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TITLE PAGE

Title: Screening for Celiac Disease in Irritable Bowel Syndrome: An Updated Systematic Review and Meta-analysis.

Short running head: Celiac Disease in IBS.

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Abbreviations:

AGA	antigliadin antibody
CD	celiac disease
CI	confidence interval

EMA	endomysial antibody
FODMAP	fermentable oligo-, di-, or monosaccharide and polyol
GI	gastrointestinal
IBS	irritable bowel syndrome
IBS-C	constipation-predominant IBS
IBS-D	diarrhea-predominant IBS
IBS-M	mixed stool pattern IBS
NCGS	non-celiac gluten sensitivity
OR	odds ratio
tTG	tissue transglutaminase

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ABSTRACT

Objectives: Celiac disease (CD) and irritable bowel syndrome (IBS) share similar symptoms, leading to confusion between the two and diagnostic delay. International guidelines recommend screening individuals with IBS for CD, via serological testing. However, studies published recently have cast doubt on the utility of this. We updated a previous meta-analysis examining this issue.

Methods: MEDLINE, EMBASE, and EMBASE Classic were searched through to May 2016. Eligible studies recruited adults with IBS according to symptom-based criteria, physician's opinion, or questionnaire data. Tests for CD included IgA-class antigliadin antibodies (AGA), endomysial antibodies (EMA), tissue transglutaminase antibodies (tTG), or duodenal biopsies following positive serology. The proportion of individuals meeting criteria for IBS testing positive for CD was combined to give a pooled prevalence for all studies, and compared between cases with IBS and, healthy controls without (where reported), using an odds ratio (OR) with a 95% confidence interval (CI).

Results: There were 36 eligible studies, recruiting 15,256 individuals, of whom 9275 (60.8%) met criteria for IBS. Pooled ORs for positive IgA AGAs, EMA and/or tTG, and biopsy-proven CD in IBS subjects vs. controls were 3.21 (95% CI 1.55-6.65), 2.75 (95% CI 1.35-5.61), and 4.48 (95% CI 2.33-8.60) respectively. There was no increase in ORs for any test for CD among cases with IBS in North American studies, and results were inconsistent in population-based studies. The prevalence of biopsy-proven CD was significantly higher across all subtypes of IBS. Limitations included heterogeneity in some analyses, and few North American studies.

Conclusions: Overall, prevalence of positive celiac serology and biopsy-proven CD was significantly higher in subjects with symptoms suggestive of IBS vs. healthy controls.

However, the utility of screening for CD in individuals with suspected IBS in North America or in the community is less clear.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common symptom-based condition, characterized by abdominal pain in association with alterations in bowel habits (1). The pathogenesis of IBS is incompletely understood, but abnormalities of motility, visceral sensation, brain-gut interactions, gut microbiome, and mucosal immune function and permeability have been identified (2-6). Estimates of prevalence vary between studies, and according to the criteria used for diagnosis, but it is generally believed to affect somewhere between 10% and 25% of the general population globally (7). Although IBS is not a diagnosis of exclusion, with physicians advised to minimize the use of investigations (8, 9), the gastrointestinal (GI) tract has a limited repertoire of symptoms, meaning that abdominal pain and a change in bowel habit is not specific to the disorder (10).

In contrast, celiac disease (CD) is a well-defined immune-mediated organic enteropathy, triggered by exposure to gluten in genetically susceptible individuals (11), which results in structural damage to the small intestinal mucosa and may lead to malabsorption. In studies conducted in the USA and Europe the prevalence of CD is estimated to be between 0.3% and 1% (12-15). The presenting features of CD are variable, but there is considerable overlap with IBS-type symptoms including abdominal pain, bloating, and change in bowel habit (16, 17). These symptoms may be overlooked, leading to mislabeling as IBS, and a delay until the diagnosis of CD is established (18).

Although IBS and CD can share similar symptoms, it is imperative to differentiate between the two conditions, as their management is different, and CD carries with it the risk of other long-term sequelae if a gluten-free diet is not implemented. In 2009 we published a meta-analysis examining the yield of various diagnostic tests for CD in patients meeting diagnostic criteria for IBS, and showed among those with symptoms suggestive of IBS, the

prevalence of biopsy-proven CD was four-fold that of controls without such symptoms (19). Economic modeling studies have suggested that excluding CD in patients with symptoms compatible with IBS could be cost-effective (20-22). Partly as a result of these studies, current guidelines for the management of CD recommend opportunistic screening of patients with IBS-type symptoms for CD, via serological testing (23, 24).

However, several high-profile studies that have been published since the conduct of this meta-analysis have suggested that opportunistic screening for CD in people reporting GI symptoms, or IBS-type symptoms, is not a worthwhile exercise. Two population-based studies from the USA reported that a positive serological test for CD was not strongly associated with GI symptoms or IBS (12, 25), although the manifestations of CD are protean, and patients may present in a variety of ways, meaning that not all will report GI symptoms. However, a third US study conducted in a referral population reported that the prevalence of positive celiac serology and biopsy-proven CD was similar in non-constipated IBS patients and non-IBS controls (26). In light of this, we aimed to update our previous meta-analysis in order to re-appraise the evidence for the role of screening for CD among people with symptoms compatible with IBS.

METHODS

Search Strategy and Study Selection

A thorough literature search was conducted using MEDLINE (1950 to May 2016), EMBASE, and EMBASE Classic (1980 to May 2016). Cross-sectional surveys recruiting unselected adult subjects meeting diagnostic criteria for IBS, with or without healthy controls who did not report symptoms compatible with IBS, and that applied serological tests for CD to all enrolled individuals were eligible for inclusion. Diagnostic criteria for IBS included a physician's opinion, questionnaire data, or specific symptom-based criteria, including the Manning (27) and Rome criteria (28-30), or the Kruis scoring system (31). These could be supplemented by results of GI investigations, if individual studies performed these. We considered IgA-class antigliadin (AGAs), endomysial (EMAs), or tissue transglutaminase (tTG) antibodies as valid serological markers of possible CD. It was not compulsory for studies to perform distal duodenal biopsy to confirm CD in individuals with positive serological tests in order to be eligible for inclusion, although we also extracted these data, where reported. Due to a priori concerns about statistical handling of rare events, studies were only eligible for inclusion if they contained ≥90 individuals. Detailed eligibility criteria for study inclusion are provided in Box 1.

Studies relating to IBS were identified with the following medical subject headings and free text terms: irritable bowel syndrome, spastic colon, irritable colon, functional adj5 bowel, Manning, Rome 1, Rome I, Rome 2, Rome II, Rome 3 or Rome III. These were combined together using the 'OR' set operator. We then combined these using the set operator 'AND' with studies identified using the following: coeliac, celiac, sprue, gluten sensitive enteropathy, villous atrophy, antigliadin, endomyseal, tissue transglutaminase, or

duodenal biopsy. There were no language restrictions, and abstracts of the papers identified were assessed for appropriateness to the study question. The bibliographies of all identified relevant studies were used to perform a recursive search of the literature. All potentially relevant papers were obtained and evaluated in detail by two reviewers, using predesigned eligibility forms, with all disagreements resolved by consensus.

Data Extraction

Data were extracted from identified papers independently by two reviewers and inputted into a spreadsheet (Microsoft Excel 2010, Microsoft Corp, Redmond, Washington), again with discrepancies resolved by consensus. For each eligible study, the following data were extracted: year of publication, country, setting, number of centers, criteria used to define IBS, whether recruited subjects were consecutive, and whether the study design was prospective. The proportion of individuals meeting diagnostic criteria for IBS, as well as healthy controls without IBS (where recruited), who were found to have positive celiac serology or biopsy-proven CD was calculated as a percentage of the total number of IBS patients or controls. Where data were incomplete for individual studies, the lead author was contacted in all cases in an attempt to obtain the information of interest.

For cross-sectional surveys that reported the prevalence of a positive test for CD in both individuals meeting criteria for IBS, and healthy controls without IBS, study quality was assessed independently by two reviewers using the Newcastle-Ottawa scale (32), which judges quality based on the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest. For cross-sectional surveys that only recruited individuals with suspected IBS there are no formal recommended methods for assessing study quality.

Data Synthesis and Analysis

The degree of agreement between the two investigators, in terms of judging study eligibility, was measured using the Kappa statistic. The proportion of individuals meeting diagnostic criteria for IBS with either a positive serological test, or biopsy-proven CD, were combined for all cross-sectional surveys to give a pooled prevalence in these individuals. In addition, for cross-sectional surveys that also recruited healthy controls without IBS, data were pooled for both cases and controls, and the prevalence of positive celiac serology and biopsy-proven CD were compared between the two groups with an odds ratio (OR) with a 95% confidence interval (CI). Given the findings from recently published studies (12, 25, 26), we conducted sensitivity analyses according to study setting (population-based versus referral population), geographical region, and IBS subtype (diarrhea predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), and mixed stool pattern IBS (IBS-M)) in order to examine whether this had any effect on the prevalence or odds of either positive celiac serology or biopsy-proven CD.

Heterogeneity between studies was assessed using the I^2 statistic with a cut-off of 50%, and the χ^2 test with a P value <0.10 used to define a statistically significant degree of heterogeneity (33). Data were pooled using a random effects model (34), to give a more conservative estimate of the prevalence of a positive serological test for CD, or biopsy-proven CD, in individuals with IBS-type symptoms. Review Manager version 5.3.5 (RevMan for Windows 2014, the Nordic Cochrane Centre, Copenhagen, Denmark) and Stats-Direct version 2.7.2 were used to generate Forest plots of pooled prevalences and pooled ORs with 95% CIs. Evidence of publication bias was assessed for by applying Egger's test to funnel plots of pooled ORs (35), where a sufficient number of studies (≥10) were available (36).

RESULTS

The literature search identified 8360 published citations, of which 50 appeared to be relevant to the study question (Figure 1). Following eligibility assessment, 36 were deemed to be relevant and included in the final analysis, with good agreement between investigators (Kappa = 0.65). Twenty-two of these studies, including 10,742 individuals, of whom 6869 met diagnostic criteria for IBS, were published subsequent to our previous meta-analysis studying this issue (25, 37-57). A further study we identified was a fully published version of an abstract identified and included in the previous meta-analysis. We therefore included data from the fully published paper (26), in lieu of the abstract data (58). There were another 4514 subjects identified in 14 studies (16, 17, 26, 59-69) from the previous meta-analysis, of whom 2406 met diagnostic criteria for IBS. In total, therefore, the 36 studies recruited 15,256 individuals, of whom 9275 (60.8%) met diagnostic criteria for IBS. Detailed characteristics of all identified studies are provided in Table 1.

Yield of IgA-class AGA Testing in Suspected IBS

Of the 36 identified studies, 10 reported data on IgA-class AGAs in 4524 subjects, of whom 2094 had IBS. Seven of these studies were identified in the previous literature search (16, 17, 26, 60, 61, 63, 69), with the remaining three studies identified in the updated search (37, 55, 57). The pooled prevalence of a positive IgA-class AGA in IBS subjects was 5.7% (95% CI 1.7% to 11.8%) (Table 2), but with significant heterogeneity between studies (I^2 = 95.9%, $P < 0.001$).

Of these 10 studies, seven also reported prevalence of a positive IgA-class AGA in non-IBS subjects (16, 17, 26, 57, 60, 63, 69). Overall, there were 50 (3.3%) of 1530

individuals with symptoms compatible with IBS with a positive IgA-class AGA, compared with 26 (1.1%) of 2430 healthy controls without IBS. The OR for a positive IgA-class AGA was significantly higher among those with IBS-type symptoms (3.21; 95% CI 1.55 to 6.65) (Figure 2 and Table 2), but with borderline heterogeneity between studies (I^2 = 41.0%, P = 0.11). There were too few studies to assess for publication bias.

Two studies examined screening for CD with IgA-class AGAs in a population-based setting (17, 60). These studies compared 173 subjects who met diagnostic criteria for IBS with 1127 subjects who served as controls, with a pooled OR for a positive IgA-class AGA of 3.89 (95% CI 1.06 to 14.3) (Figure 2 and Table 2). The remaining five studies were conducted in secondary or tertiary care settings (16, 26, 57, 63, 69). The OR for a positive IgA-class AGA in 1357 cases with suspected IBS versus 1303 controls was 2.87 (95% CI 1.07 to 7.66) (Figure 2 and Table 2). Only one of these studies was conducted in North America, and the prevalence of a positive IgA-class AGA was not higher among subjects meeting criteria for IBS (26). In contrast, there were three European studies, and the OR for a positive IgA-class AGA was significantly higher among those with IBS-type symptoms (4.38; 95% CI 1.74 to 11.0) (Figure 2 and Table 2) (16, 17, 60). When prevalence of a positive IgA-class AGA was examined according to IBS subtype, this was highest in those meeting criteria for IBS-M, but the odds of a positive IgA-class AGA was only significantly higher among those with IBS-D (OR 17.1; 95% CI 4.77 to 61.1) (Table 3).

Yield of EMA and/or tTG Testing in Suspected IBS

32 studies reported data on EMA and/or tTG antibodies in 14,150 subjects of whom 8219 met diagnostic criteria for IBS. Thirteen of these studies were identified in the previous literature search (16, 17, 26, 59-61, 63-69), with the remaining 19 studies identified in the

updated search (25, 37-42, 44-48, 50, 51, 53-57). The pooled prevalence of a positive EMA and/or tTG was 2.6% (95% CI 1.6% to 3.8%) (Table 2), but with significant heterogeneity between studies (I^2 = 89.5%, P < 0.001). When studies using EMA or tTG were separated, the prevalence of a positive EMA was 1.1% (95% CI 0.4% to 2.3%), compared with 3.1% (95% CI 1.8% to 4.6%) for tTG.

Twelve of these 32 studies also reported prevalence of a positive EMA and/or tTG in non-IBS subjects (16, 17, 25, 26, 41, 45, 56, 57, 60, 63, 65, 69). Among 2677 cases with IBS-type symptoms, 57 (2.1%) had a positive EMA and/or tTG, compared with 49 (0.8%) of 5931 controls. The OR for a positive EMA and/or tTG in those with suspected IBS, compared with non-IBS controls was 2.75 (95% CI 1.35 to 5.61) (Figure 3 and Table 2), and no significant heterogeneity between studies (I^2 = 31.0%, P = 0.17). When EMA and tTG were considered separately, the OR for a positive EMA in cases with IBS compared with controls was 3.92 (95% CI 1.32 to 11.7), and that for a positive tTG was 3.02 (95% CI 1.44 to 6.36). There was no evidence of funnel plot asymmetry to suggest publication bias or other small study effects (Egger test, P = 0.28).

Four of the 12 studies were population based (17, 25, 60, 65) comparing 657 cases meeting diagnostic criteria for IBS with 3967 controls. The OR for a positive EMA and/or tTG subjects with suspected IBS, compared with healthy controls was 1.01 (95% CI 0.20 to 5.09) (Figure 3 and Table 2). The remaining eight studies were conducted in secondary or tertiary care (16, 26, 41, 45, 56, 57, 63, 69). The OR for a positive EMA and/or tTG in 2020 individuals meeting criteria for IBS, compared with 1964 controls, was 4.32 (95% CI 2.17 to 8.58) (Figure 3 and Table 2). Three of these studies were conducted in North America, and the prevalence of a positive EMA and/or tTG was no higher among subjects meeting criteria for IBS (25, 26, 65). Again, there were three European studies, and the OR for a positive EMA and/or tTG was significantly higher among those with IBS-type symptoms (4.05; 95%

CI 1.36 to 12.1) (Table 2) (16, 17, 60). When prevalence of a positive EMA and/or tTG was examined according to IBS subtype, this was highest in those meeting criteria for IBS-D. The odds of a positive EMA and/or tTG was significantly higher among those with IBS-D (OR 6.09; 95% CI 1.88 to 19.7) and IBS-C (OR 4.84; 95% CI 1.32 to 17.7) (Table 3).

Yield of Duodenal Biopsy after Positive Celiac Serology

There were 22 studies that offered duodenal biopsy to individuals with a positive serological test for CD of any type. Seven of these studies were identified in the previous literature search (16, 17, 26, 62, 63, 68, 69). The remaining 15 studies were identified in the updated search (37, 39, 40, 43, 44, 48-57). These studies contained 9784 subjects, of whom 6991 met diagnostic criteria for IBS. The pooled prevalence of biopsy-proven CD in these studies was 3.3% (95% CI 2.3% to 4.5%) (Table 2), but with significant heterogeneity between study results (I^2 = 84.6%, P < 0.001).

Of the 22 studies, eight recruited 2025 subjects with IBS-type symptoms and 2793 healthy controls without. (16, 17, 26, 49, 56, 57, 63, 69) Overall, there were 49 (2.4%) individuals meeting criteria for IBS with duodenal biopsy findings consistent with CD, compared with 16 (0.6%) subjects who did not meet criteria for IBS, with an OR of 4.48 (95% CI 2.33 to 8.60) (Figure 4 and Table 2), and no significant heterogeneity between studies (I^2 = 0%, P = 0.45). There were too few studies to assess for publication bias.

Only one of these studies was population based (17), and compared 123 cases meeting diagnostic criteria for IBS with 1077 controls. The OR for a duodenal biopsy consistent with CD in IBS cases compared with controls was 4.49 (95% CI 1.33 to 15.1) (Figure 4 and Table 2). The remaining seven studies were based in secondary or tertiary care settings (16, 26, 49,

56, 57, 63, 69), and contained 1902 IBS cases and 1716 controls, with an OR for biopsy-proven CD of 4.46 (95% CI 1.88 to 10.6) (Figure 4 and Table 2). Only the study by Cash et al. was conducted in North America, and the prevalence of a biopsy-proven CD was no higher among subjects meeting criteria for IBS (26). Again, there were three European studies, and the OR for biopsy-proven CD was significantly higher among those with IBS-type symptoms (5.45; 95% CI 2.13 to 14.0) (Table 2) (16, 17, 60). When prevalence of biopsy-proven CD was examined according to IBS subtype, this was highest in those meeting criteria for IBS-D. The odds of biopsy-proven CD were significantly increased across all subtypes of IBS, but were highest among those with IBS-D (OR 12.4; 95% CI 4.98 to 30.9) (Table 3).

DISCUSSION

The results of this updated systematic review and meta-analysis demonstrate that the pooled prevalence of a positive serological test for CD in individuals with suspected IBS is between 2.6% and 5.7%, and the OR for a positive test was up to three-fold higher among those meeting criteria for IBS. The pooled prevalence of biopsy-proven CD was similar, at 3.3%, and again this was significantly more common in those with IBS-type symptoms, with an OR of almost 4.5. However, in some of our analyses, when only North American studies, or when only studies conducted in the general population, were considered, the odds of a positive serological test for CD, and of biopsy-proven CD, were no longer significantly greater. This suggests that the utility of screening for CD among individuals reporting, or presenting with, symptoms compatible with IBS in these settings is less clear. Only one study reported data on biopsy-proven CD in a population-based setting (17), and although the OR was significantly higher in those with presumed IBS, compared with controls, this finding should be interpreted with caution. Although the OR for a positive serological test for CD was not consistently elevated across all IBS subtypes, the OR for biopsy-proven CD was significantly higher for IBS-D, IBS-C, and IBS-M, versus controls without symptoms meeting criteria for IBS. There is a highly effective treatment for CD, in the form of a gluten-free diet, and important long-term consequences from non-treatment including increased rates of lymphoma, infertility, anemia, and osteoporosis. Given all this, clinicians should continue to pursue the diagnosis of CD aggressively in patients with suspected IBS, acknowledging that around 30 people will need to be tested to diagnose one new case of biopsy-proven CD.

The prevalence of both IBS and CD vary, depending on ethnicity and geographical location (7, 70-72), likely reflecting differences in diet, genetics, and culture. This meta-analysis included studies from multiple countries, recruiting patients of different ethnic origins. This is a potential strength, in that it increases the generalizability of the findings to

patients consulting with symptoms compatible with IBS in different countries, but is also a weakness in that the pooled results from the meta-analysis may not be applicable to all patient groups. Nine of the 37 included studies, which recruited 3122 of the 15,256 subjects in the meta-analysis, were conducted in Iranian populations (38, 41, 44, 45, 47, 51, 53, 54, 63). Having such a large proportion of the included subjects from one geographical location and ethnicity has the potential to skew the results, and in our subgroup analyses according to geographic location of the study, the OR for biopsy-proven CD in studies conducted in the Middle East appeared substantially larger than that derived from studies conducted in Europe or North America.

Other limitations of this meta-analysis include heterogeneity in some of our analyses when data from individual studies were pooled, and the fact that we did not conduct a search of the grey literature in order to identify unpublished studies. In addition, there is the possibility that the prevalence of a positive serological test for CD has been inflated, due to false positive test results. However, the specificity of these tests for a diagnosis of CD is around 95% (73), and we still observed rates of biopsy-proven CD in excess of 3% among those with symptoms suggestive of IBS, more than four-fold those of individuals who did not meet criteria for IBS. In addition, it is equally plausible that the rate of biopsy-proven CD has been underestimated in this meta-analysis. The sensitivity of these tests is 88% to 93% (73) and, in the majority of studies, distal duodenal biopsy was not performed in those with a negative test, meaning that a diagnosis of CD will have been missed in those with a false negative result. This issue may have been further compounded by the fact that not all patients with a positive serological test agreed to undergo upper GI endoscopy and biopsy.

The quality of any meta-analysis relies on the quality of the included studies, leading many authors to utilize validated assessment tools to assess study quality. We applied the Newcastle-Ottawa scale (32), which is used to assess the quality of case-control studies, to

cross-sectional surveys that recruited subjects with symptoms meeting criteria for IBS as well as healthy controls without IBS-type symptoms. Six of these 13 studies scored 7 or more out of a possible 9 on the scale. With respect to other measures of the rigor of individual study design, 28 studies stated specifically that they were prospective, and 16 that they recruited consecutive patients. In addition, almost all used validated criteria for the diagnosis of IBS, with 27 using the Rome II or Rome III criteria, and one using the Manning criteria.

Internationally, guidelines suggest that tTG antibody testing (+/- EMA testing) should be used over AGAs for the diagnosis of CD (23, 24), due to the higher sensitivity and specificity of these tests (74), and that opportunistic screening of individuals with IBS using these serological tests for CD should be considered (23, 24). As such, if we focus on the data from studies that used EMA and/or tTG in this meta-analysis, overall, the results support screening for CD in patients presenting to secondary or tertiary care. However, a benefit of screening people at either a population level, or within primary care, is not supported by our results. It is important to point out that there were fewer studies in these analyses, and more data are probably required in order to judge the utility of screening in both of these settings, particularly as primary care is where the majority of patients with IBS are managed (75). The recent evidence casting doubt on the role of CD screening in patients with IBS-type symptoms, and particularly in the community, comes mainly from North American studies (12, 25, 26). We conducted a subgroup analysis of data from North America and, although the small number of studies limits the strength of these findings, it showed little difference in CD prevalence, or a positive serological test for CD, between those with symptoms meeting diagnostic criteria for IBS and controls without GI symptoms, even in a secondary or tertiary care setting.

Several studies have shown that testing for CD in patients with IBS-type symptoms is likely to be cost-effective (20-22). Spiegel et al. reported that histological testing for CD had

an acceptable cost when CD prevalence was more than 1%, and became the dominant strategy, cheaper than empirical symptom-based therapy for presumed IBS, when the prevalence reached 8% (21). Another study reported that at a CD prevalence of 3% there was only a 1% increase in lifetime costs of managing IBS with tTG testing for CD, with the cost per quality adjusted life year falling to $4900 if the prevalence of CD in IBS was assumed to be 5% (20), close to the upper confidence limit of the estimate from our meta-analysis. Mohseninejad et al found testing for CD in patients presenting with non-constipated IBS was almost certainly cost-effective at a prevalence of 4.7% (22), again similar to the upper limit we estimated. It is therefore likely, from the up-to-date synthesis of data in this meta-analysis, that testing for CD remains acceptable in terms of cost, although the prevalence of CD falls slightly short of making serological testing the dominant strategy.

Many patients with IBS believe their symptoms relate to food sensitivity (76), and some individuals who have no genetic, serological, or mucosal markers of CD report symptom improvement following withdrawal of gluten from their diet (77), a phenomenon referred to as non-celiac gluten sensitivity (NCGS). However, the existence of this entity is not without controversy. As wheat also contains high levels of fructans, in addition to gluten, another explanation for the benefit of gluten withdrawal in patients with IBS could be a simultaneous reduction in fructans, which is one of the fermentable oligo-, di-, or monosaccharides and polyols (FODMAPs). In a recent trial examining a combination of a low FODMAP diet and a gluten-free diet in IBS, there was no additive effect of a gluten-free diet (78), suggesting that reduced fructans consumption explains the beneficial effect of gluten exclusion in IBS. In addition, a recent pooled analysis of double-blind, placebo-controlled trials of gluten challenge in presumed NCGS demonstrated that only one-in-six patients exhibited gluten-specific symptoms, and 40% of these individuals also reported an exacerbation of their symptoms with placebo (79). Regardless of these issues, it is likely that

clinicians will come under increasing pressure from patients to exclude CD, by means of serological testing, irrespective of the likely yield or cost-effectiveness of this strategy.

In conclusion, this updated meta-analysis, containing data from a further 22 studies published after the previous version (19), demonstrates a pooled prevalence of biopsy-proven CD of 3.3% among individuals with IBS-type symptoms, with a more than four-fold odds of CD, compared with healthy controls, and this was consistent across all IBS subtypes. Despite the recent publication of some studies that have cast doubt on the value of screening individuals with symptoms suggestive of IBS for CD, these findings are similar to the previous pooled estimates from our meta-analysis published in 2009. These data, along with those from economic modeling studies, support continued screening of patients with symptoms meeting diagnostic criteria for IBS in secondary and tertiary care, outside of North America. The value of screening individuals with IBS symptoms in the community or in primary care is less clear. Further studies to improve our understanding of the yield and cost-effectiveness of screening for CD in these settings are encouraged.

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Guarantor of the article: ACF is guarantor.

Specific author contributions: AJI, WDC, and ACF conceived and drafted the study. AJI and ACF collected all data. ACF analyzed and interpreted the data. AJI, WDC, and ACF drafted the manuscript. All authors contributed to and approved the final draft of the manuscript.

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Box 1. Eligibility Criteria for Study Inclusion.

Adults (with 90% of participants aged >16 years) with a presumed diagnosis of IBS (either according to a clinician's opinion, questionnaire, after negative investigation(s), or meeting specific diagnostic criteria*).

Cross-sectional surveys.

Participants not specially selected.

Serological tests for celiac disease applied to all patients and results recorded†.

≥90 subjects included.

*Manning, Kruis score, Rome I, II, or III.

† IgA-class antigliadin antibodies, endomysial antibodies, tissue transglutaminase.

Figure 1. Flow Diagram of Studies Identified in the Systematic Review and Meta-analysis.

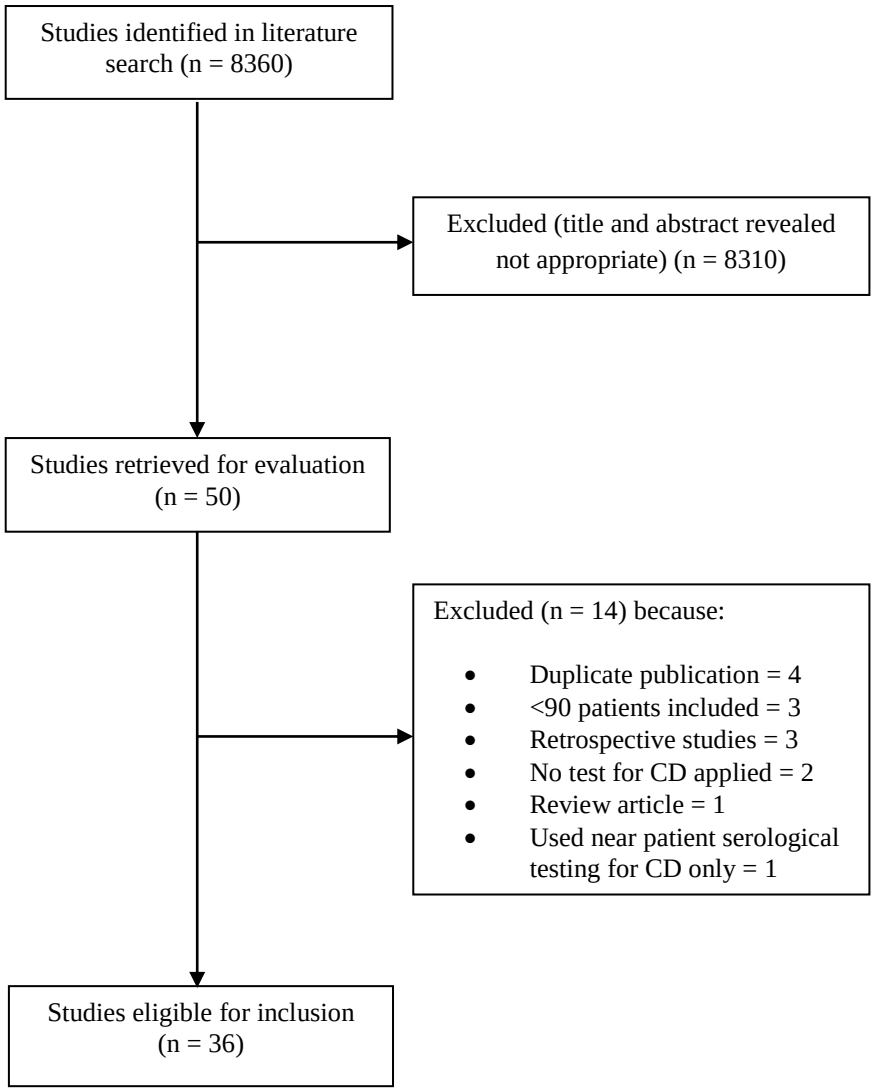

Figure 2. Pooled Odds Ratio for a Positive IgA-class AGA in Cases with IBS-type symptoms Compared with Controls without IBS-type Symptoms.

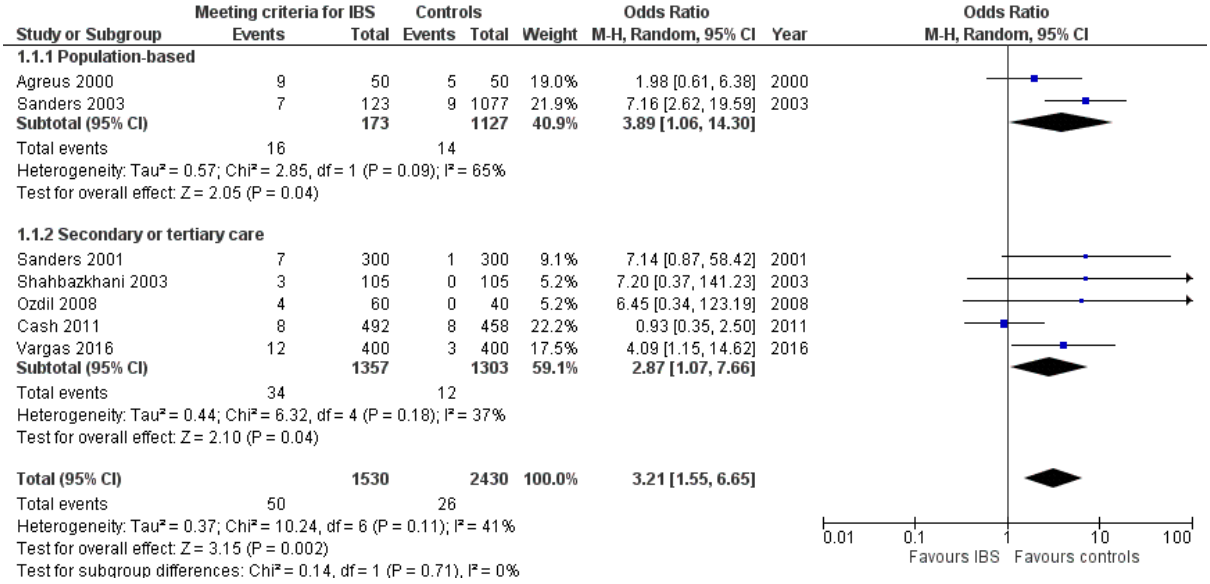

Figure 3. Pooled Odds Ratio for a Positive EMA and/or tTG in Cases with IBS-type symptoms Compared with Controls without IBS-type Symptoms.

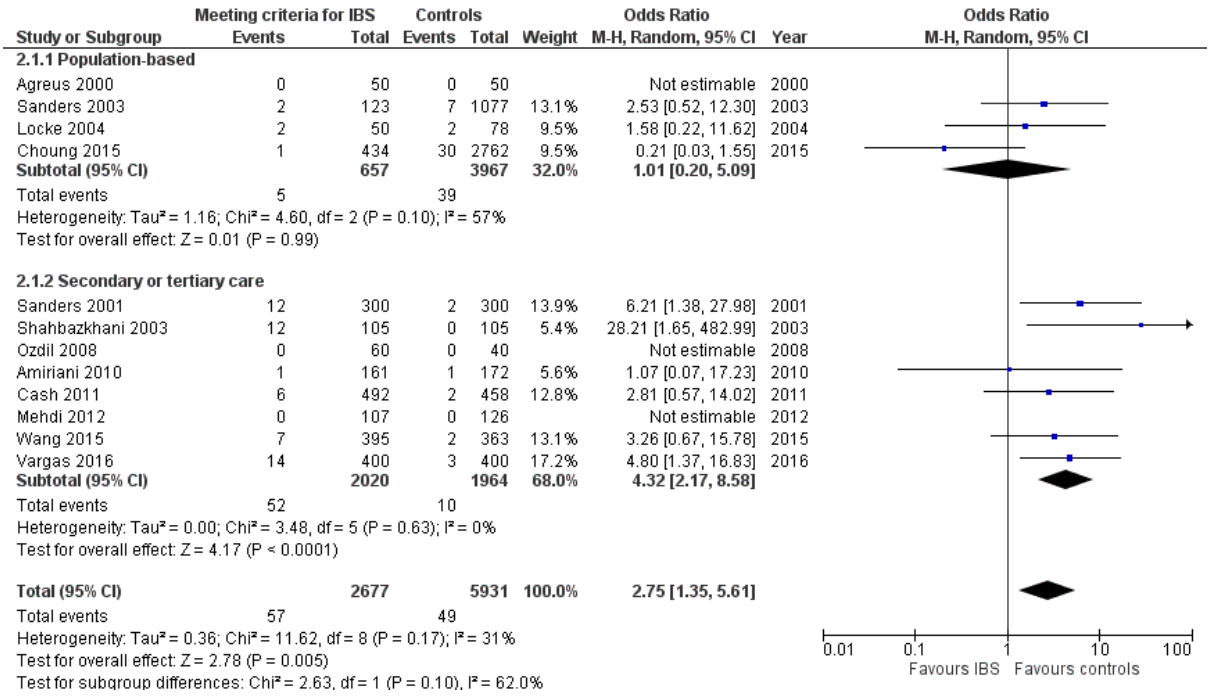

Figure 4. Pooled Odds Ratio for Biopsy-proven Celiac Disease in Cases with IBS-type symptoms Compared with Controls without IBS-type Symptoms.

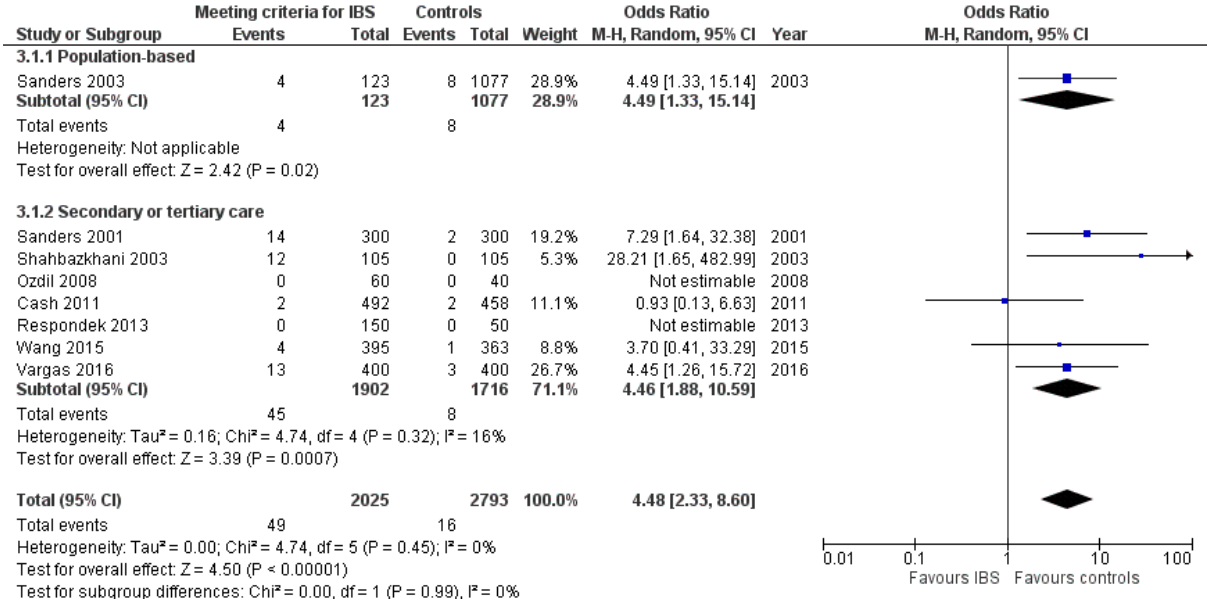

Table 1. Characteristics of Included Studies.

Study	Country	Setting (number of centers)	Consecutive patients	Prospective	Diagnostic criteria for IBS	Sample size	Diagnostic test for CD	No. with IBS (% testing positive)	No. without IBS (% testing positive)	Newcastle-Ottawa scale score
Hin (59)	UK	Primary care (9)	Unclear	Unclear	Physician's diagnosis	132	EMA	132 (0)	N/A*	N/A*
Agréus (60)	Sweden	Population -based (1)	Unclear	No	Questionnaire-based	100	IgA AGA EMA	50 (18.0) 50 (0)	50 (10.0) 50 (0)	8
Sanders (16)	UK	Secondary care (1)	Yes	Yes	Rome II	600	IgA AGA EMA Duodenal biopsy	300 (2.3) 300 (4.0) 300 (4.7)	300 (0.3) 300 (0.7) 300 (0.7)	8
Wahnschaffe (61)	Germany	Secondary care (1)	Yes	Yes	Organic disease excluded after extensive investigation	102	IgA AGA EMA tTG	102 (0) 102 (0) 102 (0)	N/A*	N/A*

DeMarchi (62)	Italy	Secondary care (1)	Yes	Yes	Rome II	257	Duodenal biopsy	257 (8.2)	N/A*	N/A*
Sanders (17)	UK	Population -based (5)	Unclear	Yes	Rome II	1200	IgA AGA EMA Duodenal biopsy	123 (5.7) 123 (1.6) 123 (3.3)	1077 (0.8) 1077 (0.6) 1077 (0.7)	5
Shahbazkhani (63)	Iran	Secondary care (1)	Yes	Yes	Rome II supplemented by investigation	210	IgA AGA EMA Duodenal biopsy	105 (2.9) 105 (11.4) 105 (11.4)	105 (0) 105 (0) 105 (0)	5
Funka (64)	Latvia	Secondary care (1)	Unclear	Unclear	Physician's diagnosis	191	EMA	191 (0.5)	N/A*	N/A*
Locke (65)	USA	Population -based (1)	Unclear	Unclear	Manning	128	EMA tTG	50 (0) 50 (4.0)	78 (0) 78 (2.6%)	8
Kennedy (66)	UK	Primary care (Multiple)	Unclear	Unclear	Physician's diagnosis	141	EMA	141 (0.7)	N/A*	N/A*
Van der Wouden (67)	Holland	Secondary care (1)	Unclear	Yes	Rome II	148	EMA	148 (0)	N/A*	N/A*

Catassi (68)	USA and Canada	Primary care (Multiple)	Unclear	Yes	Physician's diagnosis	255	tTG Duodenal biopsy	255 (2.7) 255 (2.7)	N/A*	N/A*
Ozdil (69)	Turkey	Secondary care (1)	Unclear	Yes	Rome II supplemented by investigation	100	IgA AGA EMA tTG Duodenal biopsy	60 (6.7) 60 (0) 60 (0) 60 (0)	40 (0) 40 (0) 40 (0) 40 (0)	4
Elloumi (37)	Tunisia	Tertiary care (1)	Yes	Yes	Rome II	100	IgA AGA EMA tTG Duodenal biopsy	100 (3) 100 (0) 100 (0) 100 (0)	N/A*	N/A*
Emami (38)	Iran	Secondary care (1)	Yes	Yes	Rome II	270	tTG	270 (0)	N/A*	N/A*
Jadallah (39)	Jordan	Tertiary care (1)	Yes	Yes	Rome II	742	tTG Duodenal biopsy	742 (3.2) 742 (3.2)	N/A*	N/A*

Zwolinska-Wcislo (40)	Poland	Tertiary care (1)	Unclear	Unclear	Rome II	200	tTG Duodenal biopsy	40 (20.0) 14 (7.0)	N/A*	N/A*
Amiriani (41)	Iran	Tertiary care (1)	Unclear	Yes	Rome II	333	tTG	161 (0.6)	172 (0.6)	6
Elitsur (42)	USA	Population -based (1)	Unclear	Yes	Rome III	91	tTG	91 (2.2)	N/A*	N/A*
Balasubramanian (43)	India	Secondary care (1)	Yes	Yes	Rome III	233	Duodenal biopsy	233 (9.4)	N/A*	N/A*
Cash (26)	USA	Secondary and tertiary care (4)	Yes	Yes	Rome II	950	IgA AGA EMA tTG Duodenal biopsy	492 (1.6) 492 (0.6) 492 (1.2) 492 (0.4)	458 (1.7) 458 (0.4) 458 (0.4) 458 (0.4)	7
Bakhshipour (44)	Iran	Tertiary care (1)	Yes	Yes	Rome III	364	tTG Duodenal biopsy	364 (5.5) 364 (5.5)	N/A*	N/A*
Mehdi (45)	Iran	Tertiary care (1)	Unclear	Yes	Rome II	233	tTG	107 (0)	126 (0)	6

Begtrup (46)	Denmark	Primary care (Multiple)	Unclear	Yes	Rome III	302	tTG	302 (0.3)	N/A*	N/A*
Houshiyar (47)	Iran	Tertiary care (1)	Unclear	Yes	Rome III	105	tTG	105 (13.3)	N/A*	N/A*
Pandav (48)	India	Secondary care (1)	Unclear	Yes	Rome III	200	tTG Duodenal biopsy	200 (2.0) 200 (2.0)	N/A*	N/A*
Respondek (49)	Poland	Secondary care (1)	Unclear	Yes	Rome II	200	Duodenal biopsy	150 (0)	50 (0)	6
Rodrigo (50)	Spain	Tertiary care (1)	Yes	Yes	Rome III	229	tTG Duodenal biopsy	229 (3.1) 229 (3.1)	N/A*	N/A*
Mahmoodi (51)	Iran	Tertiary care (1)	Unclear	Yes	Rome II	1000	tTG Duodenal biopsy	1000 (7.6) 1000 (5.7)	N/A*	N/A*

Mooney (52)	UK	Secondary and tertiary care (4)	Yes	Yes	Physician's diagnosis	416	Duodenal biopsy	416 (3.1)	N/A*	N/A*
Shayesteh (53)	Iran	Tertiary care (1)	Yes	Yes	Rome III	465	tTG Duodenal biopsy	465 (4.5) 465 (2.8)	N/A*	N/A*
Ahmadi (54)	Iran	Tertiary care (Unclear)	Unclear	Unclear	Rome III	143	tTG Duodenal biopsy	143 (5.6) 143 (2.8)	N/A*	N/A*
Choung (25)	USA	Population -based (1)	Unclear	No	Questionnaire-based	3196	EMA, then tTG if positive	434 (0.2)	2762 (1.1)	8
Sharma (55)	India	Tertiary care (1)	Yes	Yes	Rome III	362	IgA AGA tTG Duodenal biopsy	362 (28.7) 362 (6.1) 362 (0.8)	N/A*	N/A*

Wang (56)	China	Secondary and tertiary care (2)	Yes	Yes	Rome III	758	tTG Duodenal biopsy	395 (1.8) 395 (1.0)	363 (0.6) 363 (0.3)	6
Sanchez-Vargas (57)	Mexico	Tertiary care (1)	Yes	Yes	Rome III	800	IgA AGA tTG Duodenal biopsy	400 (3.0) 400 (3.5) 400 (3.3)	400 (0.8) 400 (0.8)	7

N/A*; not applicable

Table 2. Pooled Prevalence and Odds Ratios (Compared with Non-IBS controls) for Positive Celiac Serology and Biopsy-proven Celiac Disease in Subjects Meeting Diagnostic Criteria for IBS According to Study Country and Setting.

	Cross-sectional Surveys				**Case-control Studies**			
	Number of studies	**Number of subjects meeting diagnostic criteria for IBS**	**Pooled prevalence**	**95% confidence interval**	**Number of studies**	**Number of cases and controls**	**Odds ratio**	**95% confidence interval**
IgA-class AGAs								
All studies	**10**	**2094**	**5.7%**	**1.7% – 11.8%**	**7**	**3960**	**3.21**	**1.55 – 6.65**
North American studies	1	492	N/A*	N/A*	1	950	0.93	0.35 – 2.50
European studies	4	575	4.6%	0.8% – 11.3%	3	1900	4.38	1.74 – 11.0
Middle Eastern studies	3	265	4.1%	2.1% – 6.9%	2	310	6.81	0.84 – 55.4
Population-based studies	2	173	11.1%	2.1% – 25.8%	2	1300	3.89	1.06 – 14.3
Referral population studies	8	1921	4.6%	0.8% – 11.4%	5	2660	2.87	1.07 – 7.66

EMAs or tTG								
All studies	**32**	**8219**	**2.6%**	**1.6% – 3.8%**	**9**	**8608**	**2.75**	**1.35 – 5.61**
North American studies	5	1322	1.7%	0.6% – 3.3%	3	4274	1.05	0.21 – 5.15
European studies	11	1918	1.8%	0.3% – 4.4%	3	1900	4.05	1.36 – 12.1
Middle Eastern studies	11	3517	2.9%	1.3% – 5.1%	4	876	5.43	0.18 – 164
Population-based studies	5	748	1.4%	0.3% – 3.3%	3	4624	1.01	0.20 – 5.09
Referral population studies	27	7471	2.8%	1.7% – 4.1%	6	3984	4.32	2.17 – 8.58
Biopsy-proven celiac disease								
All studies	**22**	**6991**	**3.3%**	**2.3% – 4.5%**	**8**	**4818**	**4.48**	**2.33 – 8.60**
North American studies	2	747	1.4%	0.04% – 4.7%	1	950	0.93	0.13 – 6.63
European studies	7	1675	3.9%	2.1% – 6.3%	3	2000	5.45	2.13 – 14.0
Middle Eastern studies	8	2979	3.7%	2.2% – 5.6%	2	310	28.2	1.65 – 483
Population-based studies	1	123	N/A*	N/A*	1	1200	4.49	1.33 – 15.1
Referral population studies	21	6868	3.3%	2.2% – 4.5%	7	3618	4.46	1.88 – 10.6

N/A*; not applicable

Table 3. Pooled Prevalence and Odds Ratios (Compared with Non-IBS controls) for Positive Celiac Serology and Biopsy-proven Celiac Disease in Subjects Meeting Diagnostic Criteria for IBS According to IBS Subtype.

	Cross-sectional Surveys				Case-control Studies			
	Number of studies	**Number of subjects meeting diagnostic criteria for IBS**	**Pooled prevalence**	**95% confidence interval**	**Number of studies**	**Number of cases and controls**	**Odds ratio**	**95% confidence interval**
IBS-D								
IgA-class AGAs	4	195	6.5%	0.4% – 18.9%	2	509	17.1	4.77 – 61.1
EMAs or tTG	14	2432	5.7%	3.0% – 9.1%	6	1805	6.09	1.88 – 19.7
Biopsy-proven celiac disease	14	2678	5.4%	3.3% – 7.8%	6	1867	12.4	4.98 – 30.9
IBS-C								
IgA-class AGAs	3	273	8.0%	0.6% – 22.5%	2	597	2.86	0.61 – 13.5
EMAs or tTG	9	1002	2.1%	0.9% – 3.8%	4	931	4.84	1.32 – 17.7
Biopsy-proven celiac disease	10	1055	1.8%	0.9% – 3.0%	5	1193	4.79	1.28 – 17.9
IBS-M								
IgA-class AGAs	3	278	13.1%	0.03% – 47.2%	2	674	2.50	0.59 – 10.6
EMAs or tTG	8	748	3.4%	1.4% – 6.2%	3	821	6.46	0.53 – 78.7
Biopsy-proven celiac disease	10	933	3.1%	1.7% – 5.1%	5	1388	5.76	1.35 – 24.6