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TITLE PAGE

Title: Risk factors for Barrett's Oesophagus in Individuals with Gastro-oesophageal Reflux Symptoms: A Systematic Review and Meta-analysis

Short running title: Risk factors for Barrett's Oesophagus in Reflux: A Meta-analysis.

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Abbreviations:

BMI	Body mass index
BO	Barrett's oesophagus
CI	confidence interval
GORD	gastro-oesophageal reflux disease
MeSH	medical subject headings
NSAID	non-steroidal anti-inflammatory drug

OR odds ratio

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SUMMARY

Background: Gastro-oesophageal reflux is considered the main risk factor for Barrett's oesophagus (BO). The role of other potential risk factors for the development of BO in patients with gastro-oesophageal reflux symptoms is controversial.

Aims: To perform a systematic review and meta-analysis examining this issue.

Methods: Medline, Embase, and Embase Classic were searched (until December 2020) to identify cross-sectional studies reporting prevalence of BO based on presence of one or more proposed risk factors in individuals with gastro-oesophageal reflux symptoms. Prevalence of BO was compared according to presence or absence of each risk factor in individuals with gastro-oesophageal reflux symptoms using an odds ratio (OR), with a 95% confidence interval (CI).

Results: Of 7164 citations evaluated, 13 studies reported prevalence of BO in 11,856 subjects. Pooled prevalence of histologically-confirmed BO in individuals with gastro-oesophageal reflux symptoms in all studies was 7.0% (95% CI: 4.8% to 9.6%). Prevalence was significantly higher in subjects with hiatal hernia (OR 2.74; 95% CI 1.58 to 4.75) and in those who drank alcohol (OR 1.51; 95% CI 1.17 to 1.95). Other features including non-steroidal anti-inflammatory drugs and/or aspirin use (OR 1.19; 95% CI 1.00 to 1.42), smoking (OR 1.14; 95% CI 0.96 to 1.35), or obesity (OR 1.10; 95% CI 0.92 to 1.33) were not significantly associated with BO.

Conclusions: The prevalence of BO in individuals with gastro-oesophageal reflux symptoms was significantly higher in those who drank alcohol, although this association was modest. The strongest association found was between hiatal hernia and BO. Most potential risk factors assessed in this study did not appear to be associated with presence of BO amongst

individuals with gastro-oesophageal symptoms, questioning whether they are directly involved in its development.

INTRODUCTION

Gastro-oesophageal reflux symptoms are common in the community, affecting up to 15% of the general population, with striking variations depending on geographical region.[1] Other than the considerable impact of reflux symptoms on the quality of life of individuals who experience them,[2] the presence of chronic symptoms can lead to the development of Barrett's oesophagus (BO) and oesophageal adenocarcinoma.[3] Indeed, the presence of gastro-oesophageal reflux is one of the most frequent indications for endoscopic examination of the upper gastrointestinal tract, primarily to exclude the presence of associated lesions, such as erosive esophagitis or BO. However, only 3% to 14% of individuals who undergo endoscopy due to gastro-oesophageal reflux symptoms are found to have histologically-confirmed BO, with a significantly higher prevalence in men.[4]

Several risk factors for gastro-oesophageal reflux symptoms have been reported, including age ≥50 years, tobacco smoking, non-steroidal anti-inflammatory drug (NSAID) and/or aspirin use, and obesity, although many of these associations are modest.[1] However, the association between BO and such risk factors is less clear, and their role in the development of BO is controversial, with conflicting evidence from existing studies.[5-8] In addition, these risk factors might represent confounders associated with increased gastro-oesophageal reflux, rather than being independently associated with the development of BO.

Several case-control studies and meta-analyses have evaluated the role of risk factors in the development of BO, but these have been conducted mainly in healthy individuals in the general population, so the role of these risk factors in individuals with gastro-oesophageal reflux symptoms is uncertain.[5-7,9] Systematic analysis of studies that report these types of data is important to allow physicians consulting with patients with gastro-oesophageal reflux symptoms to provide more precise estimates of the impact of potential risk factors for BO, as well as to identify areas where further research is needed. We therefore conducted a

systematic review and meta-analysis examining the association between proposed risk factors and presence of BO, to evaluate their impact in patient with gastro-oesophageal reflux symptoms.

METHODS

Search Strategy and Selection Criteria

A literature search was performed using EMBASE CLASSIC and EMBASE (1947 to December 2020), and MEDLINE (1948 to December 2020) to identify cross-sectional studies published in full. These were required to recruit a cohort of ≥100 consecutive adult participants undergoing upper gastrointestinal endoscopy for typical gastro-oesophageal reflux symptoms (heartburn and/or regurgitation), and to report the prevalence of BO. They also had to report the number of subjects with BO according to one or more of age group, NSAID and/or aspirin use, presence of hiatal hernia, BMI, smoking habit, and alcohol consumption, in order to examine the effect of these factors on the prevalence of BO in individuals with gastro-oesophageal reflux symptoms. Definitions of gastro-oesophageal reflux symptoms included heartburn and/or regurgitation of any severity, or symptoms felt to be compatible with gastro-oesophageal reflux as diagnosed according to a questionnaire or following assessment by a clinician. Studies conducted among convenience samples, such as veterans, university students, or employees at an institution were ineligible. Studies where data collection was retrospective were also excluded. Detailed eligibility criteria for study inclusion, which were defined *a priori*, are provided in Box 1.

Studies were identified using the following terms: *heartburn, acid regurgitation*, *GERD, GORD*, *gastroesophageal reflux disease, gastroesophageal reflux, esophageal reflux* (both as a medical subject heading (MeSH) and free text terms), or *upper gastrointestinal symptoms* (as free text terms). We combined these using the set operator AND with studies identified with the following (both as MeSH and free text terms): *esophageal neoplasm, esophageal adenocarcinoma, Barrett esophagus, dysplasia, intestinal metaplasia, NERD, non-erosive reflux disease, ERD,* or *erosive esophagitis.* These terms were also combined using the set operator AND with the following: *NSAID, nonsteroidal anti-inflammatory*

drugs, aspirin, hiatal hernia, hiatus hernia, obesity, body mass index, BMI, smoking, alcohol drinking, or *age groups*.

Two investigators screened the resulting abstracts independently for potential suitability, and evaluated those that appeared relevant in more detail. There were no language restrictions; foreign language articles were translated where required. A recursive search was conducted using the bibliographies of all eligible studies. Where there appeared to be multiple studies from the same population, the most recent publication was included. Eligibility assessment was performed independently by two investigators, using pre-designed eligibility forms. The JBI Prevalence Critical Appraisal Tool was used to assess the quality of included studies (Supplementary material).[10] All disagreements were resolved by consensus. This systematic review was conducted according to the MOOSE statement.[11]

Data Analysis

Data were extracted independently by two investigators onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA), with discrepancies resolved by consensus. The following data were extracted: year(s) the study was conducted, country and geographical region, study setting, method of symptom data collection (postal questionnaire, interview-administered questionnaire, self-completed questionnaire, telephone interview, face-to-face interview), frequency and 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 a histologically-confirmed diagnosis of BO. We also extracted the number of subjects with BO according to age group, NSAID and/or aspirin use, presence of hiatal hernia, BMI, smoking habit, and alcohol consumption, all defined at the time of the upper endoscopy, in order to examine the effect of these factors on the prevalence of BO in subjects with gastro-

oesophageal reflux symptoms. We combined the proportion of individuals with BO from each study to give a pooled prevalence for all studies. The pooled prevalence of BO was also reported according to the presence or absence of each risk factor evaluated.

The prevalence of BO in patients with gastro-oesophageal reflux symptoms was compared according to age group, NSAID and/or aspirin use, presence of hiatal hernia, BMI, smoking habit, and alcohol consumption, using an unadjusted odds ratio (OR), with a 95% confidence interval (CI), using the OR command in StatsDirect. 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 used to define statistically significant heterogeneity.[12] Data were pooled using a random effects model, to give a more conservative estimate of the prevalence of BO and the odds of BO in these various groups. StatsDirect version 3.2.10 (StatsDirect Ltd, Sale, Cheshire, England) was used to generate Forest plots of pooled ORs with 95% CIs. We planned to assess for evidence of publication bias by applying Egger's test to funnel plots of ORs, where a sufficient number of studies (≥10) were available.[13]

RESULTS

The search strategy identified 7164 citations. From these, 92 articles were identified that appeared to be relevant to the study question (Figure 1). There were 13 articles that fulfilled the eligibility criteria, reporting the prevalence of histologically-confirmed BO in individuals with gastro-oesophageal reflux symptoms according to presence or absence of at least one of the proposed risk factors of interest.[14-26] Agreement between investigators for assessment of study eligibility was excellent (κ statistic=0.98). All but one of the articles were published in English.[16] Detailed characteristics of all included studies are provided in Table 1. Quality of included studies is provided in Supplementary Table 1.

The 13 included studies recruited 11,856 subjects and were geographically diverse, with three from Europe,[17,19,20] three from North America,[14,15,18] three from the Middle east,[23,25,26] two from Asia,[22,24] and one each from Africa,[21] and South America.[16] When pooling data from the 13 studies, the prevalence of histologically-confirmed BO in individuals with gastro-oesophageal reflux was 7.0% (95% CI: 4.8% to 9.6%) (Supplementary Figure 1), with statistically significant heterogeneity between studies (I^2 = 95.1%, P < 0.001).

Prevalence of Barrett's Oesophagus in Individuals with Gastro-oesophageal Reflux Symptoms According to Age

Three studies [14,20,23] reported the prevalence of BO in individuals with gastro-oesophageal reflux symptoms according to age. In one study age was dichotomized into subjects aged <50 or ≥50 years,[14] in one study <55 or ≥55 years,[20] and in one study <45 or ≥45 years.[23] When data were pooled the prevalence of BO was higher in subjects in the older age groups compared with the younger (11.3% (95% CI 1.9% to 27.0%) versus 6.6% (95% CI 0.2% to 21.3%)). The OR for BO in individuals with gastro-oesophageal reflux symptoms

in those in the older age compared with the younger groups was 2.12 (95% CI 0.65 to 6.89), with significant heterogeneity between studies (I^2 = 78.8%, P = 0.01).

Prevalence of Barrett's Oesophagus in Individuals with Gastro-oesophageal Reflux Symptoms According to NSAID and/or Aspirin Use

There were three studies reporting prevalence of BO in individuals with gastro-oesophageal reflux symptoms according to NSAID and/or aspirin use or non-use.[17,20,22] Overall, the prevalence of BO among NSAID and/or aspirin users was not significantly higher (5.7%; 95% CI 0.5% to 16.0%) than among non-users (4.9%; 95% CI 0.7% to 12.8%), with an OR of 1.19 (95% CI 1.00 to 1.42), and no heterogeneity between studies (I^2 = 0%, P = 0.68).

Prevalence of Barrett's Oesophagus in Individuals with Gastro-oesophageal Reflux Symptoms According to Presence of Hiatal hernia

The prevalence of BO in individuals with gastro-oesophageal reflux symptoms and hiatal hernia on endoscopy was reported by 10 studies.[16,18-26] When pooling the data from these studies, hiatal hernia was present in 33.6% (95% CI 22.4% to 45.8%) of individuals with gastro-oesophageal reflux symptoms. Overall, the pooled prevalence of BO was significantly higher in subjects with a hiatal hernia (9.6%; 95% CI 6.1% to 13.8%), compared with those without (4.1%; 95% CI 2.6% to 6.1%). The OR in individuals with hiatal hernia, compared with those without, was 2.74 (95% CI 1.58 to 4.75) (Figure 2), with significant

heterogeneity between studies (I^2 = 74.3%, P < 0.001), and evidence of funnel plot asymmetry (Egger test, P = 0.026).

Prevalence of Barrett's Oesophagus in Individuals with Gastro-oesophageal Reflux Symptoms According to BMI

There were five studies that reported prevalence of gastro-oesophageal reflux symptoms according to presence or absence of obesity.[15,17,20,23,25] Obesity was defined as a BMI ≥30kg/m^2 in three studies,[17,20,25] a BMI of ≥25kg/m^2 in one study,[23] and >27.3kg/m^2 in females and >27.8kg/m^2 in males in one study.[15] The pooled prevalence was identical in obese compared with non-obese subjects (6.4% (95% CI 2.7% to 11.5%) versus 6.4% (95% CI 2.7% to 11.6%)). The OR in obese subjects, compared with non-obese subjects, was 1.08 (95% CI 0.91 to 1.30), with no heterogeneity between studies (I^2 = 0%, P = 0.72). Including only the three studies that defined obesity as a BMI ≥30kg/m^2, the pooled prevalence was again similar in obese compared with non-obese individuals (5.8% (95% CI 1.1% to 13.7%) versus 5.3% (95% CI 1.1% to 12.7%), OR = 1.10; 95% CI 0.92 to 1.33, I^2 = 0%, P = 0.46).

Prevalence of Barrett's Oesophagus in Individuals with Gastro-oesophageal Reflux Symptoms According to Smoking Status

There were 11 studies [15-25] that reported the prevalence of BO in individuals with gastro-oesophageal reflux symptoms according to smoking status. The pooled prevalence of BO was higher in current smokers compared with non-smokers (7.7% (95% CI 5.7% to 9.9%) versus 6.0% (95% CI 3.8% to 8.7%)). The OR in those who smoked currently compared with those who did not was 1.14 (95% CI 0.96 to 1.35) (Supplementary Figure 2), with low heterogeneity between studies (I^2 = 3.9%, P = 0.41), and no evidence of funnel plot asymmetry (Egger test, P = 0.37).

Prevalence of Barrett's Oesophagus in Individuals with Gastro-oesophageal Reflux Symptoms According to Alcohol Use

Nine studies [16,17,19-25] reported the prevalence of BO in individuals with gastro-oesophageal reflux symptoms according to whether or not they drank alcohol. The pooled prevalence of BO was significantly higher in those who drank alcohol compared with non-drinkers (8.3% (95% CI 5.2% to 12.2%) versus 4.9% (95% CI 3.1% to 7.2%)). The OR for BO in those who drank alcohol compared with those who did not was 1.51 (95% CI 1.17 to 1.95) (Supplementary Figure 3), with low heterogeneity between studies (I^2 = 13.2%, P = 0.32).

DISCUSSION

This is the first systematic review and meta-analysis, to our knowledge, to evaluate the role of potential risk factors for BO in individuals with gastro-oesophageal reflux symptoms. We assembled data from 13 cross-sectional surveys that reported the prevalence of histologically-confirmed BO at upper gastrointestinal endoscopy in individuals with gastro-oesophageal reflux symptoms, according to several proposed risk factors. Although prevalence varied according to geographical location of the population under study, the overall prevalence of histologically-confirmed BO in individuals with gastro-oesophageal reflux symptoms was 7.0%, in line with our previous data.[4] The odds of BO were almost three-fold higher in people with hiatal hernia, compared with those without, suggesting that the presence of hiatal hernia might contribute to the development of BO via increased oesophageal exposure to gastric contents. This appeared to be the strongest potential risk factor for presence of BO in people with gastro-oesophageal reflux symptoms. The pooled prevalence was also modestly, but significantly, higher in those who drank alcohol. Other demographic features including presence of NSAID and/or aspirin use, smoking status, older age, or obesity did not show a significant association with BO among individuals with gastro-oesophageal reflux symptoms.

The literature search we used was exhaustive and contemporaneous to maximize the likelihood of identifying all relevant articles, and we translated foreign language papers where required. The judging of study eligibility and data extraction were carried out by two investigators independently, with discrepancies resolved by consensus. The use of a random effects model to pool data provided a more conservative estimate of prevalence of BO, and publication bias was assessed using funnel plots, where sufficient studies existed. Finally, we excluded studies conducted among convenience samples, in order to minimize the likelihood

of overestimating the prevalence of BO or the effect of these proposed risk factors in patients with gastro-oesophageal reflux symptoms.

Limitations arise from the available studies and the reporting of data within them, including the variability in methods and criteria used to define the presence of gastro-oesophageal reflux symptoms. The definition of gastro-oesophageal reflux symptoms varied between individual studies, according to frequency and duration of symptoms. In order to reduce variability in the diagnoses across studies, and since it is not clear whether cardia-type mucosa in the oesophagus has the same malignant predisposition,[27] we only included studies that considered specialized intestinal metaplasia (intestinal metaplasia with goblet cells) for a definitive histological diagnosis of BO in our analysis. There was significant heterogeneity between studies in some of our analyses. The reasons for this heterogeneity are speculative, and may include differences in the criteria used to define gastro-oesophageal reflux symptoms or to classify patients according to the proposed risk factors, histological sampling protocols, or other demographic or geographical differences between study populations, including ethnicity, which it was not possible to examine using the available data. Another limitation of the present meta-analysis is that the association between plausible risk factors and the occurrence of BO was assessed separately for each independent variable, thus yielding unadjusted ORs. Therefore, our analysis should be considered as exploratory rather than confirmatory. Nevertheless, the large number of included patients and the biological plausibility for the studied factors support the validity of our estimates. We were also unable to examine the cumulative effect of the presence of more than one of these risk factors, due to study reporting, nor were we able to assess causality, as all studies were cross-sectional in design.

There have been previous systematic reviews examining the role of specific factors associated with BO. However, most of the meta-analyses focused on a single issue,

evaluating its role in the general population, rather than in individuals with gastro-oesophageal reflux symptoms, and reporting conflicting results. For instance, tobacco smoking has shown a positive dose-dependent association with BO in some studies, and a meta-analysis demonstrated an increased risk of BO in smokers compared with non-smokers.[5,28] Other studies have not confirmed this. In particular, one meta-analysis showed that having ever smoked was associated with an increased risk of BO compared with non-GORD controls and population-based controls, but not GORD controls.[29] Similarly, data on the association between alcohol consumption and BO are heterogeneous. In one study, drinking alcohol was positively associated with an increased prevalence of BO,[30] but another study demonstrated that alcohol consumption was not associated with BO and interestingly, among alcohol types, drinking wine was associated with a moderately reduced odds of BO.[6]Stronger evidence is available for hiatal hernia. A prior meta-analysis showed a significant association between presence of a hiatal hernia and long segment BO, with a 12-fold higher odds.[7] This association remained significant after adjusting for presence of GORD.[7] Recently, another meta-analysis demonstrated an additive effect, with a linear incremental increase in prevalence of BO associated with the number of risk factors.[9]

Obese patients have a higher prevalence of GORD.[31] However, whether obesity has a direct effect on development of BO is controversial.[32] One meta-analysis reported that central adiposity appeared to be more strongly related to BO than overall obesity; the association persisted after adjusting for GORD symptoms.[33] Another study reported an association between BO and increased abdominal girth, although adjustment for GORD attenuated this.[34] Although the use of NSAIDs and/or aspirin has been associated with a reduced risk of oesophageal adenocarcinoma in BO,[35] whether this protects against development of BO is unclear. A pooled analysis of case-control studies from the BEACON Consortium found no evidence for an inverse association between weekly use of NSAIDs and the risk of BO.[36]

Evidence therefore suggests that NSAIDs and/or aspirin reduce the likelihood of neoplastic progression, rather than the development of BO *per se*.

The findings of this study have implications for both research and clinical practice. The potential risk factors for BO that we examined are established risk factors for gastro-oesophageal reflux symptoms,[1] which is universally recognized as the major risk factor for the development of BO.[9,37] However, based on our results, many of the associations between the risk factors assessed in this study and presence of BO were weak or non-significant among individuals with gastro-oesophageal reflux symptoms. Our findings therefore support the theory that some of these proposed risk factors might represent confounders, which are significantly associated with increased reflux-dependent mechanisms, rather than being directly involved in the development of BO in individuals with gastro-oesophageal reflux symptoms. In terms of future epidemiological studies on BO, the criteria used to categorize presence or absence of potential risk factors, as well as the use of correct landmarks to define the presence and extent of BO, as well as the biopsy sampling protocols and histological criteria utilized, may affect the prevalence of BO in observational studies. Indeed, although the use of standardized endoscopic classifications and validated biopsy protocols for BO, such as the Prague classification[38] and the Seattle protocol,[39] are widely used, up to 35% of endoscopists use incorrect landmarks to define the extent of intestinal metaplasia.[40]

In conclusion, this systematic review and meta-analysis has demonstrated that the associations between most of the risk factors assessed in this study and the presence of BO in patients with gastro-oesophageal reflux symptoms are weak. The strongest association found was between presence of hiatal hernia and BO, with an almost three-fold increase in odds, suggesting that in patients with gastro-oesophageal reflux symptoms and hiatal hernia there may be a role for more frequent endoscopic surveillance, or even surgical repair to prevent development of BO. In terms of many of the modifiable lifestyle factors we studied, only

drinking alcohol was significantly associated with BO, although the association between tobacco smoking and BO was almost significant. Finally, elucidating a direct involvement or a cumulative effect of potential risk factors in its development, could allow the prediction of patients with gastro-oesophageal reflux symptoms who might be at higher risk for the development of BO.

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- Authors contributions: LHE, RH, RMZ, FB and ACF conceived the study. LHE, AT and GGC collected all data. LHE and NEB analysed and interpreted the data. LHE, AT, RH and ACF drafted the manuscript. All authors commented on drafts of the paper.

- All authors have approved the final draft of the manuscript.

- Dr. Leonardo Henry Eusebi is the guarantor of the article.

DECLARATION OF INTERESTS

The Authors declare no competing interests.

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ETHICS COMMITTEE APPROVAL

Not required.

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Box 1. Eligibility Criteria

- Cross-sectional surveys.
- Recruited adults (aged ≥16 years).
- Recruited participants with gastro-esophageal reflux symptoms (according to a questionnaire or specific diagnostic criteria†) undergoing endoscopic examination.
- Reported prevalence of histologically-confirmed BO, defined as presence of specialized intestinal metaplasia on biopsies obtained from columnar-lined esophagus at endoscopy, according to one or more of age group, NSAID and/or aspirin use, presence of hiatal hernia, BMI, or tobacco and alcohol consumption.
- Sample size of ≥100 participants.

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

Table 1. Characteristics of Included Eligible Studies.

Author	Country	Diagnosis of gastro-oesophageal symptoms	Sample size	Definition of BO	Number with histologically diagnosed BO (%)	Risk factors	Number with risk factor (BO/cases)	Number without risk factor (BO/cases)
Gerson 2001 [14]	US	Self-completed questionnaire	517	Specialised intestinal metaplasia on biopsy	99 (19.1)	Age	54/288	42/229
Romero 2002 [15]	US	Self-completed questionnaire	200	Specialised intestinal metaplasia on biopsy	18 (9.0)	BMI Smoking	8/126 6/104	5/74 7/96
Caum 20003 [16]	Brazil	Interview-administered questionnaire	402	Specialised intestinal metaplasia on biopsy	15 (3.7)	HH smoking alcohol	12/244 2/77 11/201	3/158 13/325 4/201
Kulig 2004 [17]	Germany, Austria, Switzerland	Interview-administered questionnaire	6215	Specialised intestinal metaplasia on biopsy	702 (11.3)	NSAIDs/aspirin BMI Smoking Alcohol	204/1616 154/1250 161/1429 463/3853	498/4599 549/4965 541/4786 239/2362
Westhoff 2005 [18]	US	Self-completed questionnaire	378	Specialised intestinal metaplasia on biopsy	50 (13.2)	HH Smoking	31/174 18/121	19/204 32/257

Koek 2008 [19]	Belgium	Self-completed questionnaire	422	Specialised intestinal metaplasia on biopsy	30 (7.1)	HH Smoking Alcohol	14/155 9/106 14/124	16/267 21/316 16/298
Zagari 2008 [20]	Italy	Self-completed questionnaire	458	Specialised intestinal metaplasia on biopsy	7 (1.5)	Age NSAIDs/aspirin HH BMI Smoking Alcohol	6/267 1/38 7/230 2/99 2/89 6/278	1/191 6/420 0/228 5/359 5/369 1/180
Fouad 2009 [21]	Egypt	Self-completed questionnaire	1000	Specialised intestinal metaplasia on biopsy	73 (7.3)	HH Smoking Alcohol	29/418 45/508 6/60	44/582 28/492 67/938
Kuo 2010 [22]	Taiwan	Self-completed questionnaire	344	Specialised intestinal metaplasia on biopsy	13 (3.8)	NSAIDs/aspirin HH Smoking Alcohol	0/24 7/38 2/70 1/10	13/320 6/306 11/274 12/334

Mathew 2011 [23]	India	Clinical assessment	278	Specialised intestinal metaplasia on biopsy	25 (9.0)	Age HH BMI Smoking Alcohol	16/96 8/25 6/79 7/69 5/33	9/182 17/253 19/199 18/209 20/245
Caiqiao 2012 [24]	China	Interview-administered questionnaire	528	Specialised intestinal metaplasia on biopsy	32 (6.1)	HH Smoking Alcohol	10/50 23/261 20/230	22/478 9/267 12/298
Sharifi 2014 [25]	Iran	Clinical assessment	736	Specialised intestinal metaplasia on biopsy	34 (4.6)	HH BMI Smoking Alcohol	14/281 11/299 10/205 3/69	20/455 22/432 24/531 31/670
Wani 2014 [26]	India	Clinical assessment	378	Specialised intestinal metaplasia on biopsy	9 (2.4)	HH	7/154	2/224

Abbreviations

BO: Barrett's oesophagus
NSAIDs: non-steroidal anti-inflammatory drugs
HH: hiatal hernia
BMI: body mass index

FIGURE LEGENDS

Figure 1: Flow Diagram of Studies Identified in the Systematic Review.

Figure 2: : Odds Ratio for Barrett's Oesophagus in Individuals with Gastro-oesophageal Reflux Symptoms with Hiatal Hernia Versus Those Without.