

## **TITLE PAGE**

### **Title**

Changes in prevalence, incidence, and spontaneous loss of gastroesophageal reflux symptoms: A prospective population-based cohort study, the HUNT study.

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### **Keywords**

Gastroesophageal reflux disease; Epidemiology

### **Abbreviations**

BMI: body mass index

CIs: confidence intervals

GERD: gastroesophageal reflux disease

GERS: gastroesophageal reflux symptoms

H<sub>2</sub>RAs: H<sub>2</sub>-receptor antagonists

HUNT: Nord-Trøndelag health study

NorPD: Norwegian prescription database

ORs: odds ratios

PPIs: proton pump inhibitors

SD: standard deviation

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## **ABSTRACT**

**Objective** Changes in the occurrence of gastroesophageal reflux symptoms (GERS) in the population remain uncertain. This study aimed to determine the prevalence changes, the incidence, and the spontaneous loss of GERS.

**Design** This population-based cohort study was conducted within the Nord-Trøndelag health study (the HUNT study), a longitudinal series of population-based health surveys in Nord-Trøndelag County, Norway. The study base encompassed all adult residents in the county, and the participants reported the degree of GERS during the previous 12 months. The number of participants included were 58869 (64% response rate) in 1995-1997 and 44997 (49%) in 2006-2009. Of these, 29610 persons (61%) were prospectively followed up for an average of 11 years.

**Results** Between 1995-1997 and 2006-2009, the prevalence of any, severe and at least weekly GERS increased by 30% (from 31.4% to 40.9%), 24% (from 5.4% to 6.7%) and 47% (from 11.6% to 17.1%), respectively. The average annual incidence of any and severe GERS was 3.07% and 0.23%, respectively. In women, but not men, the incidence of GERS increased with increasing age. The average annual spontaneous loss (not due to antireflux medication) of any and severe GERS was 2.32% and 1.22%, respectively. The spontaneous loss of GERS decreased with increasing age.

**Conclusion** Between 1995-1997 and 2006-2009 the prevalence of GERS increased substantially. At least weekly GERS increased by 47%. The average annual incidence of severe GERS was 0.23%, and the corresponding spontaneous loss was 1.22%. The incidence and spontaneous loss of GERS were influenced by sex and age.

**What is already known about this subject?**

- The prevalence of at least weekly gastroesophageal reflux symptoms (GERS) among adults has been reported to be in the range of 10-20% in the Western world.
- GERS are associated with a decreased health-related quality of life.
- GERS are established risk factors of adenocarcinoma of the esophagus.

**What are the new findings?**

- The prevalence of at least weekly GERS increased by 47% (from 11.6% to 17.1%) between 1995-1997 and 2006-2009.
- The average annual incidence of severe GERS was 0.23%. In women, but not men, the incidence of GERS increased with increasing age.
- The average annual spontaneous loss of severe GERS (not due to antireflux medication) was 1.22%. The spontaneous loss of GERS decreased with increasing age.

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

- The increasing prevalence of GERS found in this study may call for a strengthened effort to investigate and treat this patient population, both due to the impact on health related quality of life and the increasing incidence of adenocarcinoma of the esophagus related to GERS.

## **MAIN TEXT**

### **INTRODUCTION**

Gastroesophageal reflux disease (GERD) is defined by its cardinal symptoms, heartburn and acid regurgitation, occurring at least weekly.<sup>1 2</sup> Gastroesophageal reflux symptoms (GERS) are associated with a decreased health-related quality of life<sup>3 4</sup> and an increased risk of adenocarcinoma of the esophagus,<sup>5 6</sup> a disease with poor prognosis and rapidly rising incidence in Western countries.<sup>7-9</sup> The prevalence of at least weekly GERS among adults has been reported to be in the range of 10-20% in the Western world,<sup>10 11</sup> with a higher prevalence in more recent studies.<sup>12</sup> However, the population-based changes in prevalence remain uncertain, and the few studies that have addressed the incidence of GERS suffer from small sample sizes, short follow-up time, or use of a selected population. In addition, GERS are not always persistent and the level of spontaneous loss of GERS, not due to antireflux medication, is unknown. The aim of this study was to provide valid data on the changes in prevalence, the incidence, and the spontaneous loss of GERS in an unselected Western population.

### **MATERIAL & METHODS**

#### **Study population and design**

GERS were studied as part of the Nord-Trøndelag health study (the HUNT study), a longitudinal series of population-based health surveys conducted in the Norwegian county of Nord-Trøndelag. The county has a stable population that is representative of the Norwegian population at large.<sup>13</sup> All adult residents in Nord-Trøndelag County who turned 20 years of age during the survey year were invited to participate. The first survey (HUNT 1), which was conducted in the mid 1980s, was not included in the

present study because GERS data was not collected. However, the second survey (HUNT 2) conducted from August 1995 through June 1997 and the third survey (HUNT 3) conducted from October 2006 through June 2008 included assessment of GERS. Moreover, in 2009, a postal questionnaire study (Mini-Q) of the non-participants in HUNT 3 was conducted, also including assessment of GERS and as such eligible in our study. The HUNT data base contains approximately 5500 health related variables, including variables on exposures, complaints, and diseases, collected through self-administered questionnaires, clinical measurements, and blood samples taken at the screening stations.

### **Assessment of gastroesophageal reflux symptoms**

In HUNT 2 and HUNT 3/Mini-Q the participants were asked the following question through self-administrated questionnaires: “To what degree have you had heartburn or acid regurgitation during the previous 12 months?” and replied with one of three response alternatives: “no complaints”, “minor complaints”, or “severe complaints”. In the analyses, those who reported minor or severe complaints were included in the category “any GERS”, while those who reported severe complaints were included in the category “severe GERS”. In HUNT 2, the GERS question was part of the initial questionnaire sent by mail along with the study invitation and returned at the screening station. In HUNT 3/Mini-Q, the GERS question was part of a second questionnaire given to the participants at the screening station (HUNT 3) or the questionnaire sent to the non-participants (Mini-Q). As frequency of GERS was not directly assessed in HUNT 2 and HUNT 3, the participants were asked to report both their degree and frequency of GERS in a validation study after HUNT 2<sup>14</sup> and in Mini-Q. The following question was asked to assess the frequency of GERS: “If you have

had heartburn or acid regurgitation during the previous 12 months, how often do you have complaints?” and replied with one of three response alternatives: “daily”, “weekly”, or “less frequently”.

### **Assessment of antireflux medication**

Data on antireflux medication was collected from the HUNT questionnaires as well as from the Norwegian Prescription Database (NorPD). The NorPD is a Norwegian national health register, established in 2004, that contains data on all prescribed medication dispensed from all Norwegian pharmacies. Through the use of the unique national identity number assigned to all Norwegian residents, it was possible to link the HUNT study to the NorPD and gather information on the prescribed medication among the participants during HUNT 3. The prescription rules in Norway during the study period required a prescription from a physician for all proton pump inhibitors (PPIs) or H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs), except for small packages of low dose H<sub>2</sub>RAs. The information retrieved from the NorPD included dosage, package size, and number of packages for each single prescription. In addition, the participants in HUNT 3 reported their use of over the counter antireflux medication, i.e. small packages of low dose H<sub>2</sub>RAs and antacids during the last month, with the response alternatives “never or rarely”, “1-3 times per week”, “4-6 times per week”, or “daily”. Thus, all antireflux medication in the study population during HUNT 3 should be accounted for.

### **Statistical analyses**

Prevalence of GERS was calculated as the proportion of persons in HUNT 2 and HUNT 3/Mini-Q who reported any (minor or severe) GERS or severe GERS,

respectively. The prevalence of individuals with at least weekly GERS in HUNT 2 and HUNT 3/Mini-Q was estimated through assessment of both degree and frequency of complaints reported by those participating in the HUNT 2 validation<sup>14</sup> or in Mini-Q. The proportion of individuals with *severe* GERS and at least weekly GERS and the proportion of individuals with *minor* GERS and at least weekly GERS in the HUNT 2 validation and in Mini-Q were calculated. These proportions were multiplied with the number of individuals with severe and minor GERS in HUNT 2 and HUNT 3, respectively, to assess at least weekly GERS.<sup>11</sup> When calculating response rates, those who had deceased or were no longer resident in the county (non-eligible) were excluded from the denominator. The incidence of GERS was calculated from the proportion of those who reported no GERS in HUNT 2 and any or severe GERS in HUNT 3/Mini-Q (cumulative incidence), respectively. The loss of GERS was calculated from the proportion of those who reported any or severe GERS in HUNT 2, respectively, but no GERS in HUNT 3/Mini-Q (cumulative loss). In the latter analysis, those using at least weekly antireflux medication in HUNT 3/Mini-Q were excluded to assess spontaneous loss of GERS only. The average annual cumulative incidence and spontaneous loss of GERS were calculated using the formula  $(\text{exp}(\text{cumulative proportion}) - 1) / 11 \text{ years}$  (average annual percentage change). In addition, 95% confidence intervals (CIs) for the proportions were calculated. The prevalence, incidence, and spontaneous loss of GERS were stratified by sex and age (<40, 40-49, 50-59, 60-69, and ≥70 years). Odds ratios (ORs) between the time points were estimated to statistically assess the changes in prevalence of GERS, and adjustments were made for sex and age by using the interaction term between sex and age groups as co-variable. Generalized estimating equations with exchangeable correlation structure were used to account for the repeated assessments of GERS



among many of the participants. ORs were also estimated by logistic regression to assess differences in incidence and spontaneous loss of GERS by sex and age, using the interaction term as explanatory variable. The statistical analyses were performed with the software Stata/IC 11.1 for Windows by StataCorp LP.

### **Ethical approval and informed consent**

The study was approved by the Regional Committee for Medical and Health Research Ethics, Central-Norway. All participants signed a written consent form when they participated in the HUNT study, which stated that the data collected could be linked with health registries and patient records for research purposes in future studies.

## RESULTS

### Participants

Degree of GERS was reported by 58869 individuals (64% response rate) in HUNT 2 (1995-1997) and by 44997 individuals (49% response rate) in HUNT 3/Mini-Q (2006-2009). The number of participants in HUNT 3 and Mini-Q were 37406 and 7591, respectively. These participants were included in the assessment of prevalence of GERS (Figure 1). In HUNT 2, the mean age was 48.5 years (standard deviation (SD) 16.8 years; range 19-101 years) compared to 52.1 years (SD 16.0 years; range 19-102 years) in HUNT 3/Mini-Q. The female response rate was 52% in HUNT 2 and 55% in HUNT 3/Mini-Q, and 570 and 237 women reported to be pregnant, respectively. All analyses included pregnant women, as analyses excluding them made no differences in the results (data not shown).

In the assessment of incidence and spontaneous loss of GERS between HUNT 2 and HUNT 3/Mini-Q, the 29610 individuals who reported their degree of GERS at both occasions were included. This corresponds to a response rate of 61%, excluding the 10535 non-eligible participants who reported GERS in HUNT 2 but were deceased or no longer resident in the county at HUNT 3 (Figure 1). The mean age of this cohort was 57.3 years at follow-up (SD 13.1 years; range 29-100 years) and 54% were women.

### Changes in prevalence of gastroesophageal reflux symptoms

Between 1995-1997 and 2006-2009, the prevalence of *any* GERS increased by 30%, from 31.4% (95% CI 31.0-31.7%) to 40.9% (95% CI 40.4-41.3%), and the prevalence of *severe* GERS increased by 24%, from 5.4% (95% CI 5.2-5.6%) to 6.7% (95% CI 6.4-6.9%). Adjusted for sex and age, the OR of *any* and *severe* GERS in 2006-2009

*Occurrence of gastroesophageal reflux symptoms*

compared with 1995-1997 was 1.46 (95% CI 1.43-1.49) and 1.20 (95% CI 1.15-1.26), respectively. For *any* GERS the prevalence increased for both sexes and all age groups, but for *severe* GERS the prevalence increased mainly among the middle aged (Table 1).

Occurrence of gastroesophageal reflux symptoms

**Table 1:** Prevalence of gastroesophageal reflux symptoms (GERS) in the HUNT study, stratified by degree of GERS, time point, sex, and age groups.

Prevalence of any GERS*																						
Age (years)§	1995-1997 (HUNT 2)						2006-2009 (HUNT 3/Mini-Q)						Relative change†									
	Total N=58869						Total N=44997‡						Total									
	Number	%	95% CI			Number	%	95% CI			%											
	18460	31.4	31.0-31.7			18389	40.9	40.4-41.3			30.3											
	Women N=30608			Men N=28261			Women N=24550			Men N=20440			Women	Men								
	Number	%	95% CI			Number	%	95% CI			Number	%	95% CI			%	%					
All ages	9104	29.7	29.2-30.3			9356	33.1	32.6-33.7			9526	38.8	38.2-39.4			8860	43.3	42.7-44.0			30.5	30.9
<40	2528	23.9	23.1-24.7			2695	29.4	28.5-30.3			1886	28.3	27.2-29.4			1516	34.5	33.1-35.9			18.3	17.5
40-49	1852	28.0	26.9-29.0			2197	35.0	33.9-36.2			1762	35.7	34.4-37.0			1761	43.4	41.9-44.9			27.7	23.8
50-59	1635	31.9	30.6-33.1			1823	36.0	34.7-37.3			2157	42.1	40.7-43.4			2258	46.7	45.3-48.1			32.0	29.8
60-69	1432	36.9	35.3-38.4			1347	34.7	33.2-36.2			2092	48.3	46.9-49.8			1971	47.1	45.6-48.6			31.2	35.9
≥70	1657	37.6	36.2-39.1			1294	33.5	32.0-35.0			1629	46.6	44.9-48.2			1354	45.6	43.8-47.4			23.7	36.2

Prevalence of severe GERS*																						
Age (years)§	1995-1997 (HUNT 2)						2006-2009 (HUNT 3/Mini-Q)						Relative change†									
	Total N=58869						Total N=44997‡						Total									
	Number	%	95% CI			Number	%	95% CI			%											
	3167	5.4	5.2-5.6			2994	6.7	6.4-6.9			23.7											
	Women N=30608			Men N=28261			Women N=24550			Men N=20440			Women	Men								
	Number	%	95% CI			Number	%	95% CI			Number	%	95% CI			%	%					
All ages	1603	5.2	5.0-5.5			1564	5.5	5.3-5.8			1629	6.6	6.3-6.9			1364	6.7	6.3-7.0			26.7	20.6
<40	396	3.7	3.4-4.1			436	4.8	4.3-5.2			290	4.4	3.9-4.8			223	5.1	4.4-5.7			16.2	6.8
40-49	286	4.3	3.8-4.8			372	5.9	5.3-6.5			289	5.9	5.2-6.5			275	6.8	6.0-7.5			35.6	14.2
50-59	281	5.5	4.9-6.1			312	6.2	5.5-6.8			372	7.3	6.5-8.0			390	8.1	7.3-8.8			32.5	31.0
60-69	299	7.7	6.9-8.5			238	6.1	5.4-6.9			385	8.9	8.0-9.7			288	6.9	6.1-7.6			15.6	12.4
≥70	341	7.7	7.0-8.5			206	5.3	4.6-6.0			293	8.4	7.5-9.3			188	6.3	5.5-7.2			8.1	18.8

\*Any GERS: minor or severe complaints with heartburn or acid regurgitation; Severe GERS: severe complaints with heartburn or acid regurgitation.

†Relative change in prevalence = (prevalence HUNT 3/Mini-Q – prevalence HUNT 2) / prevalence HUNT.

‡7 participants in HUNT 3/Mini-Q had missing information on sex.

§Age at time of GERS assessment (HUNT 2 and HUNT 3/Mini-Q, respectively).

In Mini-Q, where the participants reported both their degree and frequency of GERS, 98% of the participants with *severe* GERS had at least weekly symptoms or used at least weekly antireflux medication. The corresponding rate was 31% among participants with *minor* GERS.

The prevalence of *at least weekly* GERS, estimated through assessment of data from the HUNT 2 validation and Mini-Q, increased by 47% from 11.6% (95% CI 11.4-11.9%) to 17.1% (95% CI 16.7-17.4%). The prevalence of at least weekly GERS increased for both sexes and all age groups and most among the middle aged (Table 2; Figure 2 online only).

Occurrence of gastroesophageal reflux symptoms

**Table 2:** Prevalence of at least weekly gastroesophageal reflux symptoms (GERS) in the HUNT study, stratified by time point, sex, and age groups.

Prevalence of at least weekly GERS*														
Age (years)§	1995-1997 (HUNT 2)						2006-2009 (HUNT 3/Mini-Q)						Relative change†	
	Total N=58869						Total N=44997‡						Total	
	Number		%		95% CI		Number		%		95% CI		%	
	6835		11.6		11.4-11.9		7692		17.1		16.7-17.4		47.2	
	Women N=30608			Men N=28261			Women N=24550			Men N=20440			Women	Men
	Number	%	95% CI	Number	%	95% CI	Number	%	95% CI	Number	%	95% CI	%	%
All ages	3400	11.1	10.8-11.5	3435	12.2	11.8-12.5	4036	16.4	16.0-16.9	3654	17.9	17.4-18.4	48.0	47.1
<40	910	8.6	8.1-9.2	979	10.7	10.0-11.3	778	11.7	10.9-12.5	618	14.1	13.1-15.1	35.6	31.9
40-49	663	10.0	9.3-10.8	810	12.9	12.1-13.8	738	14.9	14.0-16.0	729	18.0	16.8-19.2	49.4	39.0
50-59	606	11.8	10.9-12.7	674	13.3	12.4-14.3	916	17.9	16.8-18.9	959	19.8	18.7-21.0	51.3	49.1
60-69	568	14.6	13.5-15.8	504	13.0	11.9-14.1	905	20.9	19.7-22.2	803	19.2	18.0-20.4	43.1	47.9
≥70	653	14.8	13.8-15.9	468	12.1	11.1-13.2	700	20.0	18.7-21.4	545	18.4	17.0-19.8	34.9	51.6

\*At least weekly GERS: at least weekly complaints with heartburn or acid regurgitation.

†Relative change in prevalence = (prevalence HUNT 3/Mini-Q – prevalence HUNT 2) / prevalence HUNT 2.

‡7 participants in HUNT 3/Mini-Q had missing information on sex.

§Age at time of GERS assessment (HUNT 2 and HUNT 3/Mini-Q, respectively).

### **Incidence of gastroesophageal reflux symptoms**

During the average 11 years of follow-up from 1995-1997 to 2006-2009, the cumulative incidence of *any* GERS was 29.1% (95% CI 28.4-29.7%), which corresponded to an average annual incidence of 3.07% (95% CI 2.99-3.14%).

Women younger than 40 years of age had the lowest incidence of any GERS. The incidence increased with increasing age for women, while it was stable with age for men. In older age groups there was no difference in the incidence of any GERS between the sexes (Table 3; Figure 3 online only).

The cumulative incidence of *severe* GERS was 2.5% (95% CI 2.3-2.7%), which corresponded to an average annual incidence of 0.23% (95% CI 0.21-0.25%). There was a slightly increased incidence of severe GERS with increasing age for women, but it was stable with age for men. Women aged 60 to 69 years had the highest incidence of severe GERS (Table 3; Figure 3 online only).

**Table 3:** Cumulative incidence of gastroesophageal reflux symptoms (GERS) from 1995-1997 (HUNT 2) to 2006-2009 (HUNT3/Mini-Q), stratified by degree of GERS, sex, and age groups.\*

<b>Any GERS†</b>										
<b>Cumulative incidence</b>							<b>OR and 95% CI‡</b>			
<b>Total N=20311</b>										
<b>Number</b>										
<b>%</b>										
<b>95% CI</b>										
	5904			29.1			28.4-29.7			
<b>Age(years)§</b>	<b>Women N=11394</b>			<b>Men N=8917</b>			<b>Women</b>		<b>Men</b>	
	Number	%	95% CI	Number	%	95% CI	OR	95% CI	OR	95% CI
All ages	3209	28.2	27.3-29.0	2695	30.2	29.3-31.2				
<40	283	20.5	18.3-22.6	243	29.3	26.2-32.4	1.00	Reference	1.61	1.32-1.96
40-49	704	25.9	24.2-27.5	548	29.6	27.5-31.7	1.36	1.16-1.59	1.63	1.38-1.92
50-59	900	29.1	27.5-30.7	775	31.3	29.4-33.1	1.59	1.37-1.85	1.77	1.51-2.07
60-69	823	33.3	31.5-35.2	666	30.6	28.6-32.5	1.94	1.66-2.27	1.71	1.46-2.01
≥70	499	28.9	26.8-31.1	463	29.4	27.1-31.6	1.58	1.34-1.87	1.62	1.36-1.92

<b>Severe GERS†</b>										
<b>Cumulative incidence</b>							<b>OR and 95% CI‡</b>			
<b>Total N=20311</b>										
<b>Number</b>										
<b>%</b>										
<b>95% CI</b>										
	510			2.5			2.3-2.7			
<b>Age(years)§</b>	<b>Women N=11394</b>			<b>Men N=8917</b>			<b>Women</b>		<b>Men</b>	
	Number	%	95% CI	Number	%	95% CI	OR	95% CI	OR	95% CI
All ages	319	2.8	2.5-3.1	191	2.1	1.8-2.4				
<40	31	2.2	1.5-3.0	15	1.8	0.9-2.7	1.00	Reference	0.80	0.43-1.50
40-49	66	2.4	1.8-3.0	40	2.2	1.5-2.8	1.08	0.70-1.67	0.96	0.60-1.55
50-59	95	3.1	2.5-3.7	53	2.1	1.6-2.7	1.38	0.92-2.08	0.95	0.61-1.49
60-69	85	3.4	2.7-4.2	48	2.2	1.6-2.8	1.55	1.03-2.36	0.98	0.62-1.55
≥70	42	2.4	1.7-3.2	35	2.2	1.5-2.9	1.09	0.68-1.74	0.99	0.61-1.62

\*Cumulative incidence was calculated from no GERS in HUNT 2 to any or severe GERS in HUNT 3/Mini-Q, respectively.

†Any GERS: minor or severe complaints with heartburn or acid regurgitation;

Severe GERS: severe complaints with heartburn or acid regurgitation.

‡Odds ratio (OR) and 95% confidence interval (CI) of incident GERS for each sex and age group.

§Age at follow-up in HUNT 3/Mini-Q.

### Spontaneous loss of gastroesophageal reflux symptoms

The cumulative loss of *any* GERS during the study period was 22.7% (95% CI 21.9-23.6%), when excluding the 286 participants (12%) using antireflux medication at least weekly. This corresponded to an average annual spontaneous loss of 2.32% (95% CI 2.23-2.42%). Women younger than 40 years of age had the highest spontaneous loss of any GERS. The spontaneous loss decreased with increasing age for both sexes, but this was more pronounced among women. There was no



difference in spontaneous loss of any GERS between the sexes in older age groups (Table 4; Figure 4 online only).

The cumulative loss of severe GERS was 12.6% (95% CI 10.9-14.2%), when excluding the 89 participants (31%) using antireflux medication at least weekly. This corresponded to an average annual spontaneous loss of 1.22% (95% CI 1.05-1.40%). The spontaneous loss decreased with increasing age for both sexes, but this was particularly evident among women (Table 4; Figure 4 online only).

**Table 4:** Cumulative spontaneous loss of gastroesophageal reflux symptoms (GERS) from 1995-1997 (HUNT 2) to 2006-2009 (HUNT3/Mini-Q), stratified by degree of GERS, sex and age groups.\*

<b>Any GERSt</b>										
	<b>Cumulative spontaneous loss</b>						<b>OR and 95% CI‡</b>			
	<b>Total N=9299</b>									
	Number		%		95% CI					
	2112		22.7		21.9-23.6					
	<b>Women N=4686</b>			<b>Men N=4613</b>			<b>Women</b>		<b>Men</b>	
<b>Age(years)§</b>	Number	%	95% CI	Number	%	95% CI	OR	95% CI	OR	95% CI
All ages	1118	23.9	22.6-25.1	994	21.5	20.4-22.7				
<40	207	51.1	46.2-56.0	74	27.9	22.5-33.3	1.00	Reference	0.37	0.27-0.52
40-49	279	31.1	28.0-34.1	209	25.0	22.1-27.9	0.43	0.34-0.55	0.32	0.25-0.41
50-59	262	22.6	20.2-25.0	287	21.3	19.1-23.5	0.28	0.22-0.35	0.26	0.20-0.33
60-69	181	16.1	14.0-18.3	229	19.0	16.7-21.2	0.18	0.14-0.24	0.22	0.18-0.29
≥70	189	17.2	14.9-19.4	195	20.4	17.8-22.9	0.20	0.15-0.25	0.24	0.19-0.31

<b>Severe GERSt</b>										
	<b>Cumulative spontaneous loss</b>						<b>OR and 95% CI‡</b>			
	<b>Total N=1553</b>									
	Number		%		95% CI					
	195		12.6		10.9-14.2					
	<b>Women N=798</b>			<b>Men N=755</b>			<b>Women</b>		<b>Men</b>	
<b>Age(years)§</b>	Number	%	95% CI	Number	%	95% CI	OR	95% CI	OR	95% CI
All ages	93	11.7	9.4-13.9	102	13.5	11.1-16.0				
<40	25	37.3	25.6-49.0	9	26.5	11.4-41.5	1.00	Reference	0.60	0.24-1.50
40-49	23	17.6	11.0-24.1	20	15.6	9.3-21.9	0.36	0.18-0.70	0.31	0.16-0.62
50-59	19	10.4	6.0-14.9	32	14.7	10.0-19.5	0.20	0.10-0.39	0.29	0.16-0.54
60-69	13	7.0	3.3-10.6	22	10.6	6.4-14.8	0.13	0.06-0.27	0.20	0.10-0.39
≥70	13	5.6	2.6-8.6	19	11.3	6.5-16.1	0.10	0.05-0.21	0.21	0.11-0.43

\*Cumulative spontaneous loss was calculated from any or severe GERS in HUNT 2, respectively, to no GERS in HUNT 3/Mini-Q, excluding those using at least weekly antireflux medication.

†Any GERS: minor or severe complaints with heartburn or acid regurgitation;

Severe GERS: severe complaints with heartburn or acid regurgitation.

‡Odds ratio (OR) and 95% confidence interval (CI) of losing GERS for each sex and age group.

§Age at follow-up in HUNT 3/Mini-Q.

### Non-participant study

In Mini-Q and HUNT 3, respectively, 29.9% and 43.1% reported any GERS; 4.3% and 7.1% reported severe GERS; and 5.7% and 8.2% used at least weekly antireflux medication. These differences were retained also after stratification by sex and age (data not shown). Distributions of key variables associated with GERS were also assessed. In Mini-Q and HUNT 3, respectively, 49% and 56% were women; the mean age was 45.9 and 53.4 years; the mean body mass index (BMI) was 26.1 and 27.2 kg/m<sup>2</sup>; there were no differences in the proportions of none or daily cigarette

smokers; 34% and 38% drank at least weekly alcohol; and 69% and 79% reported at least weekly physical exercise.

## **DISCUSSION**

The present study found a substantial increase in the prevalence of GERS during the last decade. The absolute number of individuals with new GERS exceeded the number who lost GERS during the study period. Age was an important risk factor for the incidence of GERS among women, but for men the incidence was stable irrespective of age. GERS was frequently lost, especially among young women, but seemed to be more stable with increasing age. Analyses excluding pregnant women made no differences in the results. The use of regular antireflux medication could only explain the loss of GERS in a minority of participants.

There are a few methodological issues to be discussed. Major strengths were i) the population-based design, which reduced the risk of selection bias compared to studies of individuals consulting physicians or in other health care settings; ii) the large study population, which reduced the risk of chance findings and made subgroup analyses possible; and iii) the ability to account for the use of antireflux medication among participants with loss of GERS. Limitations of the study were i) the drop in participation rate from HUNT 2 to HUNT 3, making differences in selection bias between the surveys possible; and ii) the long time interval (11 years) between the surveys, which prevented evaluation of additional fluctuations in GERS during the study period. Thus, the analysis of incident GERS may also have included recurrent symptoms and not only genuinely new cases, and loss of GERS may not necessarily mean a true recovery, but rather a temporary relief of symptoms. The probability of fluctuating symptoms was, however, most likely reduced by the 12 months time

period the individuals were asked to consider when reporting GERS. Selection bias is a major concern in all population-based studies including the present study.

However, compared to other population-based cohort studies of this magnitude the overall response rate is high. In addition, the purpose of the HUNT study was to perform an extensive investigation of common diseases and exposures using a wide range of health related variables. Thus, non-participation due to GERS is highly unlikely as there were only two questions related to GERS in the HUNT study. In Mini-Q the prevalence of both any and severe GERS and the use of antireflux medication was lower than in HUNT 3, also after stratification by sex and age. The higher prevalence of GERS in Mini-Q may indicate a selection of individuals with more complaints in the study population than in the target population and possibly an overestimation of the occurrence of GERS. However, this bias is reduced with the inclusion of the participants in Mini-Q in the study population. The lower prevalence of GERS in Mini-Q may in part be explained by the lower BMI of this population.

Finally, the definition of GERD is arbitrary, but according to present guidelines it is based mainly on the frequency of GERS,<sup>2</sup> which is in line with the present study. Our previous validation study (HUNT 2 validation) showed that 95% of the participants with severe GERS had at least weekly symptoms or used at least weekly antireflux medication.<sup>14</sup> The corresponding proportion of 98% in Mini-Q confirmed this result and implies reliability of the GERS assessment in the HUNT study.

Previous research on the population-based prevalence of GERS is heterogeneous and comparisons between prevalence studies are inherently difficult since GERS are subjective and the definition of GERD varies between studies. In addition, the sample size of previous studies is generally small. A few studies have assessed the change

in prevalence of GERS by investigating the same source population at a minimum of two time points. Two US studies, conducted in the same source population in 1980 and in 1988-1991, found an increase in the prevalence of at least weekly heartburn from 13.2% (n=835; aged 30-64 years) to 17.8% (n=1511; aged 25-74 years), but no change in at least weekly acid regurgitation (6.5% and 6.3%, respectively).<sup>15 16</sup> In a Swedish study, the prevalence of any GERS increased from 20-21% in 1986 (n=337; aged 20-79 years) to 22-25% at follow-up 10 years later (n=197).<sup>17 18</sup> In another Swedish population, the prevalence of any GERS increased from 18.9% in 1988 (n=1156; aged 20-79 years) to 19.4% at follow-up in 1995 (n=877).<sup>19</sup> In a recent Danish study from 1998-1999, the prevalence of at least mild GERS at baseline was 22% (n=6781; aged 40-65 years) and was reported to be stable at follow-up 5 years later (n=5578).<sup>20</sup> Except for this last study, there was an increasing prevalence of GERS over time in all populations, but this increase was not as pronounced as in the present study. The increasing prevalence of GERS is alarming since it most likely will contribute to the increasing incidence of adenocarcinoma of the esophagus in the Western population.<sup>5 6</sup>

Only a few population-based studies have assessed the prevalence of GERS in the same cohort during at least two time points and addressed incidence or loss of GERS. Generally these studies have a small sample size, a short follow-up time, or a selected population. A Danish study with baseline in 1982-1984 and follow-up assessment in 1987-1988 (n=2987; aged 30-60 years at baseline) reported an annual incidence of any GERS of 13-19% and an annual incidence of frequent GERS of 1-3%.<sup>21</sup> A Swedish study with baseline in 1988 and 1 year follow-up (n=1059; aged 20-79 years at baseline) reported an annual incidence of predominant GERS of

0.05% and an annual incidence of GERS with other concurrent gastrointestinal symptoms of 0.75%.<sup>22</sup> A US study from 1988-1991 with 12-20 months follow-up (n=690; aged 30-64 years at baseline) reported a cumulative onset rate of heartburn several times a week or daily of 2.7%, corresponding to average annual onset rates of 1.6-2.7%.<sup>23</sup> In another Swedish population with baseline assessment in 1986 and follow-up 10 years later (n=197; aged 20-79 years at baseline), the annual incidence of any GERS was 1.2-1.8%.<sup>18</sup> In the most recent study from Denmark with baseline in 1998-1999 and follow-up assessment 5 years later (n=5578; aged 40-65 years at baseline), an annual incidence of at least mild GERS of 2.2% was reported.<sup>20</sup> Except for the first Danish study, these incidence figures comply with the results of our study, and over the last two decades the incidence seems to be quite stable among these populations. However, in our study we were able to show an effect of age on the incidence of GERS among women.

The first Danish study reported cumulative loss of any GERS of 27-37%, corresponding to average annual loss of 6.2-9.0%, and cumulative loss of frequent GERS of 59-77%, corresponding to average annual loss of 16.1-23.2%.<sup>21</sup> The US study reported cumulative loss of heartburn several times a week or daily of 47.8%, corresponding to average annual loss of 36.9-61.3%.<sup>23</sup> The second Swedish study reported annual loss of any GERS of 1.1-1.3%,<sup>18</sup> and the most recent Danish study reported annual loss of at least mild GERS of 8.6%.<sup>20</sup> Except for the second Swedish study, these figures on loss of GERS deviate from our results, but our large sample size, long follow-up time, and ability to adjust for antireflux medication argue for validity. In addition, we showed a considerable effect of age on the spontaneous loss of GERS.

There might be several reasons why the prevalence of GERS has increased during the last decade. The body weight has increased in the population, and high BMI is an established risk factor of GERS. The increasing age of the cohort may contribute, but the prevalence increased also after adjustment for age. However, it is interesting that the incidence and spontaneous loss of GERS were influenced by age, particularly for women. Postmenopausal hormone replacement therapy seems to be a risk factor of GERS and may to some extent contribute to this pattern for women.<sup>14 24</sup> The substantial loss of GERS, not due to antireflux medication, found in the present study, is partly conflicting with the presumed chronic character of GERS and the large use of regular antireflux medication in this population. Besides antireflux medication, there are few data on the prevention and treatment of GERS in a population-based setting. These issues will be addressed in depth in future studies using the HUNT study.

## **CONCLUSION**

In this large prospective population-based cohort study there was a considerable increase in the prevalence of GERS between 1995-1997 and 2006-2009, and the prevalence of at least weekly GERS increased by 47%. The average annual cumulative incidence of severe GERS was 0.23%, and the average annual spontaneous loss of severe GERS (not due to antireflux medication) was 1.22%. The incidence and spontaneous loss of GERS differed between the sexes and with age.

## **FIGURE LEGENDS**

(Figure1.pdf)

**Figure 1:** Flowchart of participants reporting gastroesophageal reflux symptoms (GERS) in HUNT 2 (1995-1997) and HUNT 3/Mini-Q (2006-2009) with number (N) of individuals at each stage and response rates (%). Response rates were calculated from those eligible, excluding those deceased or no longer resident in the county (non-eligible).

## FIGURE LEGENDS ONLINE ONLY MATERIAL

(Figure2.pdf)

**Figure 2:** Prevalence of *at least weekly* gastroesophageal reflux symptoms for each sex and age groups in 1995-1997 (HUNT 2) and 2006-2009 (HUNT 3/Mini-Q). Vertical lines represent 95% confidence intervals.

(Figure3.pdf)

**Figure 3:** Cumulative incidence of *any* and *severe* gastroesophageal reflux symptoms for each sex and age groups (age at follow-up) between 1995-1997 (HUNT 2) and 2006-2009 (HUNT 3/Mini-Q). Vertical lines represent 95% confidence intervals.

(Figure4.pdf)

**Figure 4:** Cumulative spontaneous loss of *any* and *severe* gastroesophageal reflux symptoms for each sex and age groups (age at follow-up) between 1995-1997 (HUNT 2) and 2006-2009 (HUNT 3/Mini-Q). Vertical lines represent 95% confidence intervals.

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### **Competing Interests**

The authors have no financial, professional, or personal conflict of interest relevant to the manuscript.

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### **Contributorship Statement**

Ness-Jensen, Eivind: study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; approval of the final version of the manuscript.

Lindam, Anna: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis; approval of the final version of the manuscript.

Lagergren, Jesper: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; approval of the final version of the manuscript.

Hveem, Kristian: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; approval of the final version of the manuscript.

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Figure 1

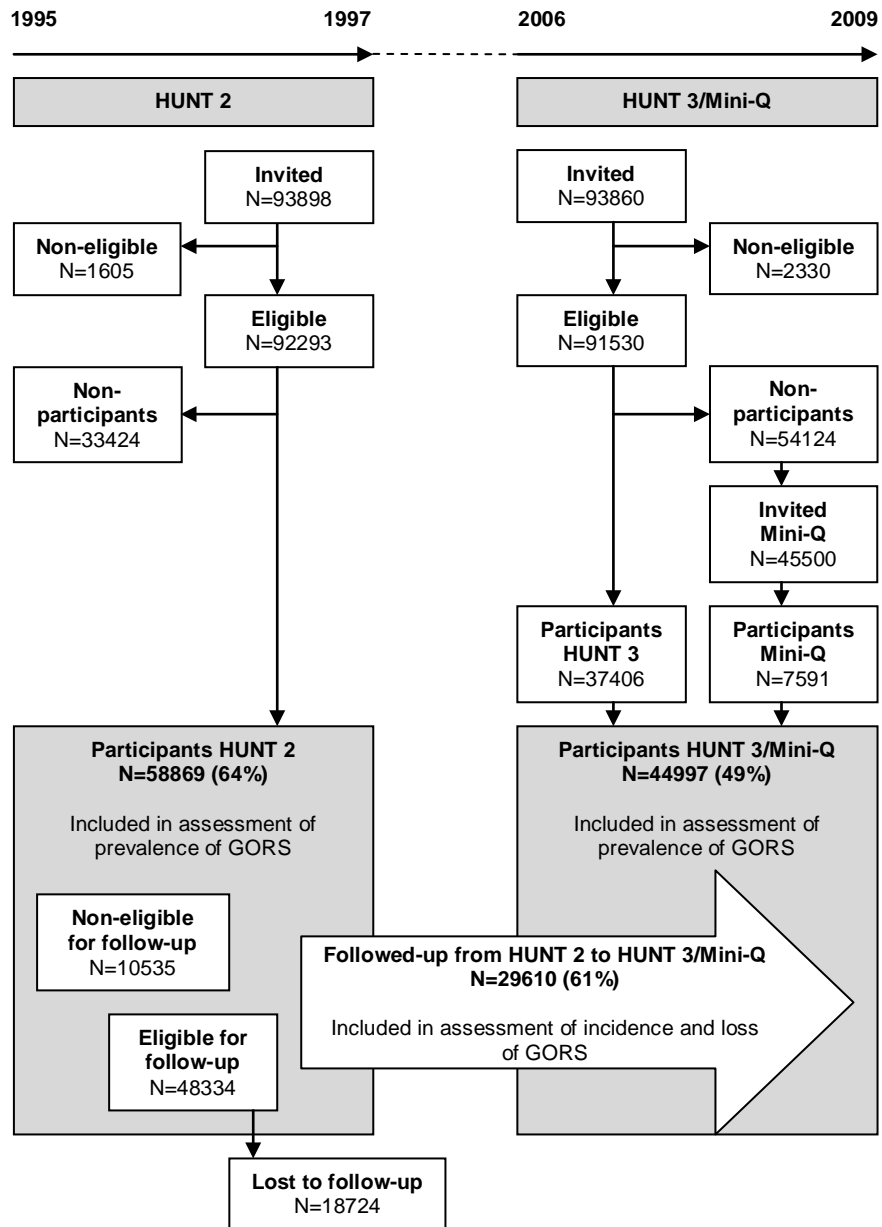


Figure 2

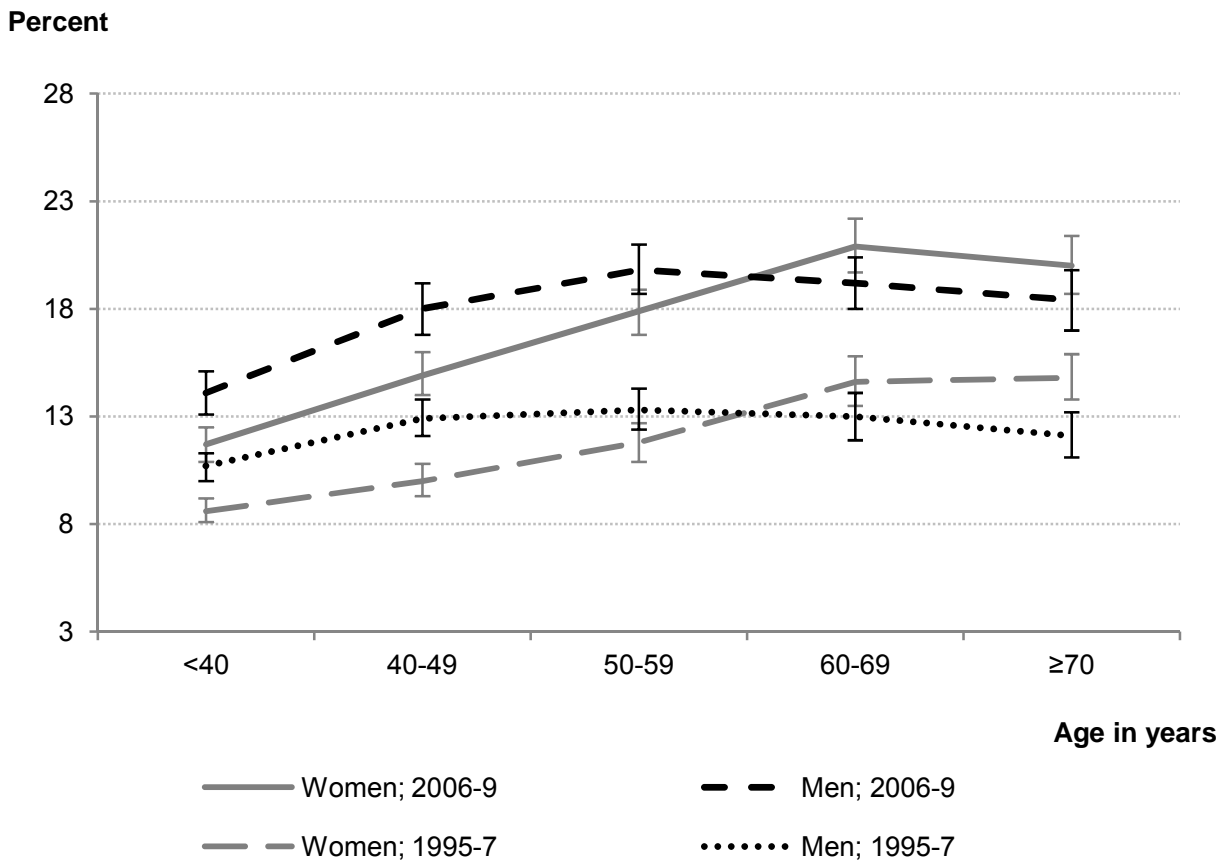
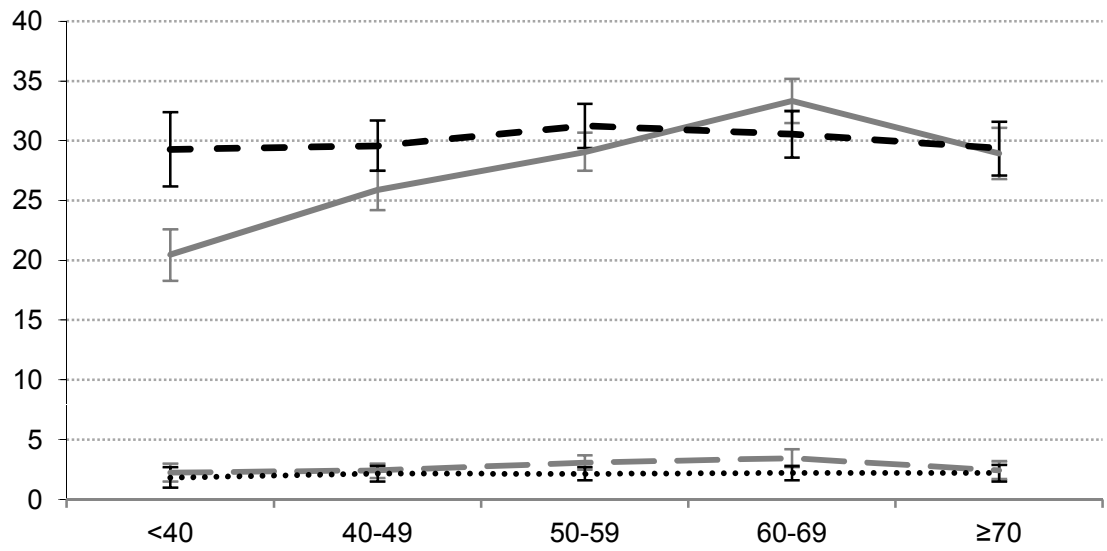


Figure 3

Percent



Age in years

— Women; any GORS

- - Men; any GORS

— Women; severe GORS

..... Men; severe GORS

Figure 4

