

Systematic review: the epidemiology of gastro-oesophageal reflux disease in primary care, using the UK General Practice Research Database

H. EL-SERAG*, C. HILL† & R. JONES‡

*Michael E DeBaakey Department of Veterans Affairs Medical Center and Baylor College of Medicine, Houston, TX, USA; †Research Evaluation Unit, Oxford PharmaGenesis LtdTM, Oxford, UK; ‡Department of General Practice and Primary Care, Kings College London School of Medicine, London, UK

Correspondence to:

Dr H. El-Serag, Gastroenterology and Hepatology Section, Department of Medicine, Michael E DeBaakey VA Medical Center and Baylor College of Medicine, Houston, TX, USA.
E-mail: hasheme@bcm.tmc.edu

Publication data

Submitted 7 October 2008
First decision 21 October 2008
Resubmitted 14 November 2008
Accepted 16 November 2008
Epub Accepted Article 25 November 2008

SUMMARY

Background

Gastro-oesophageal reflux disease (GERD) is a common diagnosis in primary care; however, there has been no comprehensive review of the epidemiology of GERD in this setting.

Aim

To review systematically articles that used the General Practice Research Database to study the epidemiology of GERD.

Methods

Systematic literature searches.

Results

Seventeen articles fulfilled the inclusion criteria. The incidence of GERD in primary care was 4.5 new diagnoses per 1000 person-years in 1996 (95% CI: 4.4–4.7). A new diagnosis of GERD was associated with being overweight, obese or an ex-smoker. Prior diagnoses of ischaemic heart disease, peptic ulcer disease, nonspecific chest pain, nonspecific abdominal pain, chronic obstructive pulmonary disease and asthma were associated with a subsequent new GERD diagnosis. A first diagnosis of GERD was associated with an increased risk of a subsequent diagnosis of oesophageal adenocarcinoma, oesophageal stricture, chronic cough, sinusitis, chest pain, angina, gallbladder disease, irritable bowel syndrome or sleep problems. Mortality may be higher in patients with a GERD diagnosis than in those without in the first year after diagnosis, but not long term.

Conclusion

The General Practice Research Database is an effective way of studying the epidemiology of GERD in a large population-based primary care setting.

Aliment Pharmacol Ther 29, 470–480

INTRODUCTION

Reflux symptoms are common, but there is a continuum of illness from infrequent heartburn through gastro-oesophageal reflux disease (GERD) to oesophagitis and Barrett's oesophagus. By convention, reflux symptoms become indicative of disease when they start to impair patients' health-related quality of life¹ or when they are associated with demonstrable oesophageal or extra-oesophageal lesions. Patient surveys have shown that impairment of health-related quality of life begins with mild symptoms at least 1 day per week.^{2, 3} Based on these criteria, the prevalence of GERD in Western countries has been estimated to be 10–20%.⁴ Surveys using 'symptomatic definitions' have also shown that GERD is associated with an increased risk of a number of extra-oesophageal syndromes, including chronic obstructive pulmonary disease (COPD), asthma, chronic cough, laryngitis and chest pain.^{4, 5} Studies in patients undergoing endoscopy have reported a strong association between GERD symptoms and oesophageal lesions, including reflux oesophagitis, strictures, Barrett's oesophagus and oesophageal adenocarcinoma.^{6–8}

Gastro-oesophageal reflux disease is also a frequent cause of consultation in primary care.⁹ However, a majority of patients with GERD do not consult about their symptoms.^{10–12} Individuals with GERD who are identified by questionnaire in population-based surveys are therefore unlikely to be the same as the patients with GERD seen in primary care, where most GERD is managed. It is therefore possible that associations seen in primary care may be different from those identified in population-based surveys. Furthermore, cross-sectional surveys conducted at a single point in time can only examine the presence of associations with potential risk factors and cannot use temporality to assess causality, whereas primary care records follow up patients over time.

This aspect of GERD epidemiology can be studied using primary care databases. The General Practice Research Database (GPRD) is the largest primary care database in the world and contains patient data that are representative of the UK general population. In the UK, general practitioners (GPs) are responsible for their patients' complete medical records, including those relating to hospitalizations and referrals. The GPRD contains anonymous patient data that are collected prospectively for research purposes. The data are entered by approximately 1500 GPs in the UK and

cover a population of over 3 million.¹³ Demographic details are recorded for each patient, as are details of all consultations involving a new diagnosis or a change of therapy, all drug prescriptions, referrals to hospital, hospitalizations and details of selected tests and their results.¹⁴

A number of studies have validated the quality of information recorded in the GPRD.^{15, 16} These validation studies have assessed the consistency of the quantitative information on the drugs prescribed and the diagnoses recorded by each participating medical practice. Studies have also compared the incidence of various illnesses and changes in the frequency of diagnosis recorded in the GPRD with those reported by other reliable sources in the UK. These studies have shown the GPRD to be an accurate and complete data source.

We wanted to study the following aspects of the epidemiology of GERD in primary care: the incidence and prevalence of GERD in individuals consulting in primary care, temporal trends in GERD diagnosis, the demographic characteristics of patients with GERD, risk factors preceding a diagnosis of GERD and also the outcomes of a GERD diagnosis (including the risks of Barrett's oesophagus, reflux oesophagitis, stricture, extra-oesophageal disorders and cancer). In recent years, a number of studies have used the GPRD to study these areas and several have examined different features of the same patient cohort. A review of these articles has the potential to provide a more complete picture of the epidemiology of GERD in the UK than would any one of the studies on their own. The aim of this paper was therefore to review these articles systematically and to provide an overview of the current literature on GERD in the GPRD.

METHODS

We identified the studies to be covered in the review by searching PubMed and EMBASE, using the search string (reflux OR heartburn OR GERD OR GORD OR gastroesophageal OR proton pump inhibitor) AND (General Practice Research Database OR GPRD OR database) AND (UK OR Great Britain). No restriction was placed on language or the year of publication. The authors performed independent searches. The GPRD bibliography and abstracts from Digestive Diseases Week and United European Gastroenterology Week in 2006 and 2007 were also searched.

RESULTS

These searches identified 16 published papers and one abstract from an otherwise unpublished study that were suitable for inclusion in the review. Only one study assessed the incidence of a GERD diagnosis and the demographic factors associated with this diagnosis.¹⁷ Eight studies addressed other potential risk factors for a GERD diagnosis,^{17–24} 14 studies examined the outcomes of a GERD diagnosis^{17–20, 23–32} and three studies assessed mortality associated with a GERD diagnosis.^{17, 26, 33} No study examined the prevalence of a GERD diagnosis or temporal trends in GERD diagnoses. Studies were published between 1999 and 2007; 14 of the 17 studies were published by the same group. All studies used a cohort design; 14 also used a nested case-control analysis.

In 13 studies, a new diagnosis of GERD was defined as the first recorded occurrence of one of the following diagnoses: gastro-oesophageal reflux, oesophagitis, acute oesophagitis, peptic oesophagitis, chronic oesophagitis, oesophageal ulcer, oesophageal reflux, reflux oesophagitis, oesophagus disease, acid regurgitation, acid reflux or heartburn.^{17–25, 29–32} One further study used the same definition but with the heartburn term removed.³³ Three studies used a cohort of patients with 'simple reflux', which was defined as a record of gastro-oesophageal reflux but no history of anti-reflux operations, oesophagitis or Barrett's oesophagus.^{26–28}

One study carried out a validation exercise.¹⁷ Questionnaires were sent to the GPs responsible for the patients in a random sample of 12% of the patients in the GERD cohort; this questionnaire requested that the GP confirm the initial diagnosis of GERD. Over 90% of the questionnaires were completed and returned. Among these questionnaires, 73% of GERD diagnoses were confirmed to be the first recorded by the GP for that patient.

Incidence of GERD and demographic characteristics of patients with newly diagnosed GERD

The single study that evaluated the incidence of GERD in the GPRD identified 7159 patients with a new GERD-related diagnosis in 1996, corresponding to an incidence among individuals aged 2–79 years of 4.5 new diagnoses per 1000 person-years [95% confidence interval (CI): 4.4–4.7].¹⁷ The incidence of GERD increased with age until 69 years, with a slight decrease

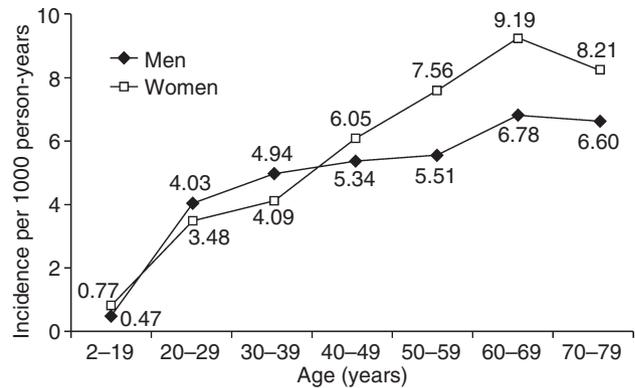


Figure 1. Incidence of gastro-oesophageal reflux disease diagnosis in UK general practice (reproduced from Ref. 17, with permission from Blackwell Publishing Ltd.).

thereafter (Figure 1). For both genders, the incidence was the highest in the 60- to 69-year age range. The only significant difference between the genders in the risk of GERD was in patients over 50 years of age, when women had a slightly higher risk of developing GERD than men (rate ratio: 1.3; 95% CI: 1.2–1.4).¹⁷

There also appeared to be a greater likelihood of a GERD diagnosis among patients with higher levels of healthcare utilization.¹⁷ Patients who visited their GP 3–10 times in the previous year had an increased risk of a new GERD diagnosis [odds ratio (OR): 1.7; 95% CI: 1.6–1.9] compared with patients who had made fewer than three visits. This risk increased even further among patients who had made more than 10 visits (OR: 2.9; 95% CI: 2.6–3.3). An increased risk of GERD diagnosis has also been found in patients who had recently been referred or hospitalized.^{17, 19}

Prevalence

No GPRD studies published to date have examined the prevalence of GERD.

Temporal trends

We did not identify any GPRD studies that examined temporal trends in the diagnosis of GERD.

Associations with lifestyle and behavioural factors

Comparing 7159 patients with a new GERD-related diagnosis with 10 000 age- and gender-matched

controls with no GERD diagnosis, Ruigómez *et al.*¹⁷ found a small but significant association between a new diagnosis of GERD and being overweight or obese [OR: 1.3; 95% CI: 1.2–1.4 for body mass index (BMI) 25–29.9 kg/m²; OR: 1.3; 95% CI: 1.2–1.5 for BMI ≥30 kg/m², compared with BMI 20–24.9 kg/m²] or an ex-smoker (OR: 1.2; 95% CI: 1.1–1.4, compared with nonsmokers). However, they found no significant association with current smoking or alcohol consumption.

Associations with other chronic diseases

Ten large longitudinal cohort studies with nested case–control analysis, two of which studied a GERD cohort and seven of which studied a cohort of a related disease, examined associations between a diagnosis of GERD and diagnoses of various chronic diseases (Tables 1 and 2). These studies showed that a prior diagnosis of asthma, COPD, irritable bowel syndrome (IBS), ischaemic heart disease, peptic ulcer disease, chest pain, dyspepsia or abdominal pain was associated with a significant increase in the risk of a first diagnosis of GERD (Table 1).^{17, 19–21, 23, 30} In the case of asthma, the risk of a new GERD diagnosis was found to be the greatest in the first year after asthma diagnosis.¹⁹ A study of 6913 patients with a dyspepsia diagnosis found that they had a likelihood of receiving a subsequent GERD diagnosis that was over 60 times greater than that of patients with no dyspepsia diagnosis ($n = 11\ 036$).²²

Patients with a GERD diagnosis were also at a significantly increased risk of subsequent diagnoses of a variety of other conditions (Table 2) including chronic cough, sinusitis, chest pain, angina, gallbladder disease, IBS and sleep problems.^{17, 20, 24, 32} However, individuals with a diagnosis of GERD did not have a significantly increased risk of a subsequent diagnosis of asthma, COPD, pneumonia, laryngitis, hoarseness, otitis or extra-oesophageal malignancies.^{17, 19, 23, 28}

Looking in detail at the association with subsequent myocardial infarction, a study of 7084 patients with a first diagnosis of GERD in 1996 found that, when compared with an age- and gender-matched control cohort, they had a nonsignificantly increased risk of myocardial infarction (RR: 1.4; 95% CI: 1.0–1.9) during a mean follow-up of 27 months.²⁵ When compared with the control cohort, the relative risk of subsequent myocardial infarction was 11.1 (95% CI: 3.3–37.0) during the first month after GERD diagnosis and 1.1 (95% CI: 0.8–1.5) thereafter, which indicates that

prodromal ischaemic symptoms may have been misdiagnosed as reflux symptoms immediately after onset. This study found no association between the use of acid-suppressive drugs and the risk of myocardial infarction.

Associations with medication use

One study found that patients with a diagnosis of GERD were more likely to have a current prescription for nonsteroidal anti-inflammatory drugs (OR: 1.5; 95% CI: 1.3–1.7) or oral steroids (OR: 1.3; 95% CI: 1.0–1.6) than individuals with no GERD diagnosis.¹⁷ However, a second study found no association between the use of oral steroids (OR: 1.6; 95% CI: 0.7–3.4) or inhaled steroids (OR: 1.4; 95% CI: 0.9–2.3) and a diagnosis of GERD in the subset of patients with a first diagnosis of asthma.¹⁹

Outcomes of a GERD diagnosis

Risk of Barrett's oesophagus and oesophagitis. Almost three-quarters (73%) of the 805 patients with GERD who underwent an endoscopy within 3 months of their diagnosis (11% of those diagnosed) had positive findings for oesophageal disease.¹⁸ Of these, 67% had oesophagitis recorded in their computerized profile, and 1% was recorded as having Barrett's oesophagus. Male gender (OR: 1.9; 95% CI: 1.3–2.8), increasing age (OR: 2.1; 95% CI: 1.0–4.1 for ages 50–69 years; OR: 2.8; 95% CI: 1.3–6.3 for ages 70–79 years, compared with patients aged 19–29 years) and a history of gastrointestinal bleeding (OR: 3.1; 95% CI: 1.1–8.8) were associated with positive oesophageal findings upon endoscopy. In a longitudinal study, patients with a GERD diagnosis had a substantially higher risk of developing an oesophageal ulcer than controls [relative risk (RR): 14.5; 95% CI: 5.1–41.7].¹⁷

Risk of oesophageal stricture. In a study with 5 years' follow-up, the risk of peptic oesophageal stricture was found to be markedly increased among patients with a new diagnosis of GERD compared with individuals with no GERD diagnosis (RR: 11.7; 95% CI: 4.0–34.1).¹⁷ This was subsequently confirmed in a second study that identified incident cases of oesophageal stricture in the GPRD between January 1994 and December 2000 ($n = 536$) and compared them with age- and gender-matched control patients who were free of stricture

Table 1. Results from cohort studies in the General Practice Research Database showing prior morbidity and medication use in patients with a subsequent diagnosis of gastro-oesophageal reflux disease (GERD) and their association with a diagnosis of GERD

Study	Study size (cohort and controls)	Diagnosis/medication use in the 12 months prior to the index date	Risk estimate (95% CI)
García Rodríguez <i>et al.</i> ²³	COPD cohort: <i>n</i> = 1628 Control cohort: <i>n</i> = 14 243 Age: 40–89 years	COPD	RR: 1.5 (1.2–1.8)
Ruigómez <i>et al.</i> ¹⁷	GERD cohort: <i>n</i> = 7159 Control cohort: <i>n</i> = 10 000 Age: 2–79 years	Irritable bowel syndrome Ischaemic heart disease Peptic ulcer disease Painful conditions Osteoarthritis Rheumatoid arthritis Inflammatory bowel disease Diabetes COPD Prescription for NSAIDs Prescription for oral steroids	OR: 1.6 (1.2–2.1) OR: 1.7 (1.4–2.1) OR: 2.5 (1.7–3.6) OR: 1.7 (1.6–1.8) OR: 1.0 (0.8–1.2) OR: 0.8 (0.5–1.3) OR: 1.0 (0.5–2.4) OR: 0.7 (0.5–0.9) OR: 1.3 (1.0–1.8) OR: 1.5 (1.3–1.7) OR: 1.3 (1.0–1.6)
Ruigómez <i>et al.</i> ¹⁹	Asthma cohort: <i>n</i> = 9712 Control cohort: <i>n</i> = 19 334 Age: 2–79 years	Asthma	Overall RR: 1.5 (1.2–1.8) In first year after asthma diagnosis RR: 2.1 (1.5–2.9)
Ruigómez <i>et al.</i> ²⁰	Chest pain cohort: <i>n</i> = 13 740 Control cohort: <i>n</i> = 20 000 Age: 2–79 years	Chest pain	OR: 3.0 (2.6–3.5)
Ruigómez <i>et al.</i> ³³	GERD cohort: <i>n</i> = 5318 Heartburn cohort: <i>n</i> = 1841 Control cohort: <i>n</i> = 10 000 Age: 2–79 years	Increased likelihood of GERD vs. heartburn diagnosis in patients with hiatus hernia abdominal pain peptic ulcer disease chest pain	OR: 2.9 (1.6–5.3) OR: 1.4 (1.1–1.6) OR: 1.6 (1.0–2.8) OR: 1.2 (1.0–1.5)
Ruigómez <i>et al.</i> ³⁰	Noncardiac chest pain cohort: <i>n</i> = 3028 Control cohort: <i>n</i> = 9000 Age: 20–79 years	Noncardiac chest pain	OR: 2.0 (1.5–2.7)
Ruigómez <i>et al.</i> ²⁴	Irritable bowel syndrome cohort: <i>n</i> = 2932 Control cohort: <i>n</i> = 4968 Age: 20–79 years	Irritable bowel syndrome	RR: 2.8 (1.7–4.9)
Wallander <i>et al.</i> ²²	Dyspepsia cohort: <i>n</i> = 6913 Control cohort: <i>n</i> = 11 036 Age: 20–79 years	Dyspepsia	OR: 62.8 (31.1–127.0)
Wallander <i>et al.</i> ²¹	Abdominal pain cohort: <i>n</i> = 29 299 Control cohort: <i>n</i> = 30 000 Age: 2–79 years	Unspecified abdominal pain	Rate ratio: 2.7 (1.9–3.8)

CI, confidence interval; COPD, chronic obstructive pulmonary disease; GERD, gastro-oesophageal reflux disease; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; RR, relative risk.

Table 2. Results from longitudinal cohort studies in the General Practice Research Database showing subsequent diagnoses in patients with a diagnosis of gastro-oesophageal reflux disease (GERD) and their association with a diagnosis of GERD

Study	Study size (cohort and controls)	Diagnosis in the 12 months following index date	Risk estimate (95% CI)
García Rodríguez <i>et al.</i> ²³	GERD cohort: <i>n</i> = 4391 Control cohort: <i>n</i> = 5118 Age: 40–79 years	COPD	RR: 1.2 (0.9–1.5)
Ruigómez <i>et al.</i> ¹⁷	GERD cohort: <i>n</i> = 7159 Control cohort: <i>n</i> = 10 000 Age: 2–79 years	Cough Sinusitis Chest pain Angina Gall bladder disease Pneumonia Asthma COPD Laryngitis Hoarseness Otitis	OR: 1.7 (1.4–2.1) OR: 1.6 (1.2–2.0) OR: 2.3 (1.8–2.8) OR: 3.2 (2.1–4.9) OR: 3.7 (2.1–6.7) OR: 1.8 (0.8–3.8) OR: 1.4 (1.0–2.1) OR: 1.1 (0.7–1.7) OR: 1.1 (0.7–1.8) OR: 1.5 (0.8–2.9) OR: 1.3 (0.9–1.9)
Ruigómez <i>et al.</i> ¹⁹	GERD cohort: <i>n</i> = 5653 Control cohort: <i>n</i> = 8105 Age: 2–79 years	Asthma	RR: 1.2 (0.9–1.6)
Ruigómez <i>et al.</i> ²⁰	Chest pain cohort: <i>n</i> = 13 740 Control cohort: <i>n</i> = 20 000 Age: 2–79 years	Unspecified chest pain	OR: 2.0 (1.7–2.3)
Ruigómez <i>et al.</i> ³⁰	Noncardiac chest pain cohort: <i>n</i> = 3028 Control cohort: <i>n</i> = 9000 Age: 20–79 years	Noncardiac chest pain	RR: 3.9 (2.7–5.7)
Ruigómez <i>et al.</i> ²⁴	GERD cohort: <i>n</i> = 6421 Control cohort: <i>n</i> = 9387 Age: 20–79 years	Irritable bowel syndrome	RR: 3.5 (2.3–5.4)
Wallander <i>et al.</i> ³²	Sleep disorder cohort: <i>n</i> = 12 437 Control cohort: <i>n</i> = 18 350 Age: 20–79 years	Sleep problems	OR: 1.4 (1.2–1.7)

CI, confidence interval; GERD, gastro-oesophageal reflux disease; OR, odds ratio; RR, relative risk.

(*n* = 5000).³¹ This study found that patients with stricture were more than eight times more likely to have a prior diagnosis of GERD than those with no diagnosis of stricture (OR 8.4; 95% CI: 6.2–11.2).

Risk of oesophageal cancer. Three GPRD studies found an increased risk of oesophageal adenocarcinoma in patients with a GERD diagnosis. Ruigómez *et al.*¹⁷ followed up patients with a GERD diagnosis for 5 years and found them to be at significantly

increased risk of oesophageal adenocarcinoma compared with those without a diagnosis of GERD (RR: 6.9; 95% CI: 1.4–32.9). This study included patients with oesophagitis in the GERD cohort, but excluded patients with a diagnosis of Barrett's oesophagus. A second study compared patients with Barrett's oesophagus (*n* = 1677), oesophagitis (*n* = 6392) or reflux (*n* = 6328) with a control cohort that was selected with no restriction other than having no diagnosis of Barrett's oesophagus (*n* = 13 416).²⁷ An

increased risk of oesophageal adenocarcinoma was observed in patients with reflux (standardized incidence rate ratio: 3.1; 95% CI: 0.6–14.2) and patients with oesophagitis (standardized incidence rate ratio: 4.5; 95% CI: 1.0–19.6) compared with patients in the control cohort. This risk was significantly higher in the patients with Barrett's oesophagus (standardized incidence rate ratio: 29.8; 95% CI: 9.6–106.0).

In a study of 287 patients with oesophageal adenocarcinoma, 195 with gastric cardia adenocarcinoma, 327 with gastric noncardia adenocarcinoma and 10 000 control patients, García Rodríguez *et al.*²⁹ found an increased risk of oesophageal adenocarcinoma in patients with a history of gastro-oesophageal reflux symptoms compared with patients with no such history (OR: 1.67; 95% CI: 1.16–2.40). As expected, no such association was found with gastric adenocarcinoma.

GERD and mortality. Ruigómez *et al.*¹⁷ found that patients with GERD had a higher risk of dying in the first year of follow-up when compared with control patients with no GERD diagnosis (adjusted RR: 1.6; 95% CI: 1.1–2.2). However, there was no increase in mortality risk when the full 5 years of follow-up were considered. In contrast, Solaymani-Dodaran *et al.*²⁶ found increased mortality among GERD patients ($n = 6328$) when compared with controls ($n = 13\ 416$) in a mean follow-up period of 1.8 person-years (hazard ratio: 1.16; 95% CI: 1.01–1.33). Only a very small part of this increased risk was due to an excess of deaths from oesophageal adenocarcinoma, as the hazard ratio remained at 1.15 (95% CI: 1.00–1.31) when these cases were removed.

DISCUSSION

Studies using the GPRD have provided information about several aspects of the epidemiology of GERD in a primary care setting. The GPRD has been used to estimate an overall incidence of GERD in UK primary care of 4.5 new diagnoses per 1000 person-years,¹⁷ which is similar to the results of an earlier database study in a US Medicaid population.³⁴ However, this is lower than estimates of the incidence of GERD from population-based surveys. For example, in a survey of 690 individuals from Olmsted County, USA, the incidence of heartburn once a week or more was 19.6 cases per 1000 person-years.³⁵ In a smaller survey of 197 individuals in Sweden, the incidence of heartburn

was 17.5 cases per 1000 person-years and that of acid regurgitation 12.4 cases per 1000 person-years.^{36, 37} This difference in incidence is likely to be due to the response bias in survey-based studies, the low consultation rate of individuals with GERD^{10, 38, 39} and the diagnosis of clinically relevant GERD in only a subset of patients consulting with reflux symptoms.

Gastro-oesophageal reflux disease may cause or be an aggravating factor in a number of extra-oesophageal syndromes (Figure 2; Table 3).^{1, 5, 40} The Montreal Definition of GERD separates these syndromes into established and proposed associations (Figure 2).¹ The GPRD studies provide more evidence to support the established associations with cough and asthma. However, this work shows that while patients with asthma are at an increased risk of a subsequent diagnosis of GERD, patients with GERD are not at a significantly increased risk of a diagnosis of asthma.¹⁹ A similar relationship has been found between GERD and COPD.²³ However, the directionality of the association between GERD and cough has not yet been established in the GPRD. It is known that a first diagnosis of GERD increases the risk of a subsequent diagnosis of cough,¹⁷ but the reverse relationship has not yet been studied in the GPRD. The Montreal Definition also classified reflux laryngitis syndrome as an established association; however, no association has been found in the GPRD between a diagnosis of GERD and a subsequent diagnosis of laryngitis.¹⁷ The relationship between GERD and reflux dental erosion syndrome has not yet been studied in the GPRD.

Of the four other extra-oesophageal associations that were proposed by the Montreal Definition, only sinusitis and otitis have been studied in the GPRD. Ruigómez *et al.*¹⁷ found that a first diagnosis of GERD was associated with a significant increase in the risk of a subsequent diagnosis of sinusitis, but no such association was seen with otitis. The relationship between GERD and pharyngitis or idiopathic pulmonary fibrosis has not yet been assessed in either direction.

GPRD studies have also identified associations between GERD and a number of other diseases. However, the directionality of these associations has not always been clear. For example, a first diagnosis of either IBS or GERD significantly increases the risk of a diagnosis of the other condition.²⁴ Similarly, a first diagnosis of either GERD or noncardiac chest pain also significantly increases the risk of a diagnosis of

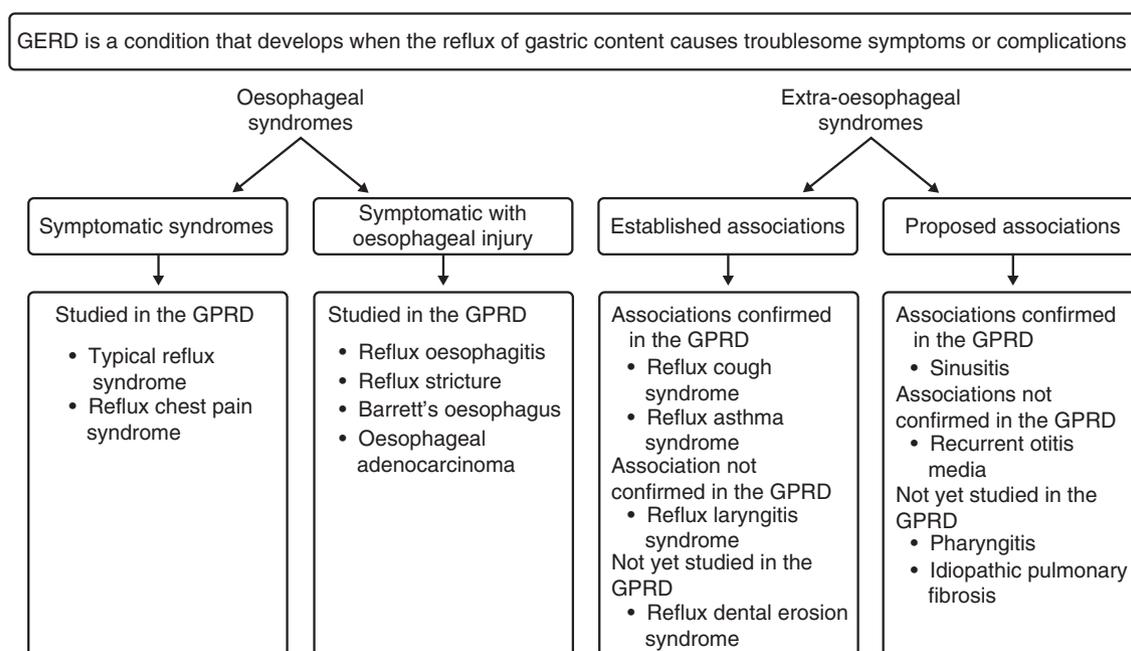


Figure 2. The constituent syndromes of gastro-oesophageal reflux disease (GERD) and the progress made in studying these in the General Practice Research Database (GPRD) (adapted from Ref. 1, with permission from Blackwell Publishing Ltd).

Table 3. Conditions that are associated with a first diagnosis of gastro-oesophageal reflux disease

Condition	Before	After
Stricture	-	✓
Oesophageal ulcer	-	✓
Oesophageal adenocarcinoma	-	✓
Hiatus hernia	✓	-
Irritable bowel syndrome	✓	✓
Dyspepsia	✓	-
Nonspecific abdominal pain	✓	-
Gall bladder disease	-	✓
Peptic ulcer disease	✓	-
Chronic obstructive pulmonary disease	✓	✗
Asthma	✓	✗
Chronic cough	-	✓
Laryngitis	-	✗
Noncardiac chest pain	✓	✓
Nonspecific chest pain	✓	✓
Ischaemic heart disease	✓	-
Myocardial infarction	-	✗
Angina	-	✓
Sinusitis	-	✓
Painful conditions	✓	-
Sleep problems	-	✓

the other condition.³⁰ A diagnosis of GERD may also be associated with a prior diagnosis of ischaemic heart disease, peptic ulcer disease or unspecified

abdominal pain.^{17, 20, 21} The directionality of these associations has not yet been clarified.

Work carried out in the GPRD also supports some of the associations with GERD that have been found in other studies, such as an increase in incidence with age^{34, 41, 42} and an association with subsequent Barrett's oesophagus and adenocarcinoma.^{43, 44} The GPRD studies have provided some evidence that certain lifestyle factors, such as being overweight or obese and perhaps a history of smoking (but not current smoking) may predispose to GERD.¹⁷ This supports the findings of studies in other settings that have also found links with these factors.⁴⁵⁻⁴⁷ One previous study also suggested a link between GERD and higher levels of alcohol consumption,⁴⁸ although no evidence of this has been found in the GPRD. However, these observed increases are only small and explain the presence of GERD in only a proportion of patients.

The GPRD has a number of strengths and weaknesses. These are summarized in Box 1.

The individual studies identified by this review also have specific strengths and weaknesses. Possibly their greatest strength is that they allow directionality and temporality to be assigned for the first time to a number of the associations that have been observed between GERD and its related extra-oesophageal

BOX 1. STRENGTHS AND WEAKNESSES OF THE GPRD

Strengths

- The database is representative of primary care for the whole UK population.
- Age and gender distributions are similar to those found in the national population census.
- Includes details of all referrals and hospitalizations.
- Medical records are accurate and complete for diagnoses of GERD,¹⁷ IBS,⁵⁵ stricture,³¹ peptic ulcer disease,⁵⁶ COPD⁵⁷ and myocardial infarction.²⁵
- Mortality data are well validated.⁵⁸
- A high response rate has been achieved for medical record requests.¹⁷
- Information submitted to the GPRD is subject to a range of quality checks; practices that fail to meet the required standard are excluded from the database.¹⁴

Weaknesses

- Only representative of the section of the population who seek health care.
- Delays in seeking health care make it more difficult to assess temporal relationships between two diagnoses or any relationship between age and disease onset.
- Only a single code is recorded when multiple symptoms and reasons for presentation are recorded.
- There can be a delay between diagnoses made in secondary care, such as those for cancer and their entry into the database.
- Does not contain complete lifestyle data.
- Relies on the accuracy of GP diagnosis; diseases such as GERD are unlikely to be diagnosed in a standardized fashion.
- Data on adherence to treatment and health-related quality of life are not recorded.

syndromes in cross-sectional studies. The follow-up period of up to 5 years is also an advantage. However, a notable weakness is the age of some of the study cohorts several of which were first identified in 1994 or 1996, although they were often followed up until 2001. A new definition of GERD has been developed in the meantime¹ and it is likely that patterns in

diagnosis and management have changed since then. Differences in diagnostic patterns and diagnostic terms could also introduce selection bias into the studies as some patients who actually have GERD may have been diagnosed with a different condition, such as dyspepsia.

Another potential source of selection bias is that GPRD studies will only identify patients who consult for their symptoms. This raises the possibility that the control groups used in GPRD studies may include individuals who do have GERD, but have not consulted for their symptoms. This is likely to lead to underestimations of the observed associations between GERD and other disorders. However, a number of studies have shown that consultation increases as symptom frequency and severity increases,^{10, 11, 38, 49–53} which suggests that those patients who do not consult are likely to be those with milder symptoms who perhaps would not fit within a 'symptomatic' definition of GERD. In addition, it has previously been argued that general practice registers in the UK are the best available means of sampling the general population.⁵⁴

This review presents an overview of the data available to date in the GPRD. This work suggests that there are a number of gaps in the literature that remain to be addressed. For example, temporal trends in the diagnosis of GERD have not yet been studied in the GPRD. It would also be interesting to study further the relationship between GERD and extra-oesophageal syndromes such as dental erosion syndrome, pharyngitis, idiopathic pulmonary fibrosis and recurrent otitis media (Figure 2). The GPRD could also be used to study the epidemiology of GERD in children and the long-term course of GERD.

ACKNOWLEDGEMENTS

Declaration of personal interests: Hashem El-Serag has served as a consultant for AstraZeneca and Takeda and has received research funding from AstraZeneca and Takeda. Catherine Hill is an employee of Oxford PharmaGenesis Ltd, which has received project funding from AstraZeneca R&D, Möln dal. Roger Jones has served as a speaker, consultant and advisory board member for AstraZeneca, Reckitt Benckiser, Pfizer, Altana and GlaxoSmithKline. *Declaration of funding interests:* The writing of this paper was funded in part by AstraZeneca R&D Möln dal.

REFERENCES

- 1 Vakil N, Veldhuyzen van Zanten S, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastro-oesophageal reflux disease (GERD) – a global evidence-based consensus. *Am J Gastroenterol* 2006; 101: 1900–20.
- 2 Wiklund I, Carlsson J, Vakil N. Gastroesophageal reflux symptoms and well-being in a random sample of the general population of a Swedish community. *Am J Gastroenterol* 2006; 101: 18–28.
- 3 Ronkainen J, Aro P, Storskrubb T, *et al.* Gastro-oesophageal reflux symptoms and health-related quality of life in the adult general population – the Kalixanda study. *Aliment Pharmacol Ther* 2006; 23: 1725–33.
- 4 Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; 54: 710–7.
- 5 Hungin AP, Raghunath A, Wiklund I. Beyond heartburn: a review of the spectrum of reflux-induced disease. *Fam Pract* 2005; 22: 591–603.
- 6 El-Serag HB, Johanson JF. Risk factors for the severity of erosive esophagitis in *Helicobacter pylori*-negative patients with gastroesophageal reflux disease. *Scand J Gastroenterol* 2002; 37: 899–904.
- 7 Winters C Jr, Spurling TJ, Chobanian SJ, *et al.* Barrett's esophagus. A prevalent, occult complication of gastroesophageal reflux disease. *Gastroenterology* 1987; 92: 118–24.
- 8 Sonnenberg A, El-Serag HB. Clinical epidemiology and natural history of gastro-oesophageal reflux disease. *Yale J Biol Med* 1999; 72: 81–92.
- 9 Jones R. Gastro-oesophageal reflux disease in general practice. *Scand J Gastroenterol Suppl* 1995; 211: 35–8.
- 10 Bretagne JF, Honnorat C, Richard-Molard B, Caekaert A, Barthelemy P. Comparative study of characteristics and disease management between subjects with frequent and occasional gastro-oesophageal reflux symptoms. *Aliment Pharmacol Ther* 2006; 23: 607–16.
- 11 Locke GR 3rd, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ 3rd. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology* 1997; 112: 1448–56.
- 12 Jones R, Ballard K. Healthcare seeking in gastro-oesophageal reflux disease: a qualitative study. *Eur J Gastroenterol Hepatol* 2008; 20: 269–75.
- 13 Garcia Rodriguez LA, Pérez Gutthann S. Use of the UK general practice research database for pharmacoepidemiology. *Br J Clin Pharmacol* 1998; 45: 419–25.
- 14 Lawson DH, Sherman V, Hollowell J. The general practice research database. Scientific and ethical advisory group. *Q J Med* 1998; 91: 445–52.
- 15 Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ* 1991; 302: 766–8.
- 16 Jick SS, Kaye JA, Vasilakis-Scaramozza C, *et al.* Validity of the general practice research database. *Pharmacotherapy* 2003; 23: 686–9.
- 17 Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Graffner H, Dent J. Natural history of gastro-oesophageal reflux disease diagnosed in general practice. *Aliment Pharmacol Ther* 2004; 20: 751–60.
- 18 Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Dent J. Endoscopic assessment patterns in a cohort of newly diagnosed GERD patients registered in a primary care database. *Dis Esophagus* 2007; 20: 504–9.
- 19 Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Thomas M, Price D. Gastroesophageal reflux disease and asthma: a longitudinal study in UK general practice. *Chest* 2005; 128: 85–93.
- 20 Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Jones R. Chest pain in general practice: incidence, comorbidity and mortality. *Fam Pract* 2006; 23: 167–74.
- 21 Wallander MA, Johansson S, Ruigómez A, García Rodríguez LA. Unspecified abdominal pain in primary care: the role of gastrointestinal morbidity. *Int J Clin Pract* 2007; 61: 1663–70.
- 22 Wallander MA, Johansson S, Ruigómez A, García Rodríguez LA, Jones R. Dyspepsia in general practice: incidence, risk factors, comorbidity and mortality. *Fam Pract* 2007; 24: 403–11.
- 23 García Rodríguez LA, Ruigómez A, Martín-Merino E, Johansson S, Wallander MA. Relationship between gastroesophageal reflux disease and COPD in UK primary care. *Chest* 2008; pre-published online 8 August 2008; 134: 1223–30.
- 24 Ruigómez A, Wallander MA, Johansson S, Rodríguez LA. Irritable bowel syndrome and gastroesophageal reflux disease in primary care: is there a link? *Dig Dis Sci* 2008; pre-published online 22 August 2008; DOI: 10.1007/s10620-008-0462-0.
- 25 Johansson S, Wallander MA, Ruigómez A, García Rodríguez LA. Is there any association between myocardial infarction, gastro-oesophageal reflux disease and acid-suppressing drugs? *Aliment Pharmacol Ther* 2003; 18: 973–8.
- 26 Soleymani-Dodaran M, Logan RF, West J, Card T. Mortality associated with Barrett's esophagus and gastroesophageal reflux disease diagnoses – a population-based cohort study. *Am J Gastroenterol* 2005; 100: 2616–21.
- 27 Soleymani-Dodaran M, Logan RF, West J, Card T, Coupland C. Risk of oesophageal cancer in Barrett's oesophagus and gastro-oesophageal reflux. *Gut* 2004; 53: 1070–4.
- 28 Soleymani-Dodaran M, Logan RF, West J, Card T, Coupland C. Risk of extra-oesophageal malignancies and colorectal cancer in Barrett's oesophagus and gastro-oesophageal reflux. *Scand J Gastroenterol* 2004; 39: 680–5.
- 29 García Rodríguez LA, Lagergren J, Lindblad M. Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case-control study in the United Kingdom. *Gut* 2006; 55: 1538–44.
- 30 Ruigómez A, García Rodríguez LA, Massó EL, Johansson S, Wallander M. Non-cardiac chest pain in general practice: increased risk of gastroesophageal reflux disease, ischaemic heart disease and mortality in the year after diagnosis. *Gut* 2007; 56(Suppl. 3): A74 (OP-G-325).
- 31 Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Eklund S. Esophageal stricture: incidence, treatment patterns and recurrence rate. *Am J Gastroenterol* 2006; 101: 2685–92.
- 32 Wallander MA, Johansson S, Ruigómez A, García Rodríguez LA, Jones R. Morbidity associated with sleep disorders in primary care: a longitudinal cohort study. *Prim Care Companion J Clin Psychiatry* 2007; 9: 338–45.
- 33 Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Dent J. Comparison of gastroesophageal reflux

- disease and heartburn diagnoses in UK primary care. *Curr Med Res Opin* 2006; 22: 1661–8.
- 34 Kotzan J, Wade W, Yu HH. Assessing NSAID prescription use as a predisposing factor for gastroesophageal reflux disease in a Medicaid population. *Pharm Res* 2001; 18: 1367–72.
- 35 Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ 3rd. Onset and disappearance of gastrointestinal symptoms and functional gastrointestinal disorders. *Am J Epidemiol* 1992; 136: 165–77.
- 36 Ruth M, Mansson I, Sandberg N. The prevalence of symptoms suggestive of esophageal disorders. *Scand J Gastroenterol* 1991; 26: 73–81.
- 37 Ruth M, Finizia C, Lundell L. The occurrence and future history of oesophageal symptoms in an urban Swedish population. Results of a questionnaire based, ten-year follow up study. *Scand J Gastroenterol* 2005; 40: 629–35.
- 38 Ho KY, Kang JY, Seow A. Patterns of consultation and treatment for heartburn: findings from a Singaporean community survey. *Aliment Pharmacol Ther* 1999; 13: 1029–33.
- 39 Kennedy T, Jones R. The prevalence of gastro-oesophageal reflux symptoms in a UK population and the consultation behaviour of patients with these symptoms. *Aliment Pharmacol Ther* 2000; 14: 1589–94.
- 40 Havemann B, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. *Gut* 2007; 56: 1654–64.
- 41 Mohammed I, Cherkas LF, Riley SA, Specator TD, Trudgill NJ. Genetic influences in gastro-oesophageal reflux disease: a twin study. *Gut* 2003; 52: 1085–9.
- 42 Isolauri J, Laippala P. Prevalence of symptoms suggestive of gastro-oesophageal reflux disease in an adult population. *Ann Med* 1995; 27: 67–70.
- 43 Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999; 340: 825–31.
- 44 Kulig M, Nocon M, Vieth M, *et al.* Risk factors of gastroesophageal reflux disease: methodology and first epidemiological results of the ProGERD study. *J Clin Epidemiol* 2004; 57: 580–9.
- 45 Nocon M, Labenz J, Jaspersen D, *et al.* Association of body mass index with heartburn, regurgitation and esophagitis: results of the Progression of Gastroesophageal Reflux Disease study. *J Gastroenterol Hepatol* 2007; 22: 1728–31.
- 46 El-Serag HB, Ergun GA, Pandolfino J, Fitzgerald S, Tran T, Kramer JR. Obesity increases oesophageal acid exposure. *Gut* 2007; 56: 749–55.
- 47 Corley DA, Kubo A, Zhao W. Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. *Gut* 2007; 56: 756–62.
- 48 Locke GR 3rd, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ 3rd. Risk factors associated with symptoms of gastroesophageal reflux. *Am J Med* 1999; 106: 642–9.
- 49 Jones R, Liker H, Ducrotte P, Ballard K. Reasons why individuals with symptoms of gastroesophageal reflux disease seek medical attention. *Gut* 2005; 54(Suppl. VII): A63.
- 50 Jones R, Armstrong D, Malfertheiner P, Ducrotte P. Does the treatment of gastro-oesophageal reflux disease (GERD) meet patients' needs? A survey-based study *Curr Med Res Opin* 2006; 22: 657–62.
- 51 Rey E, Moreno-Elola-Olaso C, Rodriguez-Artalejo F, Diaz-Rubio M. Medical consultation for gastro-oesophageal reflux symptoms: reasons and associated factors. *Digestion* 2004; 70: 173–7.
- 52 Johnston BT, Gunning J, Lewis SA. Health care seeking by heartburn sufferers is associated with psychosocial factors. *Am J Gastroenterol* 1996; 91: 2500–4.
- 53 Wong WM, Lai KC, Lam KF, *et al.* Prevalence, clinical spectrum and health care utilization of gastro-oesophageal reflux disease in a Chinese population: a population-based study. *Aliment Pharmacol Ther* 2003; 18: 595–604.
- 54 Fleming DM. Morbidity registration and the fourth general practice morbidity survey in England and Wales. *Scand J Prim Health Care Suppl* 1993; 2: 37–41.
- 55 Huerta C, Garcia Rodriguez LA, Wallander MA, Johansson S. Users of oral steroids are at a reduced risk of developing irritable bowel syndrome. *Pharmacoepidemiol Drug Saf* 2003; 12: 583–8.
- 56 Garcia Rodriguez LA, Hernandez-Diaz S. Risk of uncomplicated peptic ulcer among users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs. *Am J Epidemiol* 2004; 159: 23–31.
- 57 Soriano JB, Maier WC, Visick G, Pride NB. Validation of general practitioner-diagnosed COPD in the UK General Practice Research Database. *Eur J Epidemiol* 2001; 17: 1075–80.
- 58 Shah AD, Martinez C. A comparison of the cause of death recorded in the general practice research database with national mortality statistics in England and Wales. *Pharmacoepidemiol Drug Saf* 2004; 13: S2–3.