All-cause and cancer-specific mortality in GORD in a population-based cohort study (the HUNT study)

Ness-Jensen, Eivind; Gottlieb-Vedi, Eivind; Wahlin, Karl; Lagergren, Jesper

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TITLE PAGE

Title: All-cause and cancer-specific mortality in gastro-oesophageal reflux disease in a population-based cohort study (the HUNT study)

Corresponding author: Eivind Ness-Jensen, MD PhD

Postal address: Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, 171 76 Stockholm, Sweden

E-mail: eivind.ness-jensen@ntnu.no

Telephone number: +47 918 60 549

Authors: Eivind Ness-Jensen, MD PhD[1,2,3]; Eivind Gottlieb-Vedi[1]; Karl Wahlin, PhD[1]; Jesper Lagergren, MD PhD[1,4]

[1]Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

[2]HUNT Research Centre, Department of Public Health and General Practice, NTNU, Norwegian University of Science and Technology, Levanger, Norway

[3]Medical Department, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway

[4]Division of Cancer Studies, King's College London, London, United Kingdom

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Abbreviations:

BMI: body mass index

CI: confidence interval

ICD: International Classification of Diseases

GORD: gastro-oesophageal reflux disease

HUNT: the Nord-Trøndelag health study

HR: hazard ratio

ABSTRACT

Objective: Gastro-oesophageal reflux is a public health concern which could have associated oesophageal complications, including adenocarcinoma, and possibly also head-and-neck and lung cancer. The aim of this study was to test the hypothesis that reflux increases all-cause and cancer-specific mortality in an unselected cohort.

Design: The Nord-Trøndelag health study (HUNT), a Norwegian population-based cohort study, was used to identify individuals with and without reflux in 1995-1997 and 2006-2008, with follow-up until 2014. All-cause and cancer-specific mortality were assessed from the Norwegian Causes of Death Registry and Cancer Registry. Multivariable Cox-regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for mortality with adjustments for potential confounders.

Results: We included 4,758 participants with severe reflux symptoms and 51,381 participants without reflux symptoms, contributing 60,323 and 747,239 person-years at risk, respectively. Severe reflux was not associated with all-cause mortality, overall cancer-specific mortality, or mortality in cancer of the head-and-neck or lung. However, for men with severe reflux a 6-fold increase in oesophageal adenocarcinoma-specific mortality was found (HR 6.09, 95% CI 2.33 to 15.93) and the mortality rate was 0.27 per 1000 person-years. For women, the corresponding mortality was not significantly increased (HR 3.68, 95% CI 0.88 to 15.27) and the mortality rate was 0.05 per 1000 person-years.

Conclusion: Individuals with severe reflux symptoms do not seem to have increased all-cause mortality or overall cancer-specific mortality. Although the absolute risk is small, individuals with severe reflux symptoms have a clearly increased oesophageal adenocarcinoma-specific mortality.

What is already known about this subject?

- Gastro-oesophageal reflux disease is defined by troublesome symptoms of heartburn or regurgitation
- Gastro-oesophageal reflux disease is frequent in Western populations and the prevalence is increasing
- Gastro-oesophageal reflux disease is associated with several complications, including oesophageal adenocarcinoma and possibly cancers of the head-and-neck and lung.

What are the new findings?

- Severe reflux symptoms were not associated with any increased all-cause mortality, overall cancer-specific mortality, or head-and-neck and lung cancer-specific mortality
- Severe reflux symptoms were associated with increased oesophageal adenocarcinoma-specific mortality
- As only 14 of 4,758 individuals with severe reflux symptoms were diagnosed with oesophageal adenocarcinoma, the absolute risk is low

How might it impact on clinical practice in the foreseeable future?

- Gastro-oesophageal reflux disease can be considered a benign disorder with no increased all-cause mortality. However, the clinician should be aware of the clear association with oesophageal adenocarcinoma and oesophageal adenocarcinoma-specific mortality, and rapid endoscopy should be performed if suspected

INTRODUCTION

Gastro-oesophageal reflux disease (GORD) is a public health concern that affects as many as 10-30% of the adult population in Western countries and the prevalence is increasing [1 2]. The main established risk factors for GORD are heredity, obesity, and tobacco smoking [3-5]. GORD is defined by troublesome symptoms of heartburn or regurgitation, and is associated with substantial reductions in health-related quality of life and coincides with several other conditions, including sleep problems, asthma and other respiratory disorders [6-9]. Complications of GORD include oesophagitis, peptic strictures of the oesophagus, Barrett's oesophagus, and oesophageal and oesophagogastric junctional adenocarcinomas [10 11]. Oesophageal and junctional adenocarcinomas are characterized by poor prognosis with a 5-year survival below 20%, increasing incidence, and a male predominance [12-14]. GORD is also associated with some extra-oesophageal cancers, including head-and-neck and lung cancer [15-17]. Despite the fact that GORD is associated with all these conditions, few studies have examined whether GORD is associated with a reduced overall prognosis or increased risk of cancer-specific mortality. The results from the available literature are conflicting [18-20].

As the risk of oesophageal adenocarcinoma is known to be increased in reflux, we expected to find increased mortality from oesophageal adenocarcinoma and, thereby, also increased overall cancer-specific and all-cause mortality. Due to the association with head-and-neck and lung cancer, we also expected to find increased mortality from these cancers. The aim of this study was to test these hypotheses in a large and unselected cohort of individuals.

METHODS

Design

For the purpose of this study, data from the Norwegian population-based cohort study, the Nord-Trøndelag health study (HUNT), was used. All residents of Nord-Trøndelag county aged 20 years and older were invited to participate in three consecutive health surveys: HUNT1 (January 1, 1984 to February 28, 1986), HUNT2 (August 1, 1995 to June 30, 1997) and HUNT3 (October 1, 2006 to June 30, 2008). In addition, a separate questionnaire was sent to non-participants after HUNT3 in 2009 (questionnaire for nonparticipants). HUNT includes questionnaires that cover a wide range of health-related information, including reflux symptoms, lifestyle factors, and clinical measurements. Data on reflux symptoms were available in HUNT2, HUNT3, and the questionnaire for nonparticipants. Further information on data collection and design is available elsewhere [21]. Follow-up started from the initiation of HUNT2 (August 1, 1995) until the end of the study (December 31, 2014), thus defining the study period. If an individual participated in both HUNT2 and HUNT3 or the questionnaire for nonparticipants, follow-up started at date of participation in HUNT2.

Follow-up involved linking the HUNT data to the Norwegian Cancer Registry and the Norwegian Cause of Death Registry, using the 11-digit national identity number assigned to each Norwegian resident. All deaths in Norway are registered in the Norwegian Cause of Death Registry and the Cancer Registry of Norway has a high level of completeness (98.8% in 2001-2005) [22 23]. In addition, HUNT receives updated information on emigration from Statistics Norway every quarter. Participants diagnosed with any cancer before participation in HUNT were excluded.

Exposure

The study exposure was severe reflux symptoms. In HUNT2, HUNT3, and the questionnaire for nonparticipants the participants were asked "to what degree have you had heartburn or acid regurgitation in the last 12 months?" and answered according to three alternatives: "no", "minor" or "severe" complaints. Participants reporting severe complaints were defined as exposed, and those reporting no complaints as unexposed. This definition of severe reflux has been validated with excellent results in a previous study, showing that 95% of participants reporting severe reflux symptoms experience reflux symptoms at least once a week [24]. Those reporting minor complaints were not included in this study. Individuals participating in both HUNT2 and HUNT3 or the questionnaire for nonparticipants, and reporting different degrees of reflux symptoms (severe and never) in the different studies were excluded in order to avoid interchange in the exposure.

Outcomes

The study outcomes were all-cause mortality, overall cancer-specific mortality, oesophageal adenocarcinoma-specific mortality, and mortality from head-and-neck or lung cancer.

All-cause mortality

From the Cause of Death Registry, information was gathered on the dates of death among the participants. All deaths among the HUNT participants, i.e. independent of cause, were included in the calculations for all-cause mortality.

Overall cancer-specific mortality

From the Cancer Registry, information was gathered on the site of cancer based on the International Classification of Diseases (ICD)-7 codes, morphology based on ICD-O-3 codes, and date of cancer diagnoses. We defined cancer deaths as deaths reported in the Cause of Death Registry as caused by cancer only for participants who had a cancer diagnosis registered in the Cancer Registry as well. Participants diagnosed with any cancer as the cause of death were included in the calculations for cancer-specific mortality.

Oesophageal adenocarcinoma-specific mortality

Participants with oesophageal adenocarcinoma as the cause of death reported in the Cause of Death Registry, or deaths occurring within one year from the cancer diagnosis in the Cancer Registry, regardless of the registered cause of death in the Cause of Death Registry, were included in the calculations for oesophageal adenocarcinoma-specific mortality. We also included oesophagogastric junctional adenocarcinomas in this outcome.

Mortality from selected extra-oesophageal cancer sites

The extra-oesophageal cancer sites included cancers of the head-and-neck (labial, lingual, salivary, oral, pharyngeal, nasosinusoidal, laryngeal cancer) and lung. Participants with any of these selected extra-oesophageal cancers as the cause of death reported in the Cause of Death Registry, or deaths occurring within one year of the cancer diagnoses in the Cancer Registry, regardless of registered cause of death in the Cause of Death Registry, were included in the calculations of extra-oesophageal cancer-specific mortality.

Confounders

As potential confounders we selected age, body mass index (BMI), tobacco smoking, alcohol consumption, physical activity, education level, chronic obstructive pulmonary disease,

cardiovascular diseases, diabetes, and hypertension. Information on these factors was collected through both HUNT2 and HUNT3. Height and weight were objectively measured by trained personnel in HUNT2 and HUNT3 [21]. In the questionnaire for non-participants, height and weight were self-reported. BMI was calculated by dividing weight in kilograms by height in meters squared (kg/m^2) and categorized according to the World Health Organization's classification: <18.5 (underweight), 18.5 to 25 (normal weight), 25 to 30 (overweight), or >30 (obese) [25]. The participant's tobacco smoking status was categorized as never, previous, or current. Alcohol consumption was assessed by the number of occasions of consumption per month and categorized as less than weekly or at least weekly or consumption. Physical activity was assessed by hours or occasions of physical activity per week. High physical activity was defined as at least one hour, or at least one occasion, of physical activity per week. In addition, participants who reported high levels of walking at work were categorized into the high physical activity group. Low physical activity was anything lower than these cut-offs for high activity. Educational level was categorized as 12 years and less or more than 12 years of formal education. The presence of comorbidities was based on self-reported questionnaires. Chronic obstructive pulmonary disease included chronic bronchitis, emphysema, and cough with phlegm for periods of at least 3 months. In addition, participants reporting previous or current asthma who also reported previous or current smoking were defined as having chronic obstructive pulmonary disease. Cardiovascular disease included previous myocardial infarction, angina pectoris, or stroke/brain haemorrhage. The presence of diabetes was reported by the participants. Those participants reporting previous or current use of medication for high blood pressure were defined as having hypertension.

Statistical analysis

Time at risk was defined from the date of the first participation in HUNT2, HUNT3, or the questionnaire for nonparticipants until date of death, emigration, or the end of the study (December 31, 2014), whichever came first. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using multivariable Cox-regression comparing the mortality among individuals reporting severe reflux symptoms with those reporting no reflux symptoms. All analyses were performed separate for each sex. The HRs were adjusted for age (continuous variable), BMI (<18.5, 18.5 to 25, 25 to 30, or >30), tobacco smoking status (never, previously, or current), alcohol consumption (<weekly or ≥weekly), physical activity (high or low), education (≤12 years or >12 years), chronic obstructive pulmonary disease (yes or no), cardiovascular diseases (yes or no), diabetes (yes or no), and hypertension (yes or no). In addition, analyses were stratified by age (<40, 40 to 60, and >60 years) to evaluate effect modification.

Ethical approval

The study has ethical approval through the Regional Committee for Medical and Health Research Ethics, Central Norway (2012/1290 4.2009.328), including additional approval of the present study (approved 02.11.2015). All participants in HUNT gave written informed consent when participating stating that their data could be used in future medical research, including linkage to other registries.

RESULTS

Study participants

A flowchart showing all exclusions of individuals considered for participation is shown in the Figure. After exclusion of 750 individuals (1.3%) due to different degree of reflux symptoms reported in the different studies, 4,758 individuals with severe reflux symptoms and 51,381 without reflux symptoms participated, contributing 60,323 and 747,239 person-years at risk, respectively. The average follow-up was 14.4 years. Baseline characteristics of the study participants are shown in Table 1. The participants with reflux were older, had higher BMI, drank alcohol less frequently, were more physically active, less educated, and had more comorbidity than those without reflux, while the groups had a more similar distribution of sex and tobacco smoking status (Table 1). In total 9,093 deaths occurred in the study population. The number of deaths for each sex, outcome, and reflux status is shown in Table 2.

Table 1. Baseline characteristics of the study participants

	Severe reflux Number (%)	**No reflux** Number (%)
Total		
	4,758 (100.0)	51,381 (100.0)
Age		
Median years (range)	51.9 (19.3 to 101.1)	44.7 (19.1 to 102.1)
Sex		
Men	2,301 (48.4)	23,699 (46.1)
Women	2,457 (51.6)	27,682 (53.9)
Body mass index		
<18.5	14 (0.3)	454 (0.1)
18.5 to 25	998 (21.0)	22,761 (44.3)
25 to 30	2,245 (47.2)	20,558 (40.0)
>30	1,453 (30.5)	7,052 (13.7)
Missing	48 (1.0)	556 (1.1)

Tobacco smoking status		
Never	1,579 (33.2)	23,725 (46.2)
Previous	1,648 (34.6)	12,861 (25.0)
Current	1,447 (30.4)	14,027 (27.3)
Missing	84 (1.8)	768 (1.5)
Alcohol consumption		
<Weekly	2,944 (61.9)	29,423 (57.3)
≥Weekly	1,814 (38.1)	21,958 (42.7)
Physical Activity		
High	2,381 (50.0)	23,017 (44.8)
Low	2,123 (44.6)	26,532 (51.6)
Missing	254 (5.3)	1832 (3.6)
Education		
≤12 years	3,297 (69.3)	31,640 (61.6)
>12 years	479 (10.1)	9,563 (18.6)
Missing	982 (20.6)	10,178 (19.8)
Chronic obstructive pulmonary disease		
Yes	270 (5.7)	966 (1.9)
No	4,380 (92.1)	48,504 (94.4)
Missing	108 (2.3)	1,911 (3.7)
Cardiovascular disease		
Yes	547 (11.5)	2,950 (5.7)
No	4,150 (87.2)	46,685 (90.9)
Missing	61 (1.3)	1,746 (3.4)
Diabetes		
Yes	193 (4.1)	1,450 (2.8)
No	4,547 (95.6)	49,806 (96.9)
Missing	18 (0.4)	125 (0.2)
Hypertension		
Yes	1,030 (21.6)	5,971 (11.6)
No	3,668 (77.1)	43,659 (85.0)
Missing	60 (1.3)	1,751 (3.4)

Reflux and all-cause mortality

The crude all-cause mortality was higher in women with reflux (HR 1.61, 95% CI 1.46 to 1.78), but no difference remained after adjustment for the selected confounders (HR 1.05, 95% CI 0.92 to 1.19) (Table 2). Age was the main factor explaining the difference in the crude and adjusted mortality rates in women.

Table 2. Number of deaths, mortality rates and hazard ratios with 95% confidence intervals (CI) for all-cause, cancer-specific, oesophageal adenocarcinoma-specific, and head-and-neck and lung cancer-specific mortality among participants reporting severe and no reflux symptoms, stratified by sex

Sex	Outcome	Number of deaths		Mortality rates (per 1000 person-years)		Mortality rate ratio (95% CI)	Hazard ratio (95% CI)		
		Severe reflux	No reflux	Severe reflux	No reflux		Crude	Age adjusted	Fully adjusted*
Men	**All-cause mortality**	397	4459	13.55	13.06	1.04 (0.93 to 1.15)	1.07 (0.99 to 1.19)	0.97 (0.87 to 1.07)	0.95 (0.84 to 1.07)
	Overall cancer-specific mortality	108	1200	3.68	3.51	1.05 (0.85 to 1.28)	1.09 (0.89 to 1.32)	0.99 (0.81 to 1.21)	1.08 (0.87 to 1.34)
	Oesophageal adenocarcinoma-specific mortality	8	17	0.27	0.05	5.48 (2.05 to 13.4)	5.45 (2.35 to 12.66)	4.89 (2.10 to 11.39)	6.09 (2.33 to 15.93)
	Head-and-neck and lung cancer-specific mortality	31	303	1.06	0.89	1.19 (0.80 to 1.73)	1.24 (0.85 to 1.79)	1.13 (0.78 to 1.64)	1.09 (0.71 to 1.67)
Women	**All-cause mortality**	430	3807	13.86	9.38	1.48 (1.33 to 1.63)	1.61 (1.46 to 1.78)	1.05 (0.95 to 1.16)	1.05 (0.92 to 1.19)
	Overall cancer-specific mortality	98	943	3.16	2.32	1.36 (1.09 to 1.68)	1.49 (1.21 to 1.83)	1.07 (0.87 to 1.32)	1.11 (0.87 to 1.42)
	Oesophageal adenocarcinoma-specific mortality	4	10	0.13	0.02	5.23 (1.20 to 18.14)	5.67 (1.78 to 18.10)	3.92 (1.22 to 12.61)	3.68 (0.88 to 15.27)
	Head-and-neck and lung cancer-specific mortality	17	189	0.55	0.47	1.18 (0.67 to 1.93)	1.29 (0.78 to 2.11)	0.96 (0.59 to 1.59)	1.21 (0.68 to 2.16)

*Adjusted for age, body mass index, tobacco smoking, alcohol consumption, physical activity, education, chronic obstructive pulmonary disease, cardiovascular diseases, diabetes, and hypertension

Reflux and overall cancer-specific mortality

The crude cancer-specific mortality of all cancer types was increased in women with reflux (HR 1.49, 95% CI 1.21 to 1.83), but after adjustment for age and other confounders this increase became attenuated and statistically non-significant (HR 1.11, 95% CI 0.87 to 1.42) (Table 2).

Reflux and oesophageal adenocarcinoma-specific mortality

The oesophageal adenocarcinoma-specific mortality was higher among men with reflux than those without. A 6-fold difference remained after adjustment for confounders (HR 6.09, 95% CI 2.33 to 15.93). For women with reflux, the crude oesophageal adenocarcinoma-specific mortality was increased (HR 5.67, 95% CI 1.78 to 18.10), but after adjustments the association attenuated and became statistically non-significant (HR 3.68, 95% CI 0.88 to 15.27) (Table 2). No participants with severe reflux symptoms died of oesophageal squamous cell carcinoma, compared to 17 participants without reflux symptoms.

Reflux and mortality from head-and-neck and lung cancer

The head-and-neck and lung cancer-specific mortality was not associated with reflux (Table 2).

Reflux and mortality stratified by age

Stratification by age categories did not substantially alter the overall results regarding all-cause mortality or mortality related to cancer in men. In women, reflux became associated with increased risk of oesophageal adenocarcinoma-specific mortality among the participants above 60 years of age (HR 10.49, 95% CI 1.99 to 55.27) (Table 3).

Table 3. Hazard ratios with 95% confidence intervals (CI) for all-cause mortality, overall cancer-specific mortality, oesophageal adenocarcinoma-specific mortality, and head-and-neck and lung cancer-specific mortality, stratified by sex and age categories

Sex	Outcome	<40 years			40-60 years			>60 years		
		Number of deaths		Hazard ratio (CI 95%)*	Number of deaths		Hazard ratio (CI 95%)*	Number of deaths		Hazard ratio (CI 95%)*
		Severe reflux	No reflux		Severe reflux	No reflux		Severe reflux	No reflux	
Men	**All-cause mortality**	7	118	0.95 (0.43 to 2.09)	96	778	1.02 (0.81 to 1.29)	294	3563	0.86 (0.74 to 0.99)
	Overall cancer-specific mortality	2	28	1.08 (0.24 to 4.81)	35	314	1.09 (0.76 to 1.58)	71	858	1.02 (0.77 to 1.34)
	Oesophageal adenocarcinoma-specific mortality	0	0	-	4	3	81.73 (8.50 to 785.53)	4	14	3.59 (0.98 to 13.20)
	Head-and-neck and lung cancer-specific mortality	0	4	-	11	98	0.81 (0.40 to 1.64)	20	201	1.27 (0.74 to 2.18)
Women	**All-cause mortality**	5	96	1.36 (0.54 to 3.45)	52	589	1.02 (0.74 to 1.40)	373	3122	0.93 (0.81 to 1.07)
	Overall cancer-specific mortality	1	52	0.55 (0.07 to 4.04)	22	326	0.77 (0.48 to 1.24)	75	565	1.24 (0.92 to 1.66)
	Oesophageal adenocarcinoma-specific mortality	0	0	-	0	4	-	4	6	10.49 (1.99 to 55.27)
	Head-and-neck and lung cancer-specific mortality	0	5	-	5	84	0.80 (0.32 to 2.01)	12	100	1.32 (0.63 to 2.77)

*Adjusted for body mass index, tobacco smoking, alcohol consumption, physical activity, education, chronic obstructive pulmonary disease, cardiovascular diseases, diabetes, and hypertension

DISCUSSION

In this study severe reflux symptoms were not associated with any increase in all-cause mortality, overall cancer-specific mortality, or head-and-neck and lung cancer-specific mortality, but only an increase in oesophageal adenocarcinoma-specific mortality.

Strengths of this study include its prospective and population-based design, which counteracts recall bias and selection bias. The population of Nord-Trøndelag County is representative of the Norwegian population as a whole [26], and therefore the results can be generalized to other Western populations. The data on reflux have been well validated against a more comprehensive assessment with excellent results [24]. Cancer deaths were retrieved both from the Cancer Registry and the Cause of Death Registry in order to validate these data. The population studied was large and the time of follow-up was long, providing a robust statistical power.

Limitations include possible information bias, as most of the confounders adjusted for in this study came from self-reported questionnaires [27 28].

In this study we excluded the individuals reporting minor reflux symptoms. We believe these individuals are a heterogeneous group, most without true reflux disease. This statement is based on two validation studies performed on the questionnaire used in the HUNT study. In these validation studies, we found that 95% to 98% of the participants reporting *severe* reflux symptoms also reported at least weekly reflux symptoms, while only 25% to 31% of the participants reporting *minor* reflux symptoms also reported at least weekly reflux symptoms [1 24]. At least weekly reflux is considered the cut-off level for defining reflux disease according to the Montreal definition[29]. We believe the group of individuals reporting minor reflux symptoms mostly include individuals with physiological reflux or functional complaints

and not individuals with true reflux disease. Thus, by excluding these, we are confident that the validity of the study is increased.

In the analyses, we dichotomized three of the co-variables with large number of categories in the questionnaires, i.e. alcohol consumption, physical activity, and education, using common and previously used cut-off levels decided beforehand. This was done to maintain statistical power and to make the variables correspond well due to slight revisions of the questionnaires between the studies. We also did a sensitivity analyses with more categories of the co-variables in the model, and the results remained virtually unchanged (data not shown).

The study has low rates of missing values among the participants (<5%), except for education (20%). As education was assessed in HUNT2 only, we have missing information on education among those participants only participating in HUNT3 or the questionnaire for nonparticipants. In Cox regression analyses only “complete cases” are analysed and participants with missing information are excluded. To assess the effect of missing data on education, we ran a sensitivity analysis using data from HUNT2 participants only. In this analysis, missing for education was reduced to only 3.6%. However, the sensitivity analysis did not change the results (data not shown), meaning that the missing values did not affect the conclusion of the study.

The number of individuals (n=750) excluded from the analyses due to change in reported complaints with reflux disease between HUNT2 and HUNT3 or the questionnaire for nonparticipants was small number (1.3%) compared to the total number of included participants (n=56,139) and should not have major influence on the results.

As mortality was the main outcome of this study, we excluded participants with a cancer diagnosis in the Cancer Registry, but without this cancer reported as the cause of death in the Cause of Death Registry. However, for oesophageal adenocarcinoma and head-and-neck and lung cancers we did still include these participants if they died within one year after the date of cancer diagnosis, as we believe these deaths still could be related to these cancers as they are known to have a poor prognosis. This decision could overestimate the cancer-specific mortality of the respective cancers, but still reflux was not associated with head-and-neck and lung cancers-specific mortality.

The results of this study align with those from a smaller population-based cohort study from the US, which found no difference in all-cause mortality between 115 individuals with daily and 2,708 individuals without reflux symptoms [18]. A cohort study from the UK found that patients with GORD (n=7,159) had a 60% increased all-cause mortality within the first year of follow-up after inclusion, compared to patients without GORD (n=10,000), but no difference was seen for the remaining 4 years of follow-up [19]. In our study, reflux was neither associated with all-cause mortality after one nor five years of follow-up (data not shown). Interpreting the results from the present study and the findings of previous studies indicate that reflux does not affect overall all-cause mortality.

The findings regarding cancer-specific mortality are different from an Iranian population-based cohort study reporting that participants with severe reflux symptoms (n=172) had a 48% increase in cancer-specific mortality compared to participants without reflux symptoms (n=1,240), while no association was found for oesophageal cancer [20]. However, the Iranian study could not separate oesophageal adenocarcinoma from squamous cell carcinoma, and most oesophageal cancers in Iran are squamous cell carcinomas without any association

with reflux [10]. Moreover, differences in study design, living conditions and ethnicity, as well as chance, may explain the divergent findings.

Our study confirms the lack of association between reflux and oesophageal squamous cell carcinomas as there were no deaths due oesophageal squamous cell carcinoma among the participants with severe reflux symptoms, while there were 17 deaths due oesophageal squamous cell carcinoma among those without reflux symptoms. Reflux was also, as expected, not associated with gastric (non-cardia) cancer-specific mortality (data not shown).

The increased oesophageal adenocarcinoma-related mortality is expected, given the well-established and strong association between GORD and oesophageal adenocarcinoma incidence [10 12]. Yet, only 14 of the 4,758 individuals with severe reflux symptoms were diagnosed with an oesophageal adenocarcinoma, which emphasizes the fact that the absolute risk is low even in individuals with GORD [30]. This is, to the best of our knowledge, the first study examining the mortality related to head-and-neck and lung cancer, and no association was found.

In conclusion, this prospective and population-based cohort study with a large sample size and adjustment for confounding factors indicates that severe reflux symptoms do not entail any increased all-cause mortality or overall cancer-specific mortality, although an increase in oesophageal adenocarcinoma-specific mortality was found.

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COMPETING INTERESTS

The authors have no competing interests.

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FIGURE LEGENDS

Figure. Flowchart of inclusion and exclusion of individuals considered for participation in this study. *The Nord-Trøndelag Health Study. †Questionnaire for Nonparticipants.