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TITLE PAGE

Title: Global Prevalence of, and Risk Factors for, Uninvestigated Dyspepsia: a Meta-analysis.

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

Authors: Alexander C Ford^{1,2}, Avantika Marwaha³, Ruchit Sood^{1,2}, Paul Moayyedi³.

¹Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

²Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK.

³Gastroenterology Division, McMaster University, Health Sciences Center, Hamilton, Ontario, Canada.

Abbreviations:	CI	confidence interval
	GI	gastrointestinal
	<i>H. pylori</i>	<i>Helicobacter pylori</i>
	MeSH	medical subject headings
	NSAID	non-steroidal anti-inflammatory drug
	OR	odds ratio

Correspondence: Dr. Alex Ford
Leeds Gastroenterology Institute
D Floor
Clarendon Wing

Leeds General Infirmary

Great George Street

Leeds

United Kingdom

LS1 3EX

Email: alex12399@yahoo.com

Telephone: +441132684963

Facsimile: +441132429722

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ABSTRACT

Objectives: Many cross-sectional surveys have reported the prevalence of uninvestigated dyspepsia, but there has been no recent systematic review of data from all studies to determine its global prevalence and risk factors.

Design: MEDLINE, EMBASE, and EMBASE Classic were searched (until January 2014) to identify population-based studies that reported the prevalence of uninvestigated dyspepsia in adults (≥ 15 years old); dyspepsia was defined using symptom-based criteria or questionnaires. The prevalence of dyspepsia was extracted for all studies, and according to the 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 the 306 citations evaluated, 103 reported the prevalence of uninvestigated dyspepsia in 100 separate study populations, containing 312 415 subjects. Overall pooled prevalence in all studies was 20.8% (95% CI 17.8% to 23.9%). The prevalence varied according to country (from 1.8% to 57.0%) and criteria used to define dyspepsia. The greatest prevalence values were found when a broad definition of dyspepsia (29.5%; 95% CI 25.3%-33.8%) or upper abdominal or epigastric pain or discomfort (20.4%; 95% CI 16.3%-24.8%) were used. The prevalence was higher in women (OR 1.24; 95% CI 1.13 to 1.36), smokers (OR 1.25; 95% CI 1.12 to 1.40), NSAID users (OR 1.59; 95% CI 1.27-1.99), and *H. pylori*-positive individuals (OR 1.18; 95% CI 1.04-1.33).

Conclusion: The overall pooled prevalence of uninvestigated dyspepsia was 21%, but varied among countries and according to the criteria used to define its presence. Prevalence is significantly higher in women, smokers, NSAID users, and *H. pylori*-positive individuals, although these associations were modest.

What is already known about this subject?

Uninvestigated dyspepsia is common in the community.

Proposed risk factors include female gender, smoking, non-steroidal inflammatory drug use and *Helicobacter pylori* infection.

There has been no systematic synthesis of data concerning the prevalence of uninvestigated dyspepsia worldwide.

What are the new findings?

Up to one in five individuals report dyspepsia in the community.

Prevalence varies remarkably worldwide, and this is not explained by differing criteria used to define dyspepsia.

Female gender, smoking, non-steroidal inflammatory drug use and *Helicobacter pylori* were only modestly associated with presence of uninvestigated dyspepsia in the community.

How might it impact on clinical practice in the near future?

These data provide a robust analysis of the prevalence of uninvestigated dyspepsia, allowing for health service provision planning.

They could be plotted against other prevalence data, at individual country level, in order to determine novel risk factors for the condition.

INTRODUCTION

Dyspepsia is a symptom complex, rather than a diagnosis. Definitions of dyspepsia have evolved over the years, from one that includes any symptom felt to be referable to the upper gastrointestinal (GI) tract, [1] to the Rome criteria, [2-5] which have deliberately attempted to exclude heartburn and regurgitation from the definition, as these are felt to be indicative of underlying gastro-oesophageal reflux disease. The situation is further complicated by the fact that the classification of dyspepsia depends on whether upper GI endoscopy has been performed and, if so, whether relevant pathology was detected. Individuals who have not undergone investigation are said to have uninvestigated dyspepsia. Dyspeptic patients who undergo upper GI investigation and have pathological findings that may be responsible for the symptoms, such as peptic ulcer, are classed as having organic dyspepsia. Those without a detectable cause, who make up over three-quarters of individuals, are labelled as having functional dyspepsia, while gastro-oesophageal malignancy remains rare as a cause of dyspepsia. [6]

Although people with dyspepsia have a normal life expectancy, [7, 8] the impact on quality of life is substantial. There have been several studies reporting a reduced quality of life in patients with functional dyspepsia, compared with healthy controls or the general population. [9-12] The direction of the association between reduced quality of life and dyspepsia remains unclear, although in a 10-year follow-up of individuals from the community, one of the strongest predictors of the development of new-onset dyspepsia was poor quality of life at baseline. [13] Dyspepsia is associated with 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, [14,15] meaning that the financial implications of dyspepsia for society as a whole are huge. [16]

There have been numerous cross-sectional surveys conducted that report the prevalence of dyspepsia in the community. [17-24] As the majority of these types of study do not perform upper GI endoscopy, the cause of dyspepsia in those who report symptoms remains unclear, and it is probably best to classify these individuals as having uninvestigated dyspepsia. Despite the wealth of studies examining this issue, the prevalence of uninvestigated dyspepsia according to geographical location has not been well-reported, and no single study has synthesised data concerning potential risk factors for its presence. Systematic analysis of studies that report these types of data is important to allow physicians consulting with sufferers to provide more precise estimates of the prevalence of, as well as risk factors for, the condition, and to identify areas where further research is needed. We have therefore conducted a systematic review and meta-analysis of the prevalence of uninvestigated dyspepsia in the global community to examine these issues.

METHODS

Search Strategy and Study Selection

A literature search was performed using EMBASE CLASSIC and EMBASE (1947 to January 2014), and MEDLINE (1948 to January 2014) to identify only cross-sectional surveys published in full that reported the prevalence of dyspepsia in adults (aged 15 years and over). Studies were required to recruit participants from the general population or community. Any studies that reported the prevalence of dyspepsia in convenience samples, such as university students, employees at an institution, or those attending screening clinic health check-ups were not eligible for inclusion. In order to be eligible, studies also had to recruit at least 50 participants, and define dyspepsia according to one or more of the following: a broad definition in line with the 1988 Working Party report, including any symptom referable to the upper GI tract (including heartburn or reflux), (1) upper abdominal or epigastric pain or discomfort alone, the Rome I, (4) Rome II, (5) or Rome III criteria, (3) or according to a questionnaire. These eligibility criteria, which were defined prospectively, are provided in Box 1.

The medical literature was searched using the following terms: *dyspepsia* (both as a medical subject heading (MeSH) and free text term), *dyspep\$*, *epigastric adj5 pain*, *satiety*, *non-ulcer dyspepsia*, *functional dyspepsia*, *upper gastrointestinal symptom\$*, or *upper gastrointestinal adj5 symptom* (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). There were no language restrictions. The resulting abstracts were then screened for potential suitability, and those that appeared relevant were retrieved and examined in more detail. A recursive search was performed using the bibliographies of all obtained articles. Foreign language articles

were translated, where required. Where there appeared to be multiple study reports from the same group of subjects, we contacted study authors to clarify this issue. Eligibility assessment was performed independently by two investigators, using pre-designed eligibility forms. Any disagreements were resolved by consensus.

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 by consensus. The following data were collected for each study: year(s) conducted, country and geographical region, method of data collection (postal questionnaire, interview-administered questionnaire, self-completed questionnaire, telephone interview, face-to-face interview, web-based questionnaire), criteria used to define dyspepsia, symptom duration used to define dyspepsia, number of subjects providing complete data, mean age of subjects, proportion of male subjects, and the number of subjects with dyspepsia. Where dyspepsia prevalence was reported according to more than one set of diagnostic criteria in an individual study, the number of subjects with dyspepsia according to each individual definition was extracted.

Data Synthesis and Statistical Analysis

The proportion of individuals with dyspepsia in each study was combined to give a pooled prevalence of dyspepsia for all studies, according to the criteria used to define its presence. Heterogeneity between studies was assessed using the I^2 statistic with a cut off of 50%, and the χ^2 test with a P value <0.10, [25] used to define a statistically significant degree of heterogeneity. Subgroup analyses were conducted according to geographical region, criteria used to define dyspepsia, symptom duration used to define presence of dyspepsia,

gender, current smoking status, *H. pylori* status, and use of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, self-reported by the participants, in order to assess whether this had any effect on the pooled prevalence of dyspepsia. Finally, the prevalence of dyspepsia was compared according to gender, current smoking status, *H. pylori* status, and self-reported use or non-use of NSAIDs, using an odds ratio (OR), with a 95% confidence interval (CI). Given that the broader definition of dyspepsia, which includes any symptom referable to the upper GI tract, is likely to be more relevant to clinical situations compared with the Rome criteria, which are geared towards research into the treatment and pathophysiology of functional dyspepsia, we performed further subgroup analyses restricted to studies using only a broad definition of dyspepsia.

Data were pooled using a random effects model, [26] to give a more conservative estimate of the prevalence of dyspepsia and the odds of dyspepsia in these various groups. StatsDirect version 2.7.2 (StatsDirect Ltd, 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 odds ratios, [27] where a sufficient number of studies were available. [28]

RESULTS

The search strategy identified 42 939 citations. From these we identified 307 that appeared to be relevant to the study question. There were 103 articles that fulfilled the eligibility criteria, representing 100 separate adult study populations, containing 312 415 subjects (Supplementary Figure 1). [13, 14, 17, 19, 21-24, 29-123] There were a further three papers that reported data concerning prevalence of dyspepsia according to NSAID use, gender, and / or *H. pylori* status from one of these 100 separate study populations that were not published in the primary article arising from that study, [124-126] meaning that we extracted data from 106 separate articles in total. Agreement between investigators for assessment of study eligibility was excellent (kappa statistic = 0.90).

Detailed characteristics of all included studies are provided in Supplementary Table 1. The prevalence of dyspepsia in the community, when data from all 99 separate studies were pooled, was 20.8% (95% CI 17.8% to 23.9%). The lowest prevalence reported was 1.8% in two studies, one of which was conducted in Canada and used the Rome II criteria, and the other a Chinese study that used the Rome III criteria. The highest prevalence was 57.0%, reported in a Japanese study that used upper abdominal or epigastric pain or discomfort to define dyspepsia.

Global Prevalence of Dyspepsia

The majority of studies were conducted in Northern Europe or South-East Asia. There were no studies conducted in South Asia, one conducted in Central America, and only a few studies from South America, Africa, and the Middle East. The pooled prevalence of dyspepsia according to geographical location of the study is provided in Table 1. There was statistically significant heterogeneity between studies in all of these analyses. The lowest

Table 1. Pooled Prevalence of Uninvestigated Dyspepsia According to Geographical Location.

	Number of studies	Number of subjects	Pooled prevalence (%)	95% confidence interval	I ²	P value for I ²
All studies	100	312 415	20.8	17.8 – 23.9	99.8%	< 0.001
North European studies	41	135 966	21.7	18.4 – 25.3	99.7%	< 0.001
South East Asian studies	21	80 913	14.6	8.1 – 22.6	99.9%	< 0.001
North American studies	9	28 817	22.1	7.0 – 42.5	99.9%	< 0.001
Australasian studies	9	15 998	20.6	13.5 – 28.8	99.1%	< 0.001
South European studies	9	15 812	24.3	16.6 – 33.0	99.3%	< 0.001
Middle Eastern studies	7	26 531	15.2	8.3 – 23.8	99.5%	< 0.001
South American studies	5	6427	37.7	28.5 – 47.3	97.8%	< 0.001
African studies	2	1451	35.7	19.2 – 54.2	N/A*	N/A*
Central American studies	1	500	7.0	5.0 – 10.0	N/A*	N/A*

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

prevalence of dyspepsia occurred in the Central American study (7.0%) and the highest in South America (37.7%).

Prevalence of Dyspepsia According to Criteria Used to Define its Presence

The majority of studies used accepted diagnostic criteria to define the presence of dyspepsia, with 15 using more than one set of criteria within the same population. In total, 38 studies used a broad definition of dyspepsia, 36 used upper abdominal or epigastric pain or discomfort, 19 the Rome II criteria, 12 the Rome I criteria, and only seven the Rome III criteria. There were another seven studies that used a symptom questionnaire to define dyspepsia, and in four studies the authors stated that this was validated.

The pooled prevalence of dyspepsia according to the various criteria used to define its presence is provided in Table 2. Prevalence was highest when a broad definition was used (29.5%; 95% CI 25.3% to 33.8%), and lowest when the Rome III criteria were used (7.6%; 95% CI 4.6% to 11.3%). In the case of the Rome III criteria, the prevalence in individual countries ranged from 2% to 11%. The prevalence according to a broad definition, when upper abdominal or epigastric pain or discomfort, or the Rome II criteria were used to define dyspepsia by country are shown in Figures 1, 2, and 3. The continued disparity in prevalence of dyspepsia by country in these analyses suggests that the geographical variation was not related solely to the diagnostic criteria used in each study.

Prevalence of Dyspepsia According to Duration of Symptoms

Seventy-two studies reported the duration of symptoms required to meet diagnostic criteria for dyspepsia, with 36 using 12 months, 15 using 3 months, 11 using 6 months, four using 1 month, three using 2 weeks, two using 1 week, and one using both 3 and 12 months.

Table 2. Pooled Prevalence of Uninvestigated Dyspepsia According to Criteria Used to Define its Presence, Duration of Symptoms, and Method Used to Collect Symptom Data.

	Number of studies	Number of subjects	Pooled prevalence (%)	95% confidence interval	I ²	P value for I ²
All studies	100	312 415	20.8	17.8 – 23.9	99.8%	< 0.001
Criteria used to define dyspepsia						
Broad definition	38	106 975	29.5	25.3 – 33.8	99.6%	< 0.001
Upper abdominal or epigastric pain or discomfort	36	109 120	20.4	16.3 – 24.8	99.7%	< 0.001
Rome II	19	46 683	19.0	11.6 – 27.7	99.8%	< 0.001
Rome I	12	23 545	21.8	12.3 – 33.1	99.7%	< 0.001
Rome III	7	50 675	7.6	4.6 – 11.3	99.5%	< 0.001
Questionnaire-defined	7	11 434	21.4	10.5 – 34.9	99.5%	< 0.001
Duration of symptoms						
1 week	2	13 925	30.2	16.3 – 46.2	N/A*	N/A*
2 weeks	3	6016	19.8	2.3 – 48.4	N/A*	N/A*

1 month	4	5658	35.5	14.5 – 59.9	99.7%	< 0.001
3 months	16	72 934	19.8	12.0 – 28.9	99.9%	< 0.001
6 months	11	32 769	28.2	20.1 – 37.1	99.6%	< 0.001
12 months	37	51 671	23.3	19.3 – 27.6	99.2%	< 0.001
Method used to collect symptom data						
Postal questionnaire	35	105 123	22.7	17.4 – 28.5	99.8%	< 0.001
Interview-administered questionnaire	33	88 733	22.1	17.6 – 26.9	99.6%	< 0.001
Self-completed questionnaire	13	45 937	21.6	11.6 – 33.6	99.9%	< 0.001
Telephone interview	9	30 047	22.4	10.2 – 37.7	99.8%	< 0.001
Internet-based questionnaire	3	46 201	9.5	6.7 – 12.7	N/A*	N/A*
Face-to-face interview	2	666	41.7	33.1 – 50.5	N/A*	N/A*

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

The prevalence of dyspepsia was highest in studies that used a 1-month timeframe (35.5%), but was also higher in studies that used 6 months compared with those that used 12 months (28.2% versus 23.3%, Table 2). The prevalence of dyspepsia in the community when data from studies that required a symptom duration of 1 month or less, or studies that did not report the duration of symptoms required, were excluded was 23.1% (95% CI 19.5% to 27.0%).

When only studies that used a broad definition of dyspepsia were considered the results were as follows: 13 studies used a symptom duration of 1 year (prevalence = 26.3%; 95% CI 18.7% to 34.7%), six studies used a symptom duration of 3 months (prevalence = 26.0%; 95% CI 15.7% to 37.9%), six studies used a symptom duration of 6 months (prevalence = 32.4%; 95% CI 24.3% to 41.1%), three studies used a symptom duration of 1 month (prevalence = 45.2%; 95% CI 36.8% to 53.8%), two studies used a symptom duration of 1 week (prevalence = 30.2%; 95% CI 16.3% to 46.2%), and one study used a symptom duration of 2 weeks (prevalence = 27.5%; 95% CI 25.4% to 29.6%).

Prevalence of Dyspepsia According to Method of Symptom Data Collection

There were four studies that did not report the exact method used to collect symptom data, and a further two studies that used two separate methods within the population under study that could not be separated. In the remaining studies, 34 used a postal questionnaire, 32 used a questionnaire administered face-to-face by an interviewer, 13 a self-completed questionnaire, nine a questionnaire completed during a telephone interview, three studies an internet-based questionnaire, two conducted a face-to-face interview, and one used both a postal questionnaire and an interview-administered questionnaire at two separate time points. Pooled prevalence of dyspepsia was highest in the two studies that conducted a face-to-face interview (41.7%), and lowest in the three studies that used an internet-based questionnaire

(9.5%). The prevalence of dyspepsia using all other methods was broadly comparable (Table 2).

When only studies that used a broad definition of dyspepsia were considered the results were as follows: 13 studies used a postal questionnaire (prevalence = 27.5%; 95% CI 21.6% to 33.8%), 11 studies used an interview-administered questionnaire (prevalence = 30.4%; 95% CI 23.8% to 37.5%), eight studies used a self-completed questionnaire (prevalence = 30.2%; 95% CI 19.6% to 42.0%), four studies used a telephone interview (prevalence = 34.8%; 95% CI 20.4% to 50.9%), and two studies used a face-to-face interview (prevalence = 41.7%; 95% CI 33.1% to 50.5%).

Prevalence of Dyspepsia According to Gender

There were 55 studies that reported the prevalence of dyspepsia according to the gender of participants. Overall, the pooled prevalence of dyspepsia was slightly higher in women compared with men (25.3% (95% CI 21.1% to 29.8%) versus 21.9% (95% CI 17.6% to 26.5%)), and the OR for dyspepsia in women compared with men was 1.24 (95% CI 1.13 to 1.36), with significant heterogeneity between studies ($I^2 = 91.9\%$, $P < 0.001$), but no evidence of funnel plot asymmetry (Egger test, $P = 0.86$). We studied the effect of geographical region on prevalence according to gender. This demonstrated modestly increased ORs among women in North American, North European, South European, Middle Eastern, and South East Asian studies, but not African, South American, Australasian, or Central American studies (Figure 4). When only the 21 studies that used a broad definition of dyspepsia were included in the analysis, this difference was no longer statistically significant (OR = 1.10; 95% CI 0.99 to 1.23, $I^2 = 89.2\%$, $P < 0.001$).

Prevalence of Dyspepsia According to Smoking Status

There were 19 studies that reported the prevalence of dyspepsia according to smoking status. The pooled prevalence of dyspepsia was higher in current smokers compared with non-smokers (31.9% (95% CI 22.6% to 41.9%) versus 27.4% (95% CI 19.4% to 36.3%)). The OR for dyspepsia in those who smoked currently compared with those who did not was 1.25 (95% CI 1.12 to 1.40), with significant heterogeneity between studies ($I^2 = 76.0\%$, $P < 0.001$), but no evidence of funnel plot asymmetry (Egger test, $P = 0.21$). There were nine studies that used a broad definition of dyspepsia reporting effect of smoking status on dyspepsia prevalence. When only these studies were included in the analysis there was still a significantly higher prevalence of dyspepsia among smokers (OR = 1.35; 95% CI 1.17 to 1.56, $I^2 = 77.8\%$, $P < 0.001$).

Prevalence of Dyspepsia According to NSAID Use

There were 13 studies reporting the prevalence of dyspepsia according to NSAID use. Overall, there were 1687 (36.5%) of 4622 NSAID users reporting dyspepsia, compared with 6180 (31.7%) of 19 483 non-users. When data from these studies were pooled, the prevalence of dyspepsia was significantly higher among NSAID users (OR = 1.59; 95% CI 1.27 to 1.99), with significant heterogeneity between studies ($I^2 = 88.3\%$, $P < 0.001$), but no evidence of funnel plot asymmetry (Egger test, $P = 0.14$). When only the six studies that used a broad definition of dyspepsia were included in the analysis, the difference remained statistically significant (OR = 1.25; 95% CI 1.02 to 1.52, $I^2 = 75.3\%$, $P = 0.001$).

Prevalence of Dyspepsia According to *H. pylori* Status

There were 13 studies reporting the prevalence of dyspepsia according to *H. pylori* status. All of these studies used a broad definition of dyspepsia. Overall, there were 3223

(38.4%) of 8394 *H. pylori*-positive individuals reporting dyspepsia, compared with 5787 (34.2%) of 16 911 *H. pylori*-negatives. When data from these studies were pooled, the prevalence of dyspepsia was significantly higher among *H. pylori*-positive individuals (OR = 1.18; 95% CI 1.04 to 1.33), with significant heterogeneity between studies ($I^2 = 63.0\%$, $P < 0.001$), but no evidence of funnel plot asymmetry (Egger test, $P = 0.30$).

DISCUSSION

This systematic review and meta-analysis has assembled data from all available and identified population-based cross-sectional surveys that report the prevalence of uninvestigated dyspepsia in the community. It has demonstrated that prevalence varies strikingly, from <2% to 57%, according to the geographical location of the population under study. The criteria used also led to differences in prevalence, which was lowest when the Rome III criteria were used, and highest with a broad definition of dyspepsia. However, the variation in prevalence according to country persisted, even when the same diagnostic criteria were used. In terms of symptom duration, prevalence was highest when symptoms were present for a minimum of 1 month, although only four studies used this time interval, and higher with studies that used a 6-month time frame compared with 12 months. Prevalence remained remarkably similar according to the method of data collection, with the exception of when a face-to-face interview was used, or an internet-based questionnaire. Finally, prevalence of uninvestigated dyspepsia was significantly higher in females, smokers, NSAID users, and *H. pylori*-positive individuals.

This study has several strengths. We used an exhaustive and contemporaneous 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 in order 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 variability in methods used to collect data. It may be that more personal approaches to collecting data, such as a face-to-face or telephone interview overestimate the prevalence of dyspepsia, while for more impersonal methods, such as completion of a questionnaire over the internet, the converse is true. The paucity or absence of studies reporting the prevalence of uninvestigated dyspepsia for some geographical regions, such as Africa, Central America, and South Asia is another limitation. In addition, there was significant heterogeneity between studies in all our analyses, which was not explained by any of the subgroup analyses we conducted. The reasons for the heterogeneity are therefore speculative, but may include subtle differences in the way diagnostic criteria for dyspepsia were defined, or other demographic or cultural differences between study populations, including ethnicity, which were not possible to examine using the data that were available for extraction in the individual studies we identified. This heterogeneity may be seen, by some, as precluding the pooling of data from these studies in a meta-analysis. However, we feel that the summary data obtained using this approach are useful in order to be able to view the prevalence of uninvestigated dyspepsia in the community from an epidemiological and global perspective.

There have been few previous systematic reviews examining the prevalence of upper GI symptoms in the community. The most recent of these was published 15 years ago, [127] and also concentrated on true population prevalence surveys. Upper abdominal pain or discomfort was reported by anywhere from 8% to over 50% of study subjects, which is broadly similar to the prevalence we observed. However, this was performed by a single author, so the methodology is unlikely to be as rigorous as that used in the present study, and

no synthesis of data was conducted. In addition, there were no analyses performed to examine potential risk factors for dyspepsia. Finally, there were only 10 included studies in this systematic review, highlighting that a considerable amount of data has been published since it was conducted, and emphasising the need for a contemporaneous study such as ours.

The findings of this study have implications for both future research and clinical practice. Population-based studies using the Rome III criteria to define dyspepsia remain scarce, despite the fact that these criteria were published 8 years ago, [3] although there have been few validation studies of these criteria. [128] Extracting and analysing study data on the prevalence of uninvestigated dyspepsia has emphasised the magnitude of this disorder within the community, and thus the implications for health services worldwide, including those in some of the poorest nations in the world. A recent questionnaire survey reported that the mean yearly cost of dyspepsia to patients was almost \$700, [16] and burden of illness studies in the USA estimated that there were almost 2 million physician visits in 2009 as a result of dyspepsia, [129] and >30% of endoscopies were performed with dyspepsia as the main indication. [130] However, the prevalence of uninvestigated dyspepsia in some geographical regions, such as Africa, South Asia, and Central America needs further study. These data can also be used for ecological studies to evaluate risk factors for dyspepsia. For example, some investigators have shown that duodenal eosinophilia is associated with dyspepsia. [131, 132] This suggests that there is either an infective or an allergic component to dyspepsia and, in order to investigate this, our data could be plotted against the prevalence of asthma at a country level.

In terms of future treatment trials in uninvestigated dyspepsia, as well as epidemiological studies of the condition, our meta-analysis suggests that the methods used to collect symptom data, as well as the symptom duration used to define its presence, may affect the prevalence of dyspepsia when identifying and recruiting suitable subjects, as well as the

response of symptoms to therapy. In addition, the modest contribution of most of the risk factors that were reported in the studies we identified to the odds of reporting symptoms implies that either other factors need to be examined to identify those most at risk of dyspepsia in the community, or alternatively the cumulative effect of each of these risk factors, or the interaction between them, needs to be examined using more complex statistical methods.

In conclusion, this systematic review and meta-analysis has demonstrated a global prevalence of uninvestigated dyspepsia of almost 21%, but this varied, considerably in some instances, according to geographical region, diagnostic criteria used to define dyspepsia, and minimum symptom duration required. The striking variation in prevalence throughout the world, even when the same diagnostic criteria are used to define dyspepsia, highlights the importance of other factors such as genetic, ethnic, and cultural differences on the reporting of upper GI symptoms. Risk factors for uninvestigated dyspepsia included female gender, smoking, NSAID use, and *H. pylori* infection. However, these associations were modest, their overall importance in the aetiology of symptoms is questionable, and there are clearly other factors that are involved in the pathogenesis of dyspepsia that we were unable to elucidate via analysis of data from the studies we identified.

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CONFLICTS OF INTEREST/STUDY SUPPORT

Guarantor of the article: ACF is guarantor.

Specific author contributions: ACF, AM, RS, and PM conceived and drafted the study.

ACF, AM, and RS collected all data. ACF and AM analysed and interpreted the data. ACF drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

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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 dyspepsia (according to a questionnaire, or specific diagnostic criteria†)

Sample size of ≥ 50 participants

*Convenience samples excluded

†Broad definition of dyspepsia including any symptom referable to the upper GI tract, upper abdominal or epigastric pain or discomfort alone, Rome I, II, or III criteria

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FIGURES

Figure 1. Prevalence of Uninvestigated Dyspepsia Worldwide Using a Broad Definition.

Figure 2. Prevalence of Uninvestigated Dyspepsia Worldwide Using Upper Abdominal or Epigastric Pain or Discomfort.

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

Figure 4. Odds ratio for Uninvestigated Dyspepsia in Women Versus Men According to Geographical Location.