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Eusebi, LH, Ratnakumaran, R, Yuan, Y et al. (3 more authors) (2018) Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. Gut, 67 (3). pp. 430-440. ISSN 0017-5749

https://doi.org/10.1136/gutjnl-2016-313589

Accepted 28th January 2017

TITLE PAGE

Title: Global Prevalence of, and Risk Factors for, Gastro-oesophageal Reflux Symptoms: A Meta-analysis.

Short running head: Prevalence of Reflux Symptoms: A Meta-analysis.

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Abbreviations:

CI	confidence interval
GI	gastrointestinal
MeSH	medical subject headings
NSAID	non-steroidal anti-inflammatory drug

OR odds ratio

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Keywords: Heartburn

Regurgitation

Frequency

Prevalence

Word count: 4900

ABSTRACT

Objectives: Gastro-oesophageal reflux symptoms are common in the community, but there has been no definitive systematic review and meta-analysis of data from all studies to estimate their global prevalence, or potential risk factors for them.

Design: MEDLINE, EMBASE, and EMBASE Classic were searched (until September 2016) to identify population-based studies that reported the prevalence of gastro-oesophageal reflux symptoms in adults (≥15 years old); gastro-oesophageal reflux was defined using symptom-based criteria or questionnaires. The prevalence 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 14,132 citations evaluated, 102 reported the prevalence of gastro-oesophageal reflux symptoms in 108 separate study populations, containing 460,984 subjects. Prevalence varied according to country (from 2.5% in China to 51.2% in Greece) and criteria used to define gastro-oesophageal reflux symptoms. When only studies using a weekly frequency of heartburn or regurgitation to define presence were considered, pooled prevalence was 13.3% (95% CI 12.0%-14.6%). Prevalence was higher in subjects ≥50 years (OR 1.32; 95% CI 1.12-1.54), smokers (OR 1.26; 95% CI 1.04-1.52), non-steroidal anti-inflammatory drug/aspirin users (OR 1.44; 95% CI 1.10-1.88), and obese individuals (OR 1.73 95% CI 1.46-2.06).

Conclusion: The prevalence of gastro-oesophageal reflux symptoms varied strikingly among countries, even when similar definitions were used to define their presence. Prevalence was significantly higher in subjects ≥50 years, smokers, NSAID users, and obese individuals, although these associations were modest.

What is already known about this subject?

- Gastro-oesophageal reflux symptoms are common in the community.
- Proposed risk factors include female gender, smoking, non-steroidal anti-inflammatory drug (NSAID) and/or aspirin use, and obesity.
- There has been no definitive systematic review of data concerning the prevalence of gastro-oesophageal reflux symptoms, or risk factors for them, globally.

What are the new findings?

- Up to one in six individuals report gastro-oesophageal reflux symptoms in the community, when a stringent definition of frequency of at least once a week for 12 months is used.
- Prevalence varied remarkably throughout the world.
- Age ≥50 years, smoking, NSAID and/or aspirin use, obesity, and low socio-economic status were modestly, but significantly, associated with gastro-oesophageal reflux symptoms.

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

- These data provide an analysis of the global prevalence of gastro-oesophageal reflux symptoms, and may allow for health service provision planning.
- They highlight that the causes of gastro-oesophageal reflux symptoms are likely to be multi-factorial, and that the pathophysiology is incompletely understood.

INTRODUCTION

Gastro-oesophageal reflux disease is a condition characterised by reflux of stomach contents causing troublesome symptoms and complications.[1] Typical symptoms include heartburn (a retrosternal burning sensation), regurgitation (perception of flow of refluxed stomach content into the mouth or hypopharynx), and chest pain.[1] The condition can also present with extra-oesophageal symptoms, including chronic cough, laryngitis, asthma, and dental erosions.[2, 3]

The proposed pathogenesis of gastro-oesophageal reflux is multifactorial, involving transient lower oesophageal sphincter relaxations, and lower oesophageal sphincter pressure abnormalities.[4] Other contributing factors include delayed gastric emptying, hiatus hernias and visceral hypersensitivity.[5, 6] Due to the chronic nature of this condition, it has a substantial economic burden and impact on quality of life. Several studies have reported a reduced quality of life in patients with gastro-oesophageal reflux symptoms compared with healthy controls, with an increased disease severity associated with a worsening health-related quality of life score.[7] The considerable economic burden of the disease is driven by the costs of consultations, investigations, prescribed and over-the-counter medications, surgical costs, and costs from treatment of complications of gastro-oesophageal reflux symptoms, such as Barrett's oesophagus and oesophageal adenocarcinoma.[8, 9, 10]

Gastro-oesophageal reflux symptoms are prevalent, seen both in primary and secondary care settings [16]. There have been numerous cross-sectional surveys conducted that report the prevalence of symptoms of gastro-oesophageal reflux in the community. El Serag et al. performed a systematic review, including studies published up to 2011, which assessed

the global prevalence of gastro-oesophageal reflux,[11] but this included only 28 studies, and many surveys have been published in the interim. As a result of the limited number of studies identified, the authors were unable to systematically analyse the effect of proposed risk factors on the prevalence of gastro-oesophageal reflux symptoms.

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 and risk factors for the condition, as well as to identify areas where further research is needed. We have therefore conducted a systematic review and meta-analysis of the prevalence of, and risk factors for, gastro-oesophageal reflux symptoms in the community in order to examine these issues.

METHODS

Search Strategy and Study Selection

In order to estimate both the prevalence of gastro-oesophageal reflux symptoms in the community, and evaluate the contribution of various proposed risk factors, a literature search was performed using EMBASE CLASSIC and EMBASE (1947 to September 2016), and MEDLINE (1948 to September 2016) to identify only cross-sectional surveys published in full. These had to report the prevalence of gastro-oesophageal reflux symptoms in adults (aged 15 years and over). Studies were required to recruit participants from the general population or community. Studies that recruited convenience samples, such as those attending screening clinic health check-ups, university students, or employees at an institution were not eligible for inclusion. Other eligibility criteria included recruitment of at least 50 participants, and a definition of gastro-oesophageal reflux symptoms that included one or more of the following: heartburn and/or regurgitation of any severity, or symptoms felt to be compatible with gastro-oesophageal reflux as diagnosed by a clinician 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: heartburn, GERD, gastroesophageal reflux disease, gastroesophageal 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 then screened for potential suitability by two investigators, and those that appeared relevant were retrieved and examined in more detail. We did not restrict eligibility to studies

published only in English, with foreign language articles translated. A recursive search was performed using the bibliographies of all obtained articles. 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 data collection (postal questionnaire, interview-administered questionnaire, self-completed questionnaire, telephone interview, face-to-face interview, web-based questionnaire), criteria used to define gastro-oesophageal reflux symptoms, duration used to define presence of gastro-oesophageal reflux symptoms, number of subjects providing complete data, age range and mean age of subjects, proportion of male subjects, and the number of subjects with gastro-oesophageal reflux symptoms. Where prevalence of gastro-oesophageal reflux symptoms was reported according to more than one set of diagnostic criteria in an individual study, the number of subjects with gastro-oesophageal reflux symptoms according to each individual definition was extracted.

Data Synthesis and Statistical Analysis

The proportion of individuals with gastro-oesophageal reflux symptoms in each study, according to the criteria used to define its presence, was combined to give a pooled prevalence for all studies. Heterogeneity between studies was assessed using the I^2 statistic with a cut off of 50%, and the χ^2 test with a P value <0.10, used as the threshold for

statistically significant heterogeneity.[12] Subgroup analyses were conducted according to geographical region, criteria used to define gastro-oesophageal reflux symptoms, duration used to define presence of gastro-oesophageal reflux symptoms, and method used to collect symptom data. The prevalence of gastro-oesophageal reflux symptoms was compared according to proposed risk factors, which were chosen a priori, and included age,[13] gender,[13] current smoking status,[14] self-reported use or non-use of alcohol,[14] self-reported use or non-use of non-steroidal anti-inflammatory drugs (NSAIDs) and/or aspirin,[15] presence or absence of obesity,[14] socio-economic status,[16] and educational level,[17] using an odds ratio (OR), with a 95% confidence interval (CI).

Data were pooled using a random effects model,[18] to give a more conservative estimate of the prevalence, and the odds, of gastro-oesophageal reflux symptoms in these various groups. StatsDirect version 2.7.2 (StatsDirect Ltd, Sale, Cheshire, England) was used to generate Forest plots of pooled prevalence and pooled ORs with 95% CIs.

RESULTS

The search strategy identified 14,132 citations. From these we identified 365 that appeared to be relevant to the study question. There were 102 articles that fulfilled the eligibility criteria,[16, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119] representing 108 separate adult study populations, containing 460,984 subjects (Supplementary Figure 1). There were a further 12 papers that reported data concerning the prevalence of gastro-oesophageal reflux symptoms according to use of alcohol, smoking status, gender, and age from one of these 108 separate study populations,[120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131] which were not published in the primary article arising from that study, meaning that we extracted data from 114 separate articles in total. Agreement between investigators for assessment of study eligibility was excellent (Kappa statistic = 0.86).

Detailed characteristics of all included studies are provided in Supplementary Table 1. The prevalence of gastro-oesophageal reflux symptoms in the community, when data from all 108 separate study populations were pooled, was 14.8% (95% CI 13.5% to 16.1%). The lowest prevalence reported was 2.5% in a study conducted in China,[46] which used a Chinese version of the Mayo reflux questionnaire. The highest prevalence was 52.1%, reported in a Greek study that used the reflux symptom index questionnaire.[118]

Global Prevalence of Gastro-oesophageal Reflux Symptoms

The majority of studies were conducted in Northern Europe or Asia. There were no studies conducted in Africa, only one study conducted in Central America, and few studies

from either South America or Australasia. The pooled prevalence of gastro-oesophageal reflux symptoms in individual countries is provided in Figure 1, and the pooled prevalence of gastro-oesophageal reflux symptoms according to geographical study location is provided in Table 1. There was statistically significant heterogeneity between studies in all of these analyses. The highest prevalence of gastro-oesophageal reflux symptoms occurred in the Central American study (19.6%) and the lowest in Asia (10.0%), particularly in South-East Asian countries (7.4%).

Table 1. Pooled Prevalence of Gastro-oesophageal Reflux Symptoms According to Geographical Location.

	Number of studies	Number of subjects	Pooled prevalence (%)	95% confidence interval (%)	I^2	P value for I^2
All studies	**108**	**460,984**	**14.8**	**13.5 – 16.1**	**99.3%**	**< 0.001**
North American studies	12	43,794	15.4	10.7 – 20.9	99.5%	< 0.001
Central American studies	1	500	19.6	16.2 – 23.4	N/A*	N/A*
South American studies	6	24,164	17.6	11.0 – 25.3	99.4%	< 0.001
European studies	44	218,534	17.1	15.1 – 19.1	99.3%	< 0.001
Northern European studies	31	198,686	15.5	13.6 – 17.5	99.2%	< 0.001
Southern European studies	13	19,848	21.3	15.8 – 27.3	98.8%	< 0.001
Middle Eastern studies	13	86,428	15.0	11.5 – 19.0	99.4%	< 0.001
Asian studies	23	67,103	10.0	7.1 – 13.2	99.4%	< 0.001
South Asian studies	5	8,864	22.1	11.5 – 35.0	99.4%	< 0.001
South-East Asian studies	18	58,239	7.4	5.0 – 10.1	99.3%	< 0.001
Australasian studies	9	20,461	14.1	12.2 – 16.2	93.5%	< 0.001

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

Prevalence of Gastro-oesophageal Reflux Symptoms According to Criteria Used to Define Their Presence

The majority of studies used accepted diagnostic criteria to define the presence of gastro-oesophageal reflux symptoms, with 26 using more than one set of criteria within the same population.[16, 29, 31, 36, 42, 46, 51, 52, 53, 54, 59, 64, 65, 66, 72, 75, 83, 87, 88, 91, 92, 95, 96, 102, 108, 119] Details of symptom frequency and duration required to meet criteria for gastro-oesophageal reflux symptoms in each study are provided in Supplementary Table 1. In total, 79 studies (reporting 85 separate study populations) used a frequency of the presence of heartburn and/or regurgitation of at least once a week to define gastro-oesophageal reflux symptoms,[16, 22, 25, 27, 28, 29, 32, 33, 34, 36, 38, 40, 41, 44, 45, 46, 47, 48, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 91, 92, 93, 94, 95, 96, 97, 99, 100, 101, 102, 104, 105, 107, 108, 109, 111, 112, 113, 114, 115, 116, 117, 119] two studies used the Rome II criteria,[42, 98] and two the Rome I criteria.[23, 62]

When only studies that used a frequency of heartburn and/or regurgitation of at least once a week to define presence of gastro-oesophageal reflux symptoms were considered the pooled prevalence was 13.3% (95% CI 12.0% to 14.6%). The pooled prevalence of gastro-oesophageal reflux symptoms in individual countries, when only weekly symptoms were considered, is provided in Figure 2. The prevalence of weekly frequency of gastro-oesophageal reflux symptoms according to different criteria/questionnaires is shown in Table 2. The prevalence was generally higher when the Rome I or Rome II criteria were used (24.9% (95% CI 15.6% to 35.5%) and 21.3% (95% CI 18.9% to 23.9%), respectively).

Table 2. Pooled Prevalence of Gastro-oesophageal Reflux Symptoms According to Criteria Used to Define Their 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
Criteria used to define gastro-oesophageal reflux symptoms						
Weekly symptoms	79	378,806	13.3	12.0 – 14.6	99.2%	< 0.001
Broad weekly heartburn and/or regurgitation	22	13, 498	13.6	11.4 – 15.9	99.2%	< 0.001
Mayo reflux questionnaire	12	39,937	14.9	11.1 – 19.1	99.1%	< 0.001
Montreal criteria	10	126,207	14.7	10.5 – 19.5	99.7%	< 0.001
Digest questionnaire	1	5,581	7.0	4.5 – 9.9	93.6%	< 0.001
GerdQ questionnaire	6	14,921	11.7	4.3 – 22.0	99.6%	< 0.001
Bowel disease questionnaire	6	7,145	13.8	8.7 – 19.9	97.9%	< 0.001
Other questionnaires	22	45,517	14.2	11.6 – 16.9	98.4%	< 0.001
Rome I	2	7,103	24.9	15.6 – 35.5	N/A*	N/A*
Rome II	2	1,649	21.3	18.9 – 23.9	N/A*	N/A*

Duration of symptoms						
1 week	9	18,494	13.5	7.3-21.3	99.4%	< 0.001
1 month	7	41,191	20.1	13.2 – 28.0	99.6%	< 0.001
3 months	11	63,182	11.3	8.3 - 14.7	99.3%	< 0.001
6 months	6	34,943	17.6	9.9 – 26.9	99.7%	< 0.001
12 months	36	170,570	14.1	12.2 – 16.1	99.1%	< 0.001
Method used to collect symptom data						
Postal questionnaire	30	73,776	19.0	15.8 – 22.5	99.3%	< 0.001
Face-to-face interview	22	120,061	14.1	11.5 – 17.0	99.4%	< 0.001
Self-completed questionnaire	16	112,766	12.0	9.3 – 15.1	99.4%	< 0.001
Telephone interview	16	59,639	10.4	8.1 – 13.0	98.9%	< 0.001
Interview-administered questionnaire	17	46,715	16.4	13.4 – 19.7	98.7%	< 0.001

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

Prevalence of Gastro-oesophageal Reflux Symptoms According to Symptom Duration

Sixty-nine studies reported the duration of symptoms required to meet criteria for gastro-oesophageal reflux, with 36 using 12 months,[16, 24, 28, 29, 31, 32, 35, 36, 37, 41, 42, 46, 47, 48, 56, 62, 65, 67, 69, 70, 73, 74, 77, 79, 80, 81, 82, 83, 86, 94, 100, 102, 104, 107, 111, 115] six using 6 months,[19, 34, 38, 51, 71, 101] 11 using 3 months,[23, 26, 33, 39, 40, 43, 44, 52, 60, 87, 109] seven using 1 month,[53, 64, 78, 88, 92, 106, 118] and nine using 1 week.[27, 59, 66, 84, 99, 105, 112, 114, 117] The prevalence of gastro-oesophageal reflux symptoms was highest in studies that used a 1-month timeframe (20.1%), but was also higher in studies that used 6 months, compared with those that used 12 months (17.6% versus 14.1%) (Table 2).

Prevalence of Gastro-oesophageal Reflux Symptoms According to Frequency and Duration of Symptoms

In order to assess whether a more stringent definition of gastro-oesophageal reflux symptoms impacted on prevalence, we pooled data from only those studies that required a symptom frequency of at least weekly, according to duration of symptoms. There were seven studies that assessed prevalence using the presence of at least weekly symptoms for at least 3 months.[33, 40, 44, 52, 60, 87, 109] The prevalence using this definition was 9.4% (95% CI 9.1% to 9.7%), but heterogeneity between studies remained (I^2 = 98.7%, P <0.001). There were another 30 studies that used a frequency of symptoms of at least weekly for the last 12 months,[16, 28, 29, 32, 36, 41, 46, 47, 48, 56, 65, 67, 69, 70, 73, 74, 77, 79, 80, 81, 82, 83, 86, 94, 100, 102, 104, 107, 111, 115] and when these were pooled the prevalence was 14.0% (95% CI 12.1% to 16.1%), again with significant heterogeneity between studies (I^2 = 99.0%, P <0.001).

Prevalence of Gastro-oesophageal Reflux Symptoms According to Method of Symptom Data Collection

There was one study that used two separate methods within the population under study that could not be separated.[113] In the remaining studies, 30 used a postal questionnaire,[19, 20, 21, 22, 23, 25, 26, 27, 29, 32, 36, 37, 39, 54, 56, 60, 61, 62, 64, 66, 69, 75, 78, 81, 94, 97, 100, 106, 111, 118] 22 conducted a face-to-face interview,[16, 31, 33, 41, 45, 53, 58, 59, 63, 65, 67, 70, 71, 76, 91, 95, 99, 101, 103, 107, 115, 117] 16 used a self-completed questionnaire (including internet-based questionnaires),[24, 35, 44, 48, 50, 77, 84, 85, 87, 88, 89, 90, 96, 110, 112, 114] 17 used an interview-administered questionnaire,[28, 30, 38, 51, 55, 57, 73, 80, 82, 83, 86, 92, 98, 102, 104, 116, 119] and 16 used a questionnaire completed during a telephone interview.[34, 40, 42, 43, 46, 47, 49, 52, 68, 72, 74, 79, 93, 105, 108, 109] Pooled prevalence of gastro-oesophageal reflux symptoms was highest in the 30 studies that used a postal questionnaire (19.0%), and lowest in the 16 studies that used a questionnaire completed during a telephone interview (10.4%). The prevalence of gastro-oesophageal reflux symptoms using all other methods was broadly comparable (Table 2).

Prevalence of Gastro-oesophageal Reflux Symptoms According to Age

There were 19 studies that reported the prevalence of gastro-oesophageal reflux symptoms according to various age groups.[32, 35, 40, 43, 47, 49, 51, 58, 76, 77, 84, 88, 99, 100, 101, 107, 108, 118, 119] When these age groups were dichotomised, the pooled prevalence of gastro-oesophageal reflux symptoms was higher in subjects aged ≥50 years compared with those aged <50 years (17.3% (95% CI 13.3% to 21.7%) versus 14.0% (95% CI 9.9% to 18.7%)). The OR for gastro-oesophageal reflux symptoms in those aged ≥50 years compared with those who were aged <50 years was 1.32 (95% CI 1.12 to 1.54), with significant heterogeneity between studies (I^2 = 91.5%, P < 0.001).

Prevalence of Gastro-oesophageal Reflux Symptoms According to Gender

There were 70 studies that reported the prevalence of gastro-oesophageal reflux symptoms according to gender.[16, 20, 22, 23, 24, 25, 29, 32, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47, 49, 52, 53, 54, 55, 58, 59, 60, 61, 62, 65, 68, 69, 71, 72, 73, 75, 77, 80, 82, 83, 84, 85, 88, 89, 90, 91, 92, 93, 94, 95, 96, 98, 99, 100, 101, 102, 103, 104, 105, 107, 108, 109, 110, 112, 113, 114, 115, 116, 117, 118, 119] Overall, the pooled prevalence of gastro-oesophageal reflux symptoms was slightly higher in women compared with men (16.7% (95% CI 14.9% to 18.6%) versus 15.4% (95% CI 13.5% to 17.4%)). Although the OR was higher in women (1.13; 95% CI 1.05 to 1.21), this was extremely modest, and there was significant heterogeneity between studies (I^2 = 88.3%, P < 0.001).

We studied the effect of geographical region of the study on prevalence according to gender. This demonstrated modestly increased ORs among women in South America (OR = 1.41; 95% CI 1.15 to 1.73), the Middle East (OR = 1.36; 95% CI 1.14 to 1.63), and South-East Asia (OR = 1.11; 95% CI 1.02 to 1.20); whereas there was no statistically significant difference in North America (OR = 1.01; 95% CI 0.90 to 1.14), Northern Europe (OR = 1.05; 95% CI 0.95 to 1.17), Southern Europe (OR = 1.09; 95% CI 0.94 to 1.26), South Asia (OR = 1.13; 95% CI 0.80 to 1.59), or Australasia (OR = 1.12; 95% CI 0.97 to 1.31) (Figure 3).

Prevalence of Gastro-oesophageal Reflux Symptoms According to Smoking Status

There were 30 studies that reported the prevalence of gastro-oesophageal reflux symptoms according to smoking status.[16, 32, 36, 38, 46, 49, 51, 58, 59, 69, 71, 77, 80, 83, 84, 85, 88, 89, 92, 100, 102, 104, 105, 107, 109, 115, 117, 118, 119, 120] The pooled prevalence of gastro-oesophageal reflux symptoms was higher in current smokers compared with non-smokers (19.6% (95% CI 14.9% to 24.7%) versus 15.9% (95% CI 13.1% to 19.0%)). The OR in those who smoked currently compared with those who did not was 1.26

(95% CI 1.04 to 1.52), with significant heterogeneity between studies (I^2 = 94.6%, P < 0.001).

Prevalence of Gastro-oesophageal Reflux Symptoms According to Alcohol Use

There were 24 studies that reported the prevalence of gastro-oesophageal reflux symptoms according to alcohol use.[16, 32, 36, 38, 46, 58, 59, 69, 80, 83, 84, 85, 88, 89, 92, 100, 104, 107, 109, 115, 116, 117, 118, 120] The pooled prevalence was slightly higher in current alcohol drinkers compared with non-drinkers (20.3% (95% CI 13.6% to 28.0%) versus 18.1% (95% CI 14.3% to 22.3%)), but there was no significant difference in the OR among those who drank alcohol compared with those who did not (1.11; 95% CI 0.85 to 1.46). Again there was significant heterogeneity between studies (I^2 = 95.5%, P < 0.001).

Prevalence of Gastro-oesophageal Reflux Symptoms According to NSAID and/or aspirin Use

There were 10 studies reporting the prevalence of gastro-oesophageal reflux symptoms according to NSAID and/or aspirin use or non-use.[32, 36, 46, 59, 77, 80, 100, 105, 107, 115] Overall, the prevalence of gastro-oesophageal reflux symptoms among NSAID and/or aspirin users was significantly higher (25.5% (95% CI 18.4% to 33.3%) versus 19.6% (95% CI 14.5% to 25.1%)), with an OR of 1.44 (95% CI 1.10 to 1.88), and significant heterogeneity between studies (I^2 = 84%, P < 0.001).

Prevalence of Gastro-oesophageal Reflux Symptoms According to Presence of Obesity

There were 22 studies that reported the prevalence of gastro-oesophageal reflux symptoms according to presence of obesity,[16, 32, 44, 51, 53, 58, 59, 65, 77, 80, 84, 88, 89, 97, 100, 102, 103, 104, 105, 115, 116, 119] which was defined as a BMI ≥30kg/m^2 in all

studies, with the exception of three Chinese studies, two of which used a BMI of ≥28kg/m^2,[84, 89] and one that used ≥27.5kg/m^2.[88] The pooled prevalence was higher in obese subjects compared with non-obese (22.1% (95% CI 17.4% to 27.2%) versus 14.2% (95% CI 10.8% to 18.0%)). The OR in obese compared with non-obese subjects was 1.73 (95% CI 1.46 to 2.06), with significant heterogeneity between studies (I^2 = 86.3%, P < 0.001).

Prevalence of Gastro-oesophageal Reflux Symptoms According to Socio-economic Status

Five studies reported the prevalence of gastro-oesophageal reflux symptoms according to the income of participants.[88, 93, 104, 107, 115] Overall, the pooled prevalence was higher in subjects with lower income (16.5%; 95% CI 6.2% to 30.4%), compared with medium (11.6%; 95% CI 3.7% to 23.1%), or higher income (11.1%; 95% CI 4.8% to 19.7%). The OR in individuals with lower, compared with those with medium, income was 1.58 (95% CI 1.20 to 2.08), with significant heterogeneity between studies (I^2 = 71.8%, P < 0.001), while compared with those with higher income the OR increased to 1.68 (95% CI 1.38 to 2.05), with no heterogeneity between studies (I^2 = 0%, P < 0.001). There was no difference in prevalence of gastro-oesophageal reflux symptoms between those of medium and those of higher income (OR = 0.99; 95% CI 0.81 to 1.22) (I^2 = 0%, P = 0.43).

Prevalence of Gastro-oesophageal Reflux Symptoms According to Educational Level

There were 15 studies that reported the prevalence of gastro-oesophageal reflux symptoms according to the educational level of participants, defined as low for no education or primary school level only (or ≤8 years of education), medium for secondary or high school level (or 9-12 years of education), and high for university degree level or higher (or ≥13 years

of education).[47, 53, 59, 62, 69, 71, 72, 84, 85, 88, 89, 93, 102, 104, 119] Overall, the pooled prevalence was higher in subjects with lower education level (16.4%; 95% CI 11.6% to 21.8%) compared with medium (12.4%; 95% CI 7.5% to 18.5%), or higher educational level (10.3%; 95% CI 6.7% to 14.5%). The OR in individuals with lower educational level, compared with those of medium educational level was 1.47 (95% CI 1.25 to 1.73), with significant heterogeneity between studies (I^2 = 67.2%, P < 0.001). Compared with those with a higher level of education the OR increased to 1.78 (95% CI 1.39 to 2.28), with significant heterogeneity between studies (I^2 = 79.7%, P < 0.001). Finally, the OR for those of medium versus higher educational level was also significantly greater (1.24; 95% CI 1.05 to 1.47), with significant heterogeneity between studies (I^2 = 62.6%, P<0.001).

DISCUSSION

This systematic review and meta-analysis has assembled data from 108 population-based cross-sectional surveys, published in 102 separate articles, reporting the prevalence of gastro-oesophageal reflux symptoms in the community. It has demonstrated that prevalence varies strikingly, from 2.5% to over 52%, according to the geographical location of the population under study. This variation persisted even when identical frequencies and durations were used to define the presence of gastro-oesophageal reflux symptoms. In these analyses, the prevalence was higher in studies that used a 12-month time frame compared with 3 months, and the confidence intervals around these estimates did not overlap, suggesting that the definition used impacts on prevalence. Prevalence was also higher when study participants responded to a postal questionnaire, compared with when it was administered by an interviewer, regardless of whether this was face-to-face or via the telephone. The odds of gastro-oesophageal reflux symptoms were significantly higher in people aged 50 years or more, compared with those aged less than 50, suggesting a modest rise in symptom prevalence with increasing age. Moreover, the pooled prevalence was significantly higher in obese subjects compared with non-obese individuals. Other demographic features associated with symptoms included tobacco smoking, NSAID and/or aspirin use, lower income, and lower educational level, although in all instances, the magnitude of these effects was modest.

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 minimise the likelihood that duplicate publications from identical cohorts under extended follow-up were included and, in some cases, to obtain additional data. 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 prevalence of gastro-oesophageal reflux symptoms, and the odds of symptoms according to demographic features. Finally, we limited studies to those based in the general population, and excluded those conducted among convenience samples, meaning that the likelihood of overestimating the prevalence of gastro-oesophageal reflux symptoms has been minimised, and the data reported should therefore be generalisable to individuals in the community.

Limitations of this study include the variability in methods and criteria used to collect and define presence of gastro-oesophageal reflux symptoms. It may be that more personal approaches to collect data, such as a face-to-face or telephone interview, underestimate the prevalence, while for more impersonal methods, such as postal questionnaires, the converse may be true. Moreover, the definition of gastro-oesophageal reflux symptoms varied between individual studies, according to both frequency and duration of symptoms. Therefore, we also reported the results of studies pooled separately based on symptom duration and criteria used to define gastro-oesophageal reflux symptoms. In particular, we calculated a prevalence including only studies that reported at least weekly symptoms, which is in line with the Montreal definition of gastro-oesophageal reflux. Another limitation is the paucity or absence of studies reporting the prevalence of gastro-oesophageal reflux symptoms for some geographical regions, such as Africa, Central America, and South Asia. Despite thousands of individuals contributing data to some of our analyses, confidence intervals around estimates of prevalence were wide, suggesting a lack of precision, although our use of a random effects model will also have contributed to these wide confidence intervals. We calculated odds ratios using raw data reported by the studies, rather than being able to adjust for potential underlying differences between study participants, and therefore some of the associations we observed between gastro-oesophageal reflux symptoms and their proposed risk factors may

be due to residual confounding. Furthermore, there was significant heterogeneity between studies in almost all of our analyses. This heterogeneity was not explained by any of the subgroup analyses we conducted. The reasons for the heterogeneity are therefore speculative, and may include subtle differences in the diagnostic criteria used to define gastro-oesophageal reflux symptoms, or other demographic or cultural differences between study populations, including ethnicity, which it was not possible to examine using the data available for extraction in the individual studies. The degree of 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 could still be useful to understand the prevalence of gastro-oesophageal reflux symptoms in the community from an epidemiological and global perspective.

There have been previous systematic reviews examining the prevalence of gastro-oesophageal reflux in the community. The most recent of these was published in 2014 by El Serag et al.[11] and was an update of their previous systematic review on this topic.[132] The authors found the prevalence of gastro-oesophageal reflux to be 10%–20% in Europe and the USA, and less than 5% in East Asia, which is broadly similar to the prevalence we observed. In their review, population-based studies included those conducted among convenience samples. Despite this, there were only 28 studies included in their systematic review, highlighting that a considerable amount of data has been published since it was conducted, or that it was not included in their analysis. As a result, only a small number of studies were available to examine the effect of proposed risk factors on the prevalence of gastro-oesophageal reflux. This emphasises the need for a contemporaneous study such as ours. Other systematic reviews on this topic focused on the prevalence of gastro-oesophageal reflux limited to specific geographical areas.[133, 134, 135, 136]

The findings of this study have implications for both future research and clinical practice. It appears that the prevalence of gastro-oesophageal reflux symptoms may be lower when individuals are interviewed face-to-face or on the telephone, rather than when they complete a postal questionnaire themselves. The reasons for this are unclear, but may be partly due to under-reporting of symptoms when individuals are questioned directly, or to a stricter definition of the presence of symptoms when recorded by an interviewer. This is perhaps an area for further study. In terms of future treatment trials for gastro-oesophageal reflux, as well as epidemiological studies of the condition, our meta-analysis suggests that the criteria used to collect symptom data, as well as the symptom duration used to define its presence, may affect prevalence, when identifying and recruiting suitable subjects. Indeed, although it is widely accepted that population-based studies should be performed using the suggested Montreal criteria to define gastro-oesophageal reflux, consisting of moderate or severe symptoms occurring ≥1 day per week or mild symptoms occurring ≥2 days per week,[1] studies that have used such criteria remain scarce, despite the fact that these criteria were published 10 years ago.

In addition, most of the risk factors that were reported in the studies showed only a modest, albeit statistically significant, contribution to the odds of reporting symptoms. Part of the reason for this probably relates to the fact that only community-based studies were considered in the meta-analysis, rather than studies conducted in referral populations. Therefore, in order to identify individuals at higher risk of gastro-oesophageal reflux symptoms in the community, the cumulative effect of each of these risk factors, or the interaction between them, might need to be examined using more complex statistical methods. Finally, the prevalence of gastro-oesophageal reflux symptoms in certain geographical regions, such as Africa, Central America and South Asia is uncertain, and

further studies are required in order to enable the global prevalence to be estimated with greater precision.

In conclusion, this systematic review and meta-analysis has demonstrated that the global prevalence of gastro-oesophageal reflux symptoms varies considerably, depending on geographical region, method of data collection, criteria used to define gastro-oesophageal reflux, and minimum symptom duration required. The striking variation in prevalence throughout the world, even when similar definitions are used, or identical questionnaires within different countries, highlights the importance of other factors such as genetic, ethnic, and cultural differences on the reporting of upper GI symptoms. Risk factors for gastro-oesophageal reflux symptoms included age ≥50 years, tobacco smoking, NSAID and/or aspirin use, obesity, and lower educational level or income. However, these associations were modest, their overall importance in the aetiology of symptoms is questionable, and there are likely to be many other factors involved in the pathogenesis of gastro-oesophageal reflux symptoms that we were unable to elucidate via analysis of data from the epidemiological studies we identified.

ACKNOWLEDGEMENTS

We thank Dr. Dmitry Bordin, Dr. Oleg Reshetnikov, Dr. Javed Yakoob, and Dr. Cristina Dacoll for answering our queries about their studies.

CONFLICTS OF INTEREST/STUDY SUPPORT

Guarantor of the article: ACF is guarantor.

Specific author contributions: LHE, RR, YY, MS-D, FB, and ACF conceived and drafted the study. LHE, YY, MS-D, and RR collected all data. ACF and LHE analysed and interpreted the data. LHE and ACF drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

Financial support: None.

Potential competing interests: Leonardo H. Eusebi: none. Raguprakash Ratnakumaran: none. Yuhong Yuan: none. Masoud Solaymani-Dodaran: none. Franco Bazzoli: none. Alexander C Ford: none.

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 gastro-oesophageal reflux symptoms (according to a questionnaire, or specific diagnostic criteria†)

Sample size of ≥50 participants

*Convenience samples excluded

†Broad definition of gastroesophageal reflux including presence of heartburn or acid regurgitation alone, Montreal criteria, Rome I or II criteria

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FIGURE LEGENDS

Figure 1. Prevalence of Gastro-oesophageal Reflux Symptoms Worldwide.

Figure 2. Prevalence of Gastro-oesophageal Reflux Symptoms Worldwide Using Symptoms at a Frequency of Once a Week or More.

Figure 3. Odds ratio for Gastro-oesophageal Reflux Symptoms in Women Versus Men According to Geographical Location.