Time Trends of Gastroesophageal Reflux Disease: A Systematic Review

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There is a perception that the prevalence of gastroesophageal reflux disease (GERD) is increasing, but few studies have directly tackled this issue. By using a systematic approach, this review aimed to assess objectively whether the prevalence of GERD is changing with time. First, population-based studies that reported the prevalence of at least weekly heartburn and/or acid regurgitation were subjected to a time-trend analysis with a Poisson regression model. Second, population-based studies reporting the prevalence of GERD symptoms at 2 time points in the same source population were reviewed. Third, longitudinal studies that charted the prevalence of GERD symptoms and esophagitis in primary and secondary care were examined. The Poisson model revealed a significant ($P < .0001$) trend for an increase in the prevalence of reflux symptoms in the general population over time. Separately, significant increases with time were found for North America ($P = .0005$) and Europe ($P < .0001$) but not Asia ($P = .49$). Studies of the same source population over time indicated an increase in the prevalence of GERD in the U.S., Singapore, and China but not Sweden. An increase in the prevalence of GERD or esophagitis was found in the majority of longitudinal studies. There is evidence that the prevalence of GERD has increased during the past 2 decades. If this trend continues, it could contribute to the rapidly increasing incidence of more serious complications associated with GERD, such as esophageal adenocarcinoma, as well as costs to healthcare systems and employers.

Symptoms of gastroesophageal reflux disease (GERD) affect 10%–20% of the population in the Western world and around 5% of the population in Asia.[1] There is a perception that the prevalence of GERD is increasing. For example, a recent survey of physicians from a number of Asian countries found that 90% of gastroenterologists and 67% of primary care physicians believe that the prevalence of GERD has increased in recent years.[2] Several recent reviews have also commented on the possibility of an increase in the prevalence of GERD.[3–7] Currently, the direct costs associated with GERD in terms of consultation, referral, and treatment reach almost $10 billion per year in the U.S., whereas indirect costs caused by reduced work productivity are estimated to be as much as $75 billion per year.[8,9] A further increase in the worldwide prevalence of GERD would therefore represent a significant financial burden for both healthcare systems and employers. Furthermore, Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) are recognized complications of GERD, and so an increase in the prevalence of GERD might consequently lead to an increase in the incidence of these more serious conditions.

A recent systematic review assessed geographic variations in the prevalence of GERD,[1] but an analysis of the time trends associated with this disease was not covered. The aim of the present article, therefore, is to systematically review the findings of epidemiologic studies of GERD, including those of erosive esophagitis, to give a realistic understanding of whether the prevalence of GERD is changing with time. There are 3 main approaches that can be used to address this issue. The first approach is to examine population-based cross-sectional studies conducted in different populations at different time points; the second is to examine studies conducted in the same population at different time points; and the third is to evaluate longitudinal studies, looking at the changes in rates of the diagnosis of GERD.

Methods

Study Search

Studies were identified via PubMed searches with the search terms *heartburn*, *gastroesophageal reflux*, *reflux*, or *esophagitis*, along with *prevalence* or *incidence*. The author's existing bibliographic database and recent reviews on the epidemiology of GERD[1,10,11] were also searched for useful references.

Gastroesophageal Reflux Disease Symptoms

Cross-sectional population-based studies. The literature searches identified 45 population-based studies that measured the prevalence of GERD. To allow comparison of studies from various populations, additional criteria were imposed on the basis of those used by Dent et al[1] in their systematic review of the epidemiology of GERD. Care was taken to ensure that the sample was representative of the population as a whole. For example, with regard to the source population, studies were included if they were a survey of the general population, were part of a population that was not defined by its healthcare-seeking behavior (eg, employees at a VA hospital, blood donor studies), or were healthy controls from a case-control study. Studies were required to have included a minimum sample size of 200, which was defined as the number of eligible individuals approached to participate in the study. Studies were also required to have a response rate of at least 50% and a defined recall period of ≤1 year. To maintain a consistent definition of GERD, only studies reporting the prevalence of at least weekly symptoms of heartburn or acid regurgitation or a combination of the 2 were included. A total of 17 studies met these inclusion criteria and are presented in Table 1. Prevalence rates are reported along with accompanying 95% confidence intervals (CIs). Confidence intervals were calculated where the

Abbreviations used in this paper: BE, Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; GERD, gastroesophageal reflux disease; UK, United Kingdom.

1542-3565/07/$32.00
doi:10.1016/j.cgh.2006.09.016

Table 1. Population Studies of the Prevalence of GERD (Defined as at Least Weekly Heartburn and/or Acid Regurgitation) Used in the Analysis

Reference	Population	Time of study	Sample size	Response rate (%)	Method of data collection
Thompson and Heaton,[49] 1992	UK, employees and elderly residents	—	315	96	Physician interview
Talley et al,[13] 1992	USA, Olmsted County, MN	—	1021	82	Postal questionnaire
Isolauri and Laippala,[50] 1995	Finland, national population	—	2500	68	Postal questionnaire
Locke et al,[14] 1997	USA, Olmsted County, MN	—	2073	73	Postal questionnaire
Valle et al,[51] 1999	Italy, employees	—	768	91	Physician interview
Terry et al,[52] 2000	Sweden, national population	—	1123	73	Face to face interview
Pan et al,[53] 2000	China, population of 2 regions	July–December 1996	5000	100	Assisted self-completed questionnaire
Hu et al,[54] 2002	China, national population	1996	2640	62	Telephone interview
Mohammed et al,[55] 2003	UK, twin registry	—	8960	56	Postal questionnaire
Wong et al,[20] 2003	China, ethnic Chinese	Nov 2002	3605	61	Telephone interview
Wong et al,[21] 2004	China, ethnic Chinese	Nov 2003	825	86	Telephone interview
Diaz-Rubio et al,[56] 2004	Spain, national population	Jan 2002	8686	71	Telephone interview
El-Serag et al,[57] 2004	USA, employees	—	915	57	Postal questionnaire
Ronkainen et al,[58] 2005	Sweden	—	3000	74	Postal questionnaire
Chiocca et al,[59] 2005	Argentina	—	1000	84	Postal questionnaire
Chen et al,[60] 2005	South China	May–Dec 2003	3514	95	Face to face interview with the RDQ
Cho et al,[61] 2005	Korea	Jan 2000–Feb 2001	1417	78	Face to face interview

Hb, heartburn; R, acid regurgitation; Hb/R, heartburn and/or acid regurgitation; SD, standard deviation; RDQ, reflux disease questionnaire.

data were available. Table 2 lists the 28 studies excluded from this analysis and the reasons for exclusion. Funnel plots of the prevalence values from the 45 studies selected from the initial search and the 17 studies included in the Poisson model were constructed and tested for asymmetry by using Macaskill's test and the test proposed by Peters et al.[12]

A Poisson regression model was constructed to examine the association between the prevalence of GERD and the year in which the study was conducted (or the year of publication when the year of study was unavailable) and the geographic location of the study (continent). The offset value in this model was defined by total study subject count. GERD was defined as at least weekly heartburn or regurgitation in 12 studies or at least weekly heartburn in 5 studies.

Cross-sectional studies of the same source population. Of the studies included in the Poisson regression model, only 4 measured the prevalence of reflux symptoms in

Table 1. Continued

Age (*y*)	Men (*%*)	Recall period	At least weekly symptoms	Prevalence (*%*)	95% CI
(range, 17–91)	137 (45.5)	1 y	Hb	10.3	7.2–14.4
(range, 30–64)	—	1 y	Hb	13.2	10.9–15.5
			R	6.5	4.8–8.3
Mean, 48 (range, 20–91)	811 (47.7)	1 wk	Hb	14.8	13.3–16.7
			R	14.5	13.3–16.7
(range, 25–74)	—	1 y	Hb	17.8	15.8–19.9
			R	6.3	5.0–7.6
			Hb/R	19.8	17.7–21.9
Mean, 37.4 (range, 21–68)	362/700 (51.7)	1 y	Hb	7.7	6.0–10.0
			R	6.6	4.9–8.8
Median, 68	675 (82.8)	1 y	Hb/R	16.7	14.2–19.5
—	2346/4992 (47.0)	1 y	Hb	3.1	2.6–3.6
Mean, 37.9 ± 15 (SD)	47%	1 y	Hb/R	4.8	3.8–6.0
Mean for monozygotic twins, 51 (range, 19–81); dizygotic twins, 52 (range, 20–82)	Monozygotic twins, 167 (9); dizygotic twins, 143 (7)	1 y	Hb/R	Monozygotic, 18	16.3–19.8
				Dizygotic, 18	16.4–19.8
Mean, 40.3 ± 14 (SD)	42%	1 y	Hb/R	2.5	1.9–3.3
Mean, 42.4 ± 14 (SD)	36%	1 y	Hb/R	2.7	1.7–4.2
(range, 40–79)	1185/2500 (47.4)	1 y	Hb/R	9.8	8.6–10.9
Mean, 45 ± 10 (SD) (range, 18–75)	160/496 (32)	1 y	Hb	African Americans, 27.4	21.6–34.0
				Whites, 23.5	17.5–30.8
				Other, 23.7	16.4–32.7
			R	African Americans, 15.6	11.1–21.3
				Whites, 14.7	9.9–21.1
				Other, 14.0	8.5–22.1
			Hb/R	African Americans, 28.8	22.9–35.4
				Whites, 28.2	21.7–35.7
				Other, 25.4	18.0–34.6
Mean, 51.8	(50.5)	3 mo	Hb/R	25.9	23.2–28.8
Mean, 39.9 ± 15.4 (SD)	373 (44.5)	1 y	Hb	16.9	14.3–19.5
			R	16.5	14.0–19.1
			Hb/R	23.0	20.1–25.9
Mean, 42.6 ± 16.4 (SD)	1468 (43.9)	1 mo	Hb	1.9	1.4–2.4
			R	5.5	4.8–6.4
			Hb/R	6.2	5.5–7.1
(range, 18–69)	—	1 y	Hb	2.0	1.2–2.7
			R	2.0	1.3–2.8
			Hb/R	3.5	2.6–4.5

the same source populations at more than 1 time point. To widen the analysis to include as many of these types of studies as possible, 5 additional studies that measured the prevalence of other than weekly symptoms were also reviewed.

Longitudinal studies. Studies that assessed time trends in the incidence of GERD or complications of GERD in terms of primary or secondary care visits were also analyzed. These were required to be multicenter, population-based studies that included data from more than 1 time point. A total of 3 studies of primary and secondary care visits were found that met these inclusion criteria.

Esophagitis

Cross-sectional and longitudinal studies. Initially, we performed a literature search to find population-based studies reporting the prevalence of esophagitis. Studies were required to have included a minimum sample size of 200, have a

Table 2. Population-based Studies Reporting the Prevalence of Heartburn and/or Acid Regurgitation That Did Not Meet the Inclusion Criteria for the Poisson Regression Analysis

Reference	Sample size reported	Sample size ≥200	Response rate reported	Response rate ≥50%	Recall period reported	Recall period ≤1 *y*	At least weekly symptoms reported
Ruth et al,[16] 2005					No		No
Fujiwara et al,[62] 2005							No
Mohammed et al,[63] 2005				No			
Mishima et al,[28] 2005							No
Moraes-Filho et al,[64] 2005			No			No	
Camilleri et al,[65] 2005							No
Rajendra and Alahuddin,[66] 2004	No		No				
Wong et al ,[67] 2004							No
Fujimoto et al,[68] 2003	No		No		No		No
Khoshbaten,[69] 2003	No		No				No
Nilsson et al,[70] 2003							No
Watanabe et al,[71] 2003							No
Cameron et al,[72] 2002						No	
Conio et al,[73] 2002			No		No		
Louis et al,[74] 2002	No		No				
Agreus et al,[17] 2001							No
Avidan et al,[75] 2001		No	No		No		
Haque et al,[76] 2000							No
Kennedy and Jones,[77] 2000							No
Jasani et al,[78] 1999					No		
Lagergren et al,[79] 1999						No	
Oliveria et al,[80] 1999					No		
Ho et al,[18] 1998							No
Kennedy et al,[81] 1998							No
Corder et al,[82] 1996							No
Mold et al,[83] 1991					No		
Ruth et al,[15] 1991					No		No
Nebel et al,[84] 1976			No				

response rate of at least 50%, and be population-based. We found 3 studies that fulfilled these criteria. However, these were all performed very recently. The search was therefore extended to include time-trend longitudinal studies that reported secular trends in the incidence of esophagitis but were not strictly population-based. This strategy uncovered 5 additional studies, which were all included.

Results

Time Trends of Gastroesophageal Reflux Disease Symptoms

Cross-sectional population-based studies. The prevalence of GERD symptoms in the 17 studies included in the meta-analysis are presented graphically in Figure 1 and show a trend toward a higher prevalence of GERD in studies conducted more recently, as well as clearly demonstrating a lower prevalence in Asia compared with North America. The Asian studies and the 1 South American study are all relatively recent, whereas the European and North American studies span a greater number of years. The earlier studies also tended to record the prevalence of at least weekly heartburn, whereas the later ones report heartburn and/or regurgitation. Similar time trends, at least in North America, were clearly observed, with 9 studies reporting the prevalence of heartburn only. The results of the Poisson regression model that examined potential predictors of GERD symptoms are shown in Table 3. Overall, year of study was associated with an increase in the prevalence of weekly GERD symptoms by a factor of approximately 4% per year on average ($P < .0001$). A model including a quadratic term for the time variable in addition to the nontransformed time variable indicated a gradual but significant acceleration in this trend during more recent times. Studies conducted in Asia and Europe were associated with 81% and 41% lower prevalence of GERD symptoms, respectively, than those conducted in North America. When Poisson models were constructed to assess time trends in the main geographic areas individually, in North America there was an average annual increase of 5% ($P = .0005$), in Europe an increase of 27% ($P < .0001$), and in Asia an increase of 1% ($P = .49$) (Table 4).

Funnel plots of all 45 studies (Figure 2) and the 17 selected studies (Figure 3) were constructed by plotting the prevalence of symptoms against sample size. Macaskill's test and the test proposed by Peters et al[12] gave nonsignificant values for both funnel plots ($P < .1$), indicating that there was no significant publication bias.

Cross-sectional studies of the same source population. A total of 9 studies, 4 of which were also included in the Poisson regression analysis, were found that examined the prevalence of GERD in the same source population at different time points. Figure 4 presents changes in the prevalence of reflux symptoms among these studies. In North Amer-

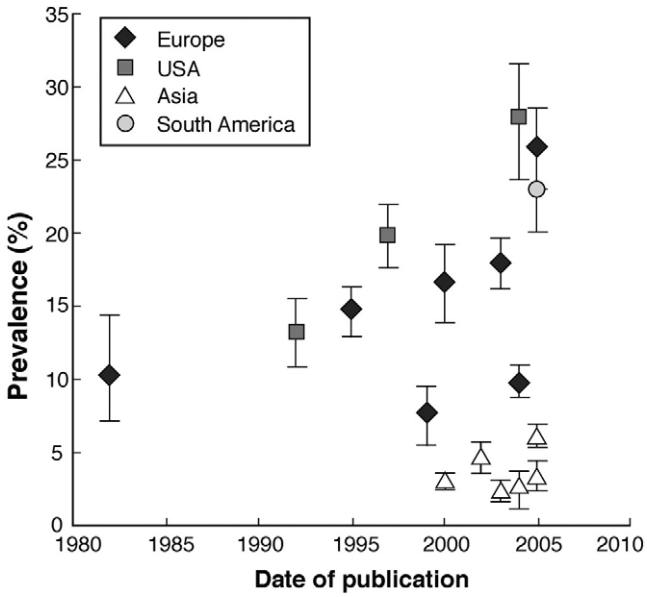

Figure 1. Prevalence of at least weekly heartburn and/or acid regurgitation, or heartburn, with regard to the publication date of the 17 studies included in the Poisson regression analysis. Studies are categorized by geographic region (continent).

ica, 2 studies have looked at the prevalence of reflux symptoms in Olmsted County, Minnesota. Although these used the same source population, the study samples were not identical. During the early 1990s, 13.2% (95% CI, 10.9–15.5) of the population reported weekly heartburn.[13] This figure increased to 17.8% (95% CI, 15.8–19.9) in a subsequent survey, suggesting that the prevalence of GERD was significantly greater.[14]

In a Swedish study conducted during the early 1990s, the prevalence of at least mild symptoms was 21% for heartburn and 20% for acid regurgitation.[15] Of 337 subjects who took part initially, 197 answered a second questionnaire 10 years later. At this point, the prevalence of at least mild symptoms of heartburn was 25% and of acid regurgitation was 22%.[16] However, the lack of any recall period affects the accuracy of this study. In another study with representative samples of the same Swedish source population, the prevalence of any troublesome heartburn and/or acid regurgitation during the past 3 months was 18.9% in 1988 (n = 1290) and 19.4% in 1995 (n = 1065).[17] A total of 843 individuals answered all 3 questionnaires. These

Table 3. Time Trends and Geographical Variations in the Prevalence of at Least Weekly Heartburn and/or Acid Regurgitation, as Shown by the Poisson Regression Model That Included all the Variables Shown

	PE	e^{PE}	SE	*P* value
Year of study	0.038	1.04	0.005	<.0001
Asia (vs N America)	−1.673	0.19	0.058	<.0001
Europe (vs N America)	−0.526	0.59	0.049	<.0001
S America (vs N America)	−0.12	1.13	0.087	.16

PE, parameter estimate; SE, standard error; e^{PE}, exponentiated value of PE.

Table 4. Time Trends in the Prevalence of at Least Weekly Heartburn and/or Acid Regurgitation in 3 Continents Examined in Separate Poisson Regression Models, Each Limited to Studies Conducted in 1 Continent

	PE	e^{PE}	SE	*P* value
N America	0.049	1.05	0.014	.0005
Europe	0.236	1.27	0.021	<.0001
Asia	0.014	1.01	0.020	.50

PE, parameter estimate; SE, standard error; e^{PE}, exponentiated value of PE.

authors did not find a statistically significant increase in the prevalence of reflux symptoms during this time period (odds ratio, 1.03; 95% CI, 0.94–1.14).

One of the most dramatic changes found among these studies was between 2 cross-sectional surveys of the general population in Singapore. The first survey, involving 696 respondents, showed that reflux symptoms were uncommon during the early 1990s. The prevalence of monthly reflux symptoms was 1.6%.[18] When this group was re-surveyed 5 years later (237 of the original group), the prevalence had increased to 10.5%.[19] The prevalence of monthly reflux symptoms among the same subgroup in the 1994 survey was 5.5%. This suggests a response bias, but there is still a substantial change in prevalence (odds ratio, 2.2; 95% CI, 1.0–5.2; $P = .05$). The upward trend in the prevalence of reflux was not related to body mass index ($P = 1.0$), smoking ($P = .59$), or alcohol consumption ($P = .68$).

A population-based study conducted in China in 2002 (n = 2209) revealed the prevalence of annual, monthly, and weekly reflux symptoms as 29.8%, 8.9%, and 2.5%, respectively.[20] A follow-up study 1 year later, which included 712 of the original subjects, showed that these figures had all increased to 34.1% for annual, 10.1% for monthly, and 2.7% for weekly symp-

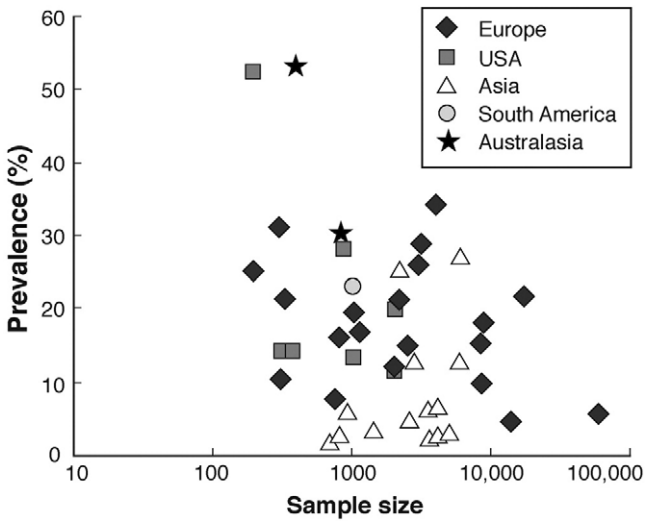

Figure 2. A funnel plot showing the prevalence of at least weekly heartburn and/or acid regurgitation, or heartburn only, with regard to the sample size of the 45 population-based studies identified by the literature search. The x-axis is in logarithmic scale.

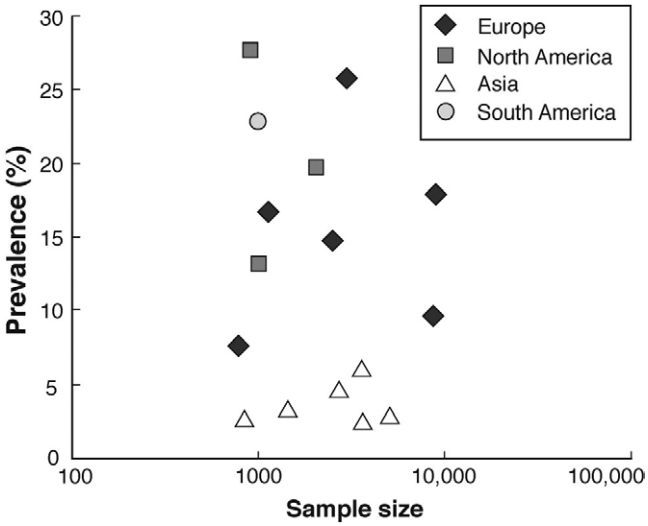

Figure 3. A funnel plot showing the prevalence of at least weekly heartburn and/or acid regurgitation, or heartburn only, with regard to the sample size of the 17 population-based studies included in the Poisson model. The x-axis is in logarithmic scale.

toms.[21] Again, however, response bias might be an issue, and the overlapping 95% CIs suggest that there was not a significant difference (Table 1).

Longitudinal studies. We identified 3 studies that met the inclusion criteria for this type of study. Data from the U.S. National Ambulatory Medical Care Survey, which covered nearly 80,000 patients, indicated an increase in the proportion of visits for GERD in U.S. primary care from 1.7% of visits in 1990–1993 to 4.7% of visits in 1998–2001.[22] Another study that used this dataset showed that the number of GERD-related visits increased by 46.5% in 3 years from 8,154,986 in 1998 to 11,944,136 in 2001.[23] During 1998, 123.4 per 10,000 visits were

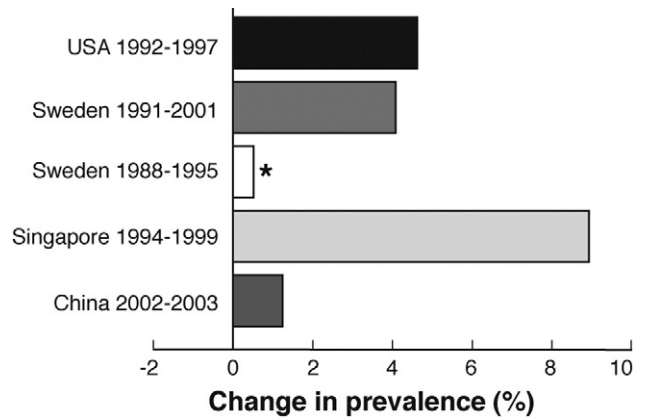

Figure 4. Change in the prevalence of reflux symptoms in studies that measured prevalence at more than 1 time point in the same source population. The reflux symptom definitions used were as follows: weekly heartburn and/or acid regurgitation in the U.S. study; "at least mild" heartburn in the 1991–2001 Swedish study; any heartburn and/or acid regurgitation during the past 3 months in the 1988–1995 Swedish study; and monthly heartburn and/or acid regurgitation for the studies in Singapore and China. *All bars* represent differences between first and second studies except for *, which represents change between 2 periods within the same study.

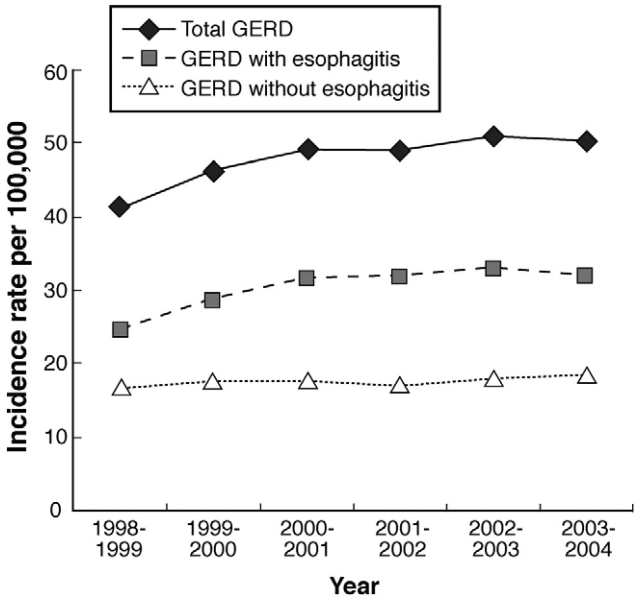

Figure 5. Frequency of hospital episodes for GERD per 10,000 hospital episodes. Data obtained from the UK hospital episodes statistics database (www.dh.gov.uk).

GERD-related, and in 2001 this had increased to 167.8 per 10,000 visits. The number of non–GERD-related visits increased by only 5.6% during this time period.

In the United Kingdom (UK), a survey of 60 primary care practices (502,493 patients) found that the number of visits in primary care for diseases of the esophagus increased from 24 per 10,000 person-years in 1981–1982 to 103 per 10,000 person-years in 1991–1992, an increase of more than 300%.[24] Meanwhile, this survey found that the total number of visits in primary care increased from 33,961 per 10,000 person-years in 1981–1982 to 34,785 per 10,000 person-years in 1991–1992, an increase of only 2.4%. In the UK, the number of hospital admissions with GERD increased between 1998–2004 from 41.6 per 10,000 episodes in 1998–1999 to 50.3 per 10,000 episodes in 2003–2004, as shown in Figure 5.[25]

Time Trends of Esophagitis

Cross-sectional studies. We found just 3 population-based studies reporting the prevalence of esophagitis that fulfilled our initial search criteria, in which a representative section of the population underwent endoscopy. A Swedish study of 1000 individuals found the prevalence of esophagitis to be 15.5%.[26] A study of a representative sample (n = 1533) of 2 Italian villages found that 11.9% of the population had esophagitis.[27] A study of randomly selected individuals attending their regular medical checkup at a Japanese hospital found the prevalence of esophagitis to be 7.1%.[28] A time-trend analysis was not possible because all 3 studies were conducted within 2 years.

Longitudinal studies. Our extended literature search identified 5 additional studies that examined secular trends in the frequency of erosive esophagitis but were not general population studies. A study with the U.S. Department of Veterans Affairs found that the proportion of hospitalizations with GERD (which comprised erosive esophagitis, esophageal stric-

tures, and hiatus hernia) increased from 61.2 per 10,000 hospitalizations in 1970–1974 to 315.6 per 10,000 hospitalizations in 1990–1995.[29] In an 11-year study in the UK (n = 8781), the proportion of patients diagnosed with esophagitis on referral increased from 3.6% in 1977 to 16.8% in 1987.[30] A large 10-year study in the Netherlands of patients referred for endoscopy (n = 11,691) showed that the proportion of these patients with esophagitis increased from 8.2% in 1992 to 16.5% in 2001.[31] In a 10-year study in Singapore of 16,375 patients who had been newly referred for endoscopy in the National University Hospital in Singapore from 1992–2001, the frequency of esophagitis increased from 3.9% to 9.8%.[32] In a Malaysian study (n = 1000) the prevalence of esophagitis in patients from a single center undergoing endoscopy for upper abdominal discomfort increased from 2.7% in 1991–1992 to 9.0% in 2000–2001.[33]

Discussion

This systematic review has used data from several types of studies that examine the prevalence of GERD to obtain as broad a perspective as possible on the issue of whether the incidence of GERD is changing with time. First, a total of 17 cross-sectional population-based studies of GERD symptoms were included in a Poisson regression analysis, which revealed a significant increasing trend in the prevalence of GERD between 1982–2005 ($P < .001$). Furthermore, it appears that this trend is gradually accelerating. North America had the highest prevalence of GERD, with the prevalence in Asia and Europe significantly lower. Second, the cross-sectional population-based studies measuring the prevalence of GERD in the same source population at more than 1 time point reviewed gave mixed evidence for a change in the prevalence of GERD with time. Neither of the 2 longitudinal studies in Sweden found significant increases in the prevalence of GERD during their 7-year and 10-year follow-up periods. However, the Asian and North American population-based studies that followed the same source population over time support the idea that the prevalence of GERD has increased in these parts of the world. Last, there were too few cross-sectional population-based studies of esophagitis to analyze a time trend; however, there is evidence that the frequency of reflux esophagitis has also increased during the last 30 years. Given that the prevalence equals incidence multiplied by the duration of disease, it seems likely that an increase over time in GERD prevalence is likely a reflection of increase over time in the incidence of GERD.

Additional indirect evidence to the increasing prevalence of GERD can be gleaned from the temporal trends of its known complications. GERD is known to be a risk factor for BE and EAC. There is substantial evidence from studies of cancer registries to support the idea that the incidence of EAC has increased with time. For example, a study with the National Cancer Institute surveillance, epidemiology, and end results database (which covers approximately 26% of the U.S. population) found that from 1975–2001 the incidence of EAC increased approximately 6-fold in the U.S. from 4 cases per million to 23 cases per million.[34] Numerous other studies of cancer registries in the U.S., Europe, and Australasia have also found that the incidence of EAC has increased during the last few decades. Similarly, several studies have reported an increase in the incidence of BE over time. A study of Olmsted County, Minnesota residents found that the incidence of BE increased 28-fold during a period of 30 years.[35] European studies have also found incidence increases of 1.6-fold to 1.8-fold during 5-year periods.[36,37] In a UK study the frequency of BE increased from 0.2% to 1.6% of all endoscopies in a study of endoscopy and histology reports for 1977–1996.[38]

Another serious complication associated with GERD is esophageal stricture. There are few data on time trends of the incidence of stricture in GERD patients, but those studies that exist have, in general, shown the incidence to be either stable[39] or decreasing.[40–42]

The reasons for the apparent increase in the prevalence of GERD symptoms and erosive esophagitis that we have identified in this systematic review are not clear and were not directly addressed in virtually all studies. The study carried out in Singapore by Lim et al[19] showed no association between the increase in frequency of heartburn and lifestyle changes such as smoking, alcohol consumption, changes in body weight, or genetic factors. Increased awareness of the disease and improved diagnostic techniques could play a role. There is evidence to suggest that eradicating *Helicobacter pylori* infection could provoke reflux esophagitis.[43,44] However, other studies have given conflicting results.[45] In contrast to GERD, peptic ulcer disease and gastric cancer are generally less common than 2–3 decades ago, and this is attributable to the decreasing prevalence of *H pylori* infection.[29] The incidence of peptic ulcer increased at the turn of the 20th century and has declined rapidly during the last 3 decades.[46] The reduced prevalence of *H pylori* infection and pangastritis in the populations of Asian countries leading to an increase in acid secretion might be responsible for the increased prevalence of GERD.[47] Last, high body mass index has been associated with an increase in the risk of GERD and its complications.[48] There is currently an epidemic of obesity in the United States as well as several European countries, which might explain part of the observed increase and contribute to additional future increases in GERD.

If the prevalence of GERD increases further in the future, it is likely to bring with it substantial clinical implications. For example, there might be an additional increase in the incidence of EAC. A growth in the prevalence of GERD would also be expected to increase the already considerable direct and indirect costs associated with the disease.

This systematic review has both limitations and strengths. First, not all of the studies covered used a consistent definition of GERD. The most informative epidemiologic studies were those that studied the same source population over time. However, few studies of this kind have been carried out, and to be able to present the results from a range of these studies, some that did not meet our criteria for the meta-analysis were also included. Indeed, the 2 Swedish studies that did not find an increase in the prevalence of reflux symptoms with time used the broadest measures of symptom definition of any of these longitudinal studies. They gave the prevalence of "mild" symptoms and "symptoms in the past 3 months," which reduces the likelihood that the prevalence of GERD is being measured. Their conclusions should therefore be taken with caution. In contrast, there are many studies of the prevalence of GERD in various source populations. Strict inclusion criteria including the use of a consistent definition for GERD as at least weekly heartburn and/or acid regurgitation, which has previously been suggested as an appropriate threshold for symptom frequency,[1] strengthened the time-trend analysis in this review and allowed 17 studies, collectively spanning more than 2 decades, to be

included. One challenge facing research into the epidemiology of GERD is that effective treatment for GERD is widespread, which means that it is impossible to study the natural history of the disease in untreated patients. Using a symptom frequency threshold in population-based studies might exclude those individuals whose disease is successfully managed by medication. However, this limitation would affect more recent studies, given the widespread use of reflux therapy, and hence would have biased the analyses toward not finding an increase in GERD during recent years. Awareness of GERD among physicians and the public has increased during the time covered by this review. Therefore it is possible that the studies showing time trends in the incidence of esophagitis and consultations for GERD could be subject to ascertainment bias. Last, most of the studies included in the analysis did not state when they were carried out, which could be substantially different from the publication date. However, in the 7 studies that reported both of these dates, there were time lags of only 1–6 years between the date that the study was performed and its publication.

In the future, use of a consistent definition of GERD will facilitate comparisons between different epidemiologic studies. Studies should also report when they were performed. Additional epidemiologic studies of GERD in areas of the world where the prevalence has been little studied, such as Africa and South America, would strengthen our understanding of worldwide prevalence trends. More longitudinal population-based studies of GERD will be crucial to enable further evaluation of long-term trends. The declining rate of peptic strictures in the face of the increasing rate of other manifestations of GERD is fascinating, and it suggests the possibility of modifying the clinical course of this disease. Meanwhile, one of the key challenges for future studies is to assess the underlying reasons for the likely increasing prevalence of GERD.

References

1. Dent J, El-Serag HB, Wallander MA, et al. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2005;54: 710–717.
2. Wong WM, Lim P, Wong BC. Clinical practice pattern of gastroenterologists, primary care physicians, and otolaryngologists for the management of GERD in the Asia-Pacific region: the FAST survey. J Gastroenterol Hepatol 2004;19:S54–S60.
3. Goh K. Changing epidemiology of gastroesophageal reflux disease in the Asian-Pacific region: an overview. J Gastroenterol Hepatol 2004;19:S22–S25.
4. Shaheen N, Provenzale D. The epidemiology of gastroesophageal reflux disease. Am J Med Sci 2003;326:264–273.
5. Delaney BC. Review article: prevalence and epidemiology of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2004; 20(Suppl 8):2–4.
6. Fujimoto K. Review article: prevalence and epidemiology of gastro-oesophageal reflux disease in Japan. Aliment Pharmacol Ther 2004;20(Suppl 8):5–8.
7. Graham DY. The changing epidemiology of GERD: geography and Helicobacter pylori. Am J Gastroenterol 2003;98:1462–1470.
8. American Gastroenterological Association. The burden of gastrointestinal diseases. Volume 2006. Bethesda, MD: AGA, 2001.
9. Wahlqvist P, Reilly M, Barkun A. Systematic review: the impact of gastro-oesophageal reflux disease on health-related productivity. Aliment Pharmacol Ther 2006; 24:259–272.
10. Heading RC. Prevalence of upper gastrointestinal symptoms in the general population: a systematic review. Scand J Gastroenterol Suppl 1999;231:3–8.
11. El-Serag HB, Talley NJ. Systematic review: the prevalence and clinical course of functional dyspepsia. Aliment Pharmacol Ther 2004;19:643–654.
12. Peters JL, Sutton AJ, Jones DR, et al. Comparison of two methods to detect publication bias in meta-analysis. JAMA 2006;295: 676–680.
13. Talley NJ, Zinsmeister AR, Schleck CD, et al. Dyspepsia and dyspepsia subgroups: a population-based study. Gastroenterology 1992;102:1259–1268.
14. Locke GR 3rd, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997;112: 1448–1456.
15. Ruth M, Mansson I, Sandberg N. The prevalence of symptoms suggestive of esophageal disorders. Scand J Gastroenterol 1991;26:73–81.
16. 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;40:629–635.
17. Agreus L, Svardsudd K, Talley NJ, et al. Natural history of gastroesophageal reflux disease and functional abdominal disorders: a population-based study. Am J Gastroenterol 2001;96: 2905–2914.
18. Ho KY, Kang JY, Seow A. Prevalence of gastrointestinal symptoms in a multiracial Asian population, with particular reference to reflux-type symptoms. Am J Gastroenterol 1998;93:1816–1822.
19. Lim SL, Goh WT, Lee JM, et al. Changing prevalence of gastroesophageal reflux with changing time: longitudinal study in an Asian population. J Gastroenterol Hepatol 2005;20:995–1001.
20. 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.
21. Wong WM, Lai KC, Lam KF, et al. Onset and disappearance of reflux symptoms in a Chinese population: a 1-year follow-up study. Aliment Pharmacol Ther 2004;20:803–812.
22. Altman KW, Stephens RM, Lyttle CS, et al. Changing impact of gastroesophageal reflux in medical and otolaryngology practice. Laryngoscope 2005;115:1145–1153.
23. Niemcryk SJ, Joshua-Gotlib S, Levine DS. Outpatient experience of patients with GERD in the United States: analysis of the 1998-2001 National Ambulatory Medical Care Survey. Dig Dis Sci 2005;50:1904–1908.
24. McCormick A, Fleming DM, Charlton J. Morbidity statistics from general practice: fourth national study 1991-1992. Volume 2005. London: Office of Population Censuses and Surveys, 1995.
25. Department of Health. Hospital episode statistics. Volume 2005. London: Department of Health, 2004.
26. Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology 2005;129:1825–1831.
27. Zagari RM, Pozzato P, Damian S, et al. Relationship between gastroesophageal reflux symptoms and esophagitis in the general population: results from the Loiano-Monghidoro study. Gastroenterology 2006;130:T1018.
28. Mishima I, Adachi K, Arima N, et al. Prevalence of endoscopically negative and positive gastroesophageal reflux disease in the Japanese. Scand J Gastroenterol 2005;40:1005–1009.
29. El-Serag HB, Sonnenberg A. Opposing time trends of peptic ulcer and reflux disease. Gut 1998;43:327–333.
30. Gear MW, Wilkinson SP. Open-access upper alimentary endoscopy. Br J Hosp Med 1989;41:438, 440, 442–444.

31. Loffeld RJ, van der Putten AB. Rising incidence of reflux oesophagitis in patients undergoing upper gastrointestinal endoscopy. Digestion 2003;68:141–144.
32. Ho KY, Chan YH, Kang JY. Increasing trend of reflux esophagitis and decreasing trend of Helicobacter pylori infection in patients from a multiethnic Asian country. Am J Gastroenterol 2005;100: 1923–1928.
33. Rosaida MS, Goh KL. Opposing time trends in the prevalence of duodenal ulcer and reflux esophagitis in a multiracial Asian population. Gastroenterology 2004;126:A443.
34. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005;97:142–146.
35. Conio M, Cameron AJ, Romero Y, et al. Secular trends in the epidemiology and outcome of Barrett's oesophagus in Olmsted County, Minnesota. Gut 2001;48:304–309.
36. van Soest EM, Dieleman JP, Siersema PD, et al. Increasing incidence of Barrett's oesophagus in the general population. Gut 2005;54:1062–1066.
37. Hurschler D, Borovicka J, Neuweiler J, et al. Increased detection rates of Barrett's oesophagus without rise in incidence of oesophageal adenocarcinoma. Swiss Med Wkly 2003;133:507–514.
38. Caygill CP, Reed PI, Johnston BJ, et al. A single centre's 20 years' experience of columnar-lined (Barrett's) oesophagus diagnosis. Eur J Gastroenterol Hepatol 1999;11:1355–1358.
39. Nayyar AK, Royston C, Bardhan KD. Oesophageal acid-peptic strictures in the histamine H2 receptor antagonist and proton pump inhibitor era. Dig Liver Dis 2003;35:143–150.
40. El-Serag HB. Temporal trends in new and recurrent esophageal strictures in the Department of Veterans Affairs. Am J Gastroenterol 2006;101:1727–1733.
41. Guda NM, Vakil N. Proton pump inhibitors and the time trends for esophageal dilation. Am J Gastroenterol 2004;99:797–800.
42. Ruigomez A, Garcia Rodriguez LA, Wallander MA, et al. Esophageal strictures in primary care: incidence, treatment patterns and recurrence rate. Gastroenterology 2006;130:W1094.
43. Labenz J, Blum AL, Bayerdorffer E, et al. Curing Helicobacter pylori infection in patients with duodenal ulcer may provoke reflux esophagitis. Gastroenterology 1997;112:1442–1447.
44. Haruma K, Hamada H, Mihara M, et al. Negative association between Helicobacter pylori infection and reflux esophagitis in older patients: case-control study in Japan. Helicobacter 2000; 5:24–29.
45. Raghunath AS, Hungin AP, Wooff D, et al. Systematic review: the effect of Helicobacter pylori and its eradication on gastro-oesophageal reflux disease in patients with duodenal ulcers or reflux oesophagitis. Aliment Pharmacol Ther 2004;20:733–744.
46. Sonnenberg A. Temporal trends and geographical variations of peptic ulcer disease. Aliment Pharmacol Ther 1995;9(Suppl 2): 3–12.
47. Haruma K. Review article: influence of Helicobacter pylori on gastro-oesophageal reflux disease in Japan. Aliment Pharmacol Ther 2004;20:40–44.
48. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med 2005;143:199–211.
49. Thompson WG, Heaton KW. Heartburn and globus in apparently healthy people. Can Med Assoc J 1982;126:46–48.
50. Isolauri J, Laippala P. Prevalence of symptoms suggestive of gastro-oesophageal reflux disease in an adult population. Ann Med 1995;27:67–70.
51. Valle C, Broglia F, Pistorio A, et al. Prevalence and impact of symptoms suggestive of gastroesophageal reflux disease. Dig Dis Sci 1999;44:1848–1852.
52. Terry P, Lagergren J, Wolk A, et al. Reflux-inducing dietary factors and risk of adenocarcinoma of the esophagus and gastric cardia. Nutr Cancer 2000;38:186–191.
53. Pan G, Xu G, Ke M, et al. Epidemiological study of symptomatic gastroesophageal reflux disease in China: Beijing and Shanghai. Chin J Dig Dis 2000;1:2–8.
54. Hu WH, Wong WM, Lam CL, et al. Anxiety but not depression determines health care-seeking behaviour in Chinese patients with dyspepsia and irritable bowel syndrome: a population-based study. Aliment Pharmacol Ther 2002;16:2081–2088.
55. Mohammed I, Cherkas LF, Riley SA, et al. Genetic influences in gastro-oesophageal reflux disease: a twin study. Gut 2003;52: 1085–1089.
56. Diaz-Rubio M, Moreno-Elola-Olaso C, Rey E, et al. Symptoms of gastro-oesophageal reflux: prevalence, severity, duration and associated factors in a Spanish population. Aliment Pharmacol Ther 2004;19:95–105.
57. El-Serag HB, Petersen NJ, Carter J, et al. Gastroesophageal reflux among different racial groups in the United States. Gastroenterology 2004;126:1692–1699.
58. Ronkainen J, Aro P, Storskrubb T, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. Scand J Gastroenterol 2005;40:275–285.
59. Chiocca JC, Olmos JA, Salis GB, et al. Prevalence, clinical spectrum and atypical symptoms of gastro-oesophageal reflux in Argentina: a nationwide population-based study. Aliment Pharmacol Ther 2005;22:331–342.
60. Chen M, Xiong L, Chen H, et al. Prevalence, risk factors and impact of gastroesophageal reflux disease symptoms: a population-based study in South China. Scand J Gastroenterol 2005; 40:759–767.
61. Cho YS, Choi MG, Jeong JJ, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Asan-si, Korea. Am J Gastroenterol 2005;100:747–753.
62. Fujiwara Y, Higuchi K, Watanabe Y, et al. Prevalence of gastroesophageal reflux disease and gastroesophageal reflux disease symptoms in Japan. J Gastroenterol Hepatol 2005;20:26–29.
63. Mohammed I, Nightingale P, Trudgill NJ. Risk factors for gastro-oesophageal reflux disease symptoms: a community study. Aliment Pharmacol Ther 2005;21:821–827.
64. Moraes-Filho JP, Chinzon D, Eisig JN, et al. Prevalence of heartburn and gastroesophageal reflux disease in the urban Brazilian population. Arq Gastroenterol 2005;42:122–127.
65. Camilleri M, Dubois D, Coulie B, et al. Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study. Clin Gastroenterol Hepatol 2005;3:543–552.
66. Rajendra S, Alahuddin S. Racial differences in the prevalence of heartburn. Aliment Pharmacol Ther 2004;19:375–376.
67. Wong WM, Lam KF, Cheng C, et al. Population based study of noncardiac chest pain in southern Chinese: prevalence, psychosocial factors and health care utilization. World J Gastroenterol 2004;10:707–712.
68. Fujimoto K, Iwakiri R, Okamoto K, et al. Characteristics of gastroesophageal reflux disease in Japan: increased prevalence in elderly women. J Gastroenterol 2003;38:3–6.
69. Khoshbaten M. Gastro-esophageal reflux disease in northwestern Tabriz, Iran. Indian J Gastroenterol 2003;22:138–139.
70. Nilsson M, Johnsen R, Ye W, et al. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. JAMA 2003;290: 66–72.
71. Watanabe Y, Fujiwara Y, Shiba M, et al. Cigarette smoking and alcohol consumption associated with gastro-oesophageal reflux disease in Japanese men. Scand J Gastroenterol 2003;38:807–811.
72. Cameron AJ, Lagergren J, Henriksson C, et al. Gastroesophageal reflux disease in monozygotic and dizygotic twins. Gastroenterology 2002;122:55–59.

73. Conio M, Filiberti R, Blanchi S, et al. Risk factors for Barrett's esophagus: a case-control study. Int J Cancer 2002;97:225–229.
74. Louis E, DeLooze D, Deprez P, et al. Heartburn in Belgium: prevalence, impact on daily life, and utilization of medical resources. Eur J Gastroenterol Hepatol 2002;14:279–284.
75. Avidan B, Sonnenberg A, Giblovich H, et al. Reflux symptoms are associated with psychiatric disease. Aliment Pharmacol Ther 2001;15:1907–1912.
76. Haque M, Wyeth JW, Stace NH, et al. Prevalence, severity and associated features of gastro-oesophageal reflux and dyspepsia: a population-based study. N Z Med J 2000;113:178–181.
77. 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; 14:1589–1594.
78. Jasani K, Piterman L, McCall L. Gastroesophageal reflux and quality of life: patient's knowledge, attitudes and perceptions. Aust Fam Physician 1999;28(Suppl 1):S15–S18.
79. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825–831.
80. Oliveria SA, Christos PJ, Talley NJ, et al. Heartburn risk factors, knowledge, and prevention strategies: a population-based survey of individuals with heartburn. Arch Intern Med 1999;159:1592–1598.
81. Kennedy TM, Jones RH, Hungin AP, et al. Irritable bowel syndrome, gastro-oesophageal reflux, and bronchial hyper-responsiveness in the general population. Gut 1998;43:770–774.
82. Corder AP, Jones RH, Sadler GH, et al. Heartburn, oesophagitis and Barrett's oesophagus in self-medicating patients in general practice. Br J Clin Pract 1996;50:245–248.
83. Mold JW, Reed LE, Davis AB, et al. Prevalence of gastroesophageal reflux in elderly patients in a primary care setting. Am J Gastroenterol 1991;86:965–970.
84. Nebel OT, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux: incidence and precipitating factors. Am J Dig Dis 1976;21:953–956.

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Dr El-Serag is a VA Health Services Research & Development Awardee (grant no. ARCD 00-013-2). Also supported by an unrestricted education research grant from AstraZeneca R&D Mölndal.

The author would like to acknowledge the help of Dr Catherine Henderson and Dr Chris Winchester, who assisted with literature searches and manuscript development.