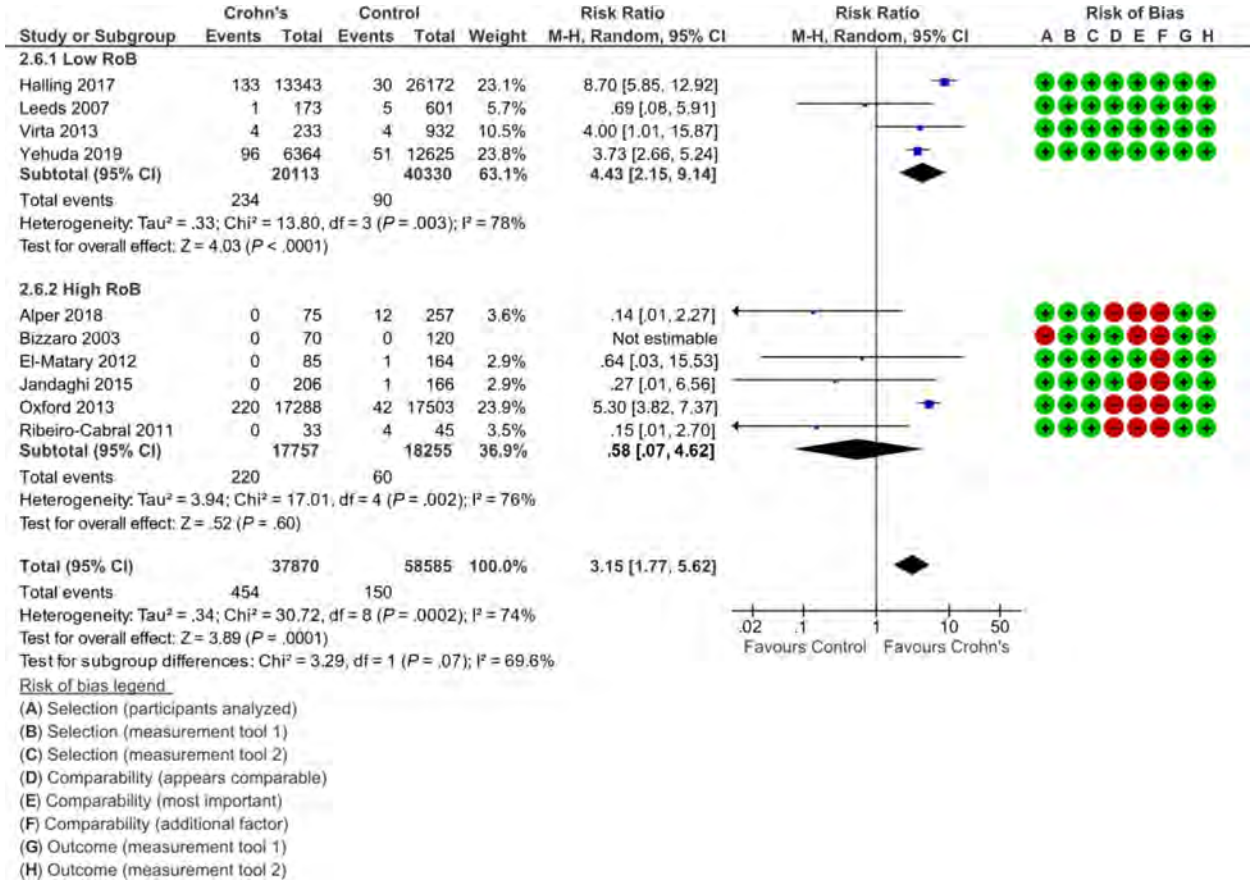
Appendix 17. CeD in Crohn's Disease vs Controls



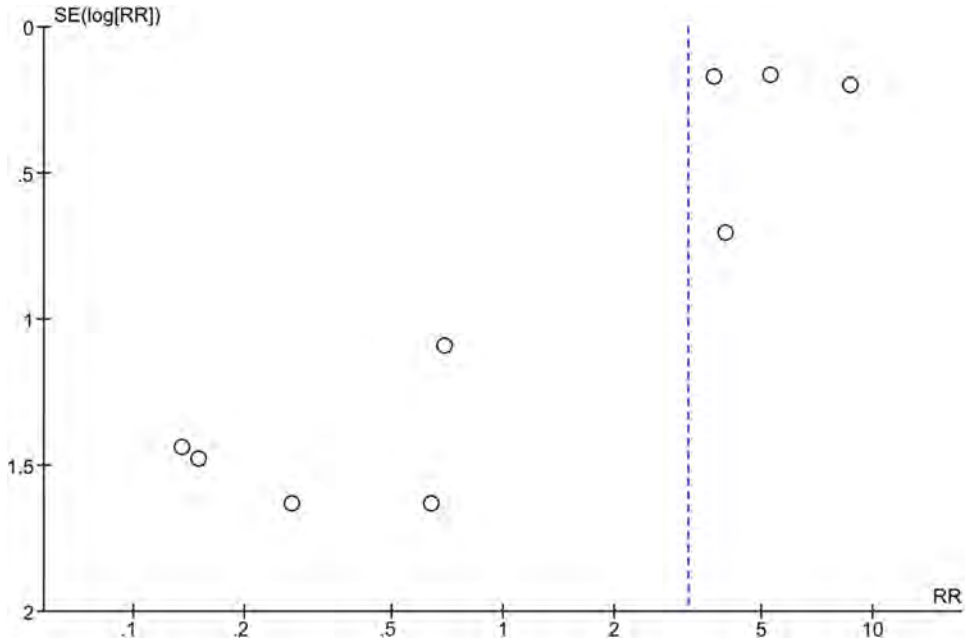
Appendix 18. CeD in Crohn's Disease vs Controls Subgrouped by Data Source



Appendix 19. CeD in Crohn's Disease vs Controls Subgrouped by Diagnosis Method

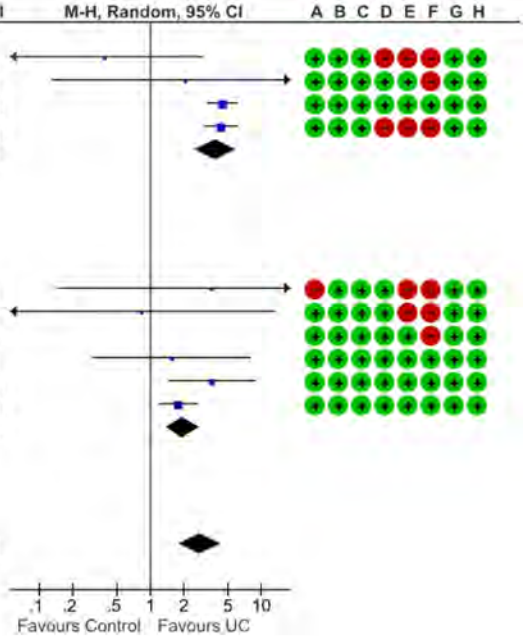


Appendix 20. CeD in Crohn's Disease vs Controls Sub-grouped by Risk of Bias



Appendix 21. CeD in Crohn's Disease vs Controls Funnel Plot

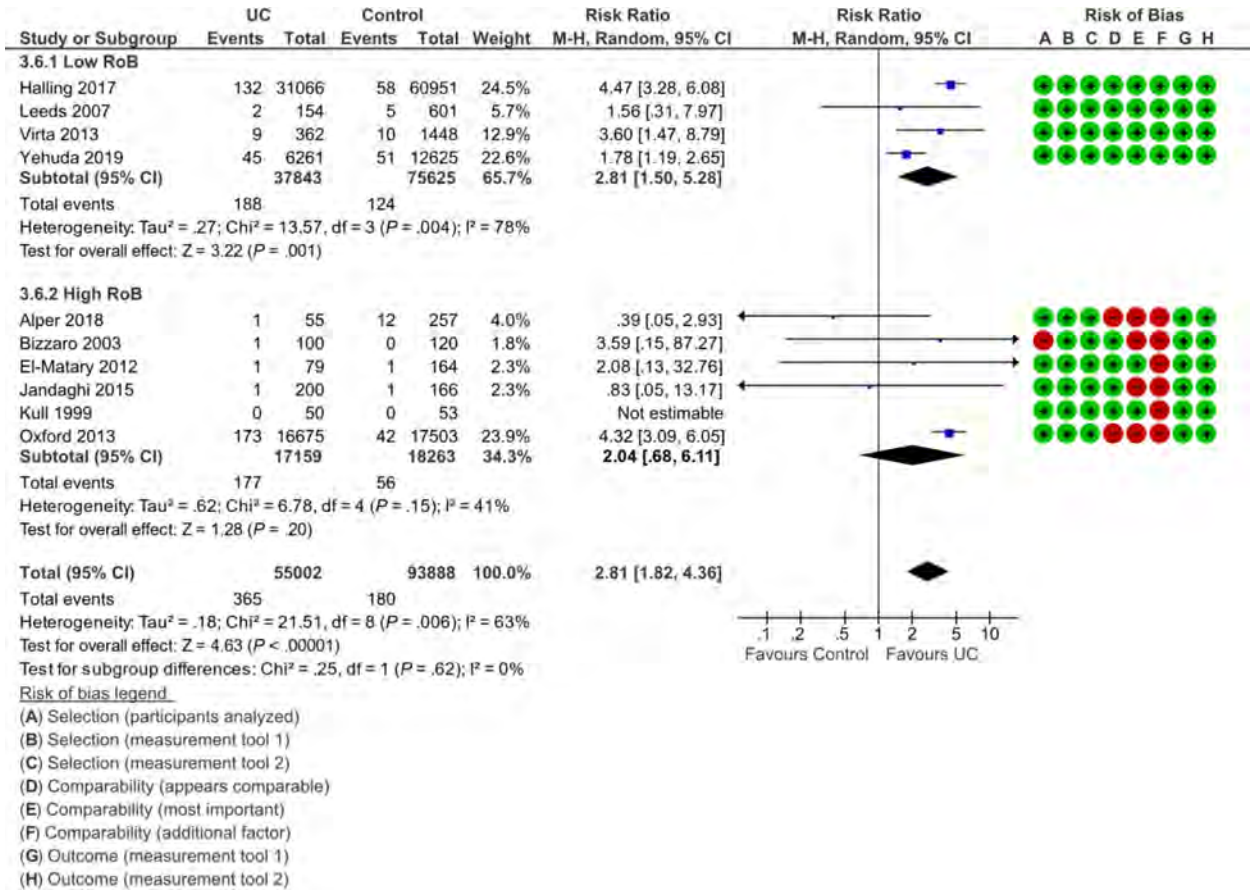
Study or Subgroup	UC Events	UC Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Country - NA						
Alper 2018	1	55	12	257	4.0%	.39 [.05, 2.93]
El-Matary 2012	1	79	1	164	2.3%	2.08 [.13, 32.76]
Halling 2017	132	31066	58	60951	24.5%	4.47 [3.28, 6.08]
Oxford 2013	173	16675	42	17503	23.9%	4.32 [3.09, 6.05]
Subtotal (95% CI)		**47875**		**78875**	**54.7%**	**3.92 [2.57, 5.96]**
Total events	307		113			
Heterogeneity: Tau² = .07; Chi² = 5.77, df = 3 (*P* = .12); I² = 48%						
Test for overall effect: Z = 6.37 (*P* < .00001)						
3.3.2 Country - Non-NA						
Bizzaro 2003	1	100	0	120	1.8%	3.59 [.15, 87.27]
Jandaghi 2015	1	200	1	166	2.3%	.83 [.05, 13.17]
Kull 1999	0	50	0	53		Not estimable
Leeds 2007	2	154	5	601	5.7%	1.56 [.31, 7.97]
Virta 2013	9	362	10	1448	12.9%	3.60 [1.47, 8.79]
Yehuda 2019	45	6261	51	12625	22.6%	1.78 [1.19, 2.65]
Subtotal (95% CI)		**7127**		**15013**	**45.3%**	**1.96 [1.38, 2.79]**
Total events	58		67			
Heterogeneity: Tau² = .00; Chi² = 2.60, df = 4 (*P* = .63); I² = 0%						
Test for overall effect: Z = 3.77 (*P* = .0002)						
Total (95% CI)		**55002**		**93888**	**100.0%**	**2.81 [1.82, 4.36]**
Total events	365		180			
Heterogeneity: Tau² = .18; Chi² = 21.51, df = 8 (*P* = .006); I² = 63%						
Test for overall effect: Z = 4.63 (*P* < .00001)						
Test for subgroup differences: Chi² = 6.10, df = 1 (*P* = .01); I² = 83.6%						



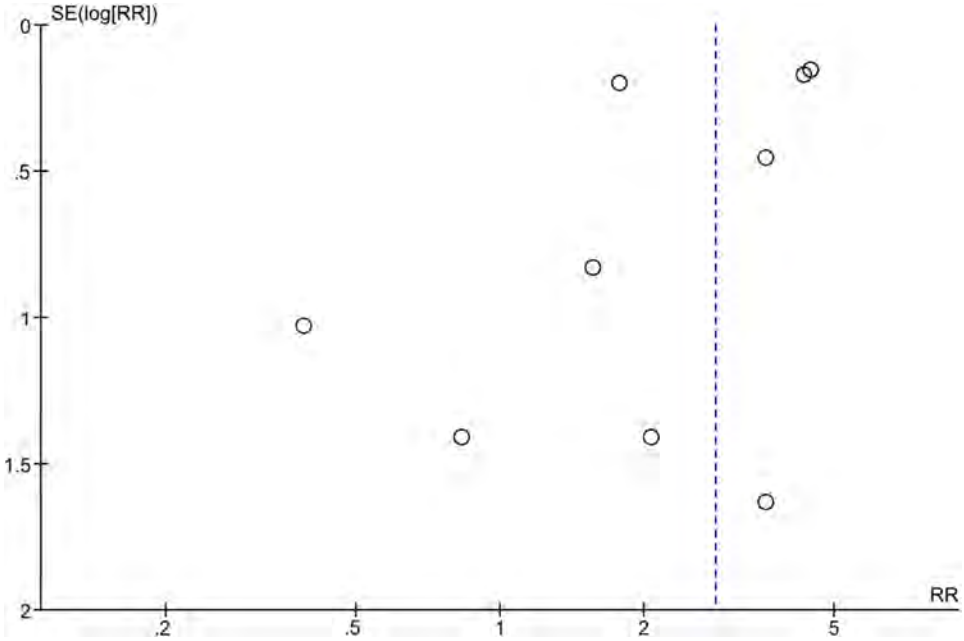
Risk of bias legend

(**A**) Selection (participants analyzed)
(**B**) Selection (measurement tool 1)
(**C**) Selection (measurement tool 2)
(**D**) Comparability (appears comparable)
(**E**) Comparability (most important)
(**F**) Comparability (additional factor)
(**G**) Outcome (measurement tool 1)
(**H**) Outcome (measurement tool 2)

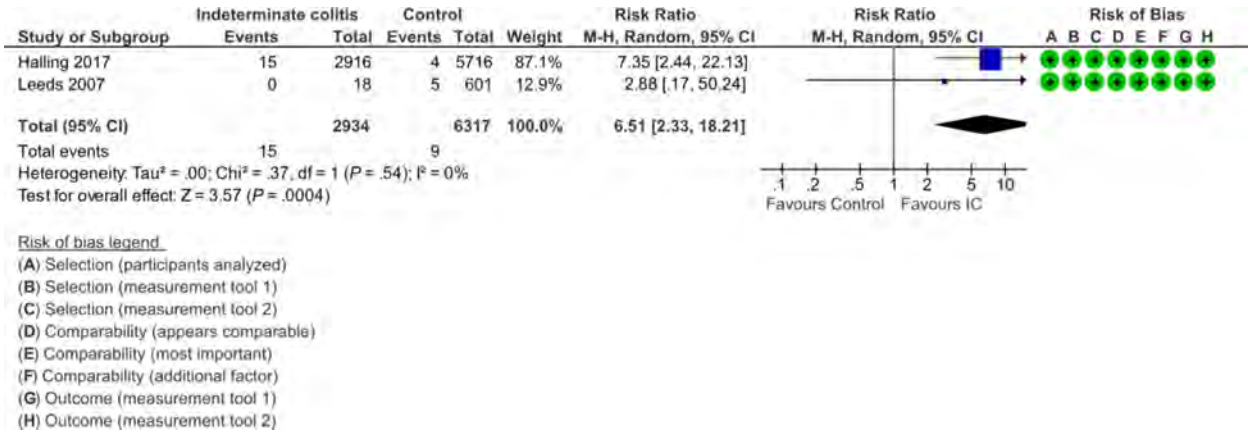
Appendix 22. CeD in UC vs Controls Subgrouped by Country



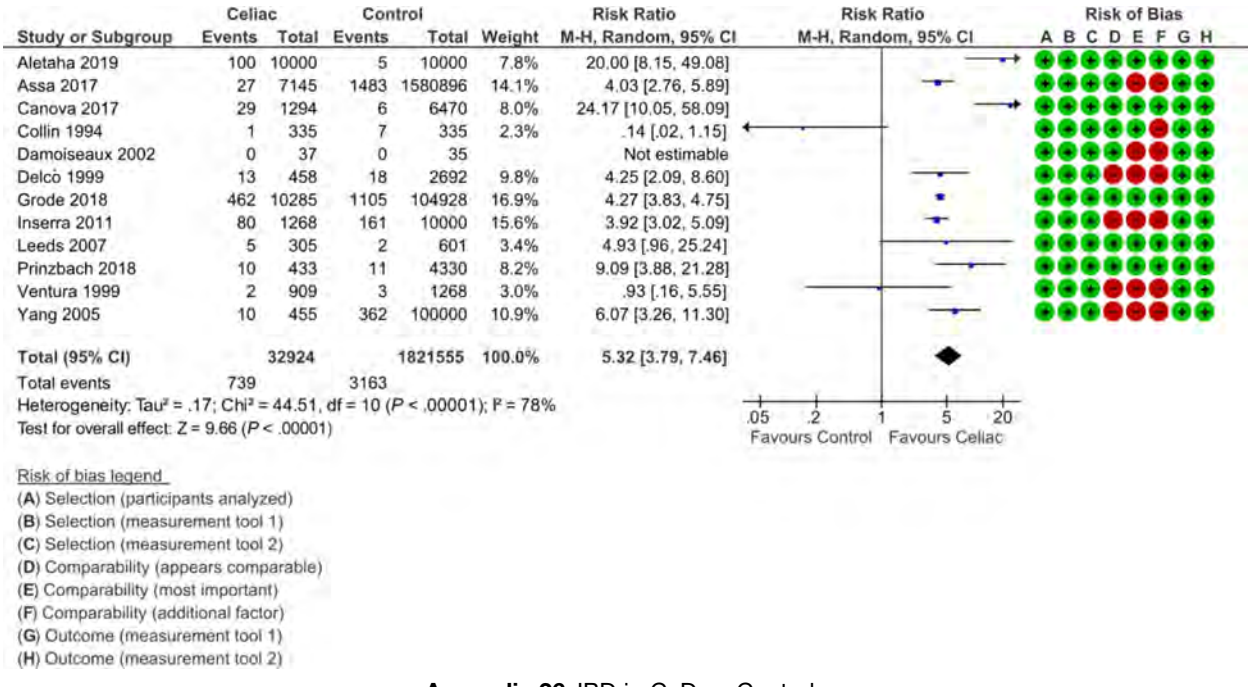
Appendix 23. CeD in UC vs Controls Sub-grouped by Risk of Bias



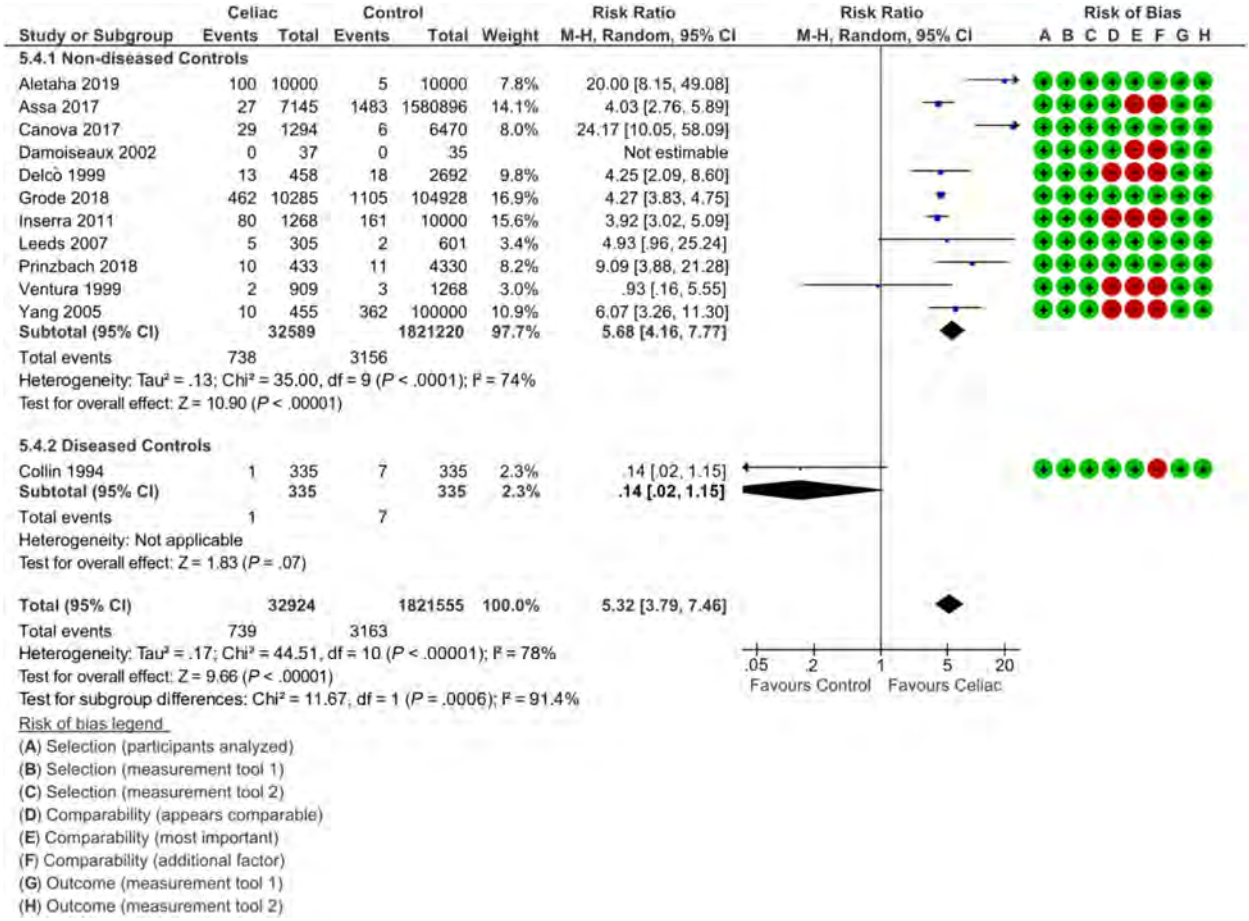
Appendix 24. CeD in UC vs Controls Funnel Plot



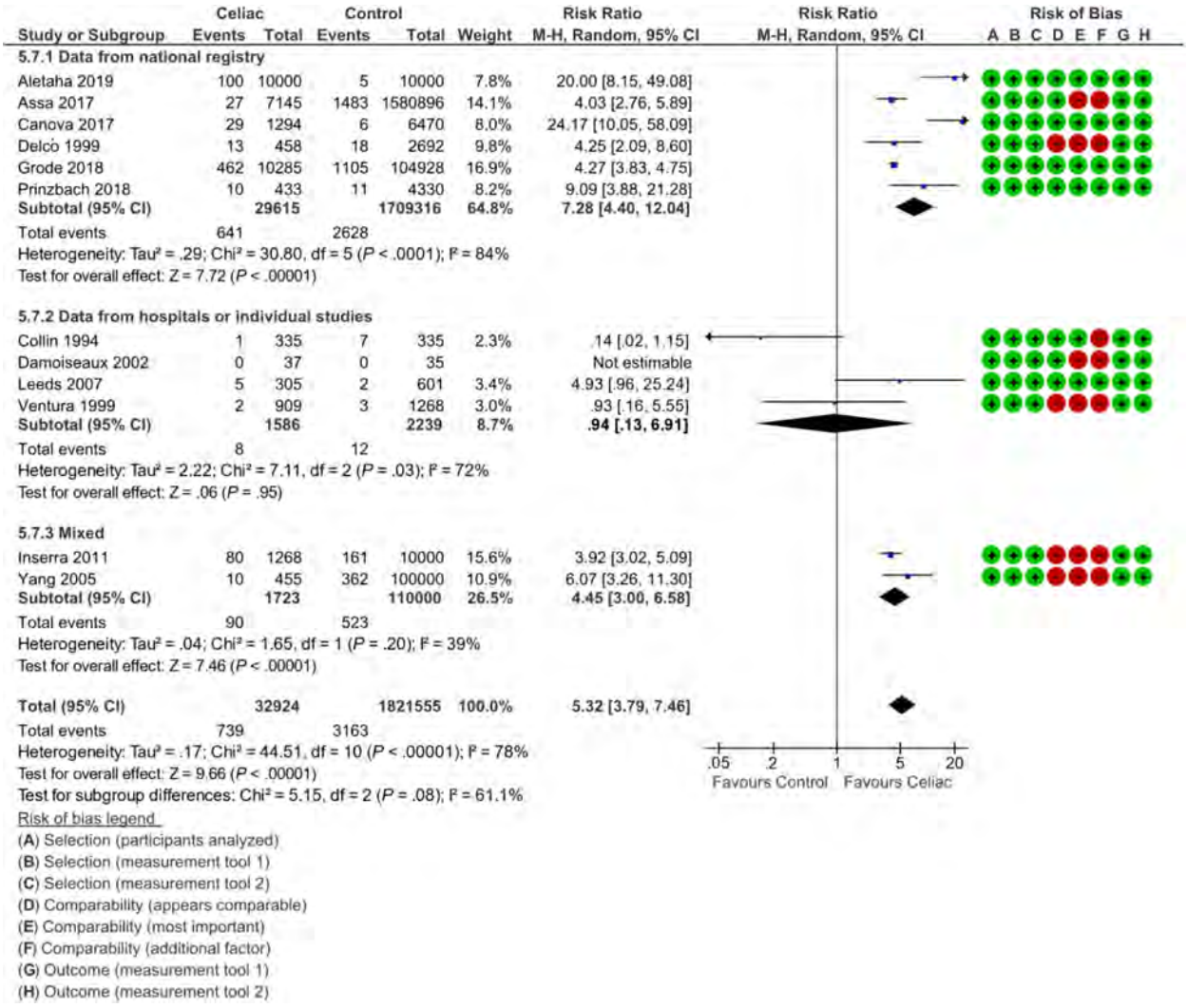
Appendix 25. CeD in IC vs Controls



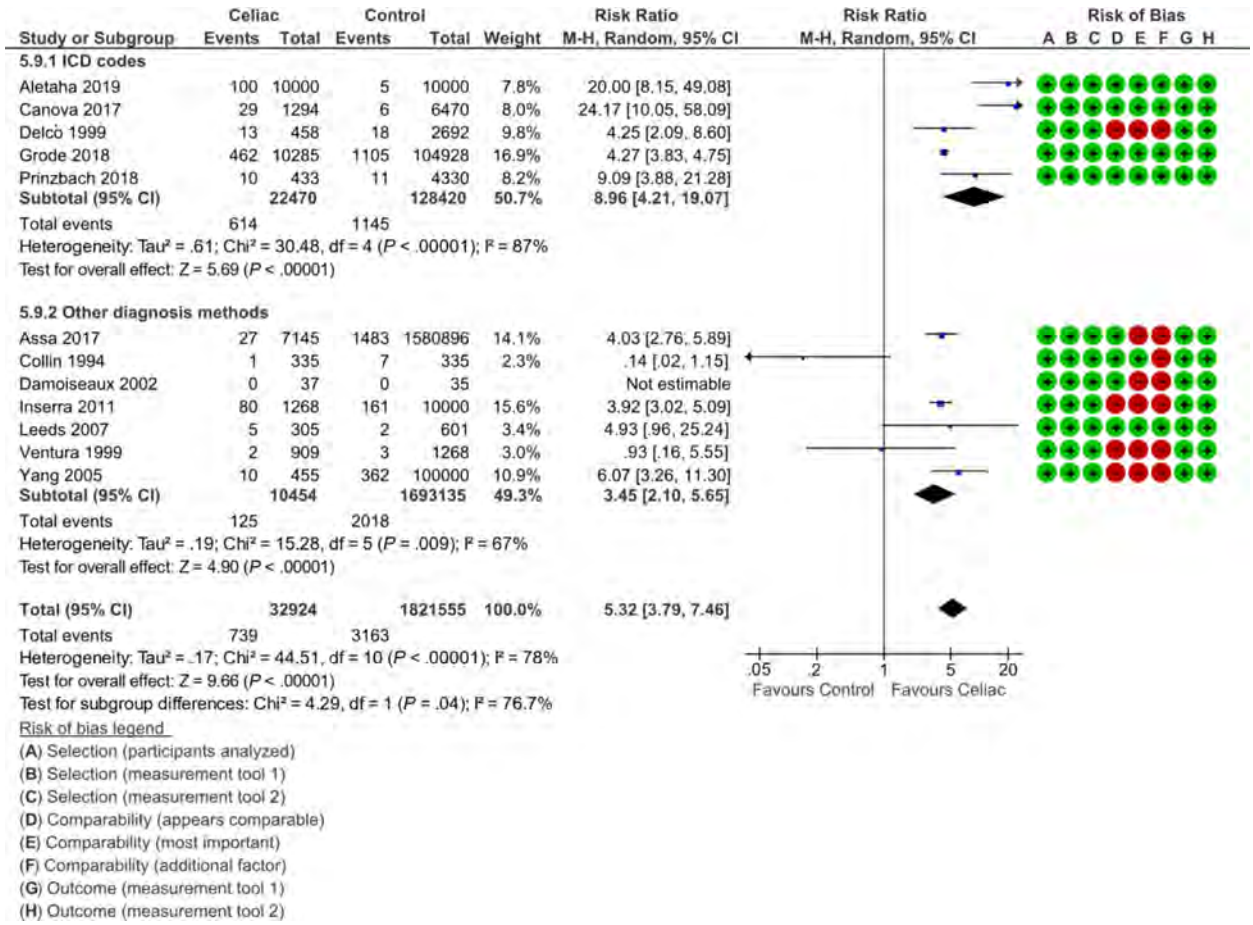
Appendix 26. IBD in CeD vs Controls



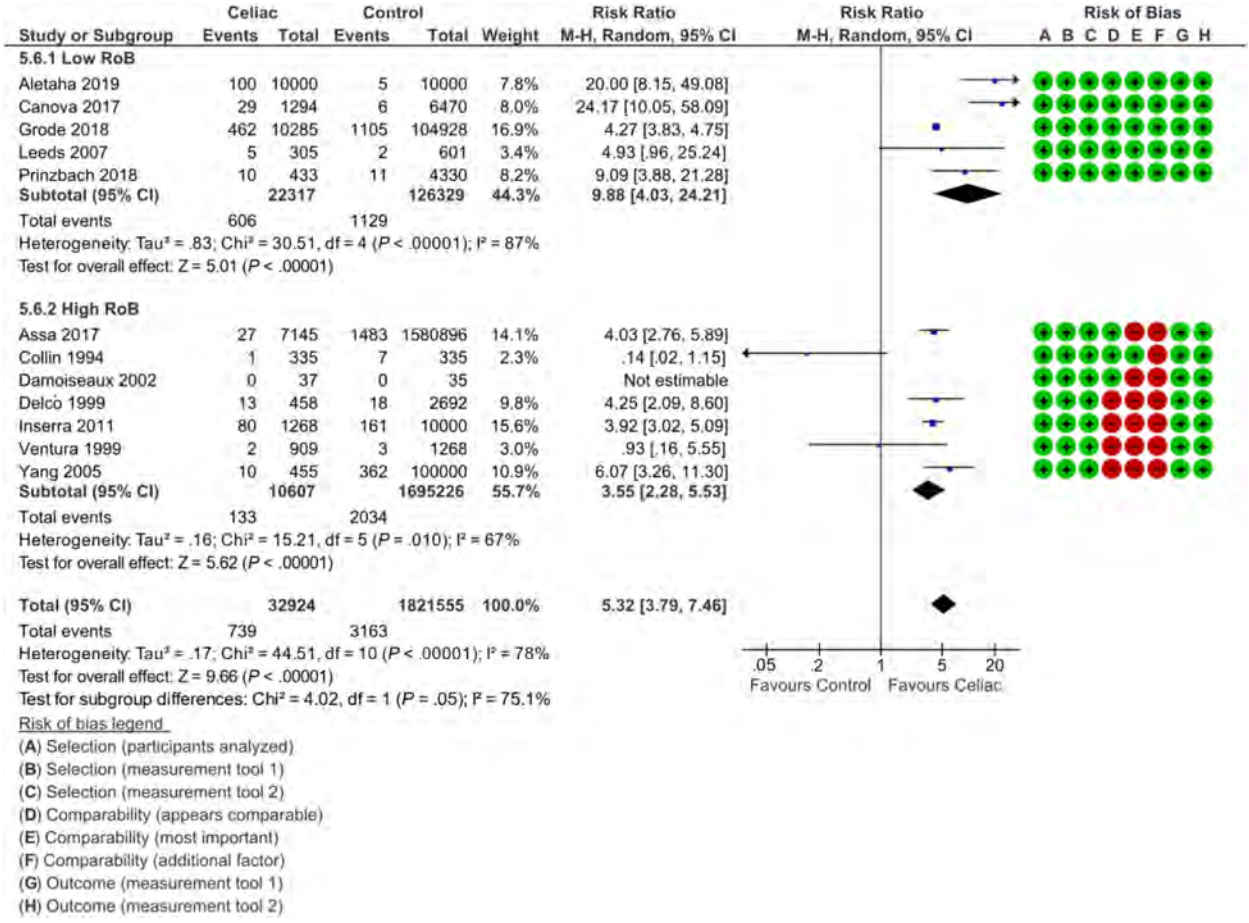
Appendix 27. IBD in CeD vs Controls Subgrouped by Control Type



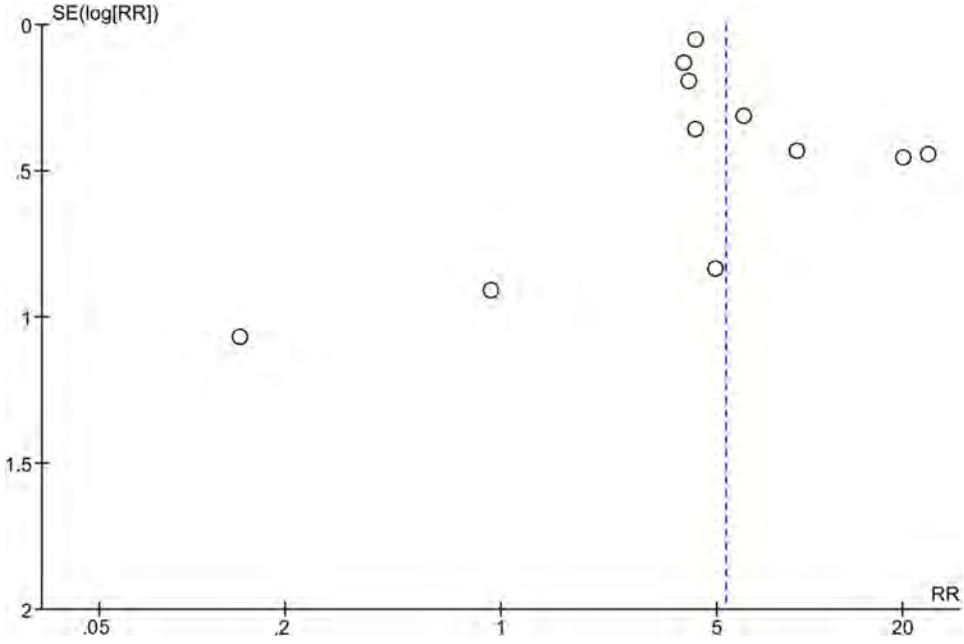
Appendix 28. IBD in CeD vs Controls Subgrouped by Data Source



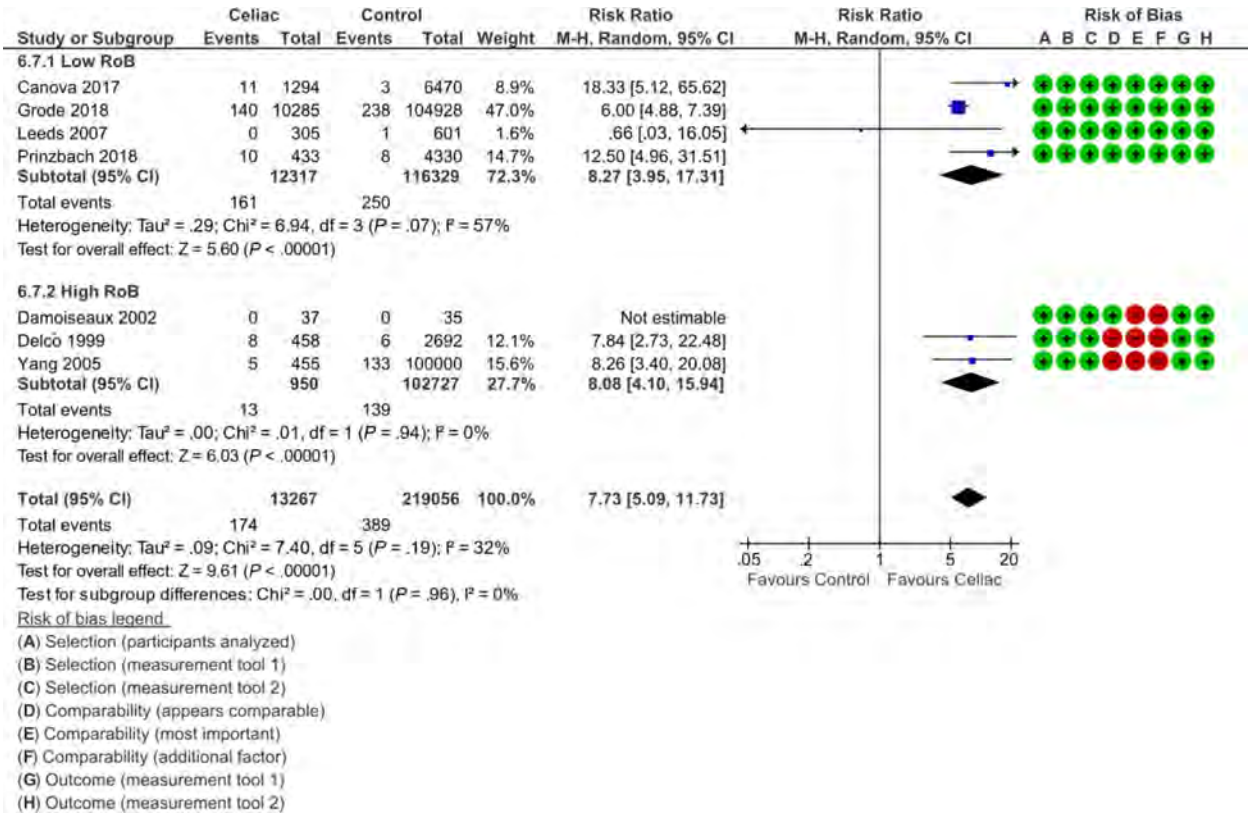
Appendix 29. IBD in CeD vs Controls Subgrouped by Diagnosis Method



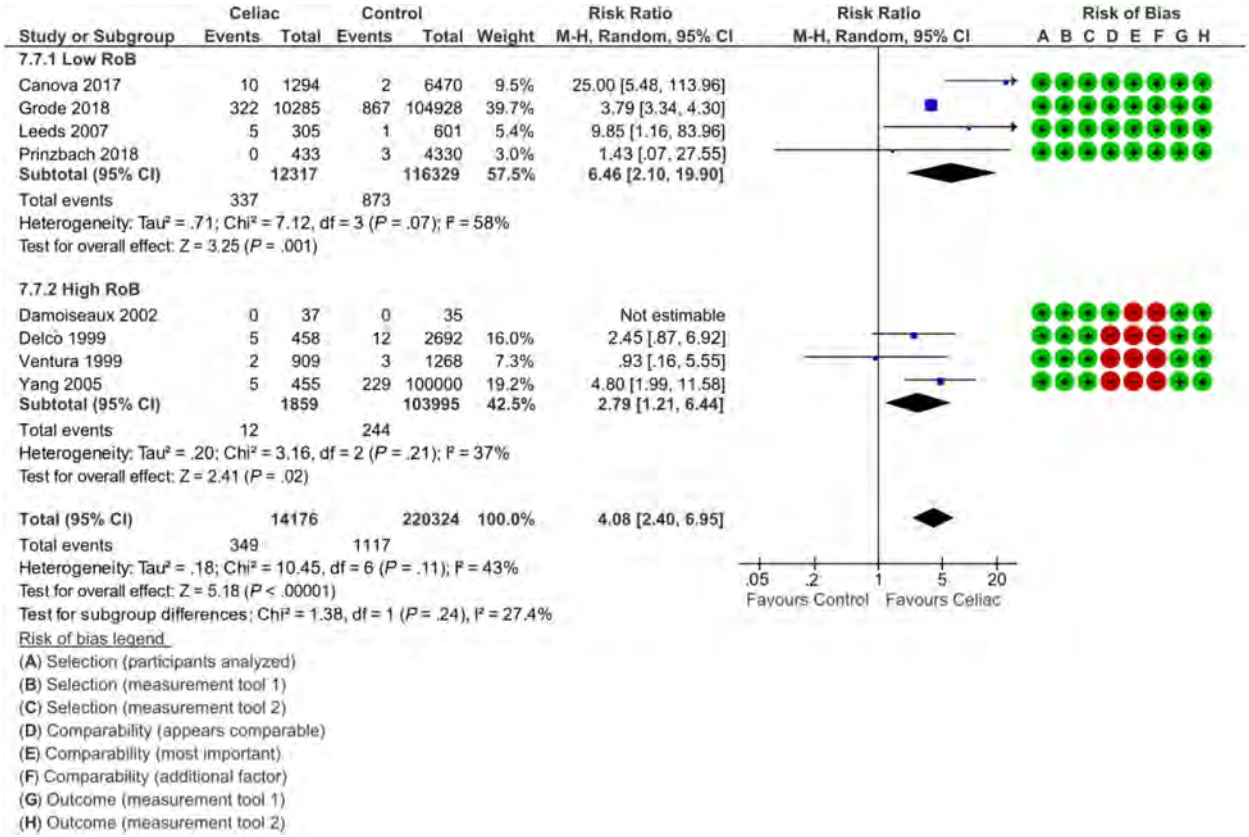
Appendix 30. IBD in CeD vs Controls Subgrouped by Risk of Bias



Appendix 31. IBD in CeD vs Controls Funnel Plot



Appendix 32. Crohn's Disease in CeD vs Controls Subgrouped by Risk of Bias



Appendix 33. UC in CeD vs Controls Sub-grouped by Risk of Bias