

**Title**

Tobacco smoking, alcohol consumption and gastro-oesophageal reflux disease

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**Abstract**

Gastro-oesophageal reflux disease (GORD) develops when reflux of gastric content causes troublesome symptoms or complications. The main symptoms are heartburn and acid regurgitation and complications include oesophagitis, strictures, Barrett's oesophagus and oesophageal adenocarcinoma. In addition to hereditary influence, GORD is associated with lifestyle factors, mainly obesity. Tobacco smoking is regarded as an aetiological factor of GORD, while alcohol consumption is considered a triggering factor of reflux episodes and not a causal factor. Yet, both tobacco smoking and alcohol consumption can reduce the lower oesophageal sphincter pressure, facilitating reflux. In addition, tobacco smoking reduces the production of saliva rich in bicarbonate, which is important for buffering and clearance of acid in the oesophagus. Alcohol also has a direct noxious effect on the oesophageal mucosa, which predisposes to acidic injury. Tobacco smoking cessation reduces the risk of GORD symptoms and avoidance of alcohol is encouraged in individuals where alcohol consumption triggers reflux.

**Keywords**

Gastroesophageal Reflux; Ethanol; Tobacco; Smoking; Causality; Disease Management

## **A. Introduction**

Gastro-oesophageal reflux disease (GORD) is defined as a condition which develops when reflux of gastric content causes troublesome symptoms or complications [1]. The main symptoms are heartburn (a burning sensation behind the breastbone) and acid regurgitation (a sour taste in the mouth or throat) [2]. These symptoms are experienced occasionally by most people in the general population without being regarded as troublesome, and throughout the population there is a continuum of frequency and severity of reflux symptoms. Mild symptoms occurring two or more days a week or moderate to severe symptoms occurring more than one day a week are often considered troublesome and usually affect the health related quality of life [3, 4]. In epidemiological research, GORD is defined as at least weekly heartburn or regurgitation [5].

GORD is highly prevalent in most parts of the world. In Europe, America and Australia the prevalence is between 9% and 28%, while in East Asia the prevalence is lower, between 3% and 8% [6]. The prevalence is higher in more recent studies and seems to be increasing over time in the same population [7]. The incidence of GORD is about 5 per 1000 person-years [6].

Complications of GORD include mucosal erosions (oesophagitis), peptic strictures, intestinal metaplasia (Barrett's oesophagus) and oesophageal adenocarcinoma. In addition, several extra-oesophageal manifestations might be associated with GORD, e.g. chronic cough, laryngitis, asthma, pneumonia and dental erosions. These manifestations are believed to be due to laryngopharyngeal reflux and micro aspirations to the lungs or due to reflexes mediated by the vagal nerves [8]. However, the extra-oesophageal manifestations are usually multifactorial and GORD is rarely the sole cause [1].

In clinical practice, the diagnosis of GORD is typically based on cardinal symptoms of heartburn or regurgitation and symptom relief after a short course of acid-inhibiting medical treatment, usually a proton pump inhibitor (PPI) [9]. If the symptoms do not resolve, the patient may be referred to an upper gastrointestinal endoscopy where oesophagitis, peptic strictures and

Barrett's oesophagus are diagnostic [10]. However, these complications are not sensitive markers of GORD. In a Swedish endoscopy survey, oesophagitis was present only in 29% of participants with weekly heartburn or regurgitation [11]. If the endoscopy is not diagnostic, a 24 hour oesophageal pH measurement might reveal pathological acidic reflux (fraction time with oesophageal pH <4) [12]. The pH measurement can also be combined with an impedance measurement to detect weakly acidic or non-acidic reflux, the latter typically refractory to acid-inhibiting medical treatment [13].

### **A. Anatomy and physiology**

The anatomy and physiology of the gastro-oesophageal junction is of great importance in GORD. The lower oesophageal sphincter (LOS), the narrow angle where the oesophagus enters the stomach (the angle of His) and the tight opening (hiatus) of the crural diaphragm where the oesophagus enters the abdomen together create an anti-reflux barrier [14]. When reflux appears the refluxed material is cleared from the oesophagus by gravity and peristaltic movements [15] and residual acid is neutralised by swallowed saliva rich in bicarbonate [16]. In addition, tight junctions in the oesophageal epithelia and the lipid-rich matrix in the intercellular spaces protect the mucosa from acidic damage and bicarbonate in the extracellular space buffers acid that reaches deeper than the mucosal surface [17, 18].

### **A. Pathophysiology**

A sliding hiatal hernia is an anatomical disruption of the anti-reflux barrier where a portion of the proximal stomach is located in the thoracic cavity. Such herniation counteracts the flap valve mechanism created by the angle of His [19]. In addition, the hernia impairs clearance of acid from the oesophagus by trapping acid in the hernia [20, 21]. A large hernia also impairs the pinchcock-like action of the diaphragm on the oesophagus [22].

The most common mechanism of reflux is transient lower oesophageal sphincter relaxations (TLOSRS) [15, 23]. TLOSRS are relaxations of the LOS and the crural diaphragm not triggered by swallowing [24], which is a physiological mechanism that allows belching [25, 26]. In GORD patients, there is an increased pressure gradient over the gastro-oesophageal junction and increased compliance of the junction which facilitates reflux when TLOSRS appear [27, 28]. In some GORD patients the LOS resting pressure is hypotensive [29], which allows reflux to occur more easily when the LOS pressure is overcome by an abrupt increase in the intra-abdominal pressure, i.e. strain-induced reflux [23, 30].

#### B. Tobacco smoking

Tobacco smoking can induce gastro-oesophageal reflux by reducing the LOS resting pressure, as shown by several studies from the 1970s [31-33]. In a study of six male healthy volunteers without GORD, inhalation of cigarette smoking decreased the LOS pressure 37% within two to three minutes, while puffing an unlit cigarette did not induce any change in the LOS pressure [31]. The pressure remained low until smoking was stopped and then the pressure returned towards normal. In a study evaluating 25 daily smokers with heartburn, cigarette smoking caused a fall in the LOS pressure with 41% within one to four minutes [32]. The pressure returned to baseline within three to eight minutes after having stopped smoking and puffing an unlit cigarette did not change the LOS pressure. In this study, pH measurements also showed increased reflux during and after tobacco smoking. In a study of 10 asymptomatic individuals and 10 symptomatic GORD patients, the LOS pressure was not significantly different at baseline, but was reduced by 19% and 21%, respectively, during cigarette smoking [33]. In a study of nine smokers without GORD and nine smokers with GORD, the majority of reflux episodes occurred during coughing and deep inspiration, associated with abrupt increased intra-abdominal pressure which overcame the LOS pressure [34]. The probable mechanism of tobacco induced LOS pressure reduction is blocking of cholinergic receptors by nicotine and subsequent relaxation of the circular LOS muscle fibres [35, 36].

Tobacco smoking is also associated with prolonged acid clearance time, probably due to reduced salivary secretion rate and bicarbonate concentration [37, 38]. In a study of eight non-smokers and 16 daily cigarette smokers without GORD, smoking resulted in an immediate prolongation of the acid clearance time and reduced salivary secretion rate [37]. Moreover, the acid clearance time was prolonged and the salivary secretion rate was lower among smokers who refrained from smoking during the study compared to non-smokers, suggesting a long-lasting negative effect of tobacco smoking. There was also a parallel, but less pronounced, reduction in the bicarbonate concentration among smokers. The reduced acid clearance time is most likely the result of reduced salivary secretion rate. In another study examining 11 daily smokers without GORD symptoms, salivary bicarbonate secretion increased following tobacco smoking cessation, suggesting a benefit in GORD patients [38].

#### B. Alcohol consumption

Similar to tobacco smoking, alcohol consumption might also reduce the LOS resting pressure. In a study of 20 healthy volunteers without GORD, white wine (8% alcohol) reduced the LOS resting pressure, but not red wine (12% alcohol), even with a higher alcoholic percentage in the red wine consumed [39]. There was no difference in the LOS resting pressure between red wine and tap-water. Consumption of white wine was also followed by increased fraction time with oesophageal pH <4. Red wine also induced GORD symptoms and reflux episodes, but not a pathological fraction time of pH <4 in the oesophagus. In a study of 24 healthy volunteers, beer (7% alcohol) also increased the median fraction time of pH <4 compared to water, but the values were still within the normal range [40]. In this study, an ethanol solution of 7.5% was also compared to tap-water, without showing any difference in the fraction time of pH <4. These findings suggest that other ingredients in wine and beer rather than alcohol promotes reflux among consumers of these alcoholic-containing beverages.

In a study of 12 healthy volunteers without GORD, pH measurements showed significantly increased reflux after ingestion of 180 ml vodka compared with 180 ml water [41]. In a study of 17

healthy volunteers without GORD, ingestion of 120 ml whiskey (40% alcohol) induced supine nightly reflux events assessed by pH measurements that were not apparent during the control night after a placebo drink [42]. A study of acute alcohol intoxication (300 ml whiskey with 43% alcohol during one hour) in twelve volunteers without GORD showed reduced incidence of primary peristalsis in the distal oesophagus, but the oesophageal motor function was normal eight hours after the intoxication [43]. One of the volunteers experienced transient heartburn after the ingestion. Deterioration of oesophageal peristalsis can be found in patients with alcoholic neuropathy [44]. However, this deterioration could have multiple causes related to alcoholism.

Alcohol might also have direct effects on the oesophageal mucosa. In a study of rabbits, an oesophageal mucosal exposure to 10% ethanol had a direct noxious effect on the epithelium, which predisposed to acidic injury [45].

### **A. Aetiology**

Large population-based cohort studies provide the best evidence of the aetiological factors of GORD. The population-based cohort design is less prone to selection bias compared to e.g. hospital-based studies or case-control studies. Large studies also provide more precise estimates of associations with sufficient statistical power to detect weaker associations and to conduct robust sub-analyses. In recent population-based studies, GORD is typically defined as at least weekly symptoms of heartburn or regurgitation.

The aetiology of GORD includes both genetic and lifestyle-related factors. The risk of GORD is increased within families [46] and there is a higher concordance in the prevalence of GORD in monozygotic over dizygotic twin pairs, suggesting a 23% to 39% genetic influence [47, 48]. Obesity is the strongest lifestyle-related risk factor of GORD, especially visceral obesity [49-52]. High dietary

fibre intake and moderate physical exercise, on the other hand, seem to protect against the development of GORD [53].

#### B. Tobacco smoking

In most studies, tobacco smoking has been associated with an increased risk of developing GORD (Table) [46, 47, 52-60]. The association between tobacco smoking and GORD is seemingly of weak or moderate strength with most reported odds ratios (ORs) below 2. In the largest study on the topic, a nested case-cohort study from Norway with 43,363 participants, the adjusted ORs for GORD were 1.7 (95% CI 1.5 to 1.9) among daily smokers with more than 20 years of smoking history and 1.6 (95% CI 1.3 to 2.0) among smokers with a lifetime number of more than 200,000 cigarettes [53]. A small case-control study from Albania with 845 participants reported very high risk estimates for GORD, with adjusted OR of 9.8 (95% CI 4.2 to 22.7) among former smokers and 29.3 (95% CI 13.9 to 61.2) among current smokers [60]. Both increased duration and amount of tobacco smoking are dose-dependently associated with an increased risk of GORD [53, 54, 56].

In a Norwegian cohort study with 14,916 participants, the adjusted OR of new-onset GORD was 1.4 (95% CI 1.1 to 1.8) among previous smokers and 1.3 (95% CI 1.0 to 1.7) among current smokers [52]. In this study, also individuals who quit smoking during the study period had remaining increased risk of new-onset GORD, with adjusted of OR 1.7 (95% CI 1.3 to 2.3), but this association was explained by gain in weight upon quitting smoking. In a smaller longitudinal case-control study from the United Kingdom with 3418 participants, the risk of new-onset GORD following tobacco smoking did not reach statistical significance at the 1% level, with adjusted OR of 1.3 (99% CI 0.9 to 2.0) [61]. Several smaller studies have failed to find any association between tobacco smoking and GORD [61-64], but this could be due to limited statistical power.

#### B. Alcohol consumption



Most studies have failed to identify any aetiological association between alcohol consumption and GORD (Table) [47, 52, 53, 62-64]. Some data, however, indicate that high alcohol intake is moderately associated with GORD. In a case-control study from the United States, intake of more than seven drinks per week was associated with increased risk of GORD, with an adjusted OR of 1.9 (95% CI 1.1 to 1.3) [46]. A Japanese case-control study found that heavy drinkers (more than 38 mL/day) had an increased risk of GORD, with an adjusted OR of 1.6 (95% CI 1.1 to 2.3) [54]. A case-control study from the United Kingdom reported an association between excessive alcohol consumption (more than 30 units per week for men and more than 20 units per week for women) and GORD, with an adjusted OR of 3.0 (95% CI 1.5 to 6.1) [55]. An Albanian case-control study found that moderate to heavy alcohol intake was associated with GORD, with an adjusted OR of 1.8 (95% CI 1.1 to 3.1) [60].

However, the largest studies have not identified any association between alcohol consumption and GORD [52, 53]. In the largest study available, a nested case-cohort study from Norway with 43,363 participants, more than ten occasions with alcohol consumption during the last two weeks were not associated with any increased risk of developing GORD, adjusted OR 1.0 (95% CI 0.8 to 1.3), and there was no dose-response association with increasing consumption ( $p$  for trend 0.54) [53]. In a Swedish case-control study of 27,717 twins, increasing alcohol intake even indicated a dose-dependent decreased risk of GORD in the monozygotic co-twin control comparison among women ( $p$  for trend 0.0093), with adjusted OR of 0.31 (95% CI 0.11 to 0.84) with an alcohol intake of more than 2400 grams per month [56]. However, when the consumption of beer, wine and spirits was analysed separately, no association with GORD was evident. This, together with lack of such association among men in the same study, suggests that chance might be an explanation of the inverse association.

A prospective Norwegian cohort study with 14,916 participants found that at least weekly consumption of alcohol did not influence the risk of new-onset GORD, with an adjusted OR of 0.9

(95% CI 0.7 to 1.2) [52], and a longitudinal case-control study from the United Kingdom with 3418 participants found no increased risk of new-onset GORD, with adjusted OR of 0.6 (95% CI 0.3 to 1.0) [65].

## **A. Management**

The management of patients with GORD can be based on lifestyle modification, medical treatment, and anti-reflux surgery.

### **B. Lifestyle modification**

The best evidence of lifestyle modification in GORD is for weight loss, tobacco smoking cessation, head of bed elevation during sleep, very low-carbohydrate diet, diet rich in dietary fibres and avoiding meals before bedtime [9, 66-70]. In addition, it is recommended to avoid dietary factors whenever these are perceived as triggering factors of reflux episodes by the individual patient, i.e. coffee, alcohol, chocolate, peppermint, citrus, carbonated drinks and spicy foods.

### ***C. Tobacco smoking cessation***

In a prospective population-based cohort study from Norway including 29,610 participants, smoking cessation was associated with decreased heartburn and acid regurgitations in normal weight individuals using acid-inhibiting medical treatment, compared to participants who continued smoking daily, with an adjusted OR of 5.7 (95% CI 1.4 to 23.6) [71]. However, smoking cessation was not associated with improvement in GORD in overweight (BMI between 25.0 and 29.9) or obese (BMI above 30.0) individuals, with adjusted ORs of 1.2 (95% CI 0.6 to 2.7) and 1.3 (95% CI 0.5 to 3.2), respectively. This could be explained by the strong association between obesity and GORD, compared to the weaker association between tobacco smoking and GORD. In obese individuals, the pathophysiological mechanism driving reflux might be dictated by weight, with tobacco smoking

playing a minor or no role, while in normal weight individuals with GORD, tobacco smoking might be a more important pathophysiological factor [71].

In addition, two small studies have assessed the immediate effects of cigarette smoking cessation on pH measurements in GORD patients [72, 73]. In eight male daily smokers with GORD, abstaining from cigarette smoking for one day decreased the number of reflux episodes in the upright position, but not the total oesophageal acid exposure [72]. In another study, examining 14 daily smokers with GORD, cigarette smoking increased the fraction time of pH<4 and reduced the frequency of heartburn after abstaining for smoking for 48 hours [73].

### *C. Alcohol abstinence*

Based on the available pathophysiological and aetiological evidence, alcohol is mainly considered an instant trigger of reflux, rather than a causal risk factor of GORD, and no long-term interventional studies of alcohol abstinence in GORD exist.

In the current clinical management guidelines avoidance of alcohol use as a treatment of GORD has little or no place [9, 68-70]. However, whenever the individual patient experiences alcohol consumption as a trigger of GORD symptoms, alcohol abstinence or moderation is recommended.

### B. Medical and surgical treatment

Medical treatment of GORD mainly consists of acid-inhibiting treatment aimed at reducing the acidity of the refluxed content. With mild and infrequent reflux symptoms without any signs of complications, antacids, sucralfate or alginate are recommended. These medications are rapidly acting, but the duration of the effect is short [69]. With more severe and frequent symptoms of GORD or in individuals with oesophagitis or Barrett's oesophagus, proton pump inhibitors (PPIs) are recommended and long-term use is often needed to prevent recurrence [74] and possibly prevent adenocarcinoma [75]. In the long-term time frame (26 to 52 weeks), PPI therapy reduces the risk of

relapsing oesophagitis and controls symptoms better than H2-receptor antagonists, which in turn are better than placebo [74, 76, 77].

Medical treatment may last for an indefinite period of time with high costs for patients and society [78, 79]. In addition, long-term and potent acid inhibition with PPIs may be associated with specific adverse effects, including secondary hypergastrinaemia with rebound hypersecretion of acid upon withdrawal of PPIs [80, 81]. Moreover, hypoacidity is associated with increased risk of infections and malabsorption [82-87].

Anti-reflux surgery with fundoplication is presently mainly used for selected patients. Fundoplication repairs the reflux barrier and controls both acid and non-acid reflux, including bile salts and pancreatic juice [88], which could be beneficial for patients intolerant of PPIs or with persistent troublesome regurgitation despite PPI therapy [69]. Fundoplication is as effective as treatment with PPIs in preventing recurrence of oesophagitis and resolving of heartburn, and better in the controlling of acid regurgitation [89, 90]. On the other hand, patients who have undergone surgery have higher rates of dysphagia, bloating and flatulence [89, 90].

#### **A. Practice Points**

- Tobacco smoking cessation should be advised to all smokers with GORD.
- Avoidance or moderation of alcohol consumption should be advised to individual patients with GORD if the patient perceives alcohol consumption as a triggering factor of reflux episodes.

#### **A. Research Agenda**

- The documentation of treatment effect of tobacco smoking cessation or alcohol abstinence in GORD is sparse.
- Randomized clinical trials assessing the role of tobacco smoking cessation and alcohol consumption in the aetiology of GORD will never be performed due to the ethical problems with continued use of tobacco and alcohol in a trial.
- Large prospective population-based observational studies should be performed to assess whether tobacco smoking cessation and alcohol abstinence are associated with reduced symptoms and complications of GORD. Ideally, such studies should include endoscopic assessments and pH and impedance measurements.
- Non-randomized intervention studies should also be performed targeting alcohol and smoking behaviours as part of lifestyle modifications in patients with GORD.

#### **A. Summary**

Tobacco smoking and alcohol consumption reduces the LOS resting pressure. In addition, tobacco smoking reduces salivary bicarbonate secretion and increases acid clearance time in the oesophagus.

Alcohol has direct noxious effects on the oesophageal mucosa, predisposing for acidic injury.

Tobacco smoking is a causal aetiological factor of GORD, while alcohol consumption is a triggering factor of reflux episodes among individuals with GORD, but not a risk factor for developing GORD.

Tobacco smoking cessation may reduce GORD symptoms. However, tobacco smoking is only a weak risk factor of GORD and other lifestyle modifications, including weight loss, and medical treatment are usually of greater importance in the treatment of GORD. Whether tobacco smoking cessation prevents or improves the complications of GORD is not known. No long-term interventional studies of alcohol abstinence in GORD exist. Ideally, randomized clinical trials of tobacco smoking cessation and alcohol abstinence should be performed to answer the question of the effect on GORD, including symptoms and complications, but such trials are not feasible due to the ethical problems. Large and

prospective population-based cohort studies and non-randomized intervention studies targeting alcohol and smoking behaviours are more realistic alternatives.

**A. Conflict of Interest Statement**

None.

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**Table.** Risk of gastro-oesophageal reflux disease (GORD) with tobacco smoking and alcohol consumption

First author	Pub. year	Country	Study design	Number of participants	Response rate	Number of cases	Data	Case definition	Prevalent or incident cases	Risk of GORD with tobacco smoking	Risk of GORD with alcohol consumption	Adjustments*
Locke <sup>46</sup>	1999	USA	Population-based cross sectional case-control	1524	72%	872	Questionnaire	At least weekly heartburn or acid regurgitation during the prior year	Prevalent	Never cigarette use, OR 1.0 (reference); current cigarette use, OR 1.3 (95% CI 0.8-2.1); past cigarette use, OR 1.6 (95% CI 1.1-2.3).	Alcohol drinks per week: None, OR 1.0 (reference); 1-2, OR 1.0 (95% CI 0.6-1.6); 3-6, OR 1.3 (95% CI 0.8-2.1); 7+, OR 1.9 (95% CI 1.1-3.3).	Age, gender, psychosomatic symptom checklist score, BMI, smoking, alcohol, coffee, ASA/NSAIDs, relative and spouse history.
Mohammed <sup>47</sup>	2003	UK	Population-based cross sectional case-control twin	5032	56%	906	Questionnaire	At least weekly heartburn or acid regurgitation during the past year	Prevalent	Ever smoked, OR 1.31 (95% CI 1.10–1.54).	Excess alcohol intake (>28 units/week for men, >21 units/week for women), OR 0.99 (95% CI 0.99–1.00).	Age, smoking, alcohol, BMI, drug therapy, sex, handedness, parental family history of upper gastrointestinal disease.
Watanabe <sup>54</sup>	2003	Japan	Population-based cross sectional case-control	4188	86%	276	Questionnaire	At least twice weekly heartburn or acid regurgitation the past one year	Prevalent	Lifelong non-smokers, OR 1.00 (reference); former smokers, OR 1.32 (95% CI 0.89–1.96); current smokers, OR 1.35 (95% CI 1.01–1.82).  Pack-years of cigarette smoking: 0, OR 1.0 (reference); 0.1-20.0, OR 1.29 (95% CI 0.87-1.90); >20.1, OR 1.45 (95% CI 1.04–2.04); p for trend 0.034.	Daily alcohol drinking (mL/day): non-drinkers, OR 1.25 (95% CI 0.85–1.85); light drinkers (0–15), OR 1.00 (reference); moderate drinkers (16–37), OR 1.47 (95% CI 1.01–2.15); heavy drinkers (38–), OR 1.60 (95% CI 1.09–2.34).	Age, BMI, smoking, alcohol.

Nilsson <sup>53</sup>	2004	Norway	Population-based nested case-cohort	43363	71%	3153	Questionnaire	Severe (95% at least weekly) heartburn or acid regurgitation during the previous 12 months	Prevalent	Daily smoking (years): <1, OR 1.0 (reference); 1–5, OR 1.2 (95% CI 0.9–1.6); 6–10, OR 1.5 (95% CI 1.2–1.8); 10–20, OR 1.7 (95% CI 1.4–1.9); >20, OR 1.7 (95% CI 1.5–1.9); p for linear trend <0.0001.  Lifetime number of cigarettes smoked (thousands): <0.1, OR 1.0 (reference); 0.1–25, OR 1.1 (95% CI 0.9–1.4); >25–50, OR 1.5 (95% CI 1.3–1.8); >50–100, OR 1.6 (95% CI 1.4–1.8); >100–200, OR 1.6 (95% CI 1.4–1.9); >200, OR 1.6 (95% CI 1.3–2.0); p for linear trend <0.0001.	Occasions of spirits, wine, or beer consumption during last two weeks: None, OR 1.0 (reference); 1–4, OR 0.9 (95% CI 0.8–1.0); 5–10, OR 0.9 (95% CI 0.7–1.2); >10, OR 1.0 (95% CI 0.8–1.3); p for linear trend 0.54.	Age, sex, BMI, smoking, alcohol, coffee, asthma medication.
Nandurkar <sup>62</sup>	2004	USA	Population-based nested case-control	132	81%	16	Questionnaire	At least weekly heartburn or acid regurgitation in the past year	Prevalent	Ever smoking, OR 1.8 (95% CI 0.5–6.6).	Ever alcohol, OR 1.0 (95% CI 0.3–3.5).	Age, gender, BMI, SCL-90 somatisation score.
Mohammed <sup>55</sup>	2005	UK	Population-based cross sectional case-control	1533	41%	322	Questionnaire	At least weekly heartburn or acid regurgitation during the past year	Prevalent	Current smoking, OR 1.65 (95% CI 1.17–2.33).	Excess alcohol consumption (>30 units/week for men and >20 units/week for women), OR 2.96 (95% CI 1.45–6.06).	Log-BMI, irritable bowel syndrome, South Asian, family history of upper gastrointestinal disease, educational, alcohol, smoking, anticholinergic drugs.

Zheng <sup>56</sup>	2007	Sweden	Population-based cross sectional case-control	27717	Not stated	4083	Telephone interview	At least weekly retrosternal pain or burning with antacid relief or radiation toward the neck or regurgitation of bitter fluid	Prevalent	<p>Women - monozygotic co-twin control comparison:</p> <p>Ever smoking, 1.08 (95% CI 0.66–1.74).</p> <p>Cigarettes equivalent/day: 1–9, OR 0.82 (95% CI 0.45–1.48); 10–19, OR 1.32 (95% CI 0.71–2.44); ≥20, OR 1.10 (95% CI 0.49–2.45); p for trend 0.6390.</p> <p>Men - monozygotic co-twin control comparison:</p> <p>Ever smoking, OR 1.37 (95% CI 0.70–2.66).</p> <p>Cigarettes equivalent/day: 1–9, OR 1.21 (95% CI 0.44–3.27); 10–19, OR 1.05 (95% CI 0.47–2.37); ≥20, OR 1.82 (95% CI 0.86–3.83); p for trend 0.1034.</p>	<p>Women - monozygotic co-twin control comparison:</p> <p>Alcohol, OR 0.73 (95% CI 0.45–1.19).</p> <p>Absolute alcohol grams/month): 1–150, OR 1.13 (95% CI 0.58–2.17); 151–1200, OR 0.84 (95% CI 0.45–1.59); 1201–2400, OR 0.48 (95% CI 0.22–1.04); &gt;2400, OR 0.31 (95% CI 0.11–0.84); p for trend 0.0093.</p> <p>Men - monozygotic co-twin control comparison:</p> <p>Alcohol, OR 0.65 (95% CI 0.32–1.33).</p> <p>Absolute alcohol (grams/month): 1–150, OR 0.75 (95% CI 0.31–1.79); 151–1200, OR 0.79 (95% CI 0.34–1.83); 1201–2400, OR 0.66 (95% CI 0.26–1.64); &gt;2400, OR 0.57 (95% CI 0.24–1.32); p for trend 0.1845.</p>	Year of birth, BMI, smoking, coffee, physical activity, education.
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Zagari <sup>63</sup>	2008	Italy	Population-based cross sectional case-control	1033	67%	245	Questionnaire	At least twice weekly heartburn or acid regurgitation during the previous 12 months	Prevalent	Never smoker, RR 1.0 (reference); former smoker, RR 0.9 (95% CI 0.6-1.2); current smoker, RR 0.8 (95% CI 0.6-1.2).	Alcohol consumption: none/occasional, RR 1.0 (reference); weekly, RR 1.1 (95% CI 0.7-1.5); daily, RR 0.8 (95% CI 0.6-1.1).	Age, sex, BMI, smoking, alcohol, coffee, medication (ASA, NSAIDs, corticosteroids), history of peptic ulcer disease, helicobacter pylori infection, hiatus hernia.
Nasseri-Moghaddam <sup>57</sup>	2008	Iran	Population-based cross sectional case-control	2057	82%	374	Questionnaire	At least weekly heartburn or acid regurgitation in the past 12 months	Prevalent	Positive smoking, OR 1.83 (95% CI 1.12–2.99).		Age, gender, BMI, education, marriage, spouse and first relative GORD history, coffee, asthma, tea, NSAID.
Eslick <sup>58</sup>	2009	Australia	Population-based cross sectional case-control	672	73%	78	Questionnaire	At least weekly heartburn or acid regurgitation the past 12 months	Prevalent	Current smoker, OR 2.47 (95% CI 1.07-5.70).		Sex, age, blood pressure, diabetes, cholesterol.
Friedenberg <sup>59</sup>	2010	USA	Population-based cross sectional case-control	503	22%	129	Questionnaire	Troublesome heartburn or regurgitation ≥2 days/week or severe heartburn or regurgitation ≥1 day/week	Prevalent	Current smoking, OR 1.74 (95% CI 1.15—2.65).		Age, BMI, calcium channel blocker intake.
Pandeya <sup>64</sup>	2011	Australia	Population-based cross sectional case-control	1580	51%	174	Questionnaire	At least weekly heartburn or acid regurgitation in the past year	Prevalent	Never smoker, OR 1.0 (reference); current smoker, OR 0.83 (95% CI 0.52–1.33); ex-smoker, OR 1.30 (95% CI 0.93–1.83).	Alcohol consumption (drinks/week): Never drinkers, OR 1.00 (reference); <1, OR 1.47 (95% CI 0.78–2.78); 1–6.99, OR 1.03 (95% CI 0.61–1.74); 7–20.99, OR 1.37 (95% CI 0.79–2.38);	Age, sex, education, BMI, smoking, alcohol, ASA or NSAID use in the past 5 years, physical activity, dietary factors.

									21 or more, OR 1.33 (95% CI 0.72–2.46).			
Ford <sup>61</sup>	2013	UK	Population-based longitudinal case-control	3418	47%	253	Questionnaire	At least weekly heartburn or acid regurgitation over the preceding 6 months	Incident	Tobacco use, OR 1.33 (99% CI 0.88-2.02).	Alcohol use, OR 0.59 (99% 0.34-1.04).	Age, gender, helicobacter pylori status, marital status, tobacco, alcohol, coffee, ethnicity, social class, quality of life, irritable bowel syndrome, BMI.



Cela <sup>60</sup>	2013	Albania	Population-based cross sectional case-control	845	85%	101	Questionnaire	At least weekly heartburn or acid regurgitation during last year	Prevalent	Never smoker, OR 1.00 (reference); current smoker, OR 29.3 (95% CI 13.9–61.2); former smoker, OR 9.79 (95% CI 4.22–22.7).	Alcohol consumption: No/occasional, OR 1.00 (reference); moderate/heavy intake, OR 1.83 (95% CI 1.10–3.06).	Age, sex, socioeconomic variables, behavioural factors (smoking, alcohol, physical activity, frequency of meat and fired food consumption, BMI).
Hallan <sup>52</sup>	2015	Norway	Population-based longitudinal nested case-cohort	14916	61%	510	Questionnaire	Severe (95–98% at least weekly) heartburn or acid regurgitation during the previous 12 months	Incident	Never smokers, OR 1.00 (reference); previous smokers, OR 1.37 (95% CI 1.07–1.76); quitters, OR 1.73 (95% CI 1.31–2.27); current smokers, OR 1.29 (95% CI 1.00–1.67).	Alcohol consumption: ≤weekly, OR 1.00 (reference); >weekly, OR 0.91 (95% CI 0.70–1.19).	Age, sex, BMI change, smoking, alcohol, physical exercise, education.

\*In analyses of the risk of GORD with tobacco smoking, tobacco smoking is not included as an adjustment variable. In analyses of the risk of GORD with alcohol consumption, alcohol consumption is not included as an adjustment variable.