Global prevalence of Barrett's oesophagus and oesophageal cancer in individuals with gastro-oesophageal reflux: a systematic review and meta-analysis

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TITLE PAGE

Title: Global Prevalence of Barrett's Oesophagus and Oesophageal Cancer in Individuals with Gastro-oesophageal Reflux: A Systematic Review and Meta-analysis.

Short running head: Prevalence of Barrett's Oesophagus in GORD: A Meta-analysis.

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Abbreviations:

CI	confidence interval
GI	gastrointestinal
MeSH	medical subject headings
OR	odds ratio
GORD	gastro-oesophageal reflux disease
BO	Barrett's oesophagus

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ABSTRACT

Objectives: Chronic gastro-oesophageal reflux might lead to the development of Barrett's oesophagus (BO), or even oesophageal adenocarcinoma. There has been no definitive systematic review and meta-analysis of data to estimate global prevalence of BO or oesophageal adenocarcinoma in individuals with gastro-oesophageal reflux.

Design: We searched MEDLINE, EMBASE, and EMBASE Classic to identify cross-sectional surveys that reported prevalence of BO or oesophageal adenocarcinoma in adults with gastro-oesophageal reflux. We extracted prevalence for all studies, both for endoscopically suspected, and histologically confirmed, cases. We calculated pooled prevalence, according to study location, symptom frequency and sex, as well as odds ratios (ORs), with 95% confidence intervals (CIs).

Results: Of the 4,963 citations evaluated, 44 reported prevalence of endoscopically suspected and/or histologically confirmed BO. Prevalence of BO among individuals with gastro-oesophageal reflux varied according to different geographic regions ranging from 3%-14% for histologically confirmed BO, with a pooled prevalence of 7.2% (95% CI 5.4%-9.3%), whereas pooled prevalence for endoscopically suspected BO was 12.0% (95% CI 5.5%-20.3%). There was heterogeneity in many of our analyses. Prevalence of BO was significantly higher in men, both for endoscopically suspected (OR = 2.1; 95% CI 1.6-2.8) and histologically confirmed BO (OR = 2.3; 95% CI 1.7-3.2). Dysplasia was present in 13.9% (95% CI = 8.9%-19.8%) of cases of histologically confirmed BO, 80.7% of which was low-grade.

Conclusion: The prevalence of Barrett's oesophagus among individuals with gastro-oesophageal reflux varied strikingly among countries, broadly resembling the geographic

distribution of gastro-oesophageal reflux itself. Prevalence of BO was significantly higher in men.

What is already known about this subject?

- Gastro-oesophageal reflux disease is considered one of the main risk factors for the development of Barrett's oesophagus, or oesophageal adenocarcinoma.
- There has been no definitive systematic review examining prevalence of Barrett's oesophagus or oesophageal adenocarcinoma in individuals with gastro-oesophageal reflux, globally.

What are the new findings?

- Up to 14% of individuals reporting gastro-oesophageal reflux symptoms were found to have histologically confirmed Barrett's oesophagus.
- Prevalence of both endoscopically suspected and histologically confirmed Barrett's oesophagus varied widely according to country.
- Less than 40% of endoscopically suspected cases of Barrett's oesophagus were confirmed by histology.
- Barrett's oesophagus was twice as frequent in men that in women

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

- These data provide an analysis of the global prevalence of Barrett's oesophagus in individuals with gastro-oesophageal reflux symptoms, and may allow for health service provision planning.

INTRODUCTION

Gastro-oesophageal reflux is the retrograde movement of gastric content through the gastro-oesophageal junction. It is usually caused by a combination of disordered sensorimotor function in association with impairment of the normal anti-reflux mechanisms, such as lower oesophageal sphincter function and diaphragm muscles at the hiatus, and changes in normal physiology, including impaired oesophageal peristalsis, increased intragastric pressure, or excess gastric acid secretion.[1] These potential predisposing factors can be exacerbated by the presence of others abnormalities, including delayed gastric emptying, hiatus hernia, visceral hypersensitivity, or obesity.[2, 3] Typical gastro-oesophageal reflux symptoms consist of heartburn and regurgitation, and a recent meta-analysis demonstrated that these affect as many as 15% of otherwise healthy individuals in the community at any one time.[4] However, the prevalence varies substantially among individual countries, with the highest rates occurring in Central America (19.6%) and the lowest in Asia (10.0%), particularly in Southeast Asian countries (7.4%).[4]

Gastro-oesophageal reflux disease (GORD) is a condition that develops when the reflux of stomach contents is so frequent as to cause troublesome symptoms and/or complications.[5] Again, GORD is a common disorder, and the prevalence may be increasing in many developing countries, but with considerable geographic variation. Previous systematic reviews and meta-analyses have found the prevalence of GORD to be around 10–20% in Europe and the USA, and <5% in East Asia.[4, 6]

The chronic nature of symptoms of gastro-oesophageal reflux and GORD results in a substantial economic burden, due to the costs of consultations, investigations, medications, surgery, and treatment of complications. In addition, there is a considerable impact of these symptoms on the quality of life of patients. There is also the risk that chronic symptoms of gastro-oesophageal reflux, or GORD, could lead to the development of precancerous lesions,

especially Barrett's oesophagus (BO), and oesophageal adenocarcinoma.[2] Barrett's oesophagus is defined as the replacement of any length of the squamous epithelium in the distal oesophagus by columnar epithelium, with the presence of intestinal metaplasia, characterised by acid mucin-containing goblet cells. The prevalence of BO has been estimated at 1% to 2% in all patients receiving endoscopy for any indication, and may range from 5% to 15% in patients with symptoms of gastro-oesophageal reflux.[7, 8] BO is considered a precancerous lesion, with a 30- to 40-fold increased risk of oesophageal adenocarcinoma.[9] Current guidelines for its management recommend endoscopic surveillance in order to detect cancer at an early, and treatable, stage. However, only a fraction of patients with BO develop oesophageal adenocarcinoma, which raises important economic and clinical questions about whom to screen.[10]

Numerous studies have been conducted in order to assess the correlation between symptoms of gastro-oesophageal reflux, or GORD, and the presence of BO, in an attempt to inform decisions regarding how to optimise endoscopic follow-up of their patients, in order to provide early diagnosis, detect any other complications, and reduce the associated management costs. Systematic analysis of studies that report these types of data is important, in order to provide physicians with more precise estimates of the prevalence of BO in patients with symptoms of gastro-oesophageal reflux, or GORD, in order to inform clinical practice, as well as to identify areas where further research is needed. Regarding the association between symptoms of gastro-oesophageal reflux and BO, a previous meta-analysis demonstrated that symptomatic individuals had a significantly increased odds of BO, compared with those without.[11] A more recent systematic review and meta-analysis reported a pooled prevalence of BO of 3% among subjects in the general population with gastro-oesophageal reflux symptoms.[12]

However, other than the studies included in their analysis, which described the prevalence of BO in unselected samples of the general population, a considerable amount of data from other settings, such as cohorts of only individuals with GORD, has been published examining the relationship between BO and gastro-oesophageal reflux symptoms specifically. We therefore performed a systematic review and meta-analysis of the prevalence of BO, and its complications, among patients with gastro-oesophageal reflux symptoms, or GORD, in order to examine these issues.

METHODS

Search Strategy and Study Selection

We conducted a literature search using EMBASE CLASSIC and EMBASE (1947 to February 2020), and MEDLINE (1948 to February 2020) to identify only cross-sectional surveys published in full that reported the prevalence of BO in adults (aged ≥16 years) referred for upper gastrointestinal endoscopy for gastro-oesophageal reflux symptoms. Studies were required to recruit consecutive participants undergoing upper gastrointestinal endoscopy. Studies that recruited convenience samples, such as university students, veterans, or employees at an institution were not eligible for inclusion.

Other eligibility criteria included prospective recruitment of at least 50 participants; a definition of gastro-oesophageal reflux 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; a definition of endoscopic BO compatible with the presence of columnar-lined oesophagus (proximal displacement of the squamous-columnar junction above the upper end of the gastric folds or gastro-oesophageal junction), or a definition of confirmed BO in the presence of specialised intestinal metaplasia on biopsies obtained from the columnar-lined oesophagus. These eligibility criteria, which were defined prospectively, are provided in Box 1.

We searched the medical literature using the following terms: *heartburn, GERD, gastroesophageal reflux disease, gastroesophageal reflux, oesophageal reflux* (both as a medical subject heading (MeSH) and free text term), *acid regurgitation*, *GORD*, or *upper gastrointestinal symptoms* (as free text terms). We combined these using the set operator AND with studies identified with the terms: *oesophageal neoplasm, oesophageal adenocarcinoma, Barrett, dysplasia,* or *intestinal metaplasia* (both as MeSH and free text terms). Two investigators screened the resulting abstracts independently for potential

suitability, and we retrieved those that appeared relevant and examined them in more detail. Eligibility was not restricted to studies published only in English; foreign language articles were translated. We performed a recursive search using the references of all obtained articles. Where there appeared to be multiple studies from the same population, the study published most recently was included. Eligibility assessment was performed independently by two investigators, using pre-designed eligibility forms, and we resolved disagreements by consensus.

The systematic review was conducted according to the MOOSE statement.[13] The study protocol was published on the PROSPERO international prospective register of systematic reviews (registration number CRD 42020164811).

Data Extraction

Two investigators extracted data independently 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: year(s) conducted, country and geographical region, setting where the study was conducted, method of symptom data collection (postal questionnaire, interview-administered questionnaire, self-completed questionnaire, telephone interview, face-to-face interview, web-based questionnaire), symptom frequency and duration used to define gastro-oesophageal reflux, number of subjects providing complete data, age range and mean age of subjects, proportion of male subjects, the number of subjects with an endoscopically suspected and/or histologically confirmed diagnosis of BO, and the length of BO detected (short-segment BO, defined as length ≤3cm, *vs*. long-segment BO, defined as length >3cm). Where gastro-oesophageal reflux symptoms were reported according to more than one frequency of symptoms in an individual study, the number of subjects with gastro-oesophageal reflux

according to each individual frequency was extracted. Subjects undergoing upper gastrointestinal endoscopy for bothersome gastro-oesophageal reflux symptoms that were reported at a frequency of at least weekly, were considered as having GORD in line with the Montreal definition.[5]

Data Synthesis and Statistical Analysis

We combined the proportion of individuals with endoscopic and histological BO in each study to give a pooled prevalence for all studies. 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, as the threshold for statistically significant heterogeneity.[14] We conducted subgroup analyses according to geographical region, criteria used to define gastro-oesophageal reflux, symptom frequency used to define presence of gastro-oesophageal reflux (gastro-oesophageal reflux symptoms of any frequency vs. GORD as per the Montreal definition), the method used to collect symptom data, the year the study was conducted, age, sex, and length of BO, in order to assess whether this had any effect on the pooled prevalence of BO. Finally, we compared the prevalence of BO according to sex using an odds ratio (OR), with a 95% confidence interval (CI).

We pooled data using a random effects model, to give a more conservative estimate of the prevalence, and the odds, of BO in these various groups. We used StatsDirect version 3.2.10 (StatsDirect Ltd, Sale, Cheshire, England) to generate Forest plots of pooled prevalence and pooled ORs with 95% CIs. We assessed for evidence of publication bias by applying Egger's test to funnel plots of odds ratios, where a sufficient number of studies (≥10) were available.[15]

RESULTS

The search strategy identified 4963 citations. From these, we identified 105 articles that appeared to be relevant to the study question (Figure 1). There were 44 articles that fulfilled the eligibility criteria,[16, 17, 18, 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] of which two reported the prevalence of endoscopically suspected BO only,[44, 54] 30 reported the prevalence of histologically confirmed BO only,[16, 17, 18, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 37, 38, 39, 42, 43, 46, 47, 48, 49, 51, 52, 56, 58] and 12 reported the prevalence of BO according to both definitions.[19, 21, 33, 36, 40, 41, 45, 50, 53, 55, 57, 59] Agreement between investigators for assessment of study eligibility was excellent (κ statistic=0.98). All but two articles were published in English.[19, 26] Detailed characteristics of all included studies are provided in Supplementary Table 1.

Global Prevalence of Endoscopically Suspected BO in Individuals with Gastro-oesophageal Reflux Symptoms of Any Frequency

The 14 included studies [16, 19, 21, 33, 36, 41, 44, 45, 50, 53, 54, 55, 57, 59] that reported the prevalence of endoscopic BO among subjects undergoing endoscopic examination for gastro-oesophageal reflux symptoms of any frequency contained 8,817 subjects and were geographically diverse, with three studies from Europe, two from North America, four from the Middle east, three from Asia, and two from South America, respectively. There were no studies conducted in Africa or Central America. When data from all 14 separate study populations were pooled, the prevalence of endoscopically suspected BO in individuals with gastro-oesophageal reflux symptoms was 12.0% (95% CI 5.5%-20.3%) (Supplementary Figure 1). The pooled prevalence according to geographical study location confirmed that the highest prevalence of endoscopic BO among patients with gastro-

oesophageal reflux symptoms occurred in South American countries (35.7%), followed by North America (23.1%), and was lowest in Asia (1.9%). There was statistically significant heterogeneity between studies in all of these analyses.

Global Prevalence of Histologically Confirmed BO in Individuals with Gastro-oesophageal Reflux Symptoms of Any Frequency

Forty-two studies reported the prevalence of histologically confirmed BO among subjects undergoing endoscopy due to gastro-oesophageal reflux symptoms of any frequency,[16, 17, 18, 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, 45, 46, 47, 48, 49, 50, 51, 52, 53, 55, 56, 57, 58, 59] containing a total of 26,521 subjects. The majority of studies were conducted in North America (13), Europe (8) or the Middle East (8). There were few studies from South America, Africa, or Asia, and no studies conducted in Central America. When data from all 42 separate study populations were pooled, the overall prevalence of histologically confirmed BO in individuals with gastro-oesophageal reflux symptoms was 7.2% (95% CI 5.4% to 9.3%) (Supplementary Figure 2). The lowest prevalence was 0.6% reported by two studies, both of which were conducted in Turkey,[41, 58] and the highest prevalence was 29%, reported in a study from the US.[17]

The pooled prevalence of histologically confirmed BO in individual countries is provided in Figure 2, and the pooled prevalence according to geographical study location is provided in Table 1. Statistically significant heterogeneity was present between studies in all of these analyses, except for among studies conducted in Africa. The highest prevalence of histologically confirmed BO among patients with gastro-oesophageal reflux symptoms occurred in North American countries (14.0%) and the lowest in the Middle East (3.0%).

Table 1. Pooled Prevalence of Histologically Confirmed BO in Individuals with Gastro-oesophageal Reflux Symptoms of Any Frequency According to Geographical Location.

	Number of studies	Number of subjects	Pooled prevalence (%)	95% confidence interval (%)	I^2	P value for I^2
All studies	**42**	**26,521**	**7.2**	**5.4 – 9.3**	**97.1%**	**< 0.001**
North American studies [16, 17, 18, 20, 23, 25, 27, 32, 37, 38, 39, 55, 59]	13	4,158	14.0	10.8 – 17.7	89.5%	< 0.001
European studies [22, 24, 29, 34, 36, 40, 43, 45]	8	9,211	4.9	1.9 – 9.1	97.5%	< 0.001
Middle Eastern studies [31, 33, 41, 47, 53, 56, 57, 58]	8	3,392	3.0	1.7 – 4.7	82.2%	< 0.001
Asian studies [30, 35, 48, 49, 50, 51, 52]	7	7,414	4.1	1.4 – 8.2	96.4%	< 0.001
African studies [28, 42, 46]	3	1,196	8.0	6.3 – 9.9	7.8%	< 0.001
South American studies [19, 21, 26]	3	1,150	9.1	3.8 – 16.4	93.1%	< 0.001

Global Prevalence of Endoscopically Suspected BO in Individuals with GORD as per the Montreal Definition

Twelve studies reported the prevalence of endoscopically suspected BO in patients undergoing endoscopic evaluation for gastro-oesophageal reflux disease, defined as at least weekly troublesome symptoms as per the Montreal definition.[19, 21, 33, 36, 40, 41, 44, 45, 50, 53, 54, 59] When data from all 12 separate studies, including a total of 6695 subjects, were pooled the prevalence of endoscopically suspected BO in individuals with GORD was 12.0% (95% CI 4.8% to 21.8%). The highest prevalence of endoscopically suspected BO among patients with GORD occurred in South American countries (35.7%) and the lowest in Asia (2.6%), with a Chinese study reporting the lowest prevalence of 0.4%.[44]

Global Prevalence of Histologically Confirmed BO in Individuals with GORD as per the Montreal Definition

The presence of histologically confirmed BO in patients with GORD, as per the Montreal definition, was reported by 24 studies,[19, 21, 22, 25, 27, 29, 30, 32, 33, 34, 36, 37, 38, 39, 40, 41, 42, 45, 46, 50, 51, 53, 56, 59] seven of which were conducted in North America, six in Europe, four in the Middle East, three in Asia, and two each in Africa, and South America. Among 14,068 subjects with GORD, the pooled prevalence of histologically confirmed BO was 8.2% (95% CI 6.2% to 10.3%) (Supplementary Figure 3). The lowest prevalence was 0.6%, reported by a study conducted in Turkey,[41] and the highest prevalence was 20.7%, reported in a study from the US.[59]

The pooled prevalence of histologically confirmed BO in individual countries is provided in Figure 3 and the pooled prevalence according to geographical study location is provided in Table 2. Statistically significant heterogeneity was present between studies in all

of these analyses. The highest prevalence of histologically confirmed BO among individuals with GORD occurred in North American countries (14.3%) and the lowest in the Middle East (3.8%).

Table 2. Pooled Prevalence of Histologically Confirmed BO in Individuals with GORD as per the Montreal Definition According to Geographical Location.

	Number of studies	**Number of subjects**	**Pooled prevalence (%)**	**95% confidence interval (%)**	**I^2**	**P value for I^2**
All studies	**24**	**14,068**	**8.2**	**6.2 – 10.3**	**93.6%**	**< 0.001**
North American studies [25, 27, 32, 37, 38, 39, 59]	7	1,066	14.3	11.0 – 18.0	57.6%	0.03
European studies [22, 29, 34, 36, 40, 45]	6	7,616	5.7	2.3 – 10.6	95.9%	< 0.001
Middle Eastern studies [33, 41, 53, 56]	4	2,422	3.8	1.6 – 6.9	89.6%	< 0.001
Asian studies [30, 50, 51]	3	1,125	6.1	1.9 – 12.6	91.8%	< 0.001
African studies [42, 46]	2	1,091	7.1	6.1 – 9.2	0%	0.33
South American studies [19, 21]	2	748	12.5	10.2 – 15.0	0%	0.41

Correlation Between Endoscopically Suspected and Histologically Confirmed BO

In order to assess the proportion of cases of endoscopically diagnosed BO that were also confirmed by histological examination, we pooled data from those studies that reported the prevalence of both endoscopically suspected and histological confirmed BO. There were 12 studies that assessed the prevalence of BO according to both definitions among subjects with gastro-oesophageal reflux symptoms,[19, 21, 33, 36, 40, 41, 45, 50, 53, 55, 57, 59] and 10 among subjects with GORD.[19, 21, 33, 36, 40, 41, 45, 50, 53, 59] The proportion of endoscopically suspected BO cases that were confirmed by histology among subjects with reflux symptoms was 38.4% (95% CI 28.1% to 49.2%) (Supplementary Figure 4); the lowest proportion occurred in a study from India (16.1%),[57] whereas a study conducted in Taiwan reported the highest proportion, confirming the endoscopic diagnosis in 61.2% of cases.[50] A similar pooled analysis among subjects with GORD revealed the proportion of histologically confirmed cases, when an endoscopic diagnosis of BO was suspected, was 39.9% (95% CI 30.0% to 50.2%). A study conducted in the US reported the highest proportion (85.7%),[59] while the lowest was found in a Swedish study (17.9%).[36]

Global Prevalence of Short-segment and Long-segment BO in Individuals with Gastro-oesophageal Reflux Symptoms

Six studies reported the length of endoscopically suspected BO in subjects with gastro-oesophageal reflux symptoms.[19, 21, 41, 45, 55, 57] The overall prevalence of short- and long-segment BO among all subject with gastro-oesophageal reflux symptoms was 13.9% (95% CI = 5.6% to 25.1%) and 0.3% (95% CI = 0.1% to 0.5%), respectively. Among 595 subjects with endoscopically suspected BO, the proportion of short-segment BO was 81.6% (95% CI = 77.7% to 85.2%) and 18.4% (95% CI = 14.8% to 22.3%) for long-segment BO.

There were 18 studies that reported the prevalence of histologically confirmed BO among subjects with gastro-oesophageal reflux symptoms according to the length of oesophageal intestinal metaplasia.[17, 19, 20, 21, 22, 23, 25, 26, 27, 32, 33, 36, 37, 39, 40, 45, 46, 55] The overall prevalence of histologically confirmed short-segment BO among subjects with gastro-oesophageal reflux symptoms, when data from all 18 separate study populations were pooled, was 6.7% (95% CI = 4.6% to 9.1%), whereas the prevalence of histologically confirmed long-segment BO was 3.1% (95% CI = 2.0% to 4.6%). As expected, among all the 721 subjects with histologically confirmed BO included in the 18 studies, the proportion of short-segment BO was significantly higher than long-segment BO ($p<0.001$), accounting for 68.0% (95% CI = 61.5% to 74.1%) and 32.0% (95% CI = 25.9% to 38.5%) of cases, respectively.

Prevalence of BO According to Sex in Individuals with Gastro-oesophageal Reflux Symptoms

There were five[21, 45, 53, 55, 57] and 12 studies[17, 23, 26, 37, 38, 45, 46, 49, 50, 53, 56, 57] that reported the prevalence of endoscopically suspected and histologically confirmed BO, respectively, according to sex among subjects with gastro-oesophageal reflux symptoms. Overall, the pooled prevalence of endoscopically suspected BO was higher in men with gastro-oesophageal reflux symptoms compared with women (19.1% (95% CI = 12.0% to 27.3%) vs. 10.1% (95% CI = 4.2% to 18.2%); OR = 2.1 (95% CI 1.6 to 2.8)), with no heterogeneity between studies ($I^2=0\%$, $p<0.001$). Similarly, the pooled prevalence of histologically confirmed BO was higher in men compared with women (10.8% (95% CI = 6.6% to 15.9%) vs. 4.8% (95% CI = 2.7% to 7.5%); OR = 2.3 (95% CI 1.7 to 3.2)), with low heterogeneity between studies ($I^2=24.6\%$, $p<0.001$). We studied the effect of geographical region of the study on prevalence of histologically confirmed BO according to sex. This

demonstrated a significantly increased OR among men in South America (OR = 4.40; 95% CI 1.33 to 16.70) and North America (OR = 2.72; 95% CI 1.80 to 4.10), and a more modest increase in the Middle East (OR = 1.76; 95% CI 1.03 to 3.01) (Figure 4). ORs were generally higher in men in Europe (OR = 2.79; 95% CI 0.45 to 29.60), Africa (OR = 2.46; 95% CI 0.98 to 7.95) and Asia (OR = 2.31; 95% CI 0.14 to 36.80), although not statistically significant.

Prevalence of Dysplasia or Oesophageal Adenocarcinoma in Individuals with Gastro-oesophageal Reflux Symptoms

The prevalence of any degree of dysplasia among subjects with gastro-oesophageal reflux symptoms was reported by seven studies,[17, 19, 21, 39, 50, 53, 59] containing 234 cases of histologically confirmed BO. Three studies were conducted in the US, two studies in Chile, and one each in India and in Taiwan. Among all cases of histologically confirmed BO, the prevalence of dysplasia was 13.9% (95% CI = 8.9% to 19.8%) (Supplementary Figure 5). Overall, 33 cases of dysplasia were diagnosed, of which 27 (80.7% (95% CI = 66.3% to 91.8%)) were low-grade and six (19.3% (95% CI = 8.2% to 33.7%)) were high-grade. When data from all seven studies were pooled, the prevalence of dysplasia in subjects with gastro-oesophageal reflux symptoms was 1.7% (95% CI = 0.9% to 2.9%). In particular, the pooled prevalence of low-grade and high-grade dysplasia were 1.4% (95% CI = 0.7% to 2.3%) and 0.4% (95% CI = 0.1% to 0.8%).

The prevalence of oesophageal adenocarcinoma among subjects with gastro-oesophageal reflux symptoms was reported by seven studies, [17, 19, 21, 39, 53, 56, 59] containing 2224 subjects, with 255 cases of histologically confirmed BO. Only two cases of oesophageal adenocarcinoma were diagnosed, with a pooled prevalence of 0.1% among subjects with gastro-oesophageal reflux symptoms (95% CI = 0.03% to 0.3%), and a

prevalence among subjects with histologically confirmed BO of 1.2% (95% CI = 0.3% to 2.9%).

DISCUSSION

This systematic review and meta-analysis has assembled data from 44 endoscopy-based cross-sectional surveys that reported the prevalence of endoscopically suspected and/or histologically confirmed BO in individuals with gastro-oesophageal reflux symptoms. We have demonstrated that prevalence varies strikingly, from 1.9% to 35.7% for endoscopically suspected BO, and from 3% to 14% for histologically confirmed BO, according to the geographical location of the population under study. This variation persisted even when only a weekly frequency was used to define the presence of gastro-oesophageal reflux symptoms. The overall prevalence of BO increased only slightly, from 7.2% to 8.2% for histologically confirmed BO, between individuals with gastro-oesophageal reflux symptoms and those with weekly symptoms that would be considered to be compatible with GORD, suggesting that the frequency of symptoms impacts only marginally on the prevalence of BO. The odds of both endoscopically suspected and histologically confirmed BO were more than two-fold higher in men compared with women. Therefore, although previous studies have shown that gastro-oesophageal reflux symptoms are slightly more prevalent in females,[4] our results confirm that male sex appears to be significantly associated with BO.

Regarding the length of BO in individuals with gastro-oesophageal reflux symptoms, approximately 20% of endoscopically suspected BO cases were classified as long-segment, whereas among the histologically confirmed cases, 32% were long-segment BO, suggesting that the endoscopically suspected long-segment BO is more often confirmed by histology compared with short-segment. Moreover, only around 40% of endoscopically suspected BO cases were confirmed by histopathology, with considerable variation across studies. These results show that more than half of endoscopically suspected BO cases are not confirmed by histological examination, and particularly short-segment BO, underlining that waiting for

histopathologic confirmation is mandatory before making a diagnosis of BO. The meta-analysis also demonstrated that the overall prevalence of dysplasia in individuals who underwent endoscopic examination for gastro-oesophageal reflux symptoms was less than 2%; more specifically, dysplasia was present in 13.9% of cases of histologically confirmed BO, 80.7% of which was low-grade. The overall prevalence of oesophageal adenocarcinoma in patients with gastro-oesophageal reflux symptoms was very low (0.1%), and was present in only 1.2% of BO cases. However, these results were based on a small number of studies. Larger cohort studies would be needed to examine this important issue in more detail, particularly given the fact that the incidence of oesophageal cancer is increasing rapidly.[7]

We used an exhaustive and contemporaneous search strategy in order to maximise the likelihood of identifying all relevant studies. The evaluation of study eligibility and data extraction was carried out by two investigators independently, with discrepancies resolved by consensus. The corresponding authors of studies were contacted, where necessary, in order to minimise the likelihood of including duplicate publications from the same cohort of patients, and to obtain additional data in some cases. We also included, after translation, foreign-language articles. We used a random effects model to pool data, in order to provide a more conservative estimate of the prevalence of BO in patients with gastro-oesophageal reflux symptoms, and the odds of BO according to sex. Finally, we excluded studies conducted among convenience samples, in order to minimise the likelihood of overestimating the prevalence of BO.

Limitations of this study include the variability in methods and criteria used to define the presence of gastro-oesophageal reflux symptoms. More personal approaches to collect data, such as a face-to-face interviews, might underestimate the prevalence and severity of symptoms, whereas for more impersonal methods, such as questionnaires, the converse may

be true. Furthermore, the definition of gastro-oesophageal reflux symptoms varied between individual studies, according to frequency and severity of symptoms. Therefore, we also reported the results of studies pooled separately based on symptom frequency. In particular, we estimated the prevalence of BO only in studies that reported at least weekly symptoms, which is in line with the Montreal definition of GORD.[5] The definition of endoscopically suspected BO was homogeneous across the studies, using the displacement of the squamous-columnar junction above the proximal end of the gastric folds or gastro-oesophageal junction as landmarks. Moreover, all studies, with the exception of one where endoscopy was performed also by primary care practitioners, were conducted in secondary or tertiary healthcare centres, suggesting that the endoscopic examination was performed by experienced endoscopists. However, this is likely to have affected our estimates of the prevalence of BO in individuals with gastro-oesophageal reflux, as there will be differences between patients with gastro-oesophageal reflux in secondary and tertiary care in whom endoscopy is deemed necessary, and those in primary care or the community who are not endoscoped. In addition, the sampling of endoscopically suspected Barrett's mucosa across the studies was not standardised, and was conducted according to local experience, which may have led to an underestimation of the prevalence of BO. Although in some countries cardiac mucosa in the oesophagus is also considered diagnostic for BO,[60] in order to reduce variability in the diagnoses and since it is not clear whether cardiac mucosa has the same malignant predisposition,[61] we only included studies that considered intestinal metaplasia with goblet cells (specialised intestinal metaplasia) for a definitive diagnosis of BO in our analysis. Current guidelines require the presence of at least 1cm of columnar-lined oesophagus to make a diagnosis of BO, but very few included studies published in the intervening years since this guidance mandated this. Another limitation is the paucity or absence of studies reporting the prevalence of BO for some geographical regions, such as

Africa, Central America, and Australasia. There were no eligible studies from many Western countries where BO is known to be common, such as the UK, France, or Australia, and some of the studies from developing countries were small, and may have overestimated the prevalence of BO in patients with gastro-oesophageal reflux.

Despite thousands of individuals included in our analyses, CIs 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 CIs. Furthermore, there was significant heterogeneity between studies in almost all of our analyses. This heterogeneity was not explained by the subgroup analyses we conducted. The reasons for this heterogeneity are therefore speculative, but may include subtle differences in the inclusion criteria used to define gastro-oesophageal reflux symptoms, histological sampling protocols, or other demographic or geographic differences between study populations, including ethnicity, which it was not possible to examine using the available data. The degree of heterogeneity may be seen as precluding the pooling of data from these studies in a meta-analysis, and may limit the utility of the pooled estimates we report. Nevertheless, we feel that the summary data obtained using this approach could still be useful to understand the prevalence of Barrett's oesophagus in individuals with gastro-oesophageal reflux symptoms from an epidemiological and global perspective.

To the best of our knowledge this is the first study to systematically provide an overall estimate of the prevalence of endoscopically suspected and histologically confirmed BO worldwide in individuals with gastro-oesophageal reflux symptoms or GORD. A recent systematic review and meta-analysis by Qumseya *et al.* evaluated the prevalence of BO in the general population, as well as based on the presence of potential risk factors, including gastro-oesophageal reflux symptoms.[12] The authors pooled data from 13 studies in which

reflux symptoms were reported as a risk factor, reporting a pooled prevalence of BO of 3% among 5975 included participants. The studies included in their analysis described the prevalence of BO in the general population, however, several other studies have been published reporting the prevalence of BO among individuals with gastro-oesophageal reflux symptoms specifically, emphasising the need for a contemporaneous study such as ours. Another meta-analysis of 26 studies was conducted by Taylor and Rubenstein, to estimate the association between GORD symptoms and BO.[11] The authors reported a significant increase in the odds of BO in those with GORD symptoms (OR 2.9; 95% CI, 1.86-4.45) compared with those without such symptoms. This increased to 4.5 (95% CI, 2.1-9.29) when including patients reporting symptoms occurring at least weekly.[11] A systematic review and meta-analysis by Cook *et al.* focused on the sex ratio for Barrett's oesophagus, reporting an overall pooled male/female sex ratio of 1.96:1 (95% confidence interval (CI): 1.77:1 to 2.17:1).[62] This result is broadly similar to the prevalence we observed according to sex, confirming that BO is approximately twice as frequent in men that in women.

The findings of this study have implications for both future research and clinical practice. In terms of future trials on BO, as well as epidemiological studies of the condition, the criteria used to collect gastro-oesophageal reflux symptom data, as well as the biopsy sampling protocols and the histological criteria, may affect the prevalence of BO in clinical trials. Indeed, although it is widely accepted that population-based studies should be performed using the suggested Montreal criteria to define GORD, consisting of moderate or severe symptoms occurring ≥1 day/ week or mild symptoms occurring ≥2 days/week,[5] studies that have used such criteria remain scarce, despite the fact that these were published more than 10 years ago. Similarly, the use of standardised endoscopic classifications and validated biopsy protocols for BO, such as the Prague classification[63] and the Seattle protocol,[64] should be used to assess the extent of intestinal metaplasia more accurately.

Moreover, the use of advanced imaging endoscopic techniques, such as high definition endoscopy, narrow-band imaging, and chromoendoscopy, may further improve the diagnosis of BO. The histological diagnosis of BO and the presence and severity of dysplasia can be challenging even among experienced pathologists, and the extent of interobserver agreement when diagnosing low-grade dysplasia can be less than 50%,[65, 66] suggesting the need for pathologists to specialise in oesophageal pathology.

In conclusion, this systematic review and meta-analysis has demonstrated that the global prevalence of histologically confirmed BO in individuals with gastro-oesophageal reflux symptoms and GORD varies considerably, ranging from 3% to 14% across different geographic regions. Higher rates were found worldwide for endoscopically suspected BO. However, histopathological confirmation should be considered mandatory for a definitive diagnosis, as less than 40% of endoscopically suspected cases were confirmed by histology. Besides male sex, which was confirmed by our analysis as significantly associated with BO, there are likely to be many other factors involved in the pathogenesis that we were unable to elucidate via analysis of data from the epidemiological studies we identified. Screening models could be based on these risk factors, allowing the identification of populations at higher risk for BO.

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Guarantor of the article: ACF is guarantor.

Specific author contributions: LHE, GGC, RMZ, and ACF conceived and drafted the study. LHE, GGC 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.

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PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

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ETHICS APPROVAL

Ethical approval was not required as the study is a systematic review and meta-analysis of previously published data.

Box 1

- Cross-sectional surveys.
- Recruited adult (>90% aged ≥16 years) participants with gastro-oesophageal reflux symptoms (according to a questionnaire or specific diagnostic criteria†) undergoing endoscopic examination prospectively.
- Reported prevalence of endoscopically suspected Barrett's oesophagus, defined as presence of columnar-lined oesophagus at endoscopy, histologically confirmed Barrett's oesophagus, defined as presence of specialised intestinal metaplasia on biopsies obtained from columnar-lined oesophagus, or both.
- Sample size of ≥50 participants.

†Broad definition of gastro-oesophageal reflux including presence of heartburn or acid regurgitation alone, Montreal criteria

FIGURE LEGENDS

Figure 1. Flow diagram of studies identified in the systematic review.

Figure 2. Prevalence of histologically confirmed Barrett's oesophagus in individuals with gastro-oesophageal reflux symptoms of any frequency by individual country.

Figure 3. Prevalence of histologically confirmed Barrett's oesophagus in individuals with GORD by individual country.

Figure 4. Odds ratio for histologically confirmed Barrett's oesophagus in men versus women according to geographical location.