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TITLE PAGE

Title: Systematic Review and meta-analysis: Global Prevalence of Uninvestigated Dyspepsia According to the Rome criteria.

Short running head: Meta-analysis: Prevalence of Dyspepsia.

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Abbreviations:

CI	confidence interval
EPS	epigastric pain syndrome
FD	functional dyspepsia
OR	odds ratio
PDS	postprandial distress syndrome

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SUMMARY

Background: Prevalence of uninvestigated dyspepsia varies across cross-sectional surveys. This may be due to differences in definitions used or study methodology, rather than global variability.

Aim: We performed a systematic review of studies using comparable methodology, and all iterations of the Rome criteria, to determine global prevalence.

Methods: MEDLINE and EMBASE were searched to identify population-based studies reporting prevalence of uninvestigated dyspepsia in adults (≥18 years old) according to Rome I, II, III, or IV criteria. Prevalence of uninvestigated dyspepsia was extracted, according to criteria used to define it. Pooled prevalence, according to study location and certain other characteristics, odds ratios (OR), and 95% confidence intervals (CIs) were calculated.

Results: Of 2133 citations evaluated, 67 studies fulfilled eligibility criteria, representing 98 separate populations, containing 338,383 subjects. Pooled prevalence ranged from 17.6% (95% CI 9.8% to 27.1%) in studies defining uninvestigated dyspepsia according to Rome I criteria, to 6.9% (95% CI 5.7% to 8.2%) in those using Rome IV criteria. Postprandial distress syndrome was the commonest subtype, occurring in 46.2% of participants using Rome III criteria, and 62.8% with Rome IV. Prevalence of uninvestigated dyspepsia was up to 1.5-fold higher in women, irrespective of definition used. There was significant heterogeneity between studies in all our analyses, which persisted even when the same criteria were applied and similar methodology used.

Conclusions: Even when uniform symptom-based criteria are used to define the presence of uninvestigated dyspepsia, prevalence varies between countries. This suggests there are environmental, cultural, ethnic, dietary, or genetic influences determining symptoms.

INTRODUCTION

Dyspepsia is a complex of symptoms referable to the gastroduodenal region of the gastrointestinal tract, rather than a diagnosis. Definitions of dyspepsia have evolved over the years, from a broad one that includes any symptom referable to the upper gastrointestinal tract,[1] to the Rome criteria (Supplementary Table 1).[2-5] These were first described in 1991, and were developed by consensus among experts in the field. These criteria moved to exclude heartburn and regurgitation deliberately from the definition of dyspepsia, as these were felt to be indicative of underlying gastro-oesophageal reflux disease. Notably, further major changes were made with the Rome III criteria in 2006,[3] wherein two distinct syndromes were proposed: postprandial distress syndrome (PDS), consisting of early satiety or postprandial fullness at least several times per week, and epigastric pain syndrome (EPS), characterised by intermittent epigastric pain or burning at least once per week. The Rome IV classification, put forward in 2016,[2] uses similar definitions, although symptoms of PDS must occur at least three times per week, meaning that these criteria are slightly more restrictive,[6] and epigastric pain related to meals is considered part of the PDS symptom complex.

The situation is further complicated by the fact that the classification of dyspepsia depends on whether upper gastrointestinal endoscopy has been performed and, if so, whether relevant pathology is detected. Individuals who have not undergone investigation are said to have uninvestigated dyspepsia. Patients with dyspepsia who undergo endoscopy and have pathological findings that may be responsible for the symptoms, such as peptic ulcer, are classed as having organic dyspepsia. Finally, those without a detectable cause, including *Helicobacter pylori* infection, who make up approximately 80% of individuals with uninvestigated dyspepsia,[7] are labelled as having functional dyspepsia (FD). Thus, the majority of individuals in the community reporting dyspeptic symptoms will likely have FD as the cause, and this condition represents a substantial economic burden.[8] Despite this, there

is considerable diagnostic confusion between FD and other causes of upper gastrointestinal symptoms, such as gastro-oesophageal reflux.[9] FD is associated with increased health-care usage, somatoform-type behaviour, psychological co-morbidity, and impaired quality of life,[10-12] as well as higher rates of absenteeism from employment, lower productivity at work, missed leisure time, reduced activity around the house, and greater medical and prescription medicine costs per year.[13,14] Patients with FD are willing to accept considerable risks in return for a cure of their symptoms. In one study almost 50% would accept a mean 12.7% risk of death in return for a 99% chance of cure of symptoms.[15]

Although dyspepsia is perceived to be common, its prevalence has shown wide variation in cross-sectional surveys, even within similar geographical regions.[16-19] As only a few studies have evaluated the prevalence of uninvestigated dyspepsia simultaneously across multiple countries using uniform methodology,[17,20,21] it is difficult to know the exact reasons for this variability. It may be that differences in sampling methods, administration of questionnaires, or the criteria used to define the presence of uninvestigated dyspepsia are responsible, but this is speculative. In our previous systematic review and meta-analysis of 100 separate study populations, containing 312,415 subjects, the overall pooled prevalence of uninvestigated dyspepsia was over 20%, but this varied significantly between individual studies, and between countries.[22] Many of the definitions of uninvestigated dyspepsia used in the studies included in this meta-analysis were outdated. Only 34 of the 103 studies reported prevalence according to one of the iterations of the Rome criteria, only seven used Rome III, and Rome IV had not been described at the time it was conducted.

In order to improve our understanding of the epidemiology of uninvestigated dyspepsia, as well as how evolving definitions have affected this, we have updated this systematic review, restricting the analysis to only studies using the Rome criteria. This type

of information is important, in order to inform health care planning decisions, as well as identify priorities for future research in this field.

METHODS

Search Strategy and Study Selection

We searched EMBASE (1990 to April 2020) and MEDLINE (1990 to April 2020) to identify only cross-sectional surveys that reported the prevalence of uninvestigated dyspepsia in adults (≥90% aged ≥18 years) according to the Rome I, II, III, or Rome IV criteria.[2,3] As the Rome criteria were first described in 1991, we limited the search from 1990 to the present. We hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) in order to identify studies published only in abstract form. Studies were required to recruit participants from the general population or community. We deemed as ineligible studies that reported the prevalence of uninvestigated dyspepsia in convenience samples, such as university students, employees at an institution, or those attending screening clinic health check-ups. In order to be eligible, studies also had to recruit at least 50 participants, and define dyspepsia according to the Rome I, II, III, or IV criteria. These eligibility criteria, which were defined prospectively, are provided in Table 1.

We searched the medical literature using the following terms: *dyspepsia* (both as a medical subject heading and free text term), *non-ulcer dyspepsia*, *non ulcer dyspepsia*, *nonulcer dyspepsia*, or *functional dyspepsia* (as free text terms). We combined these using the set operator AND with studies identified with the terms: *Rome I*, *Rome 1*, *Rome II*, *Rome 2*, *Rome III*, *Rome 3*, *Rome IV*, or *Rome 4* (as free text terms). There were no language restrictions. We screened the titles and abstracts of all citations identified by our search for potential suitability, and retrieved those that appeared relevant in order to examine them in more detail. We performed a recursive search, using the bibliographies of all eligible articles. We translated foreign language articles, where required. Where there appeared to be multiple

study reports from the same group of subjects, we contacted study authors to clarify this issue. We also contacted authors if a study appeared potentially eligible, but did not report the data required, in order to obtain supplementary information and, therefore, maximise available studies. We performed eligibility assessment independently. This was done by two investigators (ACF, BB), using pre-designed eligibility forms. We resolved any disagreements by consensus, and measured the degree of agreement with a kappa statistic. Ethical approval was not required.

Data Extraction

Data were extracted independently by two investigators (ACF, BB) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA). Again, we resolved any discrepancies by consensus. We collected the following data for each study: country, method of data collection (self-completed postal questionnaire, self-completed questionnaire given to the participant at an appointment, self-completed internet-based questionnaire, or interviewer-administered questionnaire either face-to-face or over the telephone), criteria used to define uninvestigated dyspepsia, whether the study used the Rome I, II, III, or IV diagnostic questionnaire, or approximated these definitions of dyspepsia using another questionnaire, the number of subjects providing complete data, the mean age of subjects, the number of male and female subjects, the number of subjects with uninvestigated dyspepsia, the proportion of male and female subjects with uninvestigated dyspepsia and, in the case of studies using the Rome III or IV criteria, the proportion of participants with PDS, EPS, or overlap of both subtypes. Where uninvestigated dyspepsia prevalence was reported according to more than one set of criteria within an individual study, the number of subjects with uninvestigated dyspepsia according to each individual definition was extracted.

Data Synthesis and Statistical Analysis

We combined the proportion of individuals with uninvestigated dyspepsia in each study, using a random effects model, to give a pooled prevalence of uninvestigated dyspepsia for all studies, according to the Rome I, II, III, or IV criteria. We assessed heterogeneity between studies 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.[23] We conducted subgroup analyses according to country, whether the Rome I, II, III, or IV criteria were defined strictly or approximated via another questionnaire, how the questionnaire was completed (self-completed versus interview-administered), sex, and subtype (EPS, PDS, or overlap). Finally, we compared the proportion of male and female subjects with uninvestigated dyspepsia using an odds ratio (OR), with a 95% confidence interval (CI). We used StatsDirect version 3.2.7 (StatsDirect Ltd, Sale, Cheshire, England) to generate Forest plots of pooled prevalences and pooled ORs with 95% CIs. We planned to assess for evidence of publication bias by applying Egger's test to funnel plots of odds ratios,[24] where a sufficient number of studies were available.[25]

RESULTS

The search strategy generated 2133 citations. From these we identified 125 that appeared to be relevant to the study question. In total, 67 of these articles fulfilled the eligibility criteria, representing 98 separate adult study populations (Figure 1)**,** and containing 338,383 subjects recruited from 45 different countries worldwide.[20,21,26-90] Almost all studies were conducted in a single country, with the exception of a three-nation study conducted in Canada, the UK, and the USA,[20,80] and a multi-national survey conducted in 33 different countries.[21] Agreement between investigators for assessment of study eligibility was good (kappa statistic = 0.73). Detailed characteristics of all included studies are provided in Supplementary Table 2. The lowest prevalence of uninvestigated dyspepsia reported was 0.7% in one Indian study that administered the Rome IV questionnaire during a face-to-face interview. The highest prevalence was 44.4%, reported in a Brazilian study that used the Rome I questionnaire during a face-to-face interview.[43]

Prevalence of Uninvestigated Dyspepsia According to Criteria Used to Define its Presence

In total, 13 studies, reported in stated that they used the Rome I criteria,[26-28,30,31,33,35,38,39,42,42,51,60] 19 the Rome II criteria, [29,32,36-39,41,43-47,49,50,52,53,55,56,61] 34 the Rome III criteria[34,40,48,54,57-59,62-88] and four the Rome IV criteria.[20,21,89,90] The pooled prevalence of uninvestigated dyspepsia, according to the criteria used to define its presence, is provided in Table 2. This decreased with each successive iteration of the Rome criteria; pooled prevalence was highest when the Rome I criteria were used (17.6%; 95% CI 9.8% to 27.1%), in eight different countries,[26-28,30,31,33,35,38,39,42,43,51,60] and lowest when the Rome IV criteria were used (6.9%; 95% CI 5.7% to 8.2%), in 34 different countries.[20,21,89,90] Figures 2 and 3 provide the prevalence of uninvestigated dyspepsia worldwide, according to country, using

the two most recent definitions, with the most number of countries studied; the Rome III or Rome IV criteria, respectively. The prevalence in individual countries, according to the Rome I, II, III, and IV criteria, is provided in Table 3. When the Rome I criteria were used, prevalence of uninvestigated dyspepsia was lowest in Thailand at 4.9% and highest in Brazil, at 44.4%. According to Rome II, prevalence was lowest in Canada at 1.8%, and highest in New Zealand at 34.2%. Using the Rome III criteria, prevalence of uninvestigated dyspepsia was lowest in France at 4.0% and highest in Portugal at 40.4%. Finally, when the Rome IV criteria were used prevalence was lowest in India at 0.7%, and highest in Bangladesh at 19.4%. The continued disparity in prevalence of uninvestigated dyspepsia by country in these analyses suggests that geographical variation was not related solely to the diagnostic criteria used in each study. We therefore conducted further analyses to explore reasons for this variability.

Prevalence of Uninvestigated Dyspepsia According to the Questionnaire Used and Method of Questionnaire Administration

Table 2 shows how the pooled prevalence varied on the basis of the method used to define the presence of uninvestigated dyspepsia. When the validated Rome questionnaire was used, the highest prevalence was found in 23 studies that used the Rome III criteria (11.4%; 95% CI 9.4% to 13.5%),[48,62-66,68-71,73-77,79-81,83-87] while the prevalence was lowest in three studies using the Rome I criteria (5.2%; 95% CI 2.5% to 8.8%)).[26,33,60] Among the studies that approximated the Rome criteria using another questionnaire, the prevalence was highest when the Rome I criteria were used in 10 studies (22.6%; 95% CI 15.8% to 30.3%),[27,28,30,31,35,38,39,42,43,51] while it was lowest in 11 studies using the Rome III criteria (11.8%; 95% CI 7.7% to 16.7%).[34,40,54,57-59,67,72,78,82,88]

When a self-completed questionnaire was administered, the pooled prevalence of uninvestigated dyspepsia was highest according to the Rome I criteria (15.4%; 95% CI 8.4% to 23.9%) in nine studies,[26-28,30,31,33,39,42,51] and lowest with Rome IV in three studies (7.6%; 95% CI 6.6% to 8.7%).[20,21,89] When an interview-administered questionnaire was used the highest prevalence was again found with Rome I in three studies (31.3%; 95% CI 17.7% to 46.7%),[35,38,43] and lowest with Rome IV in two studies (5.0%; 95% CI 2.4% to 8.7%).[21,90]

Prevalence of Uninvestigated Dyspepsia According to Rome III and IV Criteria by Subtype

Given the subtypes of dyspepsia proposed by the Rome I and II definitions have been superseded, we restricted this analysis to studies using only Rome III or IV criteria. Eight studies that used the Rome III criteria reported the prevalence of EPS, PDS, or overlap of both subtypes.[62,63,69,71,73,86-88] Overall, the pooled prevalence of PDS was higher (46.2%; 95% CI 33.4% to 59.3%) than the pooled prevalence of either EPS (20.8%; 95% CI 11.7% to 31.8%) or overlap of both (28.6%; 95% CI 15.3% to 44.2%). Two studies that used the Rome IV criteria reported the prevalence of the different subtypes of dyspepsia.[20,21] In this multinational-study, as well as the three-nation study conducted in Canada, the UK, and the USA, again the pooled prevalence of PDS was higher (62.8%; 95% CI 58.9% to 66.6%) than the pooled prevalence of either EPS (19.2%; 95% CI 13.6% to 25.4%) or overlap (17.8%; 95% CI 14.1% to 21.9%).

Prevalence of Uninvestigated Dyspepsia According to Sex

Overall, the prevalence of uninvestigated dyspepsia according to sex of the participants was reported in six,[26,30,31,35,43,51] eight [32,36,37,46,52,53,56,61] and 16 studies[34,48,57,58,62,63,47,70-72,74-76,78,79,86] using the Rome I, II, or III criteria respectively. Two

studies using the Rome IV criteria examined this issue. [20,21] The pooled prevalence of uninvestigated dyspepsia was higher in women compared with men, irrespective of the definition used (Table 4). There were only a sufficient number of studies to examine for funnel plot asymmetry for the Rome III criteria, with no evidence of asymmetry (Egger test, P = 0.96).

DISCUSSION

This systematic review and meta-analysis has assembled data from all available and identified population-based cross-sectional surveys that report prevalence of uninvestigated dyspepsia in the community using the Rome criteria. It has demonstrated that, even when the same definitions are applied, and similar methodology utilised, the prevalence of uninvestigated dyspepsia varies widely between countries, from <1% to >44%. Pooled prevalence was higher with the Rome I criteria, at 17.6%, compared with 6.9% using the Rome IV criteria, and decreased with each successive iteration. However, when the Rome criteria were applied, as intended, in a validated questionnaire, differences in prevalence were much smaller, and prevalence with Rome I was similar to Rome IV. PDS was the most prevalent subtype. This was particularly evident when using the Rome IV criteria, and overlap between PDS and EPS was substantially lower with Rome IV. Finally, odds of uninvestigated dyspepsia were significantly higher in female compared with male subjects, irrespective of the definition used.

We used an exhaustive search strategy in order to maximise the likelihood of identifying all pertinent literature. The judging of study eligibility and data extraction were carried out by two investigators independently, with discrepancies resolved by consensus. We contacted primary or senior authors of studies to ensure that duplicate publications from identical cohorts under extended follow-up were not included and, in some cases, to obtain extra data. We also included data from eligible foreign language articles, after translation, in order to be as inclusive as possible. We used a random effects model to pool data to provide a more conservative estimate of the prevalence of uninvestigated dyspepsia, and assessed for publication bias, where sufficient studies existed. Finally, we limited studies to those based in the general population, and excluded those conducted among convenience samples, meaning that the likelihood that the prevalence of uninvestigated dyspepsia has been inflated has been

minimised, and the data we report should therefore be generalisable to individuals in the community.

Limitations of this study include the paucity or absence of studies reporting the prevalence of uninvestigated dyspepsia for some geographical regions, such as Africa, South America, and Central America, and the limited number of studies reporting prevalence of uninvestigated dyspepsia according to gender or subtype. In addition, there was some variability in methods used to collect symptom data. It may be that these different approaches to collecting data, such as face-to-face or telephone interview versus self-completed internet-based or paper questionnaires, lead to different estimates of the prevalence of uninvestigated dyspepsia. This certainly appeared to be the case in the Rome Foundation global survey, which used both interview-administered and internet-based questionnaires.[21] There was significant heterogeneity between studies in all our analyses, which was not explained by any of the subgroup analyses we conducted. Given that the heterogeneity persisted even when the analysis was limited to studies that applied the same diagnostic criteria, and used exactly the same method of data collection, this suggests the variation in prevalence of uninvestigated dyspepsia that we observed between different countries is genuine. Reasons for this may include environmental, genetic, ethnic, dietary, or cultural differences between individual study populations. Finally, the findings of our study could be criticised as being superfluous, given the recent publication of a definitive 33-nation global study conducted by the Rome Foundation, using the Rome IV criteria to estimate prevalence of uninvestigated dyspepsia.[21] However, given the variation seen in prevalence rates between countries, even in this study, which used uniform methodology, we feel that a contemporaneous evidence synthesis of all available population-based cross-sectional surveys, using all definitions of the Rome criteria, still has merit.

There have been few previous systematic reviews examining the prevalence of uninvestigated dyspepsia in the community. The most recent of these was our own meta-analysis,[22] which considered the prevalence of uninvestigated dyspepsia, irrespective of the criteria used to define it, including historical classification systems, such as a broad definition. [1] Pooled prevalence in this meta-analysis was over 20%, but was lower with all iterations of the Rome criteria, compared with either a broad definition or a definition that encompassed epigastric pain or discomfort without a required minimum symptom frequency. There have been two large multi-national cross-sectional surveys published in the intervening years since this meta-analysis, one a three-nation survey,[20] and one a 33-nation global study,[21] both conducted by the Rome Foundation and included in the current meta-analysis. Even in these two studies, which applied the Rome IV criteria using near identical methodology, the prevalence of uninvestigated dyspepsia varied according to country. In countries that used an internet-based survey, prevalence varied from 2.4% in Japan and 3.6% in Israel,[21] to 11.9% in the USA and 12.3% in Egypt.[20,21] Participants in some of the countries included in the 33-nation study received an interview-administered questionnaire.[21] Pooled prevalence of uninvestigated dyspepsia was higher at 7.2% with the internet-based survey, compared with 4.8% with the interview-administered questionnaire. In both of these studies PDS was the commonest subtype of uninvestigated dyspepsia. Overlap was reduced when the Rome IV criteria were used, which is expected given that meal-related epigastric pain is now considered as part of PDS, and has been reported by other investigators.[91]

The findings of our study have implications for both clinical practice and future research. Although the pooled prevalence is lower than previous estimates, due to the more restrictive criteria applied in eligible studies, dyspepsia still affects somewhere between one in six and one in 15 people in the community at any point in time. From a research perspective, it appears that the method of questionnaire administration affects the likelihood

of symptom reporting, and therefore the prevalence of uninvestigated dyspepsia in the community. In addition, studies that claim to have applied the Rome criteria for dyspepsia, but have approximated this from another questionnaire, rather than using the validated Rome questionnaires, appear to inflate prevalence. Based on these issues, consideration should be given to standardising methodology of all population-based cross-sectional surveys in the future, in order to be able to make direct comparisons between them more readily. Finally, data mining of the 33-nation global study conducted by the Rome Foundation may allow valuable insights into why prevalence of uninvestigated dyspepsia varies between countries, even when identical criteria and methods are used to define its presence.[21]

Although the prevalence of uninvestigated dyspepsia in some geographical regions requires further study, data from this meta-analysis re-emphasise the magnitude of this disorder within the global community, and thus the implications for health services worldwide, including those in some of the poorest nations in the world. In an economic study, based on patients with FD attending a tertiary care centre in the USA, Lacy *et al.* estimated that the combined direct and indirect costs were $18.4 billion for the entire nation.[8] In their burden of illness study, Everhart *et al.* reported that >30% of endoscopies were performed with dyspepsia as the main indication.[92] A previous 10-year longitudinal follow-up study demonstrated that up to two-thirds of people with uninvestigated dyspepsia at the time of an initial cross-sectional survey remained symptomatic in the long-term, and one in three of those who were asymptomatic at baseline developed new onset uninvestigated dyspepsia during follow-up.[93] Effective treatments for dyspepsia are lacking, particularly for those with PDS. Proton pump inhibitors, prokinetics, and *Helicobacter pylori* eradication therapy have only modest efficacy.[94-96] In the Far East, the acetylcholinesterase inhibitor acotiamide has shown efficacy in PDS and is licensed,[97,98] but in the West there are no approved treatments

for PDS, and most prokinetic drugs have been withdrawn due to safety concerns. This therefore represents a substantial unmet need.

In conclusion, this systematic review and meta-analysis has demonstrated that the global prevalence of uninvestigated dyspepsia ranged from 17.6% using the Rome I criteria to 6.9% when the Rome IV criteria were applied. This varied, considerably in some instances, according to country, whether diagnostic criteria were applied strictly or approximated, and how symptom data were collected in individual studies. However, even when uniform diagnostic criteria and methodology were applied in different countries prevalence varied substantially suggesting that this is due to true variation. Reasons for this variability are unclear, and should be the subject of future research.

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AUTHOR CONTRIBUTIONS

BB, SM, CJB, EVS, and ACF conceived and drafted the study. BB, SM, CJB, and ACF collected, analysed, and interpreted all data. ACF and BB drafted the manuscript. BB, SM, CJB, EVS, and ACF commented on drafts of the paper. All authors have approved the final draft of the manuscript.

DECLARATION OF INTERESTS

Brigida Barberio: none. Sanjiv Mahadeva: none. Christopher J. Black: none. Edoardo V. Savarino: has acted as a consultant for and received teaching fee funding from Abbvie, Takeda, Janssen, MSD, Fresenius Kabi, Sandoz, Malesci, Sofar, which are outside the submitted work. Alexander C. Ford: none.

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ETHICS COMMITTEE APPROVAL

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FIGURE LEGENDS

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

Figure 2. Prevalence of Uninvestigated Dyspepsia Worldwide Using the Rome III Criteria

Figure 3. Prevalence of Uninvestigated Dyspepsia Worldwide Using the Rome IV Criteria.

Table 1. Eligibility Criteria.

Cross-sectional surveys
Recruited adults (>90% of participants aged ≥18 years)
Participants recruited from the general population or community*
Reported prevalence of uninvestigated dyspepsia (according to specific diagnostic criteria†)
Sample size of ≥50 participants

*Convenience samples excluded (e.g. university employees, hospital employees, blood donors, health check-up populations).

†Rome I, II, III, or IV criteria

Table 2. Pooled Prevalence of Uninvestigated Dyspepsia According to Criteria Used to Define its Presence, Questionnaire Used, and Method of Questionnaire Administration.

	Number of studies	Number of subjects	Pooled prevalence (%)	95% confidence interval	I^2	P value for χ^2
Criteria used to define dyspepsia						
Rome I	13	26,665	17.6	9.8 to 27.1	99.7%	<0.001
Rome II	19	44,330	13.0	8.4 to 18.5	99.6	<0.001
Rome III	34	186,244	11.5	9.8 to 13.3	99.2%	<0.001
Rome IV	4	81,144	6.9	5.7 to 8.2	98.0%	<0.001
Questionnaire used						
Defined as per Rome I questionnaire	3	11,460	5.2	2.5 to 8.8	98.3%	<0.001
Approximated Rome I using another questionnaire	10	15,205	22.6	15.8 to 30.3	99.1%	<0.001
Defined as per Rome II questionnaire	11	30,576	8.3	4.5 to 13.2	99.3	<0.001
Approximated Rome II using another questionnaire	8	13,754	20.9	14.9 to 27.5	98.8	<0.001
Defined as per Rome III questionnaire	23	166,400	11.4	9.4 to 13.5	99.3%	<0.001
Approximated Rome III using another questionnaire	11	19844	11.8	7.7 to 16.7	98.9%	<0.001
Defined as per Rome IV questionnaire	3	79,882	6.7	5.6 to 7.9	97.9%	<0.001
Approximated Rome IV using another questionnaire	1	1322	17.9	15.9 to 20.1	N/A*	N/A*

Method of questionnaire administration						
Rome I: self-completed questionnaire	9	15662	15.4	8.4 to 23.9	99.4%	<0.001
Rome I: interview-administered questionnaire	3	7883	31.3	17.7 to 46.7	99.5%	<0.001
Rome II: self-completed questionnaire	8	26716	10.6	3.8 to 20.2	99.7	<0.001
Rome II: interview-administered questionnaire	11	17614	15.0	11.8 to 18.4	97.4	<0.001
Rome III: self-completed questionnaire	19	144,119	10.8	8.6 to 13.3	99.4%	<0.001
Rome III: interview-administered questionnaire	14	40991	11.9	9.3 to 14.8	98.4%	<0.001
Rome IV: self-completed questionnaire	3	61,380	7.6	6.6 to 8.7	95.7%	<0.001
Rome IV: interview-administered questionnaire	2	19,764	5.0	2.4 to 8.7	99.0%	<0.001

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

Table 3. Prevalence of Uninvestigated Dyspepsia According to Rome I, II, III, and IV Criteria by Country.

Country	Rome I criteria (%)	95% confidence interval	Rome II criteria (%)	95% confidence interval	Rome III criteria (%)	95% confidence interval	Rome IV criteria (%)	95% confidence interval
Argentina	No studies	N/A*	No studies	N/A*	No studies	N/A*	7.2	6.1 – 8.4
Australia	15.1	4.5 – 30.5	24.4	22.6 – 26.2	14.3	12.2 – 16.6	12.1	3.7 – 24.4
Bangladesh	No studies	N/A*	No studies	N/A*	8.4	7.4 – 9.5	19.4	17.7 – 21.2
Belgium	No studies	N/A*	No studies	N/A*	No studies	N/A*	5.0	4.1 – 6.0
Brazil	44.4	42.8 – 46.0	15.9	14.8 – 17.1	10.6	8.1 – 13.5	10.6	9.3 – 12.0
Canada	No studies	N/A*	1.8	1.1 – 2.8	7.2	6.1 – 8.4	8.1	7.3 – 9.0
China	No studies	N/A*	10.6	0.0 – 39.0	5.6	1.3 – 12.7	5.1	3.7 – 6.8
Colombia	No studies	N/A*	No studies	N/A*	No studies	N/A*	7.2	6.1 – 8.4
Croatia	No studies	N/A*	No studies	N/A*	16.6	13.8 – 19.6	No studies	N/A*
Denmark	No studies	N/A*	No studies	N/A*	7.7	7.4 – 7.9	No studies	N/A*
Egypt	No studies	N/A*	No studies	N/A*	No studies	N/A*	12.3	10.9 – 13.8
Finland	No studies	N/A*	7.9	7.0 – 8.8	No studies	N/A*	No studies	N/A*
France	No studies	N/A*	No studies	N/A*	4.0	3.8 – 4.2	8.5	7.3 – 9.8
Germany	No studies	N/A*	No studies	N/A*	No studies	N/A*	6.9	5.8 – 8.1
Ghana	No studies	N/A*	No studies	N/A*	No studies	N/A*	7.2	5.8 – 8.8

Honduras	No studies	N/A*	No studies	N/A*	No studies	N/A*	10.1	8.1 – 12.3
Hong Kong	18.4	16.6 – 20.4	No studies	N/A*	8.0	6.9 – 9.3	No studies	N/A*
Iceland	17.8	15.8 – 20.0	No studies	N/A*	No studies	N/A*	No studies	N/A*
India	No studies	N/A*	No studies	N/A*	19.0	17.6 – 20.5	0.7	0.5 – 1.0
Indonesia	No studies	N/A*	No studies	N/A*	No studies	N/A*	4.4	3.3 – 5.7
Iran	No studies	N/A*	No studies	N/A*	8.5	8.1 – 8.9	2.9	2.2 – 3.7
Israel	No studies	N/A*	No studies	N/A*	No studies	N/A*	3.6	2.8 – 4.5
Italy	No studies	N/A*	15.1	13.0 – 17.4	21.4	19.1 – 23.9	9.1	7.9 – 10.4
Japan	No studies	N/A*	No studies	N/A*	11.3	2.9 – 24.3	2.4	1.8 – 3.1
Malaysia	No studies	N/A*	19.2	10.7 – 29.6	No studies	N/A*	3.3	2.5 – 4.2
Mexico	No studies	N/A*	7.0	4.9 – 9.6	10.0	9.0 – 11.0	6.6	5.5 – 7.8
Netherlands	No studies	N/A*	No studies	N/A*	No studies	N/A*	4.0	3.3 – 5.0
New Zealand	No studies	N/A*	34.2	30.8 – 37.6	No studies	N/A*	No studies	N/A*
Nicaragua	No studies	N/A*	10.3	8.8 – 11.9	22.4	20.3 – 24.5	No studies	N/A*
Nigeria	No studies	N/A*	No studies	N/A*	No studies	N/A*	6.0	4.9 – 7.4
Norway	No studies	N/A*	No studies	N/A*	6.9	5.4 – 8.6	No studies	N/A*
Poland	No studies	N/A*	No studies	N/A*	No studies	N/A*	8.3	7.2 – 9.6
Portugal	No studies	N/A*	No studies	N/A*	40.4	32.8 – 48.2	No studies	N/A*
Romania	No studies	N/A*	No studies	N/A*	7.6	4.2 – 12.4	7.4	6.3 – 8.6

Russia	37.5	34.5 – 40.5	No studies	N/A*	No studies	N/A*	10.3	9.0 – 11.7
Singapore	No studies	N/A*	No studies	N/A*	33.3	28.0 – 39.0	5.9	4.9 – 7.0
South Africa	No studies	N/A*	No studies	N/A*	No studies	N/A*	11.0	9.6 – 12.4
South Korea	No studies	N/A*	11.1	9.5 – 12.8	14.1	3.2 – 31.1	4.9	4.0 – 5.9
Spain	No studies	N/A*	2.0	0.9 – 3.8	No studies	N/A*	7.4	6.3 – 8.6
Sweden	17.5	10.8 – 25.5	22.5	4.2 – 49.8	20.2	17.7 – 22.8	8.2	7.0 – 9.5
Taiwan	No studies	N/A*	No studies	N/A*	4.5	3.9 – 5.2	No studies	N/A*
Thailand	4.9	4.2 – 5.7	No studies	N/A*	No studies	N/A*	No studies	N/A*
Turkey	No studies	N/A*	9.5	7.4 – 11.9	No studies	N/A*	2.8	0.2 – 8.1
UK	No studies	N/A*	No studies	N/A*	5.9	4.9 – 7.0	7.1	6.2 – 8.1
USA	11.0	0.0 – 37.8	No studies	N/A*	11.6	8.1 – 15.6	11.0	9.3 – 12.8

* N/A; not applicable, no studies

Table 4. Prevalence of Uninvestigated Dyspepsia According to Sex for Each of the Rome Definitions.

	No. of studies	Proportion of men with uninvestigated dyspepsia (%)	Proportion of women with uninvestigated dyspepsia (%)	Odds ratio for women versus. men	95% confidence interval
Rome I	6	17.3	24.4	1.44	1.22 to 1.70
Rome II	8	6.5	8.6	1.33	1.16 to 1.52
Rome III	16	6.7	8.5	1.52	1.32 to 1.75
Rome IV	2	5.5	8.1	1.51	1.38 to 1.65