Alimentary Pharmacology & Therapeutics

Meta-analysis: yield of diagnostic tests for coeliac disease in dyspepsia

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Publication data
Submitted 19 February 2009
First decision 12 March 2009
Resubmitted 18 March 2009
Accepted 23 March 2009
Epub Accepted Article 27 March 2009

SUMMARY

Background
The prevalence of coeliac disease (CD) may be increased in individuals with dyspepsia, but evidence is conflicting.

Aims
To conduct a systematic review and meta-analysis of studies reporting prevalence of CD in dyspepsia.

Methods
MEDLINE, EMBASE, and CINAHL were searched up to February 2009. Case series and case-control studies applying serological tests and/or distal duodenal biopsy for CD to unselected adults with dyspepsia were eligible. Prevalence of positive coeliac serology and biopsy-proven CD were pooled for all studies and compared between cases and controls using an odds ratio (OR) and 95% confidence interval (CI).

Results
Fifteen studies were identified. Prevalence of positive coeliac serology was higher in cases with dyspepsia (7.9%) compared with controls (3.9%), but not significantly so (OR for positive endomysial antibodies or tissue transglutaminase 1.89; 95% CI 0.90–3.99). Prevalence of biopsy-proven CD following positive serology was also higher (3.2% in cases vs. 1.3% in controls), but again this was not statistically significant (OR 2.85; 95% CI 0.60–13.38). Prevalence of biopsy-proven CD was 1% in ten studies performing duodenal biopsy first-line.

Conclusion
Prevalence of biopsy-proven CD in subjects with dyspepsia was 1% and was higher than in controls, although this difference was not statistically significant.

Aliment Pharmacol Ther **30**, 28–36

doi:10.1111/j.1365-2036.2009.04008.x

INTRODUCTION

Coeliac disease is a chronic inflammatory enteropathy of the small intestine caused by an immune-mediated response to gluten, which is found in barley, rye and wheat. If gluten is ingested by individuals with coeliac disease, it causes malabsorption, as a result of architectural changes in the small intestinal mucosa. Coeliac disease is common, with prevalence in the general population of between 0.5% and 1% following distal duodenal biopsy.[1, 2] While some individuals with coeliac disease present with the cardinal features of diarrhoea and weight loss,[3, 4] many individuals report other less classical gastrointestinal (GI) symptoms, such as abdominal bloating, pain, nausea and vomiting.[3] The diagnosis is often delayed,[3, 4] but it is relatively straightforward to screen for coeliac disease with serology and confirm with histological examination of distal duodenal biopsies.

Dyspepsia is common in the general population, with a prevalence of between 20% and 40% in population-based cross-sectional surveys,[5–8] depending on the criteria used to define its presence.[5] A significant number of individuals with dyspepsia undergo upper GI endoscopy[9] and between 40% and 60% of individuals will have a structurally normal examination.[10, 11] In the absence of organic pathology to explain their symptoms, these individuals are usually labelled as having functional dyspepsia.[12] However, patients with dyspepsia are not usually tested with coeliac serology in primary care and distal duodenal biopsy is not performed routinely in those referred for upper GI endoscopy.

The latest revision of the Rome criteria for functional dyspepsia includes the symptom complex postprandial distress syndrome.[13] One of the symptoms considered to be supportive of this diagnosis is the presence of upper abdominal bloating, which is also reported by many individuals with coeliac disease.[3] Functional dyspepsia is a chronic, relapsing and remitting disorder[14] and for that reason, it is difficult to treat. Given that there is likely to be a degree of symptom overlap between coeliac disease and functional dyspepsia and that symptoms in coeliac disease usually respond to withdrawal of gluten from the diet, screening for coeliac disease with serological testing or distal duodenal biopsy may be an attractive management strategy for dyspepsia. However, this approach is not recommended by national guidelines for the management of dyspepsia,[15–17] and studies that have examined the yield of diagnostic testing for coeliac disease in individuals with symptoms suggestive of dyspepsia have reported conflicting results.[18–20] We have conducted a systematic review and meta-analysis in an attempt to examine this issue further.

MATERIALS AND METHODS

Search strategy

A search of the medical literature was conducted using MEDLINE (1950 to 15th February 2009), EMBASE (1980 to 15th February 2009), and CINAHL (1982 to 15th February 2009). Studies on dyspepsia were identified with the terms dyspepsia [both as a Medical Subject Heading (MeSH) and free text term], and epigastric pain, satiety, nausea, upper gastrointestinal symptom$, and upper gastrointestinal adj5 symptom (as free text terms). These were combined using the set operator AND with studies identified with the terms: celiac disease, gluten, gliadin, malabsorption syndromes, intestine, small, atrophy, intestinal diseases, intestinal mucosa (both as MeSH and free text terms), and sprue, coeliac, and villous atrophy (as free text terms). There were no language restrictions and abstracts of the papers identified by the initial search were evaluated for appropriateness to the study question and all potentially relevant papers were obtained and evaluated in detail. Abstract books of conference proceedings between 2000 and 2008 were handsearched to identify potentially eligible studies published only in abstract form. The bibliographies of all identified relevant studies were used to perform a recursive search of the literature.

Eligibility criteria

Case series and case-control studies that recruited unselected adult subjects with dyspepsia symptoms and which applied serological tests for coeliac disease and/or distal duodenal biopsy to the enrolled individuals were eligible for inclusion. The diagnosis of dyspepsia could be based on a physician's opinion, questionnaire data or specific symptom-based diagnostic criteria, including a broad definition of dyspepsia, consistent with the report from the 1988 Working Party,[21] or the Rome I, II, or III criteria.[12, 13, 22] We considered Ig-A class antigliadin antibodies (AGAs), endomysial antibodies (EMAs) and tissue transglutaminase (tTG) as valid serological markers of possible

Table 1. Eligibility criteria

Adults (with 90% of participants aged >16 years) with a presumed diagnosis of dyspepsia (either according to a physician's opinion, questionnaire or meeting specific diagnostic criteria*).
Case series or case-control design.
Participants not specially selected.
Serological tests for coeliac disease† or distal duodenal biopsy applied to subjects and results recorded.
More than 90 subjects included.

* 1988 Working Party report, Rome I, II, or III criteria.
† IgA-class antigliadin antibodies, anti-endomysial antibodies, tissue transglutaminase (or any combination of these).

coeliac disease. Due to *a priori* concerns about the statistical handling of rare events, studies were only eligible for inclusion if they contained 90 or more individuals. Detailed eligibility criteria for study inclusion, which were defined prospectively, are provided in Table 1. Articles were assessed independently by two reviewers (ACF and EC) according to the eligibility criteria. Any disagreement between investigators was resolved by consensus.

Data extraction

All data were extracted independently by two reviewers (ACF and EC) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) and any discrepancies were resolved by consensus. For case series, the number of individuals with positive coeliac serology or biopsy-proven coeliac disease on distal duodenal biopsy was expressed as a proportion of the total number of subjects with a diagnosis of dyspepsia. For case-control studies, the number of cases with symptoms suggestive of dyspepsia with positive serology or biopsy-proven coeliac disease was expressed as a proportion of the total number of cases and the number of non-dyspepsia controls with positive serology or biopsy-proven coeliac disease expressed as a proportion of the total number of controls.

Data synthesis and statistical analysis

The proportion of individuals with a diagnosis of dyspepsia testing positive using the aforementioned serological markers, or having biopsy-proven coeliac disease, were combined for both case series and case-control studies to give a pooled prevalence of positive coeliac serology and biopsy-proven coeliac disease in subjects with symptoms suggestive of dyspepsia in all studies. In addition, for case-control studies, the data were pooled for both cases and controls and the pooled prevalence of positive coeliac serology and biopsy-proven coeliac disease were compared between the two groups with an odds ratio (OR). If there were no cases and/or controls with positive coeliac serology or biopsy-proven coeliac disease in a single study, 0.5 subjects were added to all four cells for the purposes of the analysis, as odds ratios cannot be calculated from zero values. Heterogeneity between studies was assessed using the I^2 statistic with a cut-off of 25%,[23] and the chi-squared test with a P value <0.10, used to define a significant degree of heterogeneity. We planned to conduct sensitivity analyses according to study setting (population-based, primary care, secondary care), country of origin and diagnostic criteria used to define dyspepsia, to examine whether this had any effect on the prevalence or odds of either positive coeliac serology or biopsy-proven coeliac disease. Individual ORs were compared between these subgroups using the Cochran Q statistic.

Data were pooled using a random effects model,[24] to give a more conservative estimate of the prevalence of coeliac disease in dyspepsia. STATSDIRECT version 2.4.4 (StatsDirect Ltd, Sale, Cheshire, England) was used to generate Forest plots of pooled prevalences and pooled ORs with 95% confidence intervals (CIs). We planned to assess for evidence of publication bias for case-control studies by applying Egger's test to funnel plots.[25]

RESULTS

The search strategy identified 3045 potentially relevant citations (Figure 1). From these, we identified 15 studies containing 9105 individuals, which applied serological tests and/or distal duodenal biopsy for coeliac disease to 8719 (95.8%) subjects with symptoms suggestive of dyspepsia.[18–20, 26–37] Agreement between reviewers for assessment of study eligibility was good (kappa statistic = 0.83).

Detailed characteristics of all included studies are provided in Table 2. Five were case-control studies with controls consisting of healthy volunteers in three studies,[26, 27, 34] blood donors in one study,[37] and individuals with other GI symptoms who did not meet criteria for either dyspepsia or irritable bowel syndrome

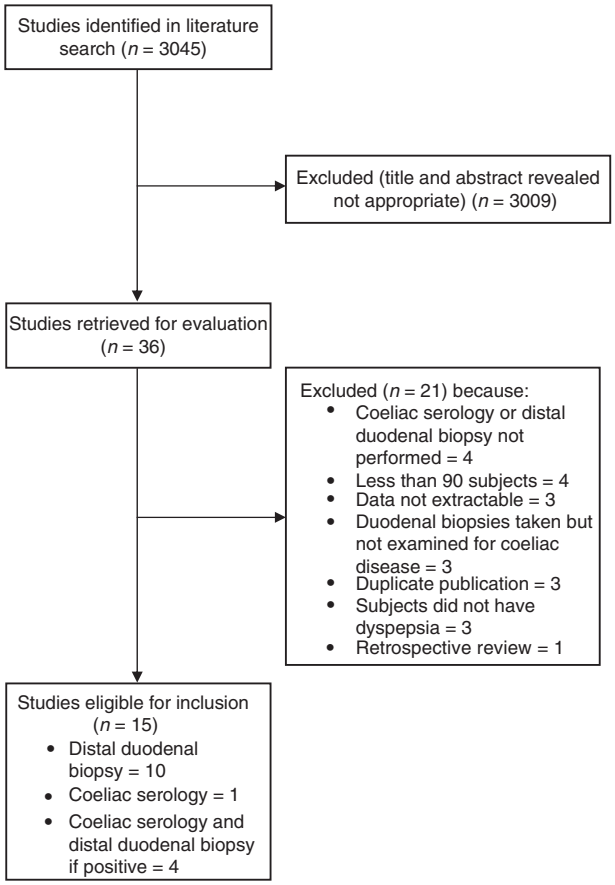

Figure 1. Flow diagram of assessment of studies identified in the systematic review and meta-analysis.

(IBS) in the fifth study.[18] Only one of these studies matched cases and controls according to age and gender.[26] Five studies used the Rome II criteria to define dyspepsia,[18, 19, 34, 36, 37] two studies used a broad definition in line with the 1988 Working Party report,[29, 32] and the remaining studies either a physician's diagnosis or questionnaire data. Ten studies used distal duodenal biopsy alone,[19, 20, 28–35] one study used coeliac serology alone[27] and the other four studies followed a positive serological test for coeliac disease with the offer of distal duodenal biopsy.[18, 26, 36, 37]

Yield of AGA-testing in subjects with dyspepsia

There were two case-control studies that screened 141 individuals with symptoms suggestive of dyspepsia and 215 controls without dyspepsia with IgA-class AGAs.[26, 37] The pooled prevalence of a positive IgA-class AGA in cases with dyspepsia was 8.2% (95% CI 0.8% to 22.1%) compared with 4.2% (95% CI 0.1% to 18.3%) in controls. The OR for positive IgA-class AGAs in subjects with symptoms suggestive of dyspepsia compared with controls was 2.01 (95% CI 0.68 to 5.89). There were too few studies to assess for evidence of heterogeneity or publication bias or to perform any of the planned sensitivity analyses.

Yield of EMA or tTG-testing in subjects with dyspepsia

Five studies used either EMA or tTG in 440 individuals with dyspepsia.[18, 26, 27, 36, 37] The proportion of subjects testing positive in these five studies ranged from 1.5% to 20.3%, with a pooled prevalence of a positive test of 5.9% (95% CI 1.5% to 13.0%; I^2 = 84%, $P < 0.001$). Four of these were case-control studies containing a total of 605 individuals, 244 (40.3%) of whom had dyspepsia.[18, 26, 27, 37] The pooled prevalence of positive EMA or tTG in cases with dyspepsia was 7.9% (95% CI 2.1% to 17.0%; I^2 = 79%, P = 0.002) compared with 3.9% in controls (95% CI 0.4% to 10.7%; I^2 = 84%, $P < 0.001$). The OR for a positive EMA or tTG in cases compared with controls was 1.89 (95% CI 0.90 to 3.99; I^2 = 0%, P = 0.71) (Figure 2). Again, there were too few studies to assess for evidence of publication bias or to perform any of the planned sensitivity analyses. One of these studies used individuals with other GI symptoms, which were not compatible with either dyspepsia or IBS, as controls rather than asymptomatic individuals.[18] Excluding this study from the analysis increased the OR for a positive EMA or tTG in cases compared with controls (OR 3.38; 95% CI 0.86 to 13.19; I^2 = 0%, P = 0.86), but this difference was not statistically significant (Cochran Q = 0.54, P = 0.46).

Yield of distal duodenal biopsy following positive coeliac serology in subjects with dyspepsia

Four studies followed a positive coeliac serology result of any type with the offer of distal duodenal biopsy in 406 individuals with dyspepsia.[18, 26, 36, 37] The prevalence of biopsy-proven coeliac disease following positive coeliac serology in subjects included in these four studies ranged from 1.4% to 3.3%, with a pooled prevalence of 2.35% (95% CI 1.1% to 4.0%; I^2 = 0%, P = 0.79). Three of these were case-control studies containing a total of 493 subjects,[18, 26, 37] 210 (42.6%) of whom had dyspepsia. The pooled prevalence of

Table 2. Characteristics of included studies

Study	Type of study	Country	Consecutive subjects recruited	Setting	Diagnostic tests applied for coeliac disease	Criteria used for diagnosis of dyspepsia	Sample size	Number of subjects with dyspepsia
Nyren 1987[20]	Case series	Sweden	Unclear	Tertiary care	Distal duodenal biopsy	Physician's diagnosis	185	185
Magazzu 1994[35]	Case series	Italy	Yes	Tertiary care	Distal duodenal biopsy	Physician's diagnosis	146	146
Heikkinen 1995[32]	Case series	Finland	Yes	Primary and tertiary care	Distal duodenal biopsy	Broad definition	400	400
Agreus 2000[26]	Case-control	Sweden	Unclear	Population-based	IgA-class AGA, EMA and distal duodenal biopsy	Questionnaire-based	99	49
Bardella 2000[28]	Case series	Italy	Yes	Tertiary care	Distal duodenal biopsy	Physician's diagnosis	517	517
Vivas 2003[37]	Case-control	Spain	Yes	Secondary care	IgA-class AGA, EMA, tTG and distal duodenal biopsy	Rome II	257	92
Cammarota 2004[29]	Case series	Italy	Yes	Tertiary care	Distal duodenal biopsy	Broad definition	396	396
Collin 2004[30]	Case series	Finland	Unclear	Primary and tertiary care	Distal duodenal biopsy	Physician's diagnosis	5459	5459
Locke 2004[27]	Case-control	USA	Unclear	Population-based	EMA and tTG	Questionnaire-based	112	34
de Lima 2005[31]	Case series	Brazil	Unclear	Tertiary care	Distal duodenal biopsy	Physician's diagnosis	142	142
Incarbone 2006[19]	Case series	Italy	Yes	Tertiary care	Distal duodenal biopsy	Rome II	626	626
Lecleire 2006[34]	Case-control	France	Yes	Tertiary care	Distal duodenal biopsy	Rome II	100	75
Ozaslan 2007[36]	Case series	Turkey	Unclear	Tertiary care	EMA and distal duodenal biopsy	Rome II	196	196
Altintas 2008[18]	Case-control	Turkey	Unclear	Tertiary care	tTG and distal duodenal biopsy	Rome II	137	69
Hopper 2008[33]	Case series	UK	Yes	Tertiary care	Distal duodenal biopsy	Physician's diagnosis	333	333

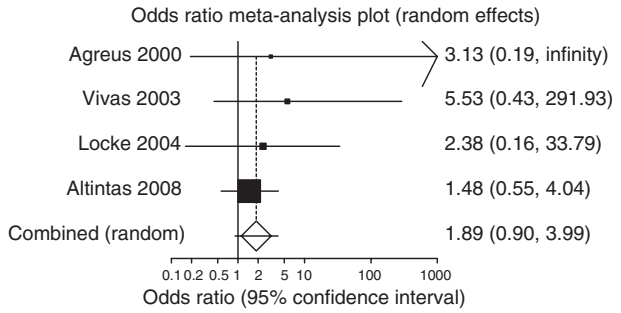

Figure 2. Pooled odds ratio for a positive EMA or tTG in dyspepsia cases vs. controls.

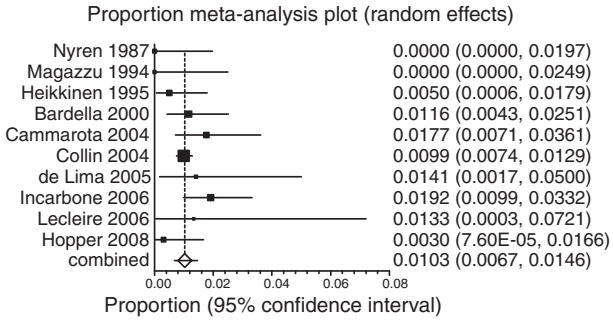

Figure 4. Pooled prevalence of biopsy-proven coeliac disease in subjects with dyspepsia.

biopsy-proven coeliac disease following positive coeliac serology in cases with dyspepsia was 3.2% (95% CI 1.3% to 5.95%; I^2 = 0%, P = 0.78), compared with 1.3% (95% CI 0.3% to 2.9%; I^2 = 0%, P = 0.73) in controls, giving an OR in cases compared with controls of 2.85 (95% CI 0.60 to 13.38; I^2 = 0%, P = 0.62) (Figure 3). If the study by Altintas *et al.*[18] which used controls with other GI symptoms, was excluded from the analysis, the OR for biopsy-proven coeliac disease increased to 4.56 (95% CI 0.71 to 29.29), although the difference between ORs was not statistically significant (Cochran Q = 0.14, P = 0.70).

Yield of distal duodenal biopsy in subjects with dyspepsia

There were ten studies that screened 8279 individuals with dyspepsia for coeliac disease using distal duodenal biopsy only.[19, 20, 28–35] The prevalence of biopsy-proven coeliac disease in individual studies ranged from 0% to 1.9%, with a pooled prevalence of biopsy-proven coeliac disease in individuals with dyspepsia of 1.0% (95% CI 0.7% to 1.5%; I^2 = 40.5%, P = 0.09) (Figure 4). Only one of these studies was a case-control study,[34] with a prevalence of biopsy-proven coeliac disease of 1.3% in cases compared to 0% in controls. Sensitivity analyses were conducted according to study setting, country and diagnostic criteria used for dyspepsia (Table 3). These did not reveal any obvious explanations for the observed heterogeneity in the prevalence of biopsy-proven coeliac disease in dyspepsia, although this was reduced when only studies from North Europe were considered in the analysis. There was a higher prevalence of biopsy-proven coeliac disease when the Rome II criteria were used to define dyspepsia compared with when either a physician's diagnosis or a broad definition was used, although this difference was only statistically significant compared with a physician's diagnosis (Cochran Q = 6.39, P = 0.01).

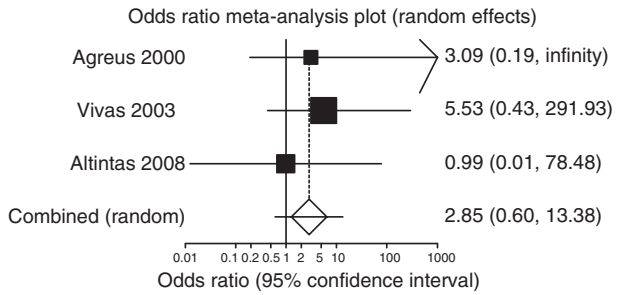

Figure 3. Pooled odds ratio for biopsy-proven coeliac disease following positive coeliac serology in dyspepsia cases vs. controls.

DISCUSSION

This study has provided an estimate of the prevalence of positive coeliac antibodies and biopsy-proven coeliac disease in individuals with dyspepsia. The pooled prevalence of positive coeliac serology varied between 6% and 8%, depending on the serological test used, whilst the pooled prevalence of biopsy-proven coeliac disease, following positive coeliac serology, was over 2%. The prevalence of positive coeliac serology and biopsy-proven coeliac disease, following a positive serological test, was generally higher in cases with dyspepsia compared with controls, but this difference was not statistically significant. In addition, when distal duodenal biopsy was performed as the first-line investigation to exclude coeliac disease, which is the

Table 3. Pooled prevalence of biopsy-proven coeliac disease in dyspepsia according to study country, setting, and diagnostic criteria used to define dyspepsia

	Number of studies	Number of dyspepsia subjects	Pooled prevalence (%)	95% confidence interval (%)	I^2 (%)	*P* value
All studies	10	8279	1.0	0.7–1.5	40.5	0.09
North European studies	5	6452	0.8	0.4–1.2	23	0.27
South European studies	4	1685	1.4	0.7–2.3	44	0.14
South American studies	1	142	1.4	0.2–5.0	*	*
Studies based in tertiary care	8	2420	1.1	0.6–1.8	49	0.06
Studies based in primary and tertiary care	2	5859	1.0	0.7–1.2	*	*
Studies using a physician's diagnosis	6	6782	0.8	0.5–1.3	30.4	0.21
Studies using a broad definition	2	796	1.2	0.25–2.7	*	*
Studies using the Rome II criteria	2	701	2.0	1.1–3.15	*	*

* Too few studies to combine.

current gold-standard for confirming the diagnosis, the pooled prevalence of biopsy-proven coeliac disease in dyspepsia fell to only 1%, which is of a similar magnitude to that in the general population of some countries,[1, 2] suggesting that subjects with dyspepsia are no more likely to harbour undiagnosed coeliac disease than these individuals. This is in contrast to subjects with suspected IBS who appear to have a four-fold increase in the prevalence of biopsy-proven coeliac disease compared to healthy controls.[38] It is interesting to note, however, that when data were pooled from the two studies that used the Rome II criteria to define dyspepsia,[19, 34] the pooled prevalence of biopsy-proven coeliac disease was 2%, which was significantly higher than that in the studies using a physician's diagnosis of dyspepsia.

Strengths of our study include the exhaustive literature search, rigorous statistical methods and pooling of data to allow synthesis of all the available published evidence to allow us to examine the yield of testing for coeliac disease in dyspepsia as well as the sensitivity analyses we conducted. Weaknesses of the study, as with any systematic review and meta-analysis, arise from the available evidence. A majority of studies were based in tertiary care, which may limit the generalizability of the findings to subjects with symptoms suggestive of dyspepsia in routine clinical practice. Another potential limitation of meta-analyses of studies evaluating the accuracy of diagnostic tests arises as a result of problems with the methodology of the type of studies included. Case series can be criticized as there is no comparison group, so it is difficult to interpret whether the reported prevalence is different from that in the general population. This is addressed by case-control studies, but these are subject to spectrum bias, because the study design often omits mild cases that are difficult to diagnose and this may lead to an overestimation of the diagnostic performance of the test being examined, compared to studies using a clinical cohort.[39] As there were only five case control studies eligible for inclusion, this systematic review and meta-analysis may not have the power to rule out a small difference in the prevalence of coeliac disease between cases and controls.

The quality of the studies included also has implications for the results of a systematic review and meta-analysis. Published recommendations exist for the evaluation of study quality in systematic reviews of diagnostic test accuracy, when an index test under evaluation is being compared to a current reference standard,[40, 41] but there are no such recommendations for assessment of studies included in this type of systematic review and meta-analysis. Assessing the quality of eligible studies included in this review informally revealed that nine of the 15 studies stated explicitly that they were prospective and eight recruited consecutive patients. However, only seven used recommended diagnostic criteria to define the presence of dyspepsia, with five studies using the Rome II criteria[18, 19, 34, 36, 37] and two a broad definition consistent with the 1988 Working Party report.[29, 32] The remainder used either a physician's diagnosis or questionnaire-based data.

We examined the effect of study setting, country of origin and dyspepsia definition utilized on the pooled prevalence of biopsy-proven coeliac disease. It would be presumed that the prevalence would be higher in studies based solely in tertiary care. This could occur as a result of selection bias, as patients with more severe dyspeptic symptoms, and therefore a greater probability of underlying organic disease, are more likely to be referred by their primary care physician for a specialist opinion. However, this did not appear to be the case from our analysis. The pooled prevalence of biopsy-proven coeliac disease was almost identical, in the two studies that recruited subjects from primary care and performed upper GI endoscopy and distal duodenal biopsy in tertiary care,[30, 32] to that in the other eight studies based solely in tertiary care. In terms of geographical setting, there were no significant differences detected in pooled prevalence of biopsy-proven coeliac disease for studies conducted in North Europe, South Europe or South America, although there was only one study from the latter region.[31]

The data derived from the studies included in this systematic review and meta-analysis demonstrate a prevalence of biopsy-proven coeliac disease in individuals with dyspepsia of 1%. This is of a magnitude similar to that amongst individuals in the general population in some countries. There were non-significant trends towards a higher prevalence of positive coeliac serology and biopsy-proven coeliac disease in cases with dyspepsia compared with controls without. Screening for coeliac disease routinely with distal duodenal biopsy during upper GI endoscopy for dyspepsia may be useful as part of the management of the condition, but more data are required before any firm recommendations can be made.

ACKNOWLEDGEMENTS

Declaration of personal interests: We are grateful to Dr David S Sanders for providing us with supplementary information regarding his study.[33] *Declaration of funding interests*: None.

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