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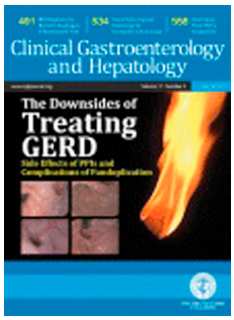

Prevalence of Dyspepsia in Individuals with Gastro-Esophageal Reflux-Type Symptoms in the Community: A Systematic Review and Meta-Analysis

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TITLE PAGE

Title: Prevalence of Dyspepsia in Individuals with Gastro-Esophageal Reflux-Type Symptoms in the Community: A Systematic Review and Meta-Analysis

Short running head: Prevalence of overlap of Dyspepsia and Reflux: Meta-analysis.

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Abbreviations:

CI	confidence interval
GERD	gastro-esophageal reflux disease
GERS	gastro-esophageal reflux symptoms
GI	gastrointestinal
H. pylori	*Helicobacter pylori*
MeSH	medical subject headings
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
SAP	symptom association probability

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ABSTRACT

Background & Aims: Dyspepsia and gastro-esophageal reflux are highly prevalent in the general population, but they are believed to be separate entities. We conducted a systematic review and meta-analysis to estimate the prevalence of dyspepsia in individuals with gastro-esophageal reflux symptoms (GERS), and to quantify overlap between the disorders.

Methods: We searched MEDLINE, EMBASE, and EMBASE Classic databases to identify population-based studies reporting the prevalence of dyspepsia and GERS in adults, defined using specific symptom-based criteria or based on answers to questionnaires. We calculated pooled prevalence values, according to study location and criteria used to define weekly GERS or dyspepsia, as well as odds ratios (ORs) with 95% CIs. The degree of overlap between dyspepsia and GERS was examined.

Results: Of 14,132 papers evaluated, 79 reported prevalence of weekly GERS. Nineteen of these study populations, comprising 111,459 participants, also reported the proportion of individuals with dyspepsia. The prevalence of dyspepsia in individuals with weekly GERS was 43.9% (95% CI, 35.1–52.9%). The pooled OR for dyspepsia in individuals with weekly GERS, compared with those without, was 6.94 (95% CI, 4.33 to 11.1). The OR for dyspepsia in individuals with weekly GERS was significantly higher in all geographical regions studied and for all diagnostic criteria. The pooled degree of overlap between dyspepsia and GERS was 25.9% (95% CI, 19.9%–32.4%).

Conclusion: The odds of dyspepsia in individuals with weekly GERS is almost 7-fold that of individuals without GERS; dyspepsia and GERS overlap in more than 25% of individuals. Reasons for this remain speculative, but might include shared pathophysiological mechanisms or residual confounding factors. However, patients with GERS should be questioned about co-existent dyspepsia, to optimize treatment approaches.

INTRODUCTION

Gastro-esophageal reflux and dyspepsia are both common conditions in the general population, with an overall pooled prevalence of approximately 15% and 21% respectively.[1, 2] Gastro-esophageal reflux is characterized by reflux of stomach contents into the esophagus, causing troublesome symptoms. Typical symptoms include heartburn, regurgitation, and chest pain [3]. The proposed pathogenesis of GERS is multifactorial, including lower esophageal pressure abnormalities, lower esophageal sphincter relaxation, hiatus hernia, delayed gastric emptying, and visceral hypersensitivity.[4-7]

Dyspepsia refers to any symptom felt to originate from the gastroduodenal region, according to the Rome Criteria.[8-11] The presence of peptic ulcer disease, or rarely gastro-esophageal malignancy, may cause symptoms of dyspepsia. However, most individuals will have no structural explanation for their symptoms and will be labelled as having functional dyspepsia.[12] There are numerous mechanisms implicated in the pathogenesis of functional dyspepsia,[13] some of which are common to GERS, including visceral hypersensitivity and delayed gastric emptying.[14-16] Other proposed mechanisms for functional dyspepsia include impaired fundal accommodation, abnormal central pain processing, acute gastroenteritis, and chronic infection with *Helicobacter pylori (H. pylori).*[17-20]

Some studies have demonstrated an overlap between GERS and dyspepsia.[21, 22] However, it is not known whether this overlap occurs by chance because they are both common disorders, or whether they share common pathophysiology or potential confounding factors, such as psychological factors or high levels of somatization. To date, there has been no study that synthesizes all available data in order to estimate the prevalence of dyspepsia in individuals with GERS. To inform future research on potential shared pathophysiological mechanisms, it is important to estimate the strength of association between the two

conditions, and whether this association remains stable depending on the criteria used to define these conditions, as well as geographic location. Therefore, we have conducted a systematic review and meta-analysis of all available population-based cross-sectional surveys, to estimate the prevalence of dyspepsia in individuals with GERS compared with those without, and to determine the degree of overlap between the two conditions.

METHODS

Search Strategy and Study Selection

A literature search was performed using EMBASE CLASSIC and EMBASE (1947 to September 2016), and MEDLINE (1948 to September 2016) in order to identify only cross-sectional surveys published in full. The studies had to report the prevalence of GERS and dyspepsia in adults (aged ≥15 years). Studies were required to recruit participants from the general population or community. Studies reporting data from convenience samples, such as those attending screening clinic health check-ups, university students, or employees at an institution were ineligible. To be eligible, studies had to recruit ≥50 participants and report prevalence of both weekly GERS and dyspepsia within the same study population. These eligibility criteria, which were defined prospectively, are provided in Box 1.

The medical literature was searched using the following terms: *heartburn*, *GERD*, *gastro-esophageal reflux disease*, *gastro-esophageal reflux*, *esophageal reflux* (both as a medical subject heading (MeSH) and free text term), *acid regurgitation*, *GORD*, or *upper gastrointestinal symptoms* (as free text terms). These were combined using the set operator AND with studies identified with the terms: *prevalence*, *incidence*, or *frequency* (both as MeSH and free text terms), or *proportion* (as a free text term). The resulting abstracts were screened for potential suitability by two investigators, and those that appeared relevant were retrieved and examined in detail. There were no language restrictions. Foreign language articles were translated, where required. A recursive search of the bibliographies of all articles was performed. Where there appeared to be multiple study reports from the same group of subjects, we contacted the authors to clarify this issue. Eligibility assessment was performed independently by two investigators, using pre-designed eligibility forms, with disagreements resolved via a third investigator.

Data Extraction

Data were extracted independently by two investigators on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA), again with any discrepancies resolved via a third investigator. The following data were collected for each study: year(s) conducted, country and geographical region, method of symptom data collection, criteria used to define GERS, criteria used to define dyspepsia, number of subjects providing complete data, number of subjects with weekly GERS, number of subjects with dyspepsia, and number of subjects meeting the criteria for dyspepsia among those with or without weekly GERS. We assessed quality of the identified and included studies using an adapted version of published, non-validated, criteria for prevalence studies such as these.[23] Studies are graded according to eight methodological criteria, with a total possible score from 0 to 8. No threshold was recommended by the authors to define a high-quality study, but we used a score of ≥5.

The degree of overlap between the two conditions was examined by extracting the total number of individuals who met the criteria for both GERS and dyspepsia simultaneously, for each study, and expressing this as a proportion of the total number of subjects who reported symptoms compatible with either condition. We studied the effect of varying the definitions of GERS or dyspepsia on the degree of overlap observed.

Data Synthesis and Statistical Analysis

The proportion of individuals with dyspepsia was combined for all studies according to presence or absence of weekly GERS. The prevalence of dyspepsia in those with and without weekly GERS was then compared using an odds ratio (OR) with a 95% confidence interval (CI). Heterogeneity between studies was assessed using the I^2 statistic, with a cut off of 50%, and the $\chi 2$ test with a P value <0.10, used as the threshold for statistically significant

heterogeneity.[24] We planned to conduct subgroup analyses according to geographical region, diagnostic criteria used to define weekly GERS, and diagnostic criteria used to define dyspepsia, to examine whether this had any effect on the ORs for dyspepsia in individuals with weekly GERS compared with those without.

Data were pooled using a random effects model to give a more conservative estimate of the prevalence of, and the odds of, dyspepsia in individuals with weekly GERS.[25] StatsDirect version 2.7.2 (StatsDirect, Sale, Cheshire, England) was 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 ORs,[26] where a sufficient number of studies (≥10) were available.[27] The degree of overlap between the two conditions was examined, whilst varying the specific diagnostic criteria used for weekly GERS or dyspepsia, where more than one study existed for each definition, by comparing the number of individuals meeting criteria for both conditions as a proportion of all individuals meeting criteria for either condition using a $\chi 2$-test.

RESULTS

The search strategy identified 14,132 citations. From these we identified 365 that appeared to be relevant to the study question. Of these, there were 79 separate adult study populations reporting the prevalence of weekly GERS, of which 19 also reported the proportion of individuals with dyspepsia (Figure 1).[21, 28-45] Agreement between investigators for assessment of study eligibility was perfect (κ-statistic = 1.0). Detailed characteristics of all included studies are provided in Table 1. Except for the article by Reshetnikov et al.[37] that was written in Russian, all other included studies were published in English language. Individual quality items for each of the included studies are provided in Supplementary Table 1. Ten studies achieved a score of ≥5 using these quality criteria.[21, 33-38, 42-44]

The 19 included studies contained 111,459 subjects and were geographically diverse, with 8 studies from Europe,[31, 34, 36, 37, 39, 43-45] four from Asia,[32, 38, 40, 42] four from North America,[21, 28, 30, 35] and one each from the Middle East,[41] Australasia,[29] and South America.[33] Six studies defined weekly GERS using the Montreal criteria,[37, 39, 40, 42, 43, 45] six the bowel disease questionnaire [21, 28-30, 32, 35], four the Mayo reflux questionnaire [33, 36, 41, 44], and three another validated questionnaire.[31, 34, 38] There was a wide variation in the prevalence of weekly GERS, which ranged from 3.1% [40] to 34.4%,[34] within the 19 included study populations. The pooled prevalence of weekly GERS was 15.4% (95% CI 12.5% to 18.6%), with statistically significant heterogeneity between studies (I^2 = 99.4%, P < 0.001).

In terms of the definition of dyspepsia used, there were four studies that used the Rome I criteria,[29, 30, 32, 37] four the Rome II criteria,[35, 38-40] five the Rome III criteria,[21, 31, 42, 43, 45] three defined presence of dyspepsia according to the Mayo reflux questionnaire (which defines dyspepsia using questions extracted directly from the previously validated bowel disease questionnaire),[33, 36, 44] and three used another validated questionnaire.[28, 31, 34] The prevalence of dyspepsia reported by included studies ranged from 2.4% [40] to 48.4%,[34] with a

pooled prevalence of 17% (95% CI 13.4% to 20.9%), again with statistically significant heterogeneity between studies (I^2 = 99.6%, P < 0.001).

Prevalence of Dyspepsia in Individuals with Weekly GERS Compared with Individuals without Weekly GERS, Regardless of Diagnostic Criteria Used

The prevalence of dyspepsia in subjects with weekly GERS varied from 6.5% [40] to 86.3%,[34] with a pooled prevalence of 43.9% (95% CI 35.1% to 52.9%). There was significant heterogeneity between studies (I^2 = 98.7%, P < 0.001). The prevalence of dyspepsia in individuals without weekly GERS varied from 0.8% [45] to 33.1%,[37] with a pooled prevalence of 11.7% (95% CI 9.0% to 14.6%), again with significant heterogeneity between studies (I^2 = 99.4%, P < 0.001). The pooled OR for dyspepsia in individuals with weekly GERS, compared with those without, was 6.94 (95% CI 4.33 to 11.1, I^2 = 98.6%, P < 0.001, Figure 2), with no evidence of funnel plot asymmetry (Egger test, P = 0.17).

A subgroup analysis was performed according to geographical location of the studies (Table 2), without revealing any obvious explanation for the heterogeneity observed between studies. The odds of dyspepsia in those with weekly GERS, compared with those without, remained significantly higher in all these analyses. The OR was highest in the study conducted in Middle East and lowest in the South American study.

Prevalence of Dyspepsia in Individuals with Weekly GERS Compared with Individuals without GERS, According to Diagnostic Criteria Used

A further subgroup analyses was conducted according to the diagnostic criteria used to define weekly GERS or dyspepsia (Table 2). When criteria for weekly GERS were examined individually, there were no obvious causes for the heterogeneity observed between

studies, although heterogeneity was somewhat lower when the bowel disease questionnaire was used. The OR was higher when the Montreal criteria were used (OR = 7.20; 95% CI 4.02 to 12.9, I^2 = 96.3%, P < 0.001), but were highest in studies that used another validated questionnaire to define the presence of weekly GERS (OR = 10.4; 95% CI 4.97 to 21.6, I^2 = 93.1%, P < 0.001).

When criteria used to define dyspepsia were examined, there was still significant heterogeneity detected between studies regardless of which criteria were used. The OR was highest when the Rome III criteria were used to define the presence of dyspepsia (20.6; 95% CI 6.86 to 61.6, I^2 = 99.4%, P < 0.001), and lowest when the Mayo reflux questionnaire was used to define dyspepsia (2.48; 95% CI 1.31 to 4.69, I^2 = 90.3%, P < 0.001).

Degree of Overlap Between Dyspepsia and Weekly GERS

The degree of overlap between weekly GERS and dyspepsia varied from 3.8% [40] to 55.9%,[34] with a pooled value of 25.9% (95% CI 19.9% to 32.4%, I^2 = 98.6%, P < 0.001). When specific diagnostic criteria for weekly GERS were applied, using any definition of dyspepsia, the degree of overlap was lowest when the bowel disease questionnaire was used (22.0%), and highest when the Mayo reflux questionnaire was used (42.6%). This difference was statistically significant ($\chi 2$ = 240.1, P < 0.001). When specific diagnostic criteria were used for dyspepsia, applying any definition of weekly GERS, overlap was lowest when the Rome II criteria were used to define presence of dyspepsia (17.0%), and highest when the Rome III criteria were used (28.9%). This difference was also statistically significant ($\chi 2$ = 125.2, P < 0.001).

DISCUSSION

This systematic review and meta-analysis has collected data from all available and identified population-based cross-sectional surveys reporting the prevalence of dyspepsia according to the presence of GERS. We have demonstrated a prevalence of dyspepsia in individuals with weekly GERS almost seven-fold that of individuals without GERS. The positive association between dyspepsia and weekly GERS remained according to all geographical locations examined. The positive association between the two persisted for almost all definitions of GERS and each definition of dyspepsia used, although the degree of association varied considerably in these analyses. The pooled OR for dyspepsia in individuals with weekly GERS was highest when the Gastrointestinal Symptom Rating Scale [34] or the Leeds Dyspepsia Questionnaire [31] were used to define GERS, and when the Rome III criteria were used to define dyspepsia. The degree of overlap between GERS and dyspepsia varied between 3.8% and 55.9%, depending on the diagnostic criteria used to define each condition. Higher amounts of overlap were found when GERS was defined according to the Mayo reflux questionnaire, and when presence of dyspepsia was defined according to Rome III criteria.

We used rigorous methodology and a contemporaneous literature search, which allowed the pooling of data from more than 100,000 individuals. Judging of study eligibility and data extraction were carried out by two investigators independently, with discrepancies resolved by consensus. Foreign language articles were also included, after translation. A random effects model was used to pool data, in order to provide a more conservative estimate of the pooled OR for dyspepsia in GERS. We also assessed for evidence of publication bias, or other small study effects, by testing funnel plots for obvious asymmetry. Finally, we limited studies to those based in the general population, and excluded those conducted among convenience samples, which should reduce the likelihood that the reported prevalence of

either GERS or dyspepsia were inflated, and the data reported should therefore be generalisable to individuals in the community.

Limitations of this study include the fact that half (10 out of 19) of the studies we identified scored 3 or less (of a possible total score of 6) on the quality scale we used,[23] although this has not been validated, and there is no recommendation as to what threshold should be used to define higher-quality studies. Since the included studies were mainly observational, the majority of the subjects were not required to undergo upper endoscopy as part of the studies, thus dyspepsia in these studies was mostly uninvestigated, rather than truly functional, despite the use of various iterations of the Rome criteria in many studies. Moreover, the methods and criteria used to define presence of GERS and dyspepsia varied between individual studies, according to both frequency and duration of symptoms in some instances. In order to minimize this variation, we included only studies that reported a weekly prevalence of GERS and, in addition, we performed subgroup analyses according to criteria used to define dyspepsia and GERS, as well as geographical location. However, significant heterogeneity between studies persisted in most of these analyses. The reasons for the heterogeneity are therefore speculative and, other than subtle differences in the diagnostic criteria used, may include other demographic or cultural differences between study populations, including ethnicity, which it was not possible to examine using the data available for extraction. Another limitation is the paucity or absence of studies reporting the prevalence of GERS and dyspepsia for some geographical regions, such as the Middle East, Central and South America, and Africa.

Although most subjects in the studies identified in this systematic review and meta-analysis had symptoms that could be classified as either GERS alone or dyspepsia alone, our results still demonstrate that, in almost half of these individuals, there was overlap between

the two conditions, and that individuals with GERS were at significantly increased risk of co-existent dyspepsia. These data suggest that the overlap of dyspepsia and GERS is not explained by chance alone, although the reasons for this overlap cannot be elucidated by a study such as ours. Although the pathophysiology of both GERS and dyspepsia has been studied extensively, there has been little research that has focused specifically on patients with both of these disorders. The two diseases are frequently chronic, and may share pathophysiological mechanisms, including visceral hypersensitivity and altered gastrointestinal (GI) motility.[14, 46, 47] In particular, impaired gastric accommodation is considered to play important role in the pathogenesis of functional dyspepsia, and has been found in approximately 40% of cases.[48] Gastric wall tension and antral over-distension are among the main mechanisms involved in generating dyspeptic symptoms. Moreover, prolonged postprandial gastric distention and increased basal intragastric pressure lead to an increased gastro-esophageal pressure gradient, favoring spontaneous reflux. Therefore, since impaired gastric accommodation has also been reported in 25-40% of patients with GERD, gastric motility issues could explain some of the overlap of GERS and dyspepsia that we observed.[49]

In addition, acid-related mechanisms have been considered to play an important role in patients with overlapping functional dyspepsia and heartburn. Several studies have reported that a subgroup of patients with functional dyspepsia have pathological acid reflux, based on abnormal 24-hour esophageal pH monitoring.[46, 50] An important role has also been attributed to psychological factors, and high levels of somatization, in particular depression, anxiety, and insomnia appear to predict symptom overlap between dyspepsia and GERS.[22] This has led some authors to suggest that the overlap group may represent a distinct syndrome.[21, 51] Moreover, not all patients reporting presence of heartburn suffer from gastro-esophageal reflux disease (GERD). Savarino *et al.* studied a cohort of patients with GERS,

but normal upper GI endoscopy. All patients underwent 24-hour pH-impedance monitoring and the symptom association probability (SAP) for typical esophageal symptoms was calculated for each subject. One-quarter of the patients were classified as having functional heartburn (negative pH-impedance study and SAP), and these patients showed significantly higher rates of dyspeptic symptoms compared with patients with a positive pH-impedance study and/or positive SAP. This led the authors to conclude that functional heartburn seemed to have more in common with functional dyspepsia than with non-erosive GERD.[52]

The role of *H. pylori* has been widely investigated in the pathogenesis of both dyspepsia and reflux disease. The infection seems to cause dyspeptic symptoms in some individuals, as confirmed by epidemiological studies [31, 53] and most of all by *H. pylori* eradication studies. Indeed, in infected patients with uninvestigated or functional dyspepsia, *H. pylori* eradication produces long-term relief of dyspepsia in about 10% of patients compared with placebo.[54] On the contrary, at a population level, *H. pylori* infection is negatively associated with GERS, and also with their sequelae, such as Barrett's esophagus and esophageal adenocarcinoma;[55-57] nevertheless, its eradication seems neither to cause nor exacerbate reflux disease. Among the studies included in our meta-analysis, only two reported the overall prevalence of *H. pylori* infection in their study population, with rates ranging from 27.7% in the UK [31] to 57.7% in Italy.[39] Two other studies reported partial data on *H. pylori* infection,[37, 40] but the majority of studies analyzed symptom questionnaires without evaluating the infection status of included individuals.

Other genetic and pathophysiological risk factors may differ according to ethnicity, and this could lead to differences in the co-existence of GERS and dyspepsia according to geographical region. Nevertheless, with the exception of the single study performed in Middle East reporting an OR of 78.2, the subgroup analyses examining this issue did not

reveal any obvious underlying differences in the degree of overlap between the two conditions, with ORs ranging from 6.23 in Asia to 6.79 in Europe, whereas ORs for dyspepsia in subjects with GERS of lesser magnitude were found in South America and Australasia, although only two studies reported data from these regions.

We also conducted subgroup analyses according to the criteria used to define each condition. We expected these to lead to a reduction in heterogeneity between studies, due to a more uniform definition of each of the two disorders. However, this was not the case, although a lower amount of heterogeneity was seen when studies that used the Rome I and II criteria to define the presence of dyspepsia were pooled. We also found a lower OR for dyspepsia in GERS when the Mayo reflux questionnaire was used to define dyspepsia. However, this questionnaire was primarily designed to identify individuals with GERS, and considers only a limited range of symptoms for the diagnosis of dyspepsia (pain or aching in the upper abdominal area only) compared with the more widely accepted Rome criteria. Therefore, using this questionnaire in the community may have underestimated the true prevalence of dyspepsia.

These methodological differences reflect the complexity of defining dyspepsia in the community, which is echoed by an evolution of the Rome criteria over the years. Within the Rome II criteria functional dyspepsia was defined as pain or discomfort centered in the upper abdomen, with no emphasis given to meal-related symptoms.[11] From Rome III onwards, different symptom clusters based on meal-induced and meal-unrelated symptoms have been introduced, distinguishing between postprandial distress syndrome and epigastric pain syndrome, with the aim being to create more homogenous patient groups.[10] The Rome III criteria also highlighted the issue that any overlap of GERD with dyspepsia needs to be carefully evaluated, in order to exclude from the diagnosis of functional dyspepsia subjects

with isolated/predominant GERS from the diagnosis of functional dyspepsia. However, in a study conducted in a primary care setting in Europe and Canada, which assessed the validity of the Rome III criteria to both distinguish between and subgroup patients with upper GI symptoms undergoing upper GI endoscopy and 48-hour pH monitoring,[58] 75% of patients with confirmed GERD met criteria for functional dyspepsia, and >50% with confirmed functional dyspepsia reported GERS. The authors concluded that, even after exhaustive investigation, discriminating between these two conditions accurately was difficult.

Our meta-analysis only included studies that reported the overlap of GERS and dyspepsia in the community, but studies from convenience samples also support our findings. In a cross-sectional survey of Japanese patients attending for upper GI endoscopy, the overlap between GERS and dyspepsia according to the Montreal definition and the Rome III criteria was 30%.[59] Similarly, Xiao *et al.* evaluated consecutive dyspeptic patients who fulfilled the Rome III criteria and who underwent upper GI endoscopy and had ambulatory 24-hour pH monitoring, confirming that evidence of pathological acid reflux was present in almost one-third of patients with dyspepsia and, in particular, the prevalence was about 50% in those with epigastric burning.[60] Moreover, the PPI test had a limited ability to distinguish those with dyspeptic symptoms from those with GERD.

In conclusion, this systematic review and meta-analysis has demonstrated that the prevalence of dyspepsia in individuals with GERS is almost seven-fold that of subjects without GERS, and that there is overlap between the two conditions in up to one-quarter of individuals. Making a diagnosis of GERD versus dyspepsia based on upper GI symptoms alone is difficult, and even when investigations are requested in an attempt to further delineate these two patient groups, overlap persists. The reasons for this remain speculative, but may include shared pathophysiological mechanisms or other demographic features that

are associated with both conditions.

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Box 1: Eligibility Criteria

Cross-sectional surveys

Recruited adults (>90% of participants aged ≥15 years)

Participants recruited from the general population / community*

Reported prevalence of both dyspepsia and gastro-esophageal reflux-type symptoms within the same study population (according to a questionnaire, or specific diagnostic criteria†)

Sample size of ≥50 participants

*Convenience samples excluded

† For dyspepsia, these included the Rome I, II, or III criteria. For gastroesophageal reflux symptoms (GERS), these included the Montreal criteria.

FIGURES

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

Figure 2. Pooled Odds Ratio for Dyspepsia in Those with Weekly GERS Compared with Those without GERS.

Table 1. Characteristics of Included Studies.

Author and publication year (ref)	Country	Method of data collection	Criteria used to define weekly GERS	Criteria used to define dyspepsia	Total no. of patients	No. with weekly GERS (%)	No. with dyspepsia (%)	Total quality score (maximum of 6)
Talley 1994 [28]	USA	Postal questionnaire	Bowel Disease Questionnaire	Bowel Disease Questionnaire	919	100 (10.9)	200 (21.8)	2
Talley 1998 [29]	Australia	Postal questionnaire	Bowel Disease Questionnaire / Bowel Symptom Questionnaire	Rome I	774	168 (21.7)	92 (11.9)	2
Locke 2000 [30]	USA	Postal questionnaire	Bowel Disease Questionnaire	Rome I	643	128 (19.9)	89 (13.8)	3
Moayyedi 2000 [31]	UK	Interview-administered questionnaire	Leeds Dyspepsia Questionnaire	Leeds Dyspepsia Questionnaire	8404	1289 (15.3)	954 (11.4)	1
Hu 2002 [32]	China	Telephone interview	Bowel Disease Questionnaire	Rome I	1649	79 (4.8)	304 (18.4)	3
Chiocca 2005 [33]	Argentina	Postal questionnaire	Mayo Reflux questionnaire	Mayo Reflux Questionnaire	837	194 (23.2)	257 (30.7)	3

Papatheodoridis 2005 [34]	Greece	Face-to-face interview	Gastrointestinal Symptom Rating Scale	Gastrointestinal Symptom Rating Scale	700	241 (34.4)	339 (48.4)	4
Choung 2007 [35] *	USA	Postal questionnaire	Bowel Disease Questionnaire	Rome II	2273	411 (18.1)	351 (15.4)	4
Kitapcioglu 2007 [36]	Turkey	Face-to-face interview	Mayo Reflux questionnaire	Mayo Reflux Questionnaire	630	126 (20)	180 (28.6)	4
Reshetnikov 2009 [37]	Russia	Self-completed questionnaire	Montreal criteria	Rome I	1040	177 (17)	390 (37.5)	4
Lee 2009 [38]	South Korea	Interview-administered questionnaire	Questionnaire (weekly heartburn and/or regurgitation)	Rome II	1443	123 (8.5)	137 (9.5)	4
Zagari 2010 [39]	Italy	Interview-administered questionnaire	Montreal criteria	Rome II	1033	258 (25)	285 (27.6)	3
Zhao 2010 [40]	China	Self-completed questionnaire	Montreal criteria	Rome II	16078	496 (3.1)	387 (2.4)	3
Moghimi-Dehkordi 2011 [41]	Iran	Face-to-face interview	Mayo Reflux questionnaire	Rome III	18180	1525 (8.4)	1411 (7.8)	3

Choung 2012 [21]	USA	Postal questionnaire	Bowel Disease Questionnaire	Rome III	3517	404 (11.5)	344 (9.8)	3
Min 2014 [42]	South Korea	Telephone interview	Montreal criteria	Rome III	5000	356 (7.1)	384 (7.7)	4
Rasmussen 2015 [43]	Denmark	Self-completed / Telephone questionnaire	Montreal criteria	Rome III	47090	5264 (11.2)	3599 (7.6)	4
Bor 2016 [44]	Russia	Face-to-face interview	Mayo Reflux questionnaire	Mayo Reflux Questionnaire	1065	251 (23.6)	360 (33.8)	4
Chirila 2016 [45]	Romania	Interview-administered questionnaire	Montreal criteria	Rome III	184	57 (31)	14 (7.6)	4

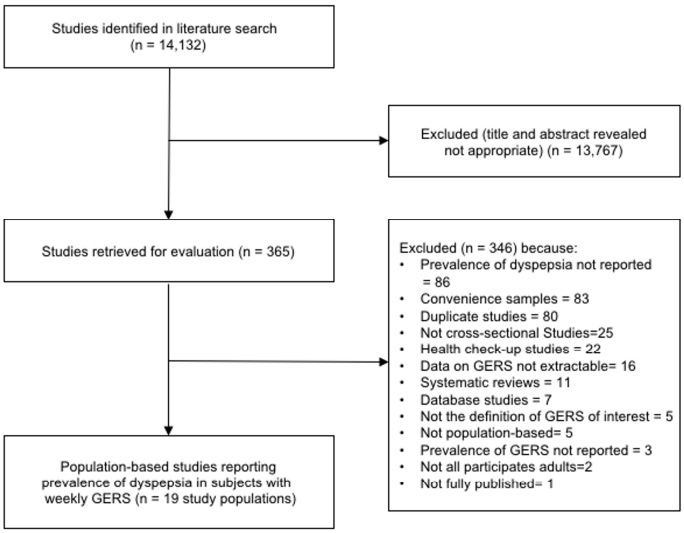
* data also extracted from Jung et al. 2007 [56]

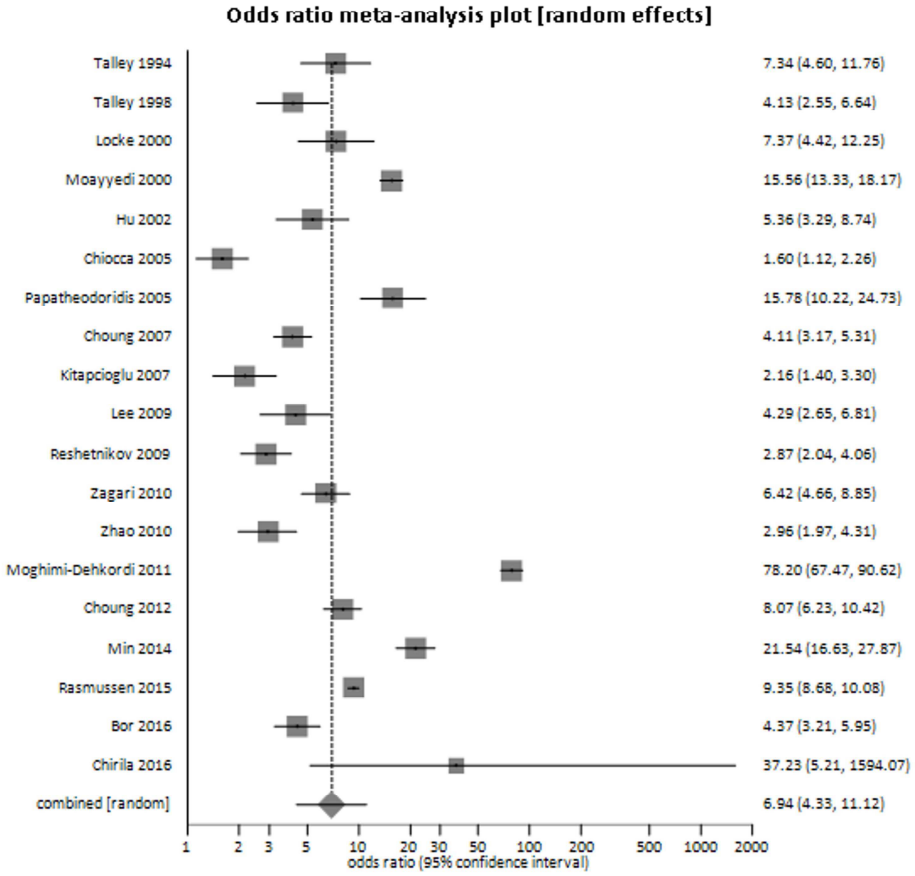
Table 2. Pooled Odds Ratios for Dyspepsia in Those with Weekly GERS Compared with Those without Weekly GERS According to Geographical Location and Criteria Used to Define Dyspepsia or Weekly GERS.

	Number of studies	Number of subjects	Odds ratio	95% confidence interval	I^2	P value for X^2
All studies	**19**	**111,459**	**6.94**	**4.33 – 11.1**	**98.6%**	**< 0.001**
Geographical region						
North American studies	4	7,352	6.41	4.37 – 9.39	81.1%	< 0.001
South American studies	1	837	1.60	1.12 – 2.26	N/A	N/A
European studies	8	60,146	6.79	4.39 – 10.5	96.1%	< 0.001
Northern European studies	*4*	*57,599*	*6.68*	*3.89 – 11.5*	*97.5%*	*< 0.001*
Southern European studies	*4*	*2,547*	*7.61*	*2.87 – 20.2*	*93.8%*	*< 0.001*
Middle Eastern studies	1	18,180	78.2	67.47 – 90.6	N/A	N/A
Asian studies	4	24,170	6.23	2.18 – 17.8	96.9%	< 0.001
Australasian studies	1	774	4.13	2.55 – 6.64	N/A	N/A

Criteria used to define GERS						
Bowel Disease Questionnaire	6	9,775	5.83	4.37 – 7.76	73.0%	< 0.001
Mayo Reflux questionnaire	4	20,712	5.88	0.60 – 57.5	99.6%	< 0.001
Montreal criteria	6	70,425	7.20	4.02 – 12.9	96.3%	< 0.001
Other questionnaires	3	10,547	10.4	4.97 – 21.6	93.1%	< 0.001
Criteria used to define Dyspepsia						
Mayo Reflux questionnaire	3	2,532	2.48	1.31 – 4.69	90.3%	< 0.001
Rome I	4	4,106	4.55	2.30 – 6.90	73.8%	< 0.001
Rome II	4	20,827	4.32	3.15 – 5.91	71.5%	< 0.001
Rome III	5	73,971	20.6	6.86 – 61.6	99.4%	< 0.001
Other questionnaires	3	10,023	12.5	8.14 – 19.3	80%	< 0.001

* N/A; not applicable, too few studies to assess heterogeneity





Supplementary Table 1. Quality Rating of Included Studies

Study	Random sample or whole population	Unbiased sampling frame (e.g. census data)	Appropriate measure used (e.g. validated questionnaire or criteria)	Outcomes measured by unbiased assessors	Adequate response rate (70%), non-responders described	Study subjects described	Total score (maximum of 6)
Talley 1994 [28]	1	0	0	0	1	0	**2**
Talley 1998 [29]	1	0	1	0	0	0	**2**
Locke 2000 [30]	1	0	1	0	1	0	**3**
Moayyedi 2000 [31]	1	0	0	0	0	0	**1**
Hu 2002 [32]	1	0	1	0	0	1	**3**
Chiocca 2005 [33]	1	0	1	0	1	0	**3**
Papatheodoridis 2005 [34]	1	0	1	0	1	1	**4**
Choung 2007 [35]	1	0	1	0	1	1	**4**
Kitapcioglu 2007 [36]	1	1	1	0	1	0	**4**
Reshetnikov 2009 [37]	1	1	1	0	0	1	**4**
Lee 2009 [38]	1	1	1	0	0	1	**4**
Zagari 2010 [39]	1	0	1	0	1	0	**3**
Zhao 2010 [40]	1	0	1	0	0	1	**3**
Moghimi-Dehkordi 2011 [41]	1	0	1	0	1	0	**3**

Choung 2012 [21]	1	0	1	0	0	1	**3**
Min 2014 [42]	1	0	1	0	1	1	**4**
Rasmussen 2015 [43]	1	1	1	0	0	1	**4**
Bor 2016 [44]	1	0	1	0	1	1	**4**
Chirila 2016 [45]	1	0	1	0	1	1	**4**