Beyond heartburn: a systematic review of the extra-oesophageal spectrum of reflux-induced disease

A Pali S Hungina, Anan S Raghunathb and Ingela Wiklunda


Background. Gastro-oesophageal reflux disease (GORD) is a chronic condition affecting up to one-quarter of the Western population. GORD is characterized by heartburn and acid regurgitation, but is reported to be associated with a spectrum of extra-oesophageal symptoms.

Objective. The aim of this systematic review was to critically evaluate postulated extra-oesophageal symptoms of GORD.

Methods. Extra-oesophageal symptoms were identified from population-based studies evaluating their association with GORD (either defined as heartburn and/or acid regurgitation, or diagnosed in general practice). The response of these symptoms to acid-suppressive therapy was investigated using randomized, double-blind, placebo-controlled studies. Pathogenic mechanisms were evaluated using clinical and preclinical studies.

Results. An association between GORD and symptoms or a diagnosis of chest pain/angina, cough, sinusitis and gall-bladder disease was evident from three eligible population-based studies of GORD. Randomized placebo-controlled studies (n = 20) showed that acid-suppressive therapy provides symptomatic relief of chest pain, asthma and, potentially, chronic cough and laryngitis. Mechanistic models, based on direct physical damage by refluxate or vagally mediated reflexes, support a causal role for GORD in chest pain and respiratory symptoms, but not in gall-bladder disease.

Conclusion. GORD is likely to play a causal role in chest pain and possibly asthma, chronic cough and laryngitis. Further investigation is desirable, particularly for other potential extra-oesophageal manifestations of GORD such as chronic obstructive pulmonary disease, sinusitis, bronchitis and otitis. Acid-suppressive therapy is likely to benefit patients with non-cardiac chest pain, but further placebo-controlled studies are needed for other symptoms comprising the extra-oesophageal spectrum of GORD.

Keywords. Asthma, chest pain, chronic cough, gastro-oesophageal reflux disease, laryngitis.

Introduction

Gastro-oesophageal reflux disease (GORD) is a chronic condition affecting up to one-quarter of the population in Western society. It is characterized by heartburn (a burning sensation rising from the stomach or lower chest towards the neck) and/or acid regurgitation. GORD can interfere with patients’ everyday living, work, enjoyment of social occasions and sleep and in clinical practice it may be appropriate to focus on these manifestations when diagnosing and managing the disease.

GORD has been implicated in a spectrum of extra-oesophageal symptoms. These have been investigated by a number of epidemiological and clinical studies, but the range of methodologies used hampers interpretation of their results. It is difficult to evaluate whether GORD patients are at increased risk of extra-oesophageal symptoms in studies that do not assess the prevalence of extra-oesophageal symptoms in a representative control group. Similarly, studies investigating the prevalence of reflux symptoms, endoscopic findings and abnormal oesophageal acid exposure (by 24-hour pH monitoring) in patients with extra-oesophageal symptoms in secondary care are of limited utility, as their subjects are often investigated by a gastroenterologist because they fail to respond to

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normal therapies. Unblinded or uncontrolled therapeutic trials are also difficult to interpret. There has been little critical appraisal of this area, particularly of relevance to primary care.

The aim of this systematic review was to characterize the extra-oesophageal spectrum of GORD by critically evaluating the role of GORD in a range of extra-oesophageal symptoms. The Bradford Hill criteria provided a useful framework. We first identified potential extra-oesophageal symptoms from epidemiological studies relevant to primary care, and assessed their temporal relationship with GORD. Secondly, the response of these symptoms to anti-reflux therapy was investigated. Finally, possible mechanisms to explain a causative relationship were examined.

Methods

We selected potential extra-oesophageal symptoms from epidemiological studies reporting associations with GORD in primary care, or the general population. For each extra-oesophageal symptom included in these studies, clinical trials evaluating their response to anti-reflux therapy were identified in the Medline database, the Cochrane database and the authors’ existing bibliographic databases using the search terms reflux, GORD, GERD, oesophagitis or esophagitis in the title or abstract. The studies highlighted by these searches were screened to identify randomized, double-blind, placebo-controlled trials conducted within the last 10 years (December 1994–December 2004) that reported the effect of anti-reflux treatment on postulated extra-oesophageal symptoms.

Results

Of 35 epidemiological studies identified, only three investigated the association between GORD and extra-oesophageal symptoms. The first of these was a symptom survey completed by an age- and sex-stratified population sample in the USA (n = 1511). Subjects with GORD (at least weekly heartburn and/or regurgitation) were more likely to report chest pain, but no more likely to report asthma, hoarseness, bronchitis, or a history of pneumonia than those without reflux symptoms. The second was an epidemiological study conducted in 2,209 ethnic Chinese individuals in Hong Kong. GORD (defined as heartburn and/or regurgitation over the past year) was associated with an increased risk of chest pain. The third was a longitudinal study that compared patients with a first-time GORD diagnosis during 1996 (n = 7159) identified in the UK General Practice Research Database (GPRD), with an age- and sex-matched control group without a GORD diagnosis (n = 10 000). A GORD diagnosis was associated with a significantly increased risk of chest pain, angina, cough, sinusitis and gall-bladder disease in the year after diagnosis, and non-significant increases in the risk of asthma, chronic obstructive pulmonary disease (COPD), pneumonia, laryngitis, hoarseness and otitis. General practice registers in the UK are a good means of sampling the general population, as patients need not necessarily consult to be included, and the validity of the GPRD has been verified.

The search strategy for the extra-oesophageal symptoms identified in the above epidemiological studies yielded a total of 2,429 papers: 635 for asthma, 539 for chest pain, 384 for pneumonia, 231 for chronic cough, 165 for laryngitis, 119 for hoarseness, 100 for bronchitis, 95 for angina, 72 for sinusitis, 42 for otitis, 26 for gall-bladder disease and 21 for COPD (Table 1). Of these papers, 21 reported randomized double-blind, placebo-controlled studies of the effect of anti-reflux therapy on postulated extra-oesophageal symptoms and were eligible for inclusion in this review (Table 2). These clinical studies were generally in highly selected populations of patients with gastro-oesophageal reflux (GOR) defined by abnormal oesophageal acid exposure, as assessed by 24-hour ambulatory pH monitoring, and/or endoscopic oesophagitis. For the purposes of this review, asthma and COPD are considered together, as are cough, bronchitis and pneumonia, chest pain and angina, and laryngitis and hoarseness.

Asthma and COPD

Association with GORD. In the US population-based survey, the prevalence of asthma was higher in patients classified as having GORD on the basis of weekly heartburn and/or regurgitation (11.6%) than in those without reflux symptoms in the previous year (7.9%), but the trend did not represent a significant increase in risk. Overall, 25.7% of individuals with asthma also had GORD, compared to 19.8% of the study population as a whole. The UK general practice study demonstrated a small increased risk of asthma in the year following a new diagnosis of GORD, although this relationship was of borderline significance [odds ratio (OR) 1.4; 95% confidence interval (CI) 1.0–2.1]. In this study, a GORD diagnosis did not significantly increase the subsequent risk of COPD (OR 1.1; 95% CI 0.7–1.7).

Effect of anti-reflux therapy. A number of randomized, placebo-controlled trials have generated data concerning GORD as a cause of asthma. A large parallel-group study in 207 patients with asthma and symptoms of acid reflux demonstrated that fewer patients had at least one asthma exacerbation when treated with lansoprazole than when given placebo (8 versus 22 patients, respectively; P < 0.05). A crossover study demonstrated that 27% of asthma patients (n = 15) with GOR achieved at least a 20% net improvement in pulmonary function (forced expiratory volume in 1 second; FEV1) during
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\(^{a}\) Symptom search used the search term ([reflux or GERD or GORD or esophagitis or oesophagitis] and [symptom name]).

\(^{b}\) Trials evaluating the response of one or more extra-oesophageal symptom identified (asthma, COPD, bronchitis, chest pain, angina, chronic cough, laryngitis, hoarseness, pneumonia, sinusitis, otitis and gall-bladder disease) to anti-reflux pharmacotherapy in patients with gastro-oesophageal reflux and/or oesophagitis and published as a randomized, double-blind, placebo controlled trial in English, including an abstract, between December 1994 and December 2004.

\(^{c}\) Patients with asthma and COPD.

\(^{d}\) Patients with laryngitis and hoarseness.
Omeprazole treatment, although modest improvements of up to 9% were observed during placebo treatment (no P-values available). A similar study of nine patients with asthma and GOR demonstrated that omeprazole treatment for 8 weeks generated a better peak expiratory flow rate (PEFR) and quality of life than placebo. A trend towards higher FEV1 following omeprazole therapy failed to reach significance.

Another crossover study identified a significant benefit of omeprazole treatment in 57 patients with GOR and asthma in terms of asthma symptoms at night (P < 0.05) but not during the day (P = 0.14). Increasing oesophageal acid exposure and body mass index (BMI) also predicted response to omeprazole treatment in this study. Similarly, a crossover study in which patients with documented asthma and GOR (n = 25) were randomized to receive omeprazole or placebo demonstrated an improvement in evening (but not morning) PEFR with omeprazole over placebo therapy (P < 0.05).

In contrast, a crossover study assessing 11 patients with GOR and nocturnal asthma showed that omeprazole afforded no benefit for relieving asthma symptoms or PEFR, although the dose of the proton pump inhibitor (PPI) in this case (20 mg/day) was relatively low. A parallel-group study of 36 patients with GOR, asthma, severe airway hyper-responsiveness and airway obstruction also found no benefit of omeprazole therapy in terms of pulmonary function or symptoms, but the inclusion of patients with both asthma and COPD make the findings of this study difficult to interpret.

Pathogenic mechanisms. Low pH or distension of the oesophagus can lead to bronchospasm via vagal reflexes. Alternatively, bronchospasm may be induced by the aspiration of refluxate into the respiratory tract. The aspiration of gastroesophageal refluxate may also contribute to the development of COPD in GORD patients, promoting a cycle of tissue damage and inflammation. Any of these mechanisms may be more active during sleep, as the duration and distance travelled by refluxate is likely to be promoted by recumbence. There are also plausible mechanisms by which asthma or COPD could stimulate GOR, as a result of a cough increasing the pressure gradient across the diaphragm, or the effect of asthma medications on lower oesophageal sphincter pressure and gastric acid secretion. These mechanisms gain support from studies showing an increased risk of GORD in patients with a prior diagnosis of asthma (OR 3.2; 95% CI 2.6–4.0) or COPD (OR 1.3; 95% CI 1.0–1.8).

### Table 2: Randomized, double-blind, placebo-controlled trials involving patients with gastro-oesophageal reflux and extra-oesophageal symptoms given anti-reflux therapy

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RDB = randomized double-blind; RSB = randomized single-blind; PC = placebo controlled trial; CO = crossover trial; PG = parallel-group trial.

* Number of patients enrolled in the trial.

* Number of patients available for analysis from the trial.
Summary. While GORD is not strongly associated with asthma or COPD in population-based studies, the results of randomized controlled trials tend to support a role for GORD in asthma symptoms (particularly at night). The suggestion that asthma may also cause GORD shows that this is an area deserving further investigation.

Chest pain

Association with GORD. In the US population-based survey, 37.0% of individuals with GORD reported non-cardiac chest pain (defined as chest pain in patients without a history of cardiac disease), compared to 7.9% of those with no reflux symptoms (OR 4.7; 95% CI 3.0–7.3).1 Conversely, the prevalence of GORD in individuals with non-cardiac chest pain was 33.2%, compared to 19.8% in the study population as a whole. The cross-sectional study in Hong Kong also identified GORD as a risk factor for non-cardiac chest pain (OR 3.4; 95% CI 2.6–4.3).11 The UK general practice study identified an increased risk of new-onset chest pain in the year following a new diagnosis of GORD, after adjustment for prior ischaemic heart disease (OR 2.3; 95% CI 1.8–2.8).10 GORD patients in this study were also shown to be at increased risk of angina (OR 3.2; 95% CI 2.1–4.9),10 possibly reflecting diagnostic confusion between ischaemic symptoms and reflux-induced chest pain.26

Effect of anti-reflux therapy. The use of anti-reflux therapy has been investigated in several studies of chest pain, including those evaluating PPIs as a diagnostic tool for reflux-induced symptoms. In a crossover study of 70 patients with GOR and chest pain, more patients experienced symptom improvement on lansoprazole than on placebo (92% versus 33%, respectively; \( P = 0.001 \)).27 In a similar crossover study of 42 patients with non-cardiac chest pain, reductions in chest pain were reported by 71% of those receiving omeprazole, compared to only 18% of those taking placebo (no \( P \)-value reported).28 In a further crossover study involving 40 patients with non-cardiac chest pain, 78% of patients with GOR (\( n = 18 \)) experienced an improvement in symptoms when receiving lansoprazole, compared with only 22% when given placebo (\( P < 0.05 \)) while in patients without GOR (\( n = 22 \)) there was no such difference (\( P = 0.75 \)).29 Another crossover trial showed that omeprazole improved chest-pain symptoms in 78% of patients with GOR (\( n = 23 \)), compared to 23% of those receiving placebo (\( P = 0.0005 \)).30 This response was even more pronounced among patients with GORD (\( n = 20 \)), 95% of whom responded to omeprazole, compared with 10% to placebo (no \( P \)-value reported).30

A parallel-group study of 36 patients with non-cardiac chest pain and GORD showed that patients given omeprazole had greater reductions in the severity of their chest pain (41% versus 8%, respectively; \( P < 0.05 \)), the number of days of chest pain (81% versus 44%, respectively; \( P < 0.05 \)) and the fraction of chest pain-free days (39% versus 10%, respectively, \( P = 0.006 \)) than those given placebo.31 Overall, 81% of subjects in the treatment arm reported symptomatic improvement compared to 6% in the placebo group (\( P = 0.001 \)).

A crossover study randomizing 19 patients with nutcracker oesophagus (high-amplitude peristaltic waves, of whom 12 had GORD) to receive lansoprazole or placebo showed that chest pain episodes were reduced in number and intensity, although there were no significant differences between the two groups (\( P > 0.05 \)).32 Given that the chest pain documented in this trial is likely to be due to nutcracker oesophagus, it is difficult to draw any conclusions from this study. The effect of omeprazole has also been investigated in a double-blind, crossover trial including patients with chest pain during strenuous exercise.33 Patients (\( n = 17 \)) were randomized to receive omeprazole or placebo for 6 days, after which their symptoms were assessed during strenuous exercise. Omeprazole did not reduce the occurrence or duration of chest pain in this study (\( P > 0.05 \)).

Pathogenic mechanisms. Exposure of the oesophageal mucosa to refluxed acid is believed to be the major mechanism underlying chest pain; given that vagal innervation is common to the oesophagus and heart, this may be misdiagnosed as angina in some patients.34,35 Sensitization of the oesophageal mucosa to gastric contents may also predispose to future reflux-induced chest pain.36 Alternatively, patients may simply describe heartburn as pain and discomfort in the chest.

Summary. Epidemiological studies support GORD as a risk factor for chest pain. With the exception of the studies conducted in patients with nutcracker oesophagus or during strenuous exercise, all eligible treatment trials demonstrated a reduction in chest pain symptoms during anti-reflux therapy. Further investigations in larger and less highly-selected study populations would be beneficial.

Cough

Association with GORD. The prevalence of bronchitis in the US population-based survey was 22.4% in individuals with GORD compared with 10.7% in those without reflux symptoms, but this difference was not statistically significant (OR 1.2; 95% CI 0.8–1.7).1 Overall, the prevalence of GORD was 30.6% in individuals with bronchitis, compared with 19.8% in the study population as a whole. The study conducted in UK general practice identified a small increase in the risk of incident cough in the year following a new GORD diagnosis (OR 1.7; 95% CI 1.4–2.1).10 GORD does not, however, appear to be associated with pneumonia or prior COPD, two potential causes of cough.1,10

Effect of anti-reflux therapy. In a parallel-group study conducted in 23 patients with acid-related chronic cough
(of whom 17 had GOR), only 1 of 8 patients responded to omeprazole treatment during the 12-week, double-blind phase, compared with none of the 9 patients in the placebo group.37 A crossover study investigating the effect of omeprazole in 29 subjects with GOR-related chronic cough showed a reduction in cough in the 12 patients receiving placebo and then omeprazole \( (P < 0.05) \), although an apparent carry-over effect in the patients receiving omeprazole and then placebo led to the original crossover design not being used in the data analysis.38

**Pathogenic mechanisms.** Two main mechanisms have been proposed to explain the relationship between GORD and cough. Similarly to asthma, cough may be induced by an oesophageal-tracheobronchial reflex in response to acid in the oesophagus,39 or by aspiration of oesophageal contents into the larynx and tracheobronchial tree.40 There is also evidence that cough may stimulate GOR, perhaps as a result of an increased pressure gradient between the thorax and abdomen.41,42

**Summary.** While GORD may be associated with a small increase in the risk of cough, evidence from randomized placebo-controlled studies of anti-reflux therapies is sparse and difficult to interpret. Further research is needed to characterize this relationship.

**Laryngitis**

**Association with GORD.** Hoarseness was reported by 23.4% of individuals with GORD in the US population-based study, compared with 10.7% of those without reflux symptoms, although this difference did not translate to a significantly increased risk.1 Similarly, the prevalence of GORD was greater in individuals with hoarseness than that in the population as a whole (31.3% versus 19.8%). The study in UK general practice did not identify a significantly increased risk of laryngitis (OR 1.1; 95% CI 0.7–1.8) or hoarseness (OR 1.5; 95% CI 0.8–2.9) following a diagnosis of GORD.10

**Effect of anti-reflux therapy.** One parallel-group study of the effects of anti-reflux therapy recruited patients \( (n = 30) \) with one or more symptoms of reflux laryngitis and more than four episodes of laryngopharyngeal reflux detected by ambulatory pH monitoring.53 Subjects treated with omeprazole reported a greater improvement in hoarseness and throat-clearing compared with placebo \( (P < 0.05) \), despite a relatively large placebo effect. However, as the omeprazole group reported much greater hoarseness at baseline than the placebo group, no firm conclusions can be drawn. In a second parallel-group study involving 22 patients with chronic laryngitis, 6 of 12 patients (50%) receiving lansoprazole achieved a complete symptomatic response, compared to 1 of 10 patients (10%) in the placebo group \( (P < 0.05) \).44 A crossover study in patients with GOR, however, reported that long-term pantoprazole therapy provided no advantage over placebo with respect to symptomatic improvement of laryngitis \( (n = 21) \).45 Furthermore, a parallel-group study conducted in 15 patients with posterior pharyngolaryngitis showed no demonstrable benefit of lansoprazole therapy over placebo.46 However, as only six of these patients had abnormal oesophageal pH levels, and symptoms of GORD were not a prerequisite for entrance into the trial, it is difficult to draw any conclusions from this trial regarding the effect of anti-reflux therapy on patients with laryngitis and GORD.

**Pathogenic mechanisms.** Chronic coughing and throat clearing, as well as laryngeal damage may occur via access of refluxate to the larynx and surrounding tissue,47 or by vagally-mediated reflexes stimulated by acid in the distal oesophagus.

**Summary.** Existing epidemiological and clinical evidence for an association between GORD and laryngitis or hoarseness are limited. Further research is needed on this topic.

**Sinusitis**

The UK general practice study identified sinusitis as a reflux-associated complication (OR 1.6; 95% CI 1.2–2.0).10 Mechanistically, it has been suggested that acid reflux could reach the nasopharynx and posterior nasal passages, particularly in the paediatric age group.48 Alternatively, a reflux-induced autonomic nervous system hyperactivity may account for reflux-associated nasal oedema and obstruction.48 There is a need for further evidence, particularly from randomized, placebo-controlled studies, to lend weight to the suggestion that sinusitis is an extra-oesophageal symptom of GORD.

**Otitis**

Newly diagnosed GORD patients were at slightly increased risk of otitis during the following year in the UK general practice study, although this relationship was not significant (OR 1.3; 95% CI 0.9–1.9).10 A postulated mechanism for reflux-induced otitis is that gastric acid could reflux into the middle ear, causing Eustachian-tube dysfunction and subsequent bacterial infection.49 Further epidemiological evidence and clinical investigations are required to elucidate this potential relationship.

**Gall-bladder disease**

The UK general practice study highlighted a considerably increased risk of gall-bladder disease in the year following a new diagnosis of GORD (OR 3.7; 95% CI 2.1–6.7).10 GORD and gall-bladder disease may share a link with smooth muscle dysfunction. Alternatively, gall-bladder disease may be initially misdiagnosed as GORD. Further evidence is required to
evaluate the relationship between gall-bladder disease and GORD.

Discussion

This review characterized the extra-oesophageal spectrum of GORD by identifying a number of potential extra-oesophageal symptoms from epidemiological studies, assessing their response to anti-reflux therapy and evaluating likely underlying mechanisms. The longitudinal study in UK general practice showed that GORD patients were at two- to fourfold increased risk of a range of extra-oesophageal symptoms (predominantly respiratory diseases and chest pain) in the year following first diagnosis. In clinical studies of patients with oesophagitis or abnormal oesophageal acid exposure, chest pain and asthma appeared to respond to anti-reflux therapy. The role of GORD in causing other extra-oesophageal symptoms was less clear, due to the limited number of treatment studies in patients with COPD, chronic cough and laryngitis/hoarseness giving often conflicting results, and a complete absence of treatment studies for otitis, sinusitis and gall-bladder disease. Our findings are summarized in Figure 1 and Table 3.

This review has a number of limitations, most notably that there were relatively few epidemiological studies and controlled clinical studies eligible for inclusion. There are also potential difficulties when interpreting their findings. Firstly, the use of multivariate analysis to evaluate the statistical relationship between GORD and its putative extra-oesophageal symptoms represents a potentially conservative approach that may understated the associated risk, since it assumes that different symptoms are independent variables, when they may in fact be co-dependent. Secondly, the exclusion of uncontrolled studies of anti-reflux surgery restricts the experimental demonstration of cause and effect to acid-suppressive therapy; a lack of effect in these studies does not, therefore, exclude the possibility that extra-oesophageal symptoms can be caused by gastrooesophageal refluxate that is either weakly acidic or alkaline. Thirdly, the patients participating in the included treatment trials were largely drawn from highly selected populations.
investigated by oesophageal pH monitoring or endoscopy in secondary care. The relevance of positive findings, therefore, to the patient consulting in primary care with uninvestigated extra-oesophageal symptoms is unclear. Finally, the included clinical studies used a diverse range of designs and assessments to measure the response of a range of extra-oesophageal symptoms to anti-reflux therapy. For this reason, combining the results of different studies in a meta-analysis was not appropriate.

Nevertheless, the findings of our review were confirmed by studies of hospital referral or hospitalization for GORD, and of oesophageal complications of GORD such as oesophagitis. A longitudinal study of participants in the first National Health and Nutrition Examination Survey demonstrated that prior hospitalization with hiatus hernia or reflux oesophagitis increased the risk of a variety of respiratory diseases, including asthma, bronchitis, emphysema and pneumonia.\(^51\) A study of patients discharged from hospitals of the Department of Veteran Affairs demonstrated an association between erosive oesophagitis or oesophageal stricture and a number of respiratory diseases, including asthma, chronic bronchitis, COPD, laryngitis, sinusitis and pneumonia.\(^52\) Similarly, a study of children aged 2–18 with GORD who were examined in the Texas Children’s Hospital demonstrated an increased risk of asthma, sinusitis, laryngitis, and pneumonia.\(^53\)

Other authors have conducted systematic reviews of the role of GORD in specific extra-oesophageal symptoms including asthma\(^54,55\) and sinusitis/otitis.\(^56\) In contrast to our review, the systematic review by Coughlan and colleagues found a weak positive association between GOR and sinusitis and a negative association between GOR and otitis media, using less stringent inclusion criteria than those used in our analysis. Also in contrast to our systematic review, neither of the systematic reviews of asthma found any overall benefit for anti-reflux therapy,\(^54,55\) although the possibility of benefit in certain sub-groups could not be excluded.\(^54\)

One such sub-group may be patients experiencing symptoms nocturnally.\(^17,57\)

The findings of our review are particularly relevant to the primary care physician. Firstly, it is clear that respiratory symptoms are common in individuals with GORD and make an important contribution to their burden of illness. Conversely, many patients presenting with respiratory symptoms will have GORD, and may be reluctant to discuss these symptoms.\(^58\) In the absence of an obvious explanation for symptoms such as chronic cough and laryngitis, or following the failure of treatment for diseases such as asthma, it may repay the physician to investigate GORD as a potential cause. Patients with respiratory symptoms who also report reflux symptoms (particularly those with a nocturnal symptom pattern) may respond to acid suppressive therapy. However, the potential extra-oesophageal symptoms of GORD may present in the absence of heartburn and regurgitation,\(^59\) particularly in the elderly,\(^60\) and the available evidence does not support the use of acid suppressive therapy in these patients.

Patients reporting chest pain warrant particular consideration. Although most chest pain is not of cardiac origin,\(^61-63\) the cause of chest pain is often left undiagnosed once cardiovascular causes have been ruled out.\(^64\) Patients with undiagnosed chest pain experience continued anxiety about the underlying cause of their symptoms and report long-term reductions in health-related quality of life.\(^65,66\) Such patients account for a substantial number of consultations and admissions, and management with PPIs opens an avenue that may reduce health resource utilization and improve patient well-being.\(^67-70\)

There is a clear need for further research into the epidemiology of GORD and its potential extra-oesophageal sequelae in the primary care setting and the general population. In particular, further longitudinal studies are needed to show whether the onset of GORD precedes the onset of its putative extra-oesophageal sequelae. Studies in healthcare databases may be used to

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**Table 3** Summary of evidence for the extra-oesophageal symptoms of GORD

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Cross-sectional studies(^a)</th>
<th>Longitudinal studies(^a)</th>
<th>Effect of anti-reflux therapy(^b)</th>
<th>Mechanistic model(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Chest pain</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Cough</td>
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<tr>
<td>Laryngitis</td>
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<tr>
<td>Sinusitis</td>
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<td>Otitis</td>
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<tr>
<td>Gall-bladder disease</td>
<td></td>
<td></td>
<td>✓</td>
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</tr>
</tbody>
</table>

\(^a\) Association with GORD symptoms or diagnosis (\(P < 0.05\)) in at least one study.

\(^b\) Improvement compared with placebo (\(P < 0.05\)) in at least one study.

\(^c\) Plausible mechanistic model available to support causative role of GORD.
assess the risk of extra-oesophageal symptoms in GORD patients who receive PPI therapy and randomized controlled studies are required in greater numbers of patients from primary care. Further mechanistic studies are also needed, to distinguish the potential role of GORD in predisposing to the development of a disease as well as in triggering symptoms in those with a pre-existing condition.

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