Gastroesophageal Reflux Disease and overall and Cause-specific Mortality: A Prospective Study of 50000 Individuals

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ABSTRACT

BACKGROUND

Only a few studies in Western countries have investigated the association between gastroesophageal reflux disease (GERD) and mortality at the general population level and they have shown mixed results. This study investigated the association between GERD symptoms and overall and cause-specific mortality in a large prospective population-based study in Golestan Province, Iran.

METHODS

Baseline data on frequency, onset time, and patient-perceived severity of GERD symptoms were available for 50001 participants in the Golestan Cohort Study (GCS). We identified 3107 deaths (including 1146 circulatory and 470 cancer-related) with an average follow-up of 6.4 years and calculated hazard ratios (HR) and 95% confidence intervals (CI) adjusted for multiple potential confounders.

RESULTS

Severe daily symptoms (defined as symptoms interfering with daily work or causing nighttime awakenings on a daily bases, reported by 4.3% of participants) were associated with cancer mortality (HR 1.48, 95% CI: 1.04-2.05). This increase was too small to noticeably affect overall mortality. Mortality was not associated with onset time or frequency of GERD and was not increased with mild to moderate symptoms.

CONCLUSION

We have observed an association with GERD and increased cancer mortality in a small group of individuals that had severe symptoms. Most patients with mild to moderate GERD can be re-assured that their symptoms are not associated with increased mortality.

KEYWORDS

Cardiovascular disease; Esophageal cancer; Gastroesophageal reflux disease; Mortality

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INTRODUCTION

Gastroesophageal reflux disease (GERD) symptoms, including heartburn and regurgitation, are among the most common gastrointestinal (GI) symptoms in Europe and the United States, with prevalence

rates of 10%–25% in population-based studies.[1-5] In 2009, GERD was the most common physician diagnosis for GI disorders in outpatient clinic visits in the United States and responsible for 8.9 million physician visits.[6] Reports from many other populations have shown a high prevalence of GERD or an increase in the prevalence in recent years.[7-11] Some of those with GERD symptoms may develop Barrett's esophagus, which can lead to esophageal adenocarcinoma (EAC); however, a recent multicenter follow-up study of individuals with Barrett's esophagus have shown that the risk of this transformation is small (<0.5% per year).[12]

Only a few prospective studies have investigated the association between GERD and mortality in the general population and they have shown mixed results. A study from the United Kingdom (UK) showed a slight (1.16-fold) increase in mortality associated with GERD in individuals without esophagitis or Barrett's esophagus, and only part of this association was attributed to esophageal cancer (EC).[13] Another study from the UK reported an increase in mortality only in the year following the diagnosis of GERD.[14] In a third study from UK, there was a significant increase in mortality among omeprazole users in the first year, but the rates fell to or below population estimated rates by the fourth year. When only those with hiatal hernia or GERD were considered, there was no association.[15] Finally, a study from the United States showed no association between daily GERD symptoms and mortality, and there were inverse associations between weekly and less than weekly symptoms and mortality.[16] There has been no published population-based study from non-Western countries on the association between GERD and overall mortality.

The prevalence of GERD in population-based studies from Iran, a middle-income country in West Asia, is high and comparable to those in Western countries.[17,18] GERD is reported as the most common outpatient diagnosis in Iran[19] where the incidence of the disease seems to be increasing.[20] We aim to investigate the association of baseline data on frequency, the time of the first episode, and patient-perceived severity of GERD symptoms with overall and cause-specific mortality in the Golestan Cohort Study (GCS), a prospective cohort study of over 50000 residents of Golestan Province in northeastern Iran. As the majority of the studies on GERD symptoms and EC are hospital-based studies, the results of this study can provide additional information about this association at the general population level, with lower risk of bias related to selection of participants in hospital-based studies. EC has a very poor prognosis in this population,[21] so EC mortality is a good surrogate for the incidence of this cancer in Golestan. Also, results of this study can provide information about whether or not GERD symptoms are associated with causes of death other than EC, and if the symptoms are noticeably associated with overall mortality at the population level.

MATERIALS AND METHODS

Study population

The design of the GCS has been described elsewhere.[22] Briefly, the GCS is a prospective population-based cohort of 40–75 year old individuals, primarily designed to investigate risk factors of upper GI cancers in eastern parts of Golestan Province. The primary goal was to recruit 50000 healthy individuals, with equal numbers of men and women, 20% from urban areas and 80% of Turkmen ethnicity. Urban inhabitants in the specified age range were selected randomly from Gonbad, the main urban area in eastern Golestan by systematic clustering based on the household number. In rural areas, all residents of 326 villages in the study catchment area in the specified age range were invited to participate. A total of 50045 adults with no history of upper GI cancers were enrolled between 2004 and 2008. The participation rate was about 70% for women and 50% for men in urban areas and 84% for women and 70% for men in rural areas.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The conduct of GCS was approved by the Institutional Review Boards of the Digestive Disease Research Institue of Tehran University of Medical Sciences, the US National Cancer Insti-

tute, and the International Agency for Research on Cancer.

Exposure measurement

At baseline, trained nurses and physicians conducted face-to-face interviews using structured questionnaires to collect data on a large number of variables. Weight and height were measured by trained research staff. Body mass index (BMI) was calculated by dividing weight (kg) by the squared value of height (m).

Only trained physicians collected data on GERD and past medical history (including history of hypertension, diabetes mellitus, and heart disease) and measured blood pressure. They asked the study participants about the history of regurgitation and heartburn. Those with either symptom were considered as having GERD. The frequency of GERD symptoms was recorded as never; occasional or only associated with certain foods or drinks; 1–3 times/month; once a week; 2–6 times/week; or daily. We re-categorized the frequency for this analysis as never, <weekly, weekly (combination of 2–6 times/week and once a week), and daily. The first episode of GERD was recorded as within the last year, 1–5 years, 6–10 years, or >10 years before the interview. We also asked about the severity of symptoms, which were categorized as: "mild", the study participant did not feel the symptoms unless actively paid attention to; "moderate", the study participant felt the symptoms without active attention but they did not interfere with daily work or nighttime sleep; or "severe", symptoms interfering with daily work or causing nighttime awakenings.

The frequency and severity of GERD symptoms were asked separately for the past year and for one year prior to the interview. As the reported frequencies and severities for these two periods were similar (Supplementary Table 1) and we had another variable on the starting time of the symptoms, we combined the data and considered the most frequent and the most severe GERD symptoms in either of the two periods as the usual frequency and severity of symptoms, respectively, in that participant.

Systolic and diastolic blood pressures were obtained twice from each arm in the sitting position. Participants were considered to be hypertensive if they used anti-hypertensive medication or fulfilled standard criteria (average systolic blood pressure ≥140 mm Hg or average diastolic blood pressure above ≥90 mm Hg).[23] Diabetes mellitus was self-reported based on the following question 'Have you ever been diagnosed by a doctor as having diabetes mellitus?' Participants were also asked 'Have you ever been diagnosed by a doctor as having angina, infarction, or heart failure?' We considered those who gave a positive response to this question as participants with heart disease as a combined entity, because we expected that a substantial proportion of patients with heart disease in the study area, particularly in the rural areas, would not be able to distinguish different types of heart disease. Individuals who used alcohol, cigarettes, water-pipe, nass (a mixture of tobacco, lime, and ash), or opium at least once a week for a period of 6 months or more were considered as users of the respective substance. In accord with our earlier publications,[24] we calculated a composite score for wealth by applying multiple correspondence analysis to appliance ownership data (including personal car, motorbike, black and white TV, color TV, refrigerator, freezer, vacuum cleaner, and washing machine), and these scores were categorized in quintiles.

Follow-up of the cohort

Details of the follow-up process are reported elsewhere.[22,25] Briefly, all participants in the GCS were actively followed through annual telephone calls by local health workers in their communities and through a review of monthly provincial death registration reports. When the death of a cohort participant was reported, copies of all available and relevant medical documents for those participants were collected from hospitals and pathology laboratories in Golestan and neighboring provinces and a validated verbal autopsy questionnaire was completed through an interview of the closest relative of the deceased.[25] This questionnaire showed high accuracy (all measures of accuracy >81%) and reliability (kappa statistics >0.75), particularly for

Supplementary Table 1: Frequency and severity of gastroesophageal reflux disease (GERD) symptoms in the last year before the interview and earlier.

Frequency Last year	Before last year				
	Never	<Weekly	Weekly	Daily	Total
Never	19560 (79.94)	737 (4.09)	123 (3.80)	301 (7.08)	20721 (41.46)
<Weekly	3139 (12.83)	16595 (92.09)	193 (5.96)	284 (6.68)	20211 (40.44)
Weekly	798 (3.26)	360 (2.00)	2555 (78.96)	105 (2.47)	3818 (7.64)
Daily	972 (3.97)	328 (1.82)	365 (11.28)	3560 (83.76)	5225 (10.46)
Total	24469 (100)	18020 (100)	3236 (100)	4250 (100)	49975 (100)
Severity Last year	**Before last year**				
	Never	Mild	Moderate	Severe	Total
Never	19558 (79.88)	164 (4.50)	774 (4.38)	232 (5.59)	20728 (41.49)
Mild	1199 (4.89)	3086 (84.64)	342 (1.93)	55 (1.33)	4682 (9.36)
Moderate	3005 (12.27)	357 (9.79)	15837 (89.45)	388 (9.35)	19587 (39.18)
Severe	725 (2.96)	39 (1.07)	751 (4.24)	3473 (83.73)	4988 (9.98)
Total	24487 (100)	3646 (100)	17704 (100)	4148 (100)	49985 (100)

The weighted kappa statistic for the agreement between the two time periods was 0.75 for frequency and 0.76 for severity of GERD symptoms.
The severity of symptoms here is defined as: mild, the study participant did not feel the symptoms unless they actively paid attention; moderate, the study participant felt the symptoms without active attention, but they did not interfere with daily work; severe, symptoms interfering with daily work or causing nighttime awakenings.

major causes of death.[25] All collected documents have been reviewed by at least two expert physicians to determine the cause of death. The success rate of the follow-up for annually contacting the participants in the GCS has been ~ 99%, and loss to follow-up was negligible. This analysis was based on follow-up data through December 17, 2012.

In this report, circulatory mortality referred to death from ischemic heart disease, cerebrovascular event, and any other cardiovascular disorder. EC included all histological subtypes. Data on histological subtypes were not available for this analysis, but esophageal squamous cell carcinoma (ESCC) constituted approximately 90% of EC in this population.[26] External causes of death included death because of motor vehicle crashes, other unintentional injury, or suicide.

Statistical analysis

Less than 0.1% of the cohort participants had missing values in all GERD variables. These participants were excluded from the current analyses. The number of individuals with missing values in individual GERD variables was also small (<0.7% for each of the variables; Table 1), so those participants were excluded from the analyses of the respective variable. Numbers and percentages were calculated and presented for categorical variables, as well as means and standard deviations for continuous variables. Cox proportional hazards regression models were used throughout this study to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the association of the frequency (<weekly, weekly, or daily), onset time (<1, 1–5, 6–10, or >10 years before the interview), and severity (mild, moderate, or severe as defined above) of GERD symptoms with overall and cause-specific mortality. In order to reduce the effect of selection bias introduced by the inclusion of patients with GERD symptoms due to complications or treatment of symptoms of undiagnosed life-threatening conditions (including cancer) that led to death soon after recruitment in the study, we conducted a sensitivity analysis by excluding deaths that occurred in the first 2 years of follow-up. Also, in order to investigate the association between the most frequent GERD symptoms and mortality, we repeated our analysis after exclusion of those with ≤weekly

Table 1: Characteristics of 50,001 individuals with baseline data on gastroesophageal reflux disease in the Golestan Cohort Study (GCS).

Sociodemographic and lifestyle factors	N (%) *	Clinical conditions	N (%)
Age, years (continuous)	52.1 (9.0)	**Gastroesophageal reflux Frequency**	
Sex			
Women	28785 (57.57)	Never	19560 (39.12)
Men	21216 (42.43)	<Weekly	20471 (40.94)
Ethnicity		Weekly	4029 (8.06)
Non-Turkmen	12786 (25.57)	Daily	5915 (11.83)
Turkmen	37215 (74.43)	Missing	26 (0.05)
Residence		**Initial onset**	
Rural	39366 (78.73)	Never	19498 (39.00)
Urban	10634 (21.27)	<1 year ago	5326 (10.65)
Education		1 – 5 years ago	12534 (25.07)
No school	35089 (70.18)	6 – 10 years ago	4444 (8.89)
1 – 8th grade	10698 (21.39)	>10 years ago	7895 (15.79)
High School	3150 (6.30)	Missing	304 (0.61)
Higher	1064 (2.13)	**Severity**	
Wealth score		Never	19558 (39.12)
Quintile 1- lowest	13455 (26.91)	Mild	4449 (8.90)
Quintile 2	8469 (16.94)	Moderate	20315 (40.63)
Quintile 3	9790 (19.58)	Severe	5663 (11.33)
Quintile 4	8345 (16.69)	Missing	16 (0.03)
Quintile 5	9942 (19.88)	**Severity of daily symptoms**	
Body mass index (BMI)		Mild daily	328 (0.66)
<18.5 kg/m^2	2410 (4.82)	Moderate daily	3424 (6.85)
18.5 – 24.9	17914 (35.84)	Severe daily	2162 (4.32)
25 – 29.9	16958 (33.92)	Missing	37 (0.07)
≥30	12710 (25.42)	**Hypertension**	
Physical activity		Normotensive	28604 (57.46)
Irregular non-intense	30619 (61.44)	Hypertensive	21177 (42.54)
Regular non-intense	13524 (27.14)	**Self-reported diabetes**	
Regular or irregular intense	5691 (11.42)	No	46550 (93.10)
Cigarette smoking		Yes	3451 (6.90)
Never	41409 (82.84)	**Self-reported heart disease**	
0.1 – 5 pack-years	2764 (5.53)	No	46951 (93.90)
5.1 – 10	1261 (2.52)	Yes	3050 (6.10)
10.1 – 20	1799 (3.60)		
≥20	2753 (5.51)		
Ever hookah smoker	533 (1.07)		
Ever Nass chewer	3773 (7.55)		
Ever opium user	8477 (16.95)		
Ever alcohol drinker	1727 (3.45)		

* For age, the value is the mean age (standard deviation). Numbers may not add to the column total because of missing data.

symptoms. As an additional analysis, we examined the association between self-reported heart disease and severity of GERD symptoms using logistic regression models, in which self-reported heart disease was the outcome.

P-values for trend were obtained from the same models by assigning consecutive numbers to categories within each categorical variable. All statistical analyses were performed using Stata statistical software version 11 (Stata Corporation, College Station, Texas, USA). All reported P-values were two-sided and $P<0.05$ was considered to be statistically significant.

RESULTS

Baseline characteristics

Data on GERD were available for 50001 individuals. Baseline characteristics of this group are shown in Table 1. Mean age was 52.1 ± 9.0 years. Approximately 58% of participants were women, 26% were of non-Turkmen ethnic groups, and 79% resided in rural areas. The majority of participants had no formal education (70%), were overweight (59% with BMI ≥25 kg/m^2), and never smoked cigarettes (83%). Alcohol drinking was an uncommon practice (ever use<4%). Approximately 8% and 12% of participants had weekly and daily GERD symptoms, respectively. Approximately 16% of participants reported GERD symptoms with the first episode happening >10 years before the interview. Also, 11% and 4% of participants reported their symptoms as severe (any frequency) and severe daily, respectively. Approximately 43% of participants were hypertensive, 7% reported a history of diabetes and 6% reported a history of heart disease.

Gastroesophageal reflux disease (GERD) and overall mortality

During 313,281 person-years of follow-up (median follow-up of 6.4 years), 3107 deaths occurred in the cohort (Table 2). There were borderline associations between daily symptoms and symptoms starting <1 year ago and overall mortality. Severe GERD was associated with a modest increase in overall mortality (HR 1.15, 95% CI 1.03–1.29). After adjustments for hypertension and self-reported diabetes and heart disease, all above positive associations attenuated and became statistically non-significant. The attenuation in risk here and in other similar situations afterwards was mainly related to adjustment for heart disease (data not shown). On the other hand, weekly symptoms, symptoms that started 1–10 years before the interview, and mild and moderate symptoms were associated with a lower mortality. The results after exclusion of the first 2 years of follow-up were similar to overall results (Table 3).

After exclusion of those with ≤weekly symptoms (Table 4), the magnitude of associations between severe symptoms and overall mortality slightly increased (HR 1.27, 95% CI 1.08–1.49), but it attenuated after adjustment for hypertension, self-reported diabetes and heart disease (HR 1.14, 95% CI 0.97–1.35). Severe GERD was associated with overall mortality after exclusion of EC and overall cancer deaths from the analysis (Supplementary Table 2), but there was no statistically significant association after adjustment for history of medical conditions.

The severity of symptoms here is defined as: mild, the study participant did not feel the symptoms unless they actively paid attention; moderate, the study participant felt the symptoms without active attention, but they did not interfere with daily work; severe, symptoms interfering with daily work or causing nighttime awakenings.

Gastroesophageal reflux disease (GERD) and circulatory mortality

There were 1591 circulatory deaths (51.2% of all deaths) in this study (Table 2). Frequency of symptoms less than weekly, moderate symptoms, and longer duration of the time period between the onset of GERD symptoms and baseline interview were associated with a lower risk of circulatory mortality. These inverse associations were similar in major categories of circulatory diseases (isch-

Table 2: The association between gastroesophageal reflux disease (GERD) and mortality in the Golestan Cohort Study (GCS).

GERD symptoms	Overall mortality			Circulatory mortality			Cancer mortality			Esophageal cancer (EC) mortality		
	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)
Frequency												
Never	1240	Referent	Referent	656	Referent	Referent	269	Referent	Referent	55	Referent	Referent
<Weekly	1203	0.95 (0.87–1.02)	0.92 (0.85–1.00)	602	0.88 (0.79–0.99)	0.85 (0.76–0.95)	265	0.95 (0.80–1.13)	0.95 (0.80–1.13)	50	0.94 (0.64–1.38)	0.95 (0.64–1.40)
Weekly	238	0.90 (0.78–1.04)	0.85 (0.74–0.98)	118	0.83 (0.68–1.02)	0.75 (0.61–0.91)	48	0.87 (0.64–1.19)	0.88 (0.64–1.19)	8	0.73 (0.34–1.54)	0.76 (0.36–1.60)
Daily	425	1.11 (0.99–1.24)	1.04 (0.93–1.17)	215	1.03 (0.88–1.21)	0.92 (0.79–1.08)	97	1.21 (0.95–1.53)	1.21 (0.95–1.54)	21	1.24 (0.73–2.09)	1.29 (0.77–2.19)
p for trend		0.33	0.80		0.70	0.06		0.32	0.32		0.70	0.57
First start												
Never	1238	Referent	Referent	655	Referent	Referent	268	Referent	Referent	54	Referent	Referent
<1 year ago	356	1.12 (0.99–1.26)	1.09 (0.97–1.23)	179	1.05 (0.89–1.24)	1.01 (0.86–1.20)	76	1.10 (0.85–1.43)	1.10 (0.85–1.43)	7	0.43 (0.17–1.01)	0.44 (0.19–1.03)
1 – 5 years ago	714	0.94 (0.85–1.03)	0.90 (0.82–0.99)	359	0.88 (0.77–1.00)	0.82 (0.72–0.93)	153	0.94 (0.77–1.15)	0.94 (0.77–1.15)	33	1.03 (0.66–1.59)	1.05 (0.68–1.62)
6 – 10 years ago	242	0.89 (0.77–1.02)	0.85 (0.74–0.97)	131	0.89 (0.74–1.08)	0.82 (0.68–0.99)	54	0.91 (0.68–1.23)	0.92 (0.68–1.23)	7	0.63 (0.29–1.40)	0.66 (0.30–1.45)
>10 years ago	539	0.97 (0.88–1.08)	0.94 (0.85–1.04)	253	0.85 (0.73–0.98)	0.79 (0.68–0.92)	126	1.04 (0.84–1.29)	1.04 (0.84–1.29)	31	1.43 (0.91–2.25)	1.46 (0.93–2.29)
p for trend		0.14	0.02		0.008	<0.001		0.92	0.92		0.21	0.17
Severity												
Never	1240	Referent	Referent	656	Referent	Referent	269	Referent	Referent	55	Referent	Referent
Mild	242	0.88 (0.76–1.01)	0.86 (0.75–0.99)	130	0.87 (0.72–1.06)	0.85 (0.70–1.03)	53	0.91 (0.67–1.22)	0.91 (0.67–1.22)	11	0.96 (0.49–1.89)	0.97 (0.49–1.91)
Moderate	1206	0.94 (0.87–1.02)	0.91 (0.84–0.99)	597	0.87 (0.78–0.97)	0.82 (0.73–0.92)	268	0.96 (0.81–1.14)	0.96 (0.81–1.14)	49	0.90 (0.61–1.33)	0.92 (0.62–1.35)
Severe	418	1.15 (1.03–1.29)	1.07 (0.96–1.20)	208	1.06 (0.91–1.24)	0.94 (0.80–1.10)	89	1.13 (0.89–1.45)	1.14 (0.89–1.45)	19	1.21 (0.71–2.06)	1.27 (0.75–2.16)
p for trend		0.46	0.68		0.35	0.02		0.69	0.68		0.90	0.77
Total		3107			1591			679			134	

CI: Confidence interval; GERD: Gastroesophageal reflux disease; HR: Hazard ratio; N: Number of deaths.
HR1 (95% CIs) are adjusted for the sociodemographic and lifestyle factors shown in Table 1; HR2 (95% CIs) are additionally adjusted for hypertension, self-reported diabetes and heart disease. The severity of symptoms here is defined as: mild, the study participant did not feel the symptoms unless they actively paid attention; moderate, the study participant felt the symptoms without active attention, but they did not interfere with daily work; and severe, symptoms interfering with daily work or causing nighttime awakenings

Table 3: The association between gastroesophageal reflux disease (GERD) and mortality after exclusion of deaths in the first two years of follow-up in the Golestan Cohort Study (GCS).

GERD symptoms	Overall mortality			Circulatory mortality			Cancer mortality			Esophageal cancer (EC) mortality		
	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)
Frequency												
Never	916	Referent	Referent	479	Referent	Referent	204	Referent	Referent	44	Referent	Referent
<Weekly	888	0.93 (0.85–1.02)	0.92 (0.84–1.01)	432	0.85 (0.74–0.97)	0.83 (0.73–0.95)	201	0.93 (0.76–1.14)	0.93 (0.76–1.14)	35	0.81 (0.52–1.27)	0.84 (0.53–1.32)
Weekly	175	0.89 (0.76–1.05)	0.84 (0.71–0.99)	90	0.85 (0.68–1.07)	0.76 (0.61–0.96)	31	0.74 (0.51–1.09)	0.75 (0.51–1.09)	7	0.79 (0.35–1.77)	0.83 (0.37–1.87)
Daily	304	1.08 (0.94–1.23)	1.00 (0.88–1.15)	160	1.05 (0.87–1.26)	0.92 (0.77–1.11)	65	1.08 (0.81–1.45)	1.09 (0.81–1.45)	13	0.96 (0.50–1.84)	1.01 (0.52–1.94)
p for trend		0.73	0.45		0.87	0.12		0.90	0.93		0.69	0.83
First start												
Never	915	Referent	Referent	478	Referent	Referent	204	Referent	Referent	44	Referent	Referent
<1 year ago	240	1.01 (0.88–1.17)	1.00 (0.87–1.16)	122	0.97 (0.79–1.19)	0.95 (0.78–1.17)	46	0.87 (0.62–1.21)	0.87 (0.63–1.22)	4	0.27 (0.08–0.86)	0.28 (0.09–0.89)
1 – 5 years ago	525	0.93 (0.83–1.03)	0.90 (0.80–1.00)	257	0.85 (0.73–0.99)	0.80 (0.69–0.94)	118	0.95 (0.75–1.20)	0.95 (0.76–1.21)	23	0.88 (0.53–1.46)	0.91 (0.54–1.52)
6 – 10 years ago	181	0.89 (0.76–1.05)	0.85 (0.72–1.00)	95	0.87 (0.70–1.09)	0.79 (0.63–0.99)	40	0.88 (0.63–1.25)	0.89 (0.64–1.27)	6	0.66 (0.28–1.56)	0.70 (0.30–1.65)
>10 years ago	408	0.97 (0.86–1.09)	0.95 (0.84–1.07)	197	0.87 (0.73–1.03)	0.83 (0.70–0.98)	92	0.98 (0.76–1.27)	0.99 (0.77–1.28)	21	1.17 (0.69–1.99)	1.22 (0.72–2.08)
p for trend		0.26	0.09		0.04	0.004		0.70	0.77		0.69	0.57
Severity												
Never	916	Referent	Referent	479	Referent	Referent	204	Referent	Referent	44	Referent	Referent
Mild	173	0.84 (0.71–0.99)	0.84 (0.71–0.99)	94	0.85 (0.68–1.06)	0.84 (0.67–1.05)	36	0.79 (0.55–1.13)	0.80 (0.56–1.15)	7	0.71 (0.30–1.66)	0.72 (0.31–1.70)
Moderate	874	0.91 (0.83–1.00)	0.89 (0.81–0.98)	430	0.84 (0.74–0.96)	0.80 (0.70–0.92)	188	0.88 (0.72–1.08)	0.88 (0.72–1.08)	33	0.76 (0.48–1.20)	0.79 (0.50–1.25)
Severe	319	1.17 (1.03–1.33)	1.11 (0.97–1.27)	158	1.07 (0.89–1.29)	0.97 (0.81–1.17)	73	1.22 (0.93–1.61)	1.23 (0.94–1.62)	15	1.20 (0.66–2.18)	1.28 (0.70–2.33)
p for trend		0.61	0.74		0.34	0.05		0.77	0.76		0.77	0.95
Total	2283			1161			501			99		

CI: Confidence interval; GERD: Gastroesophageal reflux disease; HR: Hazard ratio; N: Number of deaths.
HR1 (95% CIs) are adjusted for the sociodemographic and lifestyle factors shown in Table 1; HR2 (95% CIs) are additionally adjusted for hypertension, self-reported diabetes and heart disease. The severity of symptoms here is defined as: mild, the study participant did not feel the symptoms unless they actively paid attention; moderate, the study participant felt the symptoms without active attention, but they did not interfere with daily work; severe, symptoms interfering with daily work or causing nighttime awakenings.

Table 4: The association of daily and severity of daily gastroesophageal reflux disease (GERD) symptoms with mortality (excluding those with ≤weekly symptoms).

GERD symptoms	Overall mortality			Circulatory mortality			Cancer mortality			Esophageal cancer (EC) mortality		
	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)
All participants Any daily symptoms												
No	1240	Referent	Referent	656	Referent	Referent	269	Referent	Referent	55	Referent	Referent
Yes	425	1.13 (1.01-1.27)	1.04 (0.92-1.16)	215	1.05 (0.89-1.23)	0.89 (0.76-1.05)	97	1.23 (0.97-1.57)	1.25 (0.98-1.60)	21	1.30 (0.76-2.22)	1.38 (0.81-2.36)
Severity												
Never	1240	Referent	Referent	656	Referent	Referent	269	Referent	Referent	55	Referent	Referent
Mild	18	0.88 (0.55-1.42)	0.85 (0.52-1.40)	11	1.04 (0.57-1.89)	0.98 (0.52-1.84)	6	1.35 (0.56-3.28)	1.38 (0.57-3.36)	1	Incalculable	Incalculable
Moderate	235	1.07 (0.92-1.23)	0.98 (0.85-1.14)	125	1.03 (0.85-1.26)	0.89 (0.73-1.09)	51	1.12 (0.82-1.52)	1.12 (0.82-1.53)	11	1.23 (0.63-2.40)	1.29 (0.66-2.51)
Severe	172	1.27 (1.08-1.49)	1.14 (0.97-1.35)	79	1.07 (0.85-1.36)	0.87 (0.69-1.11)	40	1.40 (1.00-1.97)	1.48 (1.04-2.05)	9	1.57 (0.76-3.25)	1.73 (0.84-2.58)
p for trend		0.01	0.31		0.54	0.16		0.06	0.04		0.22	0.14
After exclusion of first 2 years of follow-up Any daily symptoms												
No	916	Referent	Referent	479	Referent	Referent	204	Referent	Referent	44	Referent	Referent
Yes	304	1.09 (0.95–1.25)	1.01 (0.88–1.16)	160	1.06 (0.88–1.27)	0.92 (0.76–1.11)	65	1.12 (0.83–1.50)	1.13 (0.84–1.52)	13	1.04 (0.54–2.01)	1.10 (0.56–2.14)
Severity												
Never	916	Referent	Referent	479	Referent	Referent	204	Referent	Referent	44	Referent	Referent
Mild	14	0.90 (0.52–1.55)	0.86 (0.49–1.52)	9	1.14 (0.59–2.21)	1.06 (0.53–2.14)	5	1.41 (0.52–3.80)	1.45 (0.54–3.91)	1	Incalculable	Incalculable
Moderate	163	1.00 (0.84–1.18)	0.93 (0.78–1.00)	93	1.04 (0.83–1.31)	0.92 (0.73–1.15)	27	0.79 (0.52–1.20)	0.80 (0.53–1.21)	5	0.75 (0.29–1.91)	0.77 (0.30–1.99)
Severe	127	1.26 (1.04–1.53)	1.17 (0.96–1.42)	58	1.07 (0.81–1.41)	0.91 (0.69–1.21)	33	1.58 (1.09–2.31)	1.63 (1.12–2.39)	7	1.65 (0.72–3.74)	1.81 (0.79–4.14)
p for trend		0.08	0.49		0.58	0.38		0.21	0.17		0.58	0.45

CI: Confidence interval; GERD: Gastroesophageal reflux disease; HR: Hazard ratio; N: Number of deaths.
HR1 (95% CIs) are adjusted for the sociodemographic and lifestyle factors shown in Table 1; HR2 (95% CIs) are additionally adjusted for hypertension, self-reported diabetes and heart disease. The severity of symptoms here is defined as: mild, the study participant did not feel the symptoms unless they actively paid attention; moderate, the study participant felt the symptoms without active attention, but they did not interfere with daily work; severe, symptoms interfering with daily work or causing nighttime awakenings.

emic heart disease and cerebrovascular event), although due to smaller numbers of deaths in those categories, the 95% CIs generally included the unity (Supplementary Table 3) and they persisted after exclusion of the first 2 years of follow-up (Table 3).

Self-reported heart disease and severity of GERD symptoms were correlated (Supplementary Table 4). The inverse association between GERD symp-

Supplementary Table 2: The association between severity of gastroesophageal reflux disease (GERD) symptoms and overall mortality after exclusion of esophageal cancer (EC) and all cancer deaths.

Severity of symptoms	Overall mortality All follow-up			Excluding those with≤weekly symptoms			Excluding those with≤weekly symptoms and first 2 years of follow-up		
	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)
Excluding EC deaths									
Never	1185	Referent	Referent	872	Referent	Referent	872	Referent	Referent
Mild	231	0.87 (0.76–1.01)	0.87 (0.75–1.00)	166	0.91 (0.57–1.48)	0.89 (0.54–1.46)	13	0.94 (0.54–1.62)	0.90 (0.51–1.59)
Moderate	1157	0.94 (0.87–1.02)	0.91 (0.83–0.99)	841	1.06 (0.91–1.23)	0.97 (0.84–1.13)	158	1.01 (0.85–1.20)	0.93 (0.78–1.11)
Severe	399	1.15 (1.03–1.29)	1.07 (0.95–1.20)	304	1.25 (1.06–1.48)	1.12 (0.94–1.33)	120	1.25 (1.03–1.52)	1.15 (0.94–1.40)
p for trend		0.45	0.61		0.02	0.45		0.09	0.57
Excluding all cancer deaths									
Never	971	Referent	Referent	712	Referent	Referent	712	Referent	Referent
Mild	189	0.87 (0.74–1.02)	0.86 (0.73–1.01)	137	0.78 (0.44–1.38)	0.73 (0.40–1.33)	9	0.78 (0.41–1.51)	0.72 (0.36–1.45)
Moderate	938	0.93 (0.85–1.02)	0.89 (0.81–0.98)	686	1.05 (0.89–1.24)	0.95 (0.80–1.12)	136	1.05 (0.87–1.26)	0.95 (0.78–1.15)
Severe	329	1.16 (1.02–1.32)	1.06 (0.94–1.21)	246	1.24 (1.02–1.49)	1.07 (0.89–1.29)	94	1.18 (0.95–1.48)	1.07 (0.85–1.33)
p for trend		0.51	0.48		0.05	0.89		0.19	0.93

CI: Confidence interval; EC: Esophageal cancer; GERD: Gastroesophageal reflux disease; HR: Hazard ratio; N: Number of deaths.
HR1 (95% CIs) are adjusted for the sociodemographic and lifestyle factors shown in Table 1; HR2 (95% CIs) are additionally adjusted for hypertension, self-reported diabetes and heart disease. The severity of symptoms here is defined as: mild, the study participant did not feel the symptoms unless they actively paid attention; moderate, the study participant felt the symptoms without active attention, but they did not interfere with daily work; severe, symptoms interfering with daily work or causing nighttime awakenings.

toms and circulatory mortality was mainly observed among those with self-reported heart disease.

Gastroesophageal reflux disease (GERD) and cancer mortality

There were 679 cancer deaths overall and 134 EC deaths (21.9% and 4.2% of all deaths, respectively) in this study. Daily and severe symptoms showed statistically non-significant associations with cancer and EC mortality; there was a similar association between earlier onset of GERD symptom and EC. Adjustments for clinical conditions had little influence on the association between GERD and cancer or EC mortality.

After exclusion of those with ≤weekly symptoms (Table 4), the association between severe symptoms and cancer mortality became statistically significant (HR 1.48, 95% CI 1.04–2.05). The magnitude of association between severe daily symptoms and EC was stronger than that of the above association, but the number of EC deaths was smaller than the number of all cancers, and the 95% CI for the association between EC mortality and GERD included the unity. After exclusion of the first 2 years of follow-up, severe daily symptoms were associated with death from cancers other than EC, even after adjustments for medical conditions (Table 5). Data for some of individual cancer types were available, but the number of those cancers was generally much smaller than the number of EC cases, and mortality from none of those cancer sites showed significant associations with GERD symptoms (data not shown).

Gastroesophageal reflux disease (GERD) and mortality from other causes of death

Supplementary Table 3: The association between gastroesophageal reflux disease (GERD) and death from categories of circulatory diseases after exclusion of deaths in the first two years of follow-up.

GERD symptoms	All circulatory disorders		Ischemic heart disease		Other cardiovascular disorders		Cerebrovascular event	
	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)
Frequency								
Never	479	Referent	283	Referent	156	Referent	40	Referent
<Weekly	432	0.85 (0.74–0.97)	259	0.87 (0.73–1.03)	144	0.86 (0.68–1.08)	29	0.67 (0.41–1.08)
Weekly	90	0.85 (0.68–1.07)	45	0.75 (0.55–1.03)	36	1.01 (0.69–1.46)	9	0.94 (0.45–1.96)
Daily	160	1.05 (0.87–1.26)	93	1.06 (0.84–1.35)	51	0.99 (0.71–1.37)	16	1.13 (0.63–2.05)
p for trend	0.87		0.79		0.91		0.77	
First start								
Never	478	Referent	282	Referent	156	Referent	40	Referent
<1 year ago	122	0.97 (0.79–1.19)	73	1.01 (0.78–1.32)	43	1.01 (0.72–1.43)	6	0.51 (0.21–1.20)
1 – 5 years ago	257	0.85 (0.73–0.99)	159	0.91 (0.75–1.11)	81	0.81 (0.62–1.06)	17	0.62 (0.35–1.10)
6 – 10 years ago	95	0.87 (0.70–1.09)	47	0.73 (0.53–1.00)	38	1.07 (0.75–1.53)	10	1.07 (0.53–2.14)
>10 years ago	197	0.87 (0.73–1.03)	112	0.85 (0.68–1.07)	65	0.85 (0.63–1.14)	20	1.07 (0.62–1.85)
p for trend	0.04		0.05		0.28		0.83	
Severity								
Never	479	Referent	283	Referent	156	Referent	40	Referent
Mild	94	0.85 (0.68–1.06)	60	0.91 (0.69–1.21)	31	0.86 (0.57–1.28)	3	0.34 (0.10–1.09)
Moderate	430	0.84 (0.74–0.96)	251	0.85 (0.71–1.01)	139	0.82 (0.65–1.04)	40	0.90 (0.58–1.40)
Severe	158	1.07 (0.89–1.29)	86	1.02 (0.80–1.31)	61	1.24 (0.91–1.67)	11	0.79 (0.40–1.54)
p for trend	0.34		0.31		0.97		0.55	
Total	1161		680		387		94	

The association between daily GERD and other causes of mortality are shown in Table 6. The HRs for some of the associations, including for respiratory, infectious, genitourinary, and neurologic deaths were slightly above or below unity, but these were based on modest numbers of death and none reached statistical significance after exclusion of the first two years of follow-up.

DISCUSSION

We found an association between severe symptoms defined as symptoms that interfered with daily work or caused nighttime awakenings, and occurred on a daily basis (reported by 4.3% of participants) to overall cancer and EC mortality. This association persisted even after exclusion of the first two years of follow-up and adjustments for hypertension, self-reported diabetes and heart disease. There was also a slight increase in overall mortality associated with severe GERD, but the association disappeared after adjustments for the above medical conditions. On the other hand, non-daily and mild to moderate GERD symptoms was associated with a slight reduction in risk of death from circulatory disorders. Overall mortality was not associated with onset time or frequency of GERD and was not increased with mild to moderate symptoms.

Gastroesophageal reflux disease (GERD) symptoms and cancer and overall mortality

The results of our study suggested an association between severe daily GERD and EC. Although the association was not statistically significant, it was probably due to a modest number of EC cases with severe daily symptoms. The association between GERD and EC deaths reported in this and Solaymani-Dodaran et al.[13] studies seemed to be mechanistically plausible and was supported by several other studies.[27] In our study, severe daily symptoms were also associated

Supplementary Table 4: The association between severity of gastroesophageal reflux disease (GERD) symptoms and self-reported heart disease and between severity of GERD symptoms and circulatory mortality by self-reported heart disease status.

Severity of symptoms	Association between self-reported heart disease and severity of reflux		Circulatory mortality			
			Among those with self-reported heart disease		Among those without self-reported heart disease	
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
Never	875	Referent	124	Referent	532	Referent
Mild	241	1.16 (1.00–1.35)	23	0.64 (0.41–1.01)	107	0.90 (0.73-1.11)
Moderate	1354	1.45 (1.33–1.59)	155	0.81 (0.64–1.03)	442	0.82 (0.72-0.93)
Severe	580	2.36 (2.10–2.64)	55	0.72 (0.52–0.99)	153	1.03 (0.86-1.24)
p for trend		<0.001		0.04		0.09

CI: Confidence interval; GERD: Gastroesophageal reflux disease; HR: Hazard ratio; N: Number of deaths; OR: Odds ratio.
ORs and HRs (95% CIs) are adjusted for the sociodemographic and lifestyle factors shown in Table 1. Odds ratios (95% CIs) for the association between self-reported heart disease and reflux severity was calculated using logistic regression models in which self-reported heart disease was the dependent variable.

Table 5: The association between onset time and severity of daily GERD symptoms and cancer mortality after exclusion of cases of esophageal cancer mortality

Severity of symptoms	Cancer mortality All follow-up			Excluding those with ≤weekly symptoms			Excluding those with ≤weekly symptoms and first 2 years of follow-up		
	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)
Excluding EC deaths									
Never	1185	Referent	Referent	872	Referent	Referent	872	Referent	Referent
Mild	231	0.90 (0.64–1.25)	0.91 (0.65–1.26)	166	1.67 (0.69–4.08)	1.71 (0.70–4.19)	13	1.78 (0.65–4.82)	1.84 (0.68–4.99)
Moderate	1157	0.98 (0.81–1.18)	0.96 (0.79–1.17)	841	1.09 (0.77–1.54)	1.08 (0.76–1.54)	158	0.81 (0.51–1.29)	0.81 (0.51–1.28)
Severe	399	1.12 (0.85–1.48)	1.13 (0.85–1.48)	304	1.37 (0.93–2.01)	1.40 (0.95–2.06)	120	1.58 (1.03–2.42)	1.61 (1.05–2.47)
p for trend		0.68	0.74		0.14	0.12		0.24	0.23

CI: confidence interval; GERD, gastroesophageal reflux disease; HR, hazard ratio; N, number of deaths.
HR1 (95% CIs) are adjusted for the sociodemographic and lifestyle factors shown in Table 1; HR2 (95% CIs) are additionally adjusted for hypertension and self-reported diabetes and heart disease. The severity of symptoms here was defined as: mild, the study participant did not feel the symptoms unless they actively paid attention; moderate, the study participant felt the symptoms without active attention, but they did not interfere with daily work; severe, symptoms interfering with daily work or causing nighttime awakenings.

with death from cancers other than EC after exclusion of the first two years of follow-up. As the numbers of individual cancers in our study were modest, these associations necessitate further investigation.

A study by Solaymani-Dodaran et al. was the only other study that has reported an association between GERD and increased mortality beyond one year of follow-up, suggested a modest increase in the risk, with HRs of 1.16 in individuals with GERD but without esophagitis or Barrett's esophagus, 1.16 in individuals with esophagitis, and 1.37 in individuals with Barrett's esophagus.[13] Similar to our study, the associations were attenuated after adjustment for history of ischemic heart disease: the HR (95% CI) for the first group (GERD without histological change) was 1.09 (0.95–1.26) after the adjustment.[13] This indicated

Table 6: The association between severe daily GERD symptoms and other causes of mortality

Cause of death	N Total	All follow-up excluding those with ≤weekly symptoms			Excluding first 2 years of follow-up and those with ≤weekly symptoms		
		N	HR1 (95% CI)	HR2 (95% CI)	N	HR1 (95% CI)	HR2 (95% CI)
Respiratory	160	78	1.13 (0.68–1.90)	1.16 (0.69–1.96)	58	1.32 (0.73–2.37)	1.38 (0.76–2.49)
Digestive	87	47	1.22 (0.63–2.39)	1.22 (0.62–2.38)	33	1.11 (0.50–2.47)	1.14 (0.51–2.53)
Infectious	83	39	0.62 (0.27–1.44)	0.58 (0.25–1.37)	30	0.73 (0.29–1.85)	0.70 (0.27–1.80)
Genitourinary	79	46	2.09 (1.13–3.87)	1.88 (1.00–3.53)	34	1.53 (0.73–3.19)	1.44 (0.68–3.02)
Endocrine	50	27	0.93 (0.38–2.29)	0.67 (0.27–1.70)	18	1.13 (0.39–3.32)	0.79 (0.26–2.38)
Neurologic	34	13	2.11 (0.59–7.52)	2.31 (0.65–8.27)	11	2.90 (0.75–11.27)	3.25 (0.83–12.77)
External	194	107	1.14 (0.70–1.85)	1.12 (0.69–1.82)	69	0.96 (0.50–1.82)	0.96 (0.50–1.83)
Unknown	136	63	1.44 (0.82–2.55)	1.45 (0.81–2.58)	53	0.96 (0.49–1.87)	0.96 (0.49–1.89)
Other	14	8	Incalculable *	Incalculable *	6	Incalculable *	Incalculable *

CI: confidence interval; GERD, gastroesophageal reflux disease; HR, hazard ratio; N, number of deaths.
The causes of death in this table do not include cancer or circulatory deaths. All HRs (95% CIs) are the risk of mortality associated with severe GERD symptoms (vs. no symptoms). Results for mild and moderate symptoms are not shown here.
HR1 (95% CIs) are adjusted for the sociodemographic and lifestyle factors shown in Table 1; HR2 (95% CIs) are additionally adjusted for hypertension and self-reported diabetes and heart disease. The severity of symptoms here was defined as: mild, the study participant did not feel the symptoms unless they actively paid attention; moderate, the study participant felt the symptoms without active attention, but they did not interfere with daily work; severe, symptoms interfering with daily work or causing nighttime awakenings.
* None of those who died in this category had daily severe GERD.

that a major part of the observed associations were unlikely to be causal and might be explained by other medical conditions. The effect of other chronic diseases appeared to be similar across different populations because the observed association in this Iranian population and in the UK population[13] were very similar. These results also indicated that the increased risk of EC or overall cancer associated with GERD was too small to noticeably affect overall mortality.

Inverse association between gastroesophageal reflux disease (GERD) symptoms and circulatory mortality

Another study also reported an inverse association between weekly and less than weekly GERD and mortality in the United States.[16] As circulatory diseases are the major causes of death in the United States,[28] it is likely that this inverse association was mainly related to circulatory diseases, consistent with our finding. The reason for this inverse association is unclear. However, it may not be causal. The positive association between GERD symptoms and self-reported heart disease suggest that people with known heart disease may be at higher risk of GERD due to treatment of heart disease, or individuals with GERD may refer to physicians more frequently, and because of this any heart disease is more likely to be diagnosed. This may also explain the stronger inverse association between GERD symptoms and circulatory mortality among those with known heart disease; those with undiagnosed heart disease may be more likely to present with more severe complications. Nevertheless, we do not have the data to examine this hypothesis appropriately.

Clinical implications of the results

The association between GERD and cancer mortality in this study was modest and observed only among those with severe symptoms. This has shown that the majority of individuals with GERD can also be reassured that mild or moderate GERD per se is not associated with an increased risk of death. This may reduce the extent of potential anxiety associated with the symptoms and may improve the patients' quality of life. Many individuals with GERD may be exposed to information about the association between GERD and some serious conditions, such as EAC. This may induce stress and anxiety in those individuals, as they may think that the ultimate outcome of GERD will be life-threatening. Thus individuals may repeatedly seek medical care; on the other hand, in some cases it

may cause patients to avoid seeking appropriate medical care because of their fear.[29] Furthermore, as GERD may be associated with stress,[30-32] any anxiety associated with GERD may exacerbate the symptoms. The results of this population-based study further support the results of hospital-based studies reporting a low risk of EAC in individuals with GERD, even in those with Barrett's esophagus.[12]

Generalization of the results of this study to other populations

Golestan Province has one of the highest incidence rates for EC worldwide, with age-standardized rates (ASRs) of 70.7 (men) and 42.6 (women) per 100,000 person-years in the eastern parts of the province.[33] Although the incidence of EAC in Golestan seems to be increasing,[34] ESCC is still much more common than EAC in Golestan,[26] whereas in the United States and several European countries, EAC now considerably outnumbers ESCC.[35,36] As EAC is the major fatal disease with a known association to GERD, one may argue that the results of this study may not be generalizable to the Western countries. However, although the incidence of EAC has increased in Western countries, EC overall and EAC are relatively rare cancers in those populations. For example, the ASRs for incidence (per 100,000 person-years) of EC overall in more developed countries (as defined by the United Nations: all regions of Europe plus Northern America, Australia/New Zealand and Japan) in 2008 have been reported as 6.5 in men and 1.2 in women, which was a small part of total cancer incidence rates in those regions (300.1 in men and 225.5 in women).[37] The ASR per 100,000 person-years for EAC incidence in 2009 was estimated as 2.7 in the United States (5.3 for men and 0.9 for women)[38] and 1.9 in Golestan Province (3.0 for men and 0.8 for women).[34] This information suggests that there is only a modest difference in the incidence of EAC cases in Golestan and Western countries, supporting the generalizability of our results to those populations in this regard. The similarity of the results of this and the Solaymani-Dodaran et al.[13] studies may further support this notion.

Strength and limitation of the study

Some major strengths of this study are the large sample size and the relatively high number of outcomes of interest, which has enabled us to investigate the associations by cause-specific mortality; collection of detailed information on GERD; and adjustment of the results for multiple potential confounding factors. On the other hand, we did not have data on morphologic or histological status of the esophageal lining of the study participants, so we were not able to examine the associations by these factors. The natural history of GERD-related lesions may be best studied in hospital-based follow-up studies of patients with confirmed lesions. In some populations, however, some individuals may not be included in the studies that require diagnostic interventions, such as upper GI endoscopy, as a result of their limited access to clinical care or their concerns about the procedure (selection bias). Therefore, it can be informative to also examine the association between GERD and mortality in large-scale population studies with minimal risk of the above bias.

The history of diabetes and heart disease was based on self-reports, but similar to many other large population-based studies, this was the only source for gathering such information. It was logistically impossible to do diagnostic workups for those diseases in this study. However, as adjustments for diabetes and heart disease based on known, self-reported cases of these conditions did not change the associations between GERD and EC or overall cancer, which were positive findings of this study. We do not expect that diabetes and heart disease are major confounding factors for these associations. Therefore, identifying undiagnosed cases of these medical conditions and including them in the analyses is unlikely to change the results substantially.

The results of this study suggest that cancer mortality may causally be associated with GERD, but any association between GERD and other causes of mortality may not be causal and is explainable by other chronic diseases, notably heart disease. The majority of those with GERD can be reassured that mild or moderate GERD per se are not associated with increased risk of death. This may reduce the extent of potential anxiety associated with the symptoms.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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