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Epidemiology of gastro-oesophageal reflux

A prospective population-based cohort study:
The HUNT study

Thesis for the degree of Philosophiae Doctor

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Epidemiologi ved gastroøsofageal refluks

Gastroøsofageal refluks er tilbakestrøm av mageinnhold til spiserøret. Hovedsymptomene ved refluks er halsbrann og sure oppstøt. Refluks kan gi skader på slimhinnen i spiserøret og redusert livskvalitet. Hos noen få kan refluks også bidra til utvikling av kreft i spiserøret. I Helseundersøkelsen i Nord-Trøndelag (HUNT) rapporterte 60 000 voksne deltakere i HUNT 2 (1995-1997) og 45 000 voksne deltakere i HUNT 3 (2006-2009) sine plager med halsbrann og sure oppstøt. Blant disse deltok 30 000 individer både i HUNT 2 og HUNT 3.
Gastroøsofageal reflukssykdom, definert som minst ukentlige plager med reflukssymptomer, er hyppig og økende i befolkningen. I tidsrommet mellom HUNT 2 og HUNT 3 økte andelen som anga minst ukentlige reflukssymptomer med 47 %, fra 11,6 % til 17,1 % av befolkningen. Symptomene økte for begge kjønn og i alle aldersgrupper fra 20-års alder. I gjennomsnitt oppstod nye, alvorlige reflukssymptomer årlig hos 0,23 % av befolkningen i denne perioden. I samme periode ble i gjennomsnitt 1,22 % kvitt alvorlige reflukssymptomer årlig uten bruk av medisiner. De yngste ble hyppigere kvitt plagene sine enn de eldste.
Overvekt og tobakksrøyking er kjente risikofaktor for reflukssykdom, men det har vært uklart om vektnedgang eller røykekutt bedrer sykdommen. Dette ble undersøkt blant individene som deltok i både HUNT 2 og HUNT 3. Individene som gikk ned i vekt mellom HUNT 2 og HUNT 3 hadde større sjanse for bedring av reflukssymptomene enn individene som hadde stabil vekt eller gikk opp i vekt. Individene med størst vektnedgang hadde større sjanse for bedring av plagene enn individene med mindre vektnedgang. De som hadde gått ned i vekt hadde også større sjansen for vellykket behandling med medisiner. Individene som kuttet ut dagligrøyking mellom HUNT 2 og HUNT 3 hadde også økt sjanse for bedring av alvorlige reflukssymptomer sammenlignet med de som fortsatte å røyke daglig. Røykekutt bedret bare symptomene hos normalvektige som brukte medisiner regelmessig mot plagene. Dette skyldes trolig at overvekt er en sterkere risikofaktor for reflukssykdom enn røyking, og at det hos overvektige ikke er nok å kutte ut røyken for å bedres.
Studien viser derfor at vektnedgang og røykekutt kan være gunstig for å forebygge og behandle reflukssykdom, og at individer som ikke har tilfredsstillende effekt av medikamentell behandling mot reflukssykdom kan ha nytte av vektnedgang og røykekutt.

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List of papers

I. Ness-Jensen E, Lindam A, Lagergren J, Hveem K.

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

Gut 2012; 61: 1390-1397.

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II. Ness-Jensen E, Lindam A, Lagergren J, Hveem K.

Weight loss and reduction in gastroesophageal reflux. A prospective population-based cohort study: the HUNT study.

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III. Ness-Jensen E, Lindam A, Lagergren J, Hveem K.

Tobacco smoking cessation and improved gastro-oesophageal reflux. A prospective population-based cohort study: the HUNT study.

American Journal of Gastroenterology 2014; 109:171-177.

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List of acronyms and abbreviations

ATC	Anatomical therapeutic chemical
BMI	Body mass index
BO	Barrett's oesophagus
CI	Confidence interval
GEE	Generalized estimating equations
GERD	Gastroesophageal reflux disease
GERS	Gastroesophageal reflux symptoms
GORD	Gastro-oesophageal reflux disease
GORS	Gastro-oesophageal reflux symptoms
H2RA	Histamine-2-receptor antagonist
HUNT	Nord-Trøndelag Health Study
LOS	Lower oesophageal sphincter
Mini-Q	Non-responder study after HUNT 3
NERD	Non-erosive reflux disease
NorPD	Norwegian Prescription Database

OAC	Oesophageal adenocarcinoma
OR	Odds ratio
OTC	Over the counter
PPI	Proton pump inhibitor
SD	Standard deviation
TLOSR	Transient lower oesophageal sphincter relaxation

Summary

Introduction

Heartburn and acid regurgitation are the characteristic gastro-oesophageal reflux symptoms (GORS). GORS are associated with reduced quality of life and increased risk of oesophageal adenocarcinoma. GORS are highly prevalent in Western populations, but the changes in prevalence, incidence, and loss of GORS over time are unsettled. Overweight and tobacco smoking are known risk factors of GORS. However, whether weight loss or tobacco smoking cessation improves GORS is unclear. The aims of this thesis were to address changes in the occurrence of GORS in the same population over time and the associations between weight loss and tobacco smoking cessation and improvement in GORS.

Materials and methods

The thesis is based on data from the Nord-Trøndelag Health Study (HUNT), a series of population-based health surveys conducted in Nord-Trøndelag County, Norway. In HUNT 2 (1995 to 1997) and HUNT 3 (2006 to 2009) all adult residents of the county were invited. The participants received questionnaires on several health related topics, including complaints with GORS, and clinical measurements were performed at examination sites. In addition, data on antireflux medication was collected through the Norwegian Prescription Database. The prevalence of any, severe, and at least weekly GORS during HUNT 2 and HUNT 3 and the cumulative incidence and loss of GORS

between HUNT 2 and HUNT 3 were calculated. The association between weight loss and GORS and between tobacco smoking cessation and GORS was assessed by multivariable logistic regression, providing odds ratios (OR) and 95% confidence intervals (CI), while taking potential confounding factors into consideration.

Results

In HUNT 2 and HUNT 3, 58 869 and 44 997 participants answered the GORS questionnaire, respectively. This corresponded to response rates of 64% and 49%, respectively. Of the HUNT 2 participants, 29 610 individuals were prospectively followed up at HUNT 3, corresponding to a response rate of 61%. During the average 11-year period between 1995 to 1997 and 2006 to 2009, the prevalence of any, severe, and at least weekly GORS 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 GORS was 3.07% and 0.23%, respectively. In women, but not men, the incidence of GORS increased with increasing age. The average annual spontaneous loss (not due to antireflux medication) of any and severe GORS was 2.32% and 1.22%, respectively. The spontaneous loss of GORS decreased with increasing age. Weight loss was dose-dependently associated with reduction of GORS and an increased treatment success with antireflux medication. Among individuals with >3.5 units decrease in body mass index (BMI), the OR of loss of any (minor or severe) GORS was 1.98 (95% CI 1.45 to 2.72) when using no or less than weekly antireflux medication, and 3.95 (95% CI 2.03 to 7.65) when using at least weekly antireflux medication. The corresponding ORs of loss of severe GORS was 0.90 (95% CI 0.32 to 2.55) and 3.11 (95% CI 1.13 to

8.58). Among individuals using less than weekly antireflux medication, there was no association between tobacco smoking cessation and improvement in GORS (OR 0.95, 95% CI 0.39 to 2.30). However, when antireflux medication was used at least weekly, cessation of daily tobacco smoking was associated with improvement in GORS from severe to no or minor complaints (OR 1.78, 95% CI 1.07 to 2.97), compared with persistent daily smoking. This association was present among individuals within the normal range of BMI (OR 5.67, 95% CI 1.36 to 23.64), but not among overweight individuals.

Conclusions

Between 1995 to 1997 and 2006 to 2009 the prevalence of GORS increased substantially. At least weekly GORS increased by 47%. The average annual incidence of severe GORS was 0.23%, and the corresponding spontaneous loss was 1.22%. The incidence and spontaneous loss of GORS were influenced by sex and age. Weight loss was dose-dependently associated with both a reduction of GORS and an increased treatment success with antireflux medication. Tobacco smoking cessation was associated with improvement in severe GORS in individuals of normal BMI using at least weekly antireflux medication.

1 Introduction

1.1 Gastro-oesophageal reflux

1.1.1 Definitions

Gastro-oesophageal reflux means backflow of stomach content to the oesophagus. Heartburn, a burning retrosternal sensation, and acid regurgitation, the perception of flow of stomach content into the mouth or hypopharynx, are the characteristic gastro-oesophageal reflux symptoms (GORS).(1) Other clinical presentations are also associated with gastro-oesophageal reflux disease (GORD), including epigastric and retrosternal pain, dysphagia (difficulty swallowing) and odynophagia (pain with swallowing), water brash (excessive salivation with reflux episodes), nausea, inflammation of the airways with related symptoms, and dental erosions. GORD is through "The Montreal definition and classification of GERD: A global evidence-based consensus" defined as "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications."(2) The definition further states that "In population-based studies, mild symptoms occurring 2 or more days a week, or moderate/severe symptoms occurring more than 1 day a week, are often considered troublesome by patients". A modified Delphi process was used to develop this definition, using four principal steps: 1) selection of group members and drafting of statements; 2) systematic literature reviews for each statement; 3) grading of the collected evidence; and 4) discussion and repeated anonymous voting on a series of

iterations of the statements until a consensus was reached. Traditionally, the diagnosis of GORD has been made on the grounds of morphological changes of the oesophageal mucosa and on 24-hour pH-measurements of the distal oesophagus. The Montreal definition allow both asymptomatic individuals with demonstrated reflux complications and individuals with typical symptoms alone, without further investigations, to be defined as GORD patients, thus resulting in higher sensitivity in assessing GORD.

1.1.2 Occurrence

Prevalence is a measure of an existing state and may be defined as the proportion of individuals with a given disease in a population at a specified point in time. Incidence is a measure of new events or new cases of a given disease in a population during a defined period of time. Incidence may be reported as a cumulative incidence, which is the proportion of the population that get a disease during a given period of time. Cumulative incidence is sometimes also called incidence risk or incidence proportion.(3)

GORD, defined as at least weekly GORS, is highly prevalent in Western populations. In Western Europe, North America, Australia, and New Zealand the prevalence of GORD is reported to be between 9% and 25%, with a higher prevalence in more recent studies.(4-11) However, in other parts of the world the prevalence is generally lower. In Asia, the prevalence is reported to be between 2% and 10% (12-14) and in Sub-Sahara Africa the disease is rare.(14, 15) The incidence of GORD defined as at least weekly GORS, has previously only been addressed in one population-based study of 690

participants from the United States. After 12-20 months follow-up from 1988 to 1991 the cumulative incidence was reported to be 2.7%.(16)

1.1.3 Pathophysiology

There are four main factors involved in the pathophysiology of GORD: 1) the antireflux barrier; 2) the composition of the refluxed material; 3) the clearance of the refluxed material; and 4) the oesophageal mucosal resistance.

1) The antireflux barrier

At the oesophagogastric junction between the oesophagus and stomach there is an antireflux barrier which consists of the internal muscle layers of the distal oesophagus and proximal stomach (internal part) and the diaphragm and its supporting connective tissue (external part).(17) The smooth muscles in a 3 to 4 cm long segment of the distal oesophagus are tonically contracted creating a lower oesophageal sphincter (LOS).(18) The oblique muscle fibres of the proximal stomach create a narrow angle (the angle of His) where the oesophagus enters the stomach and act as a flap valve mechanism.(19) The crural part of the diaphragm forms the opening (hiatus) through which the oesophagus enters the abdomen and contraction of the diaphragm exerts a pinchcock-like action on the oesophagus.(20)

There are three main mechanisms which compromise the antireflux barrier: a) transient lower oesophageal sphincter relaxations (TLOSRs); b) hypotensive LOS; and c) anatomic disruption of the barrier.(17)

a) TLOSRs

TLOSRs are relaxations of the LOS and the crural diaphragm not triggered by swallowing.(21) This is a physiological mechanism which allows us to belch.(22, 23) The TLOSRs are also the most common mechanism of reflux, both in normal individuals and in GORD patients.(24, 25) TLOSRs are responsible for the majority of acid reflux episodes, but the rate of TLOSRs is similar in healthy individuals and GORD patients. However, the TLOSRs are more likely to be associated with reflux episodes in GORD patients.(26, 27) In GORD patients, an increased pressure gradient over the oesophagogastric junction and an increased compliance of the junction compared with healthy individuals facilitates reflux.(28, 29) As GORD becomes more severe the other mechanisms compromising the antireflux barrier become more important.(30)

b) Hypotensive LOS

The LOS has normally a resting pressure of 10 to 30 mmHg compared with the intragastric pressure and relaxes at the initiation of swallowing to allow passage of food.(18) Hypotensive LOS is present in a minority of GORD patients.(31) Reflux occurs when the hypotensive LOS pressure is overcome by an abrupt increase in the intraabdominal pressure (strain-induced reflux) or by free reflux if the LOS pressure is very low (0 to 4 mmHg).(25, 32) In addition, the LOS pressure can be reduced by various foods, including fat,(33) chocolate,(34) caffeine,(35) and alcohol(36). Hormones,(37) including elevated progesterone levels during pregnancy,(38, 39) and

drugs, including nitrates and dihydropyridine calcium channel antagonists,(40) beta-agonists,(41) anticholinergic drugs,(42) and benzodiazepines,(43) are also known to reduce the LOS pressure.

c) Anatomic disruption of the barrier

Hiatal hernia is a condition where a portion of the stomach is pulled up through the diaphragm and into the thoracic cavity. This counteracts the flap valve mechanism of the angle of His.(44) In addition, such hernia impairs clearance of acid from the oesophagus by trapping acid in the hernia sac, which subsequently is re-refluxed with the next swallow-induced relaxations of the LOS.(45, 46) A large hernia impairs the pinchcock-like action of the diaphragm on the distal oesophagus.(47) The majority of patients with moderate to severe GORD have hiatal hernia and the severity of oesophagitis correlates with hernia size.(17, 48) Hiatal hernia is associated with an increased frequency of TLOSRs.(49) However, TLOSRs play a less important role in the occurrence of reflux than in GORD patients without hiatal hernia.(50)

2) The composition of the refluxed material

It is mainly the acid of the stomach content that can cause damage to the oesophageal mucosa. The proton (H^+) diffuses into the mucosa, leading to cellular acidification and necrosis.(51) In addition pepsin, bile acids, trypsin, and food hyperosmolality increase the susceptibility of the mucosa to acid injury.(52) The level of acidity and the length of the reflux episodes define the degree of damage.(53) In GORD, a pH < 4 in > 4% of the

time during a 24-hour pH-measurement is considered pathological.(54) The enzymatic activity of pepsin is pH dependent and pepsin is activated in an acidic environment. Non-acid reflux can also cause symptoms and appears in part to be responsible for persistent symptoms despite medical treatment.(55)

3) The clearance of the refluxed material

The oesophagus is cleared of acid content by gravity and peristalsis moving down the oesophagus into the stomach.(24) In addition, residual acid is neutralised by swallowed saliva.(56) Peristaltic dysfunction compromises oesophageal acid clearance and occurs in a substantial minority of GORD patients.(31) Delayed gastric emptying is also associated with prolonged acid contact time in the oesophagus by triggering TLOSRs.(57) Chronic xerostomia (dry mouth) is also associated with reduced clearance of acid and oesophageal injury.(58) In addition, hiatal hernias impair the oesophageal clearance by trapping of acid content in the hernia sac and re-reflux, as explained above. Head of bed elevation has been shown to improve acid clearance from the oesophagus.(59)

4) The oesophageal mucosal resistance

The oesophageal mucosal resistance consists of preepithelial, epithelial, and postepithelial defences.(60) The preepithelial defences of surface mucous and bicarbonate, which maintain a pH gradient between lumen and cell surface, are poorly developed in the oesophagus.(61) The main defence is the epithelia itself, because of

tight junctions and a lipid rich matrix in the intercellular spaces.(62) The main postepithelial defence is blood flow, which provides bicarbonate to the extracellular space where protons extruded by pH-activated pumps on the oesophageal membranes are buffered.(51)

1.1.4 Aetiology

In contrast to pathophysiology, which is the study of disease mechanisms, aetiology is the study of what causes disease. Pathophysiology is typically studied by laboratory methods on patients, volunteers, or laboratory animals, while aetiology is studied by epidemiological methods to identify risk factors and subsequently causal relations. There is an increased risk of GORS within families (63) and a higher concordance in prevalence of GORS in monozygotic over dizygotic twin pairs,(64) suggesting a genetic influence. A few lifestyle-related factors have in population-based studies been associated with an increased risk of GORS, mainly high body mass index (BMI) (6, 8, 63, 65-72) and tobacco smoking.(6, 10, 63, 69, 73) High dietary fibre intake and moderate physical exercise seem to protect against GORS.(69, 73) Low socioeconomic status and education has also been associated with an increased risk of GORS.(8, 74) Some studies also find an increasing risk of GORS with increasing age (5, 6, 66, 75) and for men.(70, 76) In pregnancy, physiological responses increase the amount of GORS. Hormonal changes during pregnancy reduce the LOS resting pressure(77) and the mechanical pressure against the LOS barrier in the later stages of the pregnancy is increased, both favouring reflux events. In addition, hormone replacement therapy is also associated with GORS, probably by reducing the LOS resting pressure.(67, 78)

1.1.5 Complications

The Montreal definition and classification recognises several complications of gastro-oesophageal reflux which is divided into different syndromes (figure 1).(2)

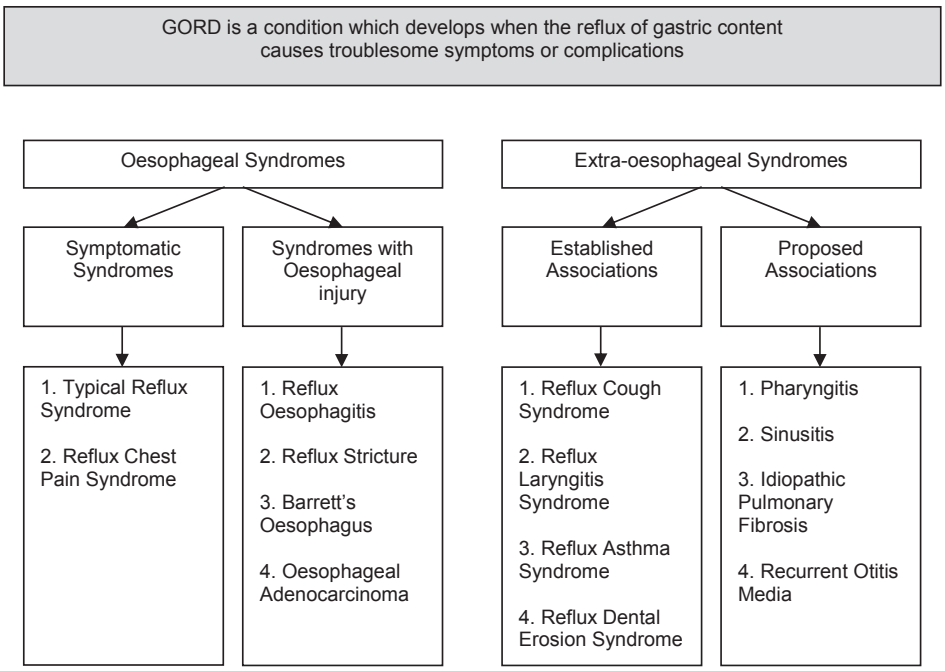

Figure 1 The overall definition of GORD and its constituent syndromes(2)

The complications are either oesophageal or extra-oesophageal. The extra-oesophageal syndromes are further divided into syndromes with established associations with GORD and conditions with proposed associations with GORD. Chronic cough, laryngitis, asthma, and dental erosions are associated with GORD, but the syndromes are usually

multifactorial where reflux rarely is the sole cause.(2) Whether reflux is a causal or exacerbation factor in pharyngitis, sinusitis, idiopathic pulmonary fibrosis, or recurrent otitis media is unclear.(2) The oesophageal syndromes are further divided into symptomatic syndromes and syndromes with oesophageal injury. The symptomatic syndromes are constellations of symptoms and further tests are not necessary to establish the diagnosis. Minor symptoms that occur for two or more days a week, or moderate to severe symptoms that occur for more than one day a week, reduces health-related quality of life.(79, 80) In addition, GORS has a considerable impact on work productivity.(81) The syndromes with oesophageal injury require further diagnostic testing to be established, i.e. by upper endoscopy. Upper endoscopy is a visualisation of the mucosa of the upper gastrointestinal tract done by passing a tube with optical lightning and camera through the mouth. The upper endoscopy provides objective signs of reflux complications. Oesophagitis, defined as endoscopically visible breaks of the distal oesophageal mucosa, is the most common consequence of oesophageal injury. Today, oesophagitis is most frequently assesses by the Los Angeles classification.(82, 83) However, oesophagitis was only seen in 29% of participants with weekly GORS in a Swedish survey (the Kalixanda study).(84) These patients might have non-erosive reflux disease (NERD) with pathological acid exposure on 24-hour pH-measurements of the distal oesophagus. Whether NERD and erosive reflux disease are distinct entities or just represent a continuum of the same disease is debated.(60, 85) A less common complication of reflux is formation of strictures, which narrows the lumen of the oesophagus and might induce dysphagia, i.e. difficulty swallowing. In a study with 7-year follow-up of patients with GORS, 0.08% and 1.9% developed strictures after a normal and erosive index upper endoscopy, respectively.(86) Peptic strictures are

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usually readily and successfully treated with endoscopic dilatation. More severe complications of reflux are Barrett's oesophagus (BO) and oesophageal adenocarcinoma (OAC). BO is the replacement of the normal squamous epithelia of the oesophagus with intestinal-type (columnar) epithelium due to oesophageal injury. In the Kalixanda study, BO was found in 1.6% of the general population and in 2.3% of those reporting GORS during the past 3 months.(87) In the 7-year follow-up study, none with a normal index upper endoscopy developed BO.(86) However, another study found that 1.4% with low-grade oesophagitis (Los Angeles grade A and B) and 5.8% with high-grade oesophagitis (Los Angeles grade C and D) had BO at 2-years follow-up.(88) BO is a premalignant condition, which may develop to OAC in about 0.1 to 0.2% per year overall.(89, 90) The risk is higher in long-segment BO or in BO with high grade dysplasia. OAC is a highly malignant disease with poor prognosis. The overall 5-year survival in patients with invasive oesophageal carcinoma is about 15 to 25%.(91) GORS are strongly associated with OAC.(92, 93) In some patients with typical GORS, pathological reflux has not been found either by upper endoscopy or by pH-measurements. The cause of symptoms in these patients are not clear, but may be related to increased sensitivity to normal acid exposure or other stimuli (oesophageal hypersensitivity).(94, 95)

1.1.6 Management

There are three main approaches to the management of GORD: 1) lifestyle modification, 2) medical therapy, and 3) surgery.

1) Lifestyle modification

As described above, a few lifestyle-related factors have a documented role in the pathophysiology of GORD and are associated with GORS in population-based studies. The lifestyle modifications broadly fall into 3 categories: a) avoidance of foods that may precipitate reflux (including coffee, alcohol, chocolate, and peppermint); b) avoidance of foods that can precipitate heartburn (including citrus, carbonated drinks, and spicy foods); and c) adoptions of behaviours that may reduce oesophageal acid exposure (including weight loss, smoking cessation, avoiding large meals, head of bed elevation, and avoiding recumbence after meals or meals before bedtime).(96, 97) If high-fat meals should be avoided is unclear. A controlled study did not find any change in LOS pressure or pH-measurements when comparing a low-fat and high-fat diet.(98) In a review of the evidence supporting lifestyle measures, only weight loss and head of bed elevation were found to be effective interventions for GORD. Both interventions improved pH profiles and weight loss also improved symptoms.(99) Head of bed elevation allows gravity to help clear the oesophagus of stomach content. A randomised controlled trail found effect on the healing of moderate oesophagitis and GORS by 20 cm elevation of the head of the bed.(100) However, the evidence supporting the effect of weight loss and head of bed elevation is from small studies of highly selected patients only. No evidence supported improvement in GORD by cessation of tobacco smoking or alcohol consumption or other dietary interventions in the review.(99) This is mainly due to lack of studies assessing these interventions. Anyhow, treatment is aimed at the individual patient and management is based on that individual's dietary intolerance or lifestyle, so avoiding exacerbating factors identified by the patient can be helpful.

2) Medical therapy

Medical therapy is aimed at reducing the acidity of the refluxate or to improve clearance of the refluxed content. Treatment is guided by the severity of symptoms and complications, as well as the effectiveness of the initial therapy. With mild and infrequent symptoms without signs of complications, lifestyle modifications and antacids on demand are the main approaches. Antacids relieve symptoms by neutralising the acid and are effective and rapidly acting.(97) Sucralphate and alginate which are cytoprotective and coats the mucosa are also used for mild GORS. With more severe and frequent symptoms or complications, H2-reseptor antagonists (H2RAs) and proton pump inhibitors (PPIs) are usually preferred. The goal is then preventing symptoms and if oesophagitis, healing of the mucosa. In the long term (26 to 52 weeks) PPI therapy reduces the risk of relapsing erosive disease and symptoms better than H2RA, which in turn is better than placebo.(101-103) With severe oesophagitis (Los Angeles grades C or D), PPIs are the preferred medical treatment and long term use is usually needed to prevent recurrence of erosive disease.(103) The role of maintenance therapy in non-erosive disease or in GORD patients were endoscopy has not been conducted is less clear.(97) However, H2RAs are usually preferred over PPIs and at the lowest effective dosage. With strictures or BO, PPIs are generally preferred for an indefinite time, but it has not been shown that this reduces the incidence of OAC in BO.(97) So, medical therapy may last for an indefinite period of time, and the costs of these treatments are huge.(104, 105) In addition, long term and potent acid inhibition with PPIs can induce secondary hypergastrinemia which is associated with rebound

hypersecretion of acid (106) and PPIs have been shown to produce GORS in healthy volunteers after withdrawal.(107) Moreover, low acid level in the stomach due to long term acid inhibition is associated with pneumonia,(108) Clostridium difficile infections,(109), reduced absorption of vitamin B-12,(110) and hypomagnesaemia.(111) The risk of hip fractures is also increased among long term users of PPIs, probably due to malabsorption of calcium.(112)

In addition to acid inhibition, medical therapy aimed at the other pathophysiological aspects of GERD is available as adjunctive therapy. Metoclopramide, a dopamine receptor antagonist which increases the oesophagogastric motility, is a potential drug against GERD. However, frequent central nervous side effects make regular use inappropriate.(113) As TLOSRs have been shown to be important in the pathophysiology of GORD, neurotransmitters and receptors involved in the regulation of TLOSRs are potentially new targets for pharmacological treatment of GORD patients.(27) This includes drugs that reduce the rate of TLOSRs, as gamma-aminobutyric acid receptor B (GABA-B) agonists (baclofen),(114) metabotropic glutamate receptor 5 (mGluR5) antagonists,(115) and cannabinoid receptor 1 (CBR1) agonists.(116) These drugs might be particularly useful in patient with refractory GORS on PPI therapy, because they can reduce symptoms due to non-acid reflux. However, central nervous system side effects are currently limiting the use of baclofen and data on side effects of the other drugs are needed.(27)

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3) Surgery

The indications for antireflux surgery are controversial. Surgery focuses on repairing the reflux barrier and controlling both acid and non-acid reflux.(117) It is believed that three mechanisms may play a role with antireflux surgery: 1) anatomical restoration of the oesophagogastric junction if a hiatal hernia is present, 2) decreased distensibility of the oesophagogastric junction,(118) and 3) a decreased rate of TLOSRs and decreased reflux associated with TLOSRs.(119) Both open and laparoscopic fundoplication are as effective as medical treatment with PPIs in preventing recurrence of oesophagitis and resolving of heartburn, but better on controlling acid regurgitation.(120, 121) On the other hand, surgically treated patients have higher rates of dysphagia, bloating, and flatulence.(120, 121) Surgery has not been shown to reduce the incidence of OAC in GORD patients (122) or BO patients.(123) So, if patients are judged to have similar effect of surgery and PPI therapy, the latter should be recommended as initial therapy because of superior safety. However, if the patient is responsive to, but intolerant of, acid suppressive therapy, surgery should be recommended as an alternative. In addition, patients with persistent troublesome regurgitation, despite PPI therapy, could benefit from surgery.(97) The potential benefits of surgery must, however, be weighed against the deleterious effects of surgery. Although the perioperative (124) and long-term (120, 121) morbidity and mortality is generally low with laparoscopic fundoplication, the otherwise low morbidity and mortality with GORD demands therapies to be very safe. Moreover, many surgical patients need medical therapy in the long run postoperatively and surgical revision is common. Nevertheless, most adult patients (92%) are satisfied with the result of laparoscopic fundoplication.(125) Traditionally, best results have been found in patients with typical symptoms, good response to medication, pathological pH

measurements, and no motility disturbances.(126) However, a systematic review concluded that there was no consistent association between surgical outcome and preoperative characteristics.(127)

1.2 Obesity and gastro-oesophageal reflux

1.2.1 Definitions

BMI is defined as the body weight in kilograms divided by the square height in metres (kg/m^2). BMI is used in the World Health Organization's International Classification of adult underweight, overweight and obesity: <18.50 is defined as underweight, 18.50 to 24.99 as normal range, ≥25.00 as overweight, and ≥30.00 as obese.(128)

1.2.2 Associations

There is good evidence that overweight is associated with GORS. (6, 8, 63, 65-72) The relation between weight and GORS seems to be dose-dependent.(67, 129) The risk of GORS has even been shown to be higher in individuals with BMI in the upper normal range (22.5 to 24.9) compared to individuals with BMI in the lower normal range (20.0 to 22.4[j]. In the same study, BMI of less than 20.0 was also associated with a reduced risk of GORS compared to individuals with BMI in the lower normal range.(129)

1.2.3 Pathophysiology

BMI and waist circumference are correlated with increased intragastric pressure and increased gastro-oesophageal pressure gradient that might lead to hiatal hernia.(130) Increasing BMI is correlated with increasing episodes of gastro-oesophageal reflux and higher acid exposure of the oesophagus.(131) Waist circumference may mediate a large part of the effect of obesity on oesophageal acid exposure.(132) Obesity is associated with an increased rate of TLOSRs, increased association of TLOSRs with reflux episodes, and increased pressure gradient over the oesophagogastric junction.(133) In addition, increasing BMI is correlated with higher volume and more proximal extent of reflux.(134) As higher acid exposure, volume, and proximal extent are associated with increased perception of GORS, obese individuals are also more likely to report symptoms.(135)

1.3 Tobacco smoking and gastro-oesophageal reflux

1.3.1 Associations

Tobacco smoking is associated with GORS.(6, 10, 63, 69, 73) Increased duration of smoking and higher amounts of smoking are both associated with a dose dependently increased risk of GORS.(73)

1.3.2 Pathophysiology

Tobacco smoking induces reflux by reducing the LOS resting pressure, facilitating gastric acid to reach the oesophagus.(136-138) In addition, tobacco smoking reduces the salivary bicarbonate secretion, which neutralises the acidity, and is associated with prolonged acid clearance time.(139, 140)

2 Objectives

As GORD is a disease with considerable impact on both patients and society, we wanted to 1) obtain valid estimates of the occurrence of GORS in the general population, including a) changes in prevalence with calendar time, b) incidence, and c) spontaneous loss. In addition, as lifestyle is related to GORD, we wanted to 2) clarify whether changes in lifestyle are associated with improvement in GORS, with focus on the associations with a) weight loss and b) tobacco smoking cessation.

2.1 Occurrence of gastro-oesophageal reflux (paper I)

2.1.1 Changes in prevalence

The prevalence of GORS has been reported from several populations, with a higher prevalence in more recent studies. However, the changes in prevalence over time in the same population remain uncertain. Our aim was to assess the changes in prevalence of GORS over time in the same population.

2.1.2 Incidence

The incidence of GORS has only been addressed in a few studies. Generally, these studies have a small sample size, a short follow-up time, or have been performed in a

selected population. Our aim was to assess the population-based cumulative incidence of GORS in a study of large sample size and long follow-up time.

2.1.3 Spontaneous loss

Loss of GORS without regular use of antireflux medication has only been addressed in a few studies with methodological issues. Our aim was to assess the population-based cumulative loss of GORS in study of large sample size and long follow-up time, excluding individuals using regular antireflux medication.

2.2 Changes in lifestyle and gastro-oesophageal reflux (papers II-III)

2.2.1 Weight loss and gastro-oesophageal reflux (paper II)

Overweight is a strong risk factor of GORS (see section 1.2.2 above). However, whether weight loss reduces GORS is unclear. Our aim was to clarify whether weight loss reduces GORS in a large population-based cohort followed prospectively over time.

2.2.2 Tobacco smoking cessation and gastro-oesophageal reflux (paper III)

Tobacco smoking increases the risk of GORS (see section 1.3.1 above). Only the very short-term effects of smoking cessation on GORD outcomes has been evaluated and a randomized clinical trial of smoking cessation would be unethical and not feasible to

perform. Our aim was to clarify if tobacco smoking cessation improves GORS in a large population-based cohort followed prospectively over time.

3 Materials and methods

3.1 The Nord-Trøndelag Health Study

3.1.1 Overview

The Nord-Trøndelag Health Study (HUNT) is a population-based cohort study based on data collected at repeated health surveys. The first survey (HUNT 1) was performed from January 1984 through February 1986, the second survey (HUNT 2) was performed from August 1995 through June 1997, and the third survey (HUNT 3) was performed from October 2006 through June 2008. In addition, a short questionnaire (Mini-Q) was sent to the non-responders in HUNT 3 in 2009. All residents of Nord-Trøndelag County from 20 years of age have been invited to participate. The participants filled in written questionnaires on health related topics, risk factors, quality of life, and socioeconomic status and clinical measurements were performed. In HUNT 1, the main focus was on hypertension and diabetes.(141, 142) In HUNT 2 and 3, the questionnaires and measurements were extended considerably, including questions on GORS, and blood and urine samples were included.(143, 144) In each survey the residents were invited to participate at temporarily located examination sites staffed by trained personnel. A basic screening questionnaire accompanied the invitational letter to each survey and additional questionnaires were handed out to the participants at the examination sites.

3.1.2 Assessment of gastro-oesophageal reflux symptoms

In HUNT 2 and HUNT 3 the questionnaires included an assessment of GORS. The participants were asked the following question: 'To what degree have you had heartburn or acid regurgitation during the previous 12 months?' The question had three response alternatives: 'no complaints', minor complaints', or 'severe complaints'. In HUNT 2 the GORS question was part of the basic screening questionnaire accompanying the invitational letter, but in HUNT 3 the GORS question was part of a second screening questionnaire that the participants received at the examination sites. However, the GORS question was also included in Mini-Q, which was sent to the non-responders in HUNT 3. In addition, frequency of GORS was assessed in Mini-Q through the following question: "If you have had heartburn or acid regurgitation during the previous 12 months, how often do you have complaints?" The question had three response alternatives: 'daily', 'weekly', and 'rarer'. Frequency of GORS was also assessed in a validation study after HUNT 2.(67) In the analyses, we have combined those who reported minor or severe complaints with GORS in the group 'any GORS' and those who reported severe complaints in the group 'severe GORS'. In addition, a group 'at least weekly GORS' has been estimated from the information on degree of GORS from HUNT 2 and HUNT 3 and the information on frequency of GORS from the validation study after HUNT 2 and Mini-Q, respectively.

3.1.3 Assessment of body mass index

Weight and height were objectively measured under standardised conditions and by trained personnel at the examination sites in both HUNT 2 and HUNT 3. In Mini-Q,

weight and height measurements were self-reported. In paper II, the absolute change in BMI units between HUNT 2 and HUNT 3/Mini-Q was calculated and five categories reflecting this change were used in the analyses: <0.5 units change (reference category), 0.5 to 1.5 units decrease, >1.5 to 3.5 units decrease, >3.5 units decrease, and ≥0.5 units increase. In paper III, the analyses were stratified by BMI categories as defined by the World Health Organization's classification: 18.5 to 24.9 units (normal weight), 25.0 to 29.9 units (pre-obese), and ≥30.0 units (obese).(128) Waist and hip circumference were also measured in HUNT 2 and HUNT 3, but not reported by the responders to Mini-Q. Thus, to increase the precision and reduce selection bias (see sections 5.1.2.2 and 5.1.2.1 1) below), BMI was chosen over waist circumference as the measure of obesity.

3.1.4 Assessment of tobacco smoking

In HUNT 2, the participants were asked about their tobacco smoking status by answering yes or no to these questions: 'Have you ever smoked daily?', 'Do you smoke cigarettes daily?', 'Do you smoke cigars or cigarillos daily?', and 'Do you smoke pipe daily?' In HUNT 3 and Mini-Q, the participants were asked: 'Do you smoke?' The response alternatives to this question were: 'no, I have never smoked', 'no, I have quit smoking', 'yes, cigarettes occasionally (parties/vacation, not daily)', or 'yes, cigarettes daily'. In paper III, those who quitted daily tobacco smoking or reduced daily smoking to only occasional smoking between HUNT 2 and HUNT 3/Mini-Q were defined as 'exposed' to tobacco smoking cessation, and those who were persistent daily tobacco smokers at both time points were regarded as 'unexposed' to such cessation. In paper II, tobacco smoking was assessed as a co-variable by using the reported status in HUNT

3/Mini-Q. The categories included were ‘never smoker’, ‘previous smoker’, or ‘current smoker’, with the latter including those responding with ‘yes, cigarettes occasionally (parties/vacation, not daily)’ or ‘yes, cigarettes daily’.

3.1.5 Assessment of co-variables

Sex and age at participation at each survey were recorded for all participants. In paper I, the prevalence, incidence and loss of GORS were assessed for each sex and in age groups: <40, 40 to 49, 50 to 59, 60 to 69, and ≥70 years. In papers II and III, sex and age at follow-up in HUNT 3/Mini-Q were included as co-variables in the analyses. In addition, categories reflecting frequency of alcohol consumption (less than weekly or at least weekly), years of education (≤12 years or >12 years), and frequency of physical exercise (less than weekly or at least weekly) were included as co-variables in the analyses in papers II and III. Frequency of alcohol consumption was assessed in HUNT 3/Mini-Q through the question: ‘About how often during the previous 12 months did you drink alcohol? (Do not include low-alcohol beer)’. This question had the following response alternatives: ‘4 to 7 times a week’, ‘2 to 3 times a week’, ‘about once a week’, ‘2 to 3 times a month’, ‘about once a month’, ‘a few times a year’, ‘not at all the last year’, and ‘never drank alcohol’. We used weekly alcohol consumption as the cut-off value and those reporting consumption ‘about once a week’ or more frequent were included in the ‘at least weekly’ category and those reporting consumption ‘2 to 3 times a month’ or less frequent were included in the ‘less than weekly’ category. Education was not assessed in Mini-Q, so to reduce the number of participants with missing information on education, questionnaire data from HUNT 2 were used. In HUNT 2,

education was assessed with the following question: ‘What is your highest level of education?’ The response alternatives reflect both old and new educational systems in Norway: ‘primary school 7 to 10 years, continuation school, folk high school’, ‘high school, intermediate school, vocational school, 1 to 2 years high school’, ‘university qualifying examination, junior college, A levels’, ‘university or other post-secondary education, less than 4 years’, and ‘university/college, 4 years or more’. We defined university, other post-secondary education, and college as the higher level of education and this will require more than 12 years of education in Norway. The other levels of education require 12 years of education or less. Physical exercise was assessed in HUNT 3/Mini-Q with the following question: ‘How often do you exercise?’ The response alternatives to this question were: ‘never’, ‘less than once a week’, ‘once a week’, ‘2 to 3 times a week’, and ‘nearly every day’. We used weekly exercise as the cut-off value and those reporting exercise ‘once a week’ or more frequent were included in the ‘at least weekly’ category and those reporting exercise ‘less than once a week’ or less frequent were included in the ‘less than weekly’ category.

3.2 The Norwegian Prescription Database

3.2.1 Overview

The Norwegian Prescription Database (NorPD) was established January 1, 2004. It contains data about drugs dispensed by prescription in Norway. All Norwegian pharmacies are required by legislation to report data on all prescriptions they are handling. Drugs that are purchased over the counter (OTC) without prescription are not

included. 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.

3.2.2 Assessment of antireflux medication

Antireflux medication includes PPIs, H2RAs, antacids, and other drugs (misoprostol, sucralfate, bismuth subcitrate, and alginic acid). Until 2010, the prescription rules in Norway required a prescription from a physician for all PPIs or H2RAs, except for small packages of low dose H2RAs. As the NorPD was not established until 2004 we do not have information on antireflux medication at the time of HUNT 2. However, we were able to gather information on the prescribed medication among the participants in HUNT 3. We retrieved information from the NorPD by using the anatomical therapeutic chemical (ATC) classification system. We included all prescriptions of medications in the ATC A02 level (alimentary tract and metabolism, drugs for acid related disorders) and lower levels to include all usual antireflux medications. We collected information on dosage, package size, and number of packages for each single prescription. The information was retrieved from the HUNT 3 study period, from October, 2006 through June, 2008. By using the number of prescriptions and number of tablets in each prescription, average frequency of antireflux medication was estimated for each participant. To comply with the definition of GORD, we defined average weekly use of antireflux medication as the cut-off level. At least weekly use of antireflux medication was considered a proxy for GORD and less than weekly use of antireflux medication was considered not sufficient to be defined as GORD. In addition to the data from the NorPD, OTC antireflux medication was assessed in HUNT 3 with the following

question: ‘How often have you taken non-prescribed medication for the following complaints during the last month: heartburn or acid regurgitation?’ The response alternatives were: “never or rarely”, “1 to 3 times per week”, “4 to 6 times per week”, or “daily”. Thus, both prescribed and OTC antireflux medication in the study population during HUNT 3 should be accounted for. Only those who actually had a prescription of antireflux medication were included in the data from the NorPD and therefore it was not possible to distinguish between never users and participants with missing information on medication use. All participants with missing data on antireflux medication were therefore regarded as never users.

3.3 Study design

3.3.1 Cross-sectional studies

Both HUNT 2 and HUNT 3 were cross-sectional surveys conducted in the same population during a defined time period, from August 1995 through June 1997 and from October 2006 through June 2008, respectively. Thus, prevalence of GORS could be assessed in this population at two time periods, approximately 11 years apart. As Mini-Q was a non-responder study of those invited to participate in HUNT 3, we could also include the participants in Mini-Q in our study (HUNT 3/Mini-Q).

3.3.2 Longitudinal study

The individuals who participated in both HUNT 2 and HUNT 3 or Mini-Q were prospectively followed from HUNT 2 to HUNT 3/Mini-Q. Thus, incidence of GORS and loss of GORS could be assessed. In addition, we could assess other variables associated with changes in GORS over time.

3.4 Analyses

3.4.1 Prevalence, incidence and loss of gastro-oesophageal reflux

In paper I, prevalence of GORS was calculated as the proportion of participants in HUNT 2 and HUNT 3/Mini-Q who reported any (minor or severe) GORS or severe GORS, respectively. The prevalence of at least weekly GORS was estimated through assessment of both degree and frequency of complaints reported by those participating in the validation study after HUNT 2 and in Mini-Q. The proportion of participants with severe GORS and at least weekly GORS and the proportion of participants with minor GORS and at least weekly GORS in the validation study and Mini-Q were calculated. These proportions were then multiplied by the number of individuals with severe and minor GORS in HUNT 2 and HUNT 3, respectively, to get an estimate of at least weekly GORS in the two surveys. Cumulative incidence of GORS was calculated from the proportion of participants who reported no GORS in HUNT 2 and any or severe GORS in HUNT 3/Mini-Q, respectively. Cumulative loss of GORS was calculated from the proportion of participants who reported any or severe GORS in HUNT 2, respectively, but no GORS in HUNT 3/Mini-Q. In the latter analysis, those using

antireflux medication at least weekly in HUNT 3/Mini-Q were excluded to assess spontaneous loss of GORS only. Average annual cumulative incidence and spontaneous loss of GORS were calculated using the formula: (exp (cumulative proportion) – 1) / 11 years (average annual percentage change). In addition, 95% CIs for the proportions were calculated. Prevalence, incidence, and spontaneous loss of GORS were assessed for each sex and by age groups: <40, 40 to 49, 50 to 59, 60 to 69, and ≥70 years.

3.4.2 Logistic regression

In paper I, logistic regression was used to statistically assess the differences in incidence and spontaneous loss of GORS for each sex and age group. The interaction term between sex and age groups was used in the model. In paper II and III, logistic regression was used to assess the association between weight loss and tobacco smoking cessation as exposures, respectively, and improvement in GORS as outcome.

3.4.3 Generalised estimating equations

Standard statistical models for analysing data, including logistic regression, assume independency between the measurements. However, repeated measurements over time in the same individual are not independent. Generalised estimating equations (GEE) are based on logistic regression and use the same model as independent data, but with a correlation structure added to adjust for the dependency over time. In paper I, the changes in prevalence of GORS from HUNT 2 to HUNT 3/Mini-Q was statistically assessed by GEE to account for the repeated assessments of GORS among many of the

participants. We used exchangeable correlation structure which assumes constant correlation over time. This is a valid assumption when the data has few measurements on a large sample of individuals as in the HUNT study.(145) In addition, we used a robust variance estimator to get valid standard errors. In the model, adjustments were made for sex and age by using the interaction term between sex and age groups as co-variable.

4 Results

4.1 Participation (papers I-III)

4.1.1 The cross-sectional studies

In HUNT 2, 93 898 residents of Nord-Trøndelag County above 20 years of age were invited. Of these, 1605 individuals were not eligible because they had moved out of the county or had died at the time of the survey. Of the eligible residents, 58 869 individuals (64%) responded to the GORS questionnaire in HUNT 2. In HUNT 3, 93 860 residents above 20 years of age were invited and 2330 of these were not eligible due to emigration or death. Of the eligible residents, 37 406 individuals responded to the GORS questionnaire in HUNT 3. In addition, 7591 of the non-participants in HUNT 3 responded to the GORS questionnaire in Mini-Q. In total, 44 997 individuals (49%) responded to the GORS questionnaire in HUNT 3/Mini-Q (figure 2).

4.1.2 The longitudinal study

Of the 58 869 participants responding to the GORS questionnaire in HUNT 2, 10 535 individuals were not eligible for follow-up in HUNT 3 due to emigration or death between the surveys. Of the eligible participants in HUNT 2, 29 610 individuals (61%) were followed up prospectively in HUNT 3/Mini-Q (figure 2).

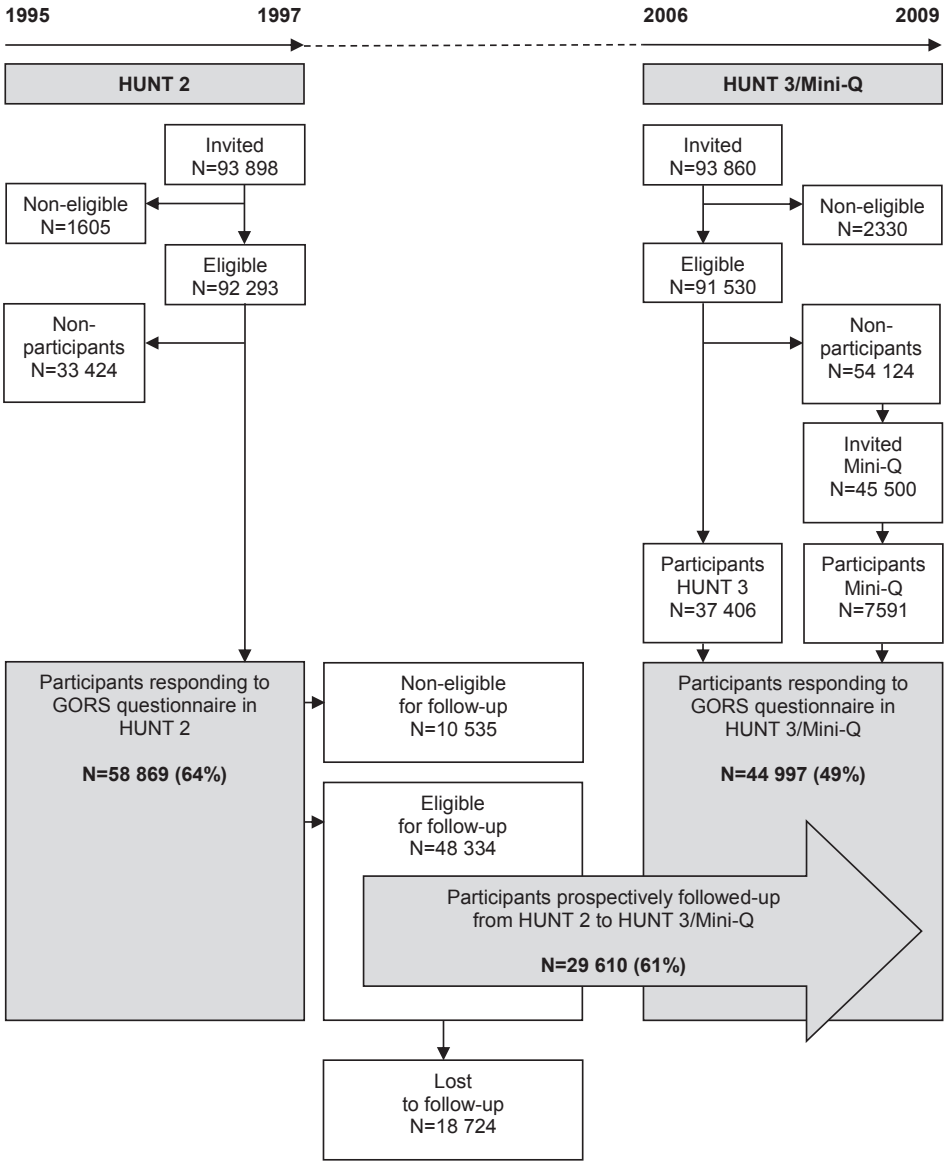

Figure 2 Flowchart of participants responding to the GORS questionnaires in HUNT 2 and HUNT 3/Mini-Q

4.2 Characteristics of participants

4.2.1 Paper I

In paper I we studied the occurrence of GORS for each sex and by age groups. In HUNT 2, 52% of the participants responding to the GORS questionnaire were women and 570 of these women reported to be pregnant. In HUNT 3/Mini-Q, 55% of the responders were women and 237 of these reported to be pregnant. All analyses included pregnant women, as analyses excluding them made no differences in the results. In HUNT 2, the mean age of the responders was 48.5 years (standard deviation (SD) 16.8 years), ranging from 19 to 101 years of age. In HUNT 3/Mini-Q, the mean age was 52.1 years (SD 16.0 years), ranging from 19 to 102 years. Among the participants who responded to the GORS questionnaire in both HUNT 2 and HUNT 3/Mini-Q, 54% were women and the mean age was 57.3 years at follow-up (SD 13.1 years), ranging from 29 to 100 years of age.

4.2.2 Paper II

In paper II we studied the association between weight loss and improvement in GORS. At baseline in HUNT 2, 9299 individuals (31.4%) reported any GORS and 1553 individuals (5.2%) reported severe GORS. Among those reporting any GORS in HUNT 2, 2398 individuals (25.8%) reported no GORS at follow-up in HUNT 3/Mini-Q, i.e. “loss of any GORS” (table 1). Among those reporting severe GORS in HUNT 2, 284 individuals (18.3%) reported no GORS at follow-up in HUNT 3/Mini-Q, i.e. “loss of

severe GORS" (table 1), 729 individuals (46.9%) reported minor GORS, and 1013 (65.2%) reported no or minor GORS, i.e. "reduction of severe GORS" (table 1).

The mean BMI among all the participants in paper II increased between HUNT 2 and HUNT 3/Mini-Q. The participants with loss or reduction of GORS had a lower increase in BMI than those with stable GORS (table 1). Those with loss or reduction of GORS were younger, had higher education, and used less antireflux medication than those with stable GORS (table 1). There was no difference in the proportion of current cigarette smokers among the subgroups (table 1). Of those reporting any GORS at baseline, the proportion of women was higher among those with loss of GORS compared to those with stable GORS at follow-up (table 1). Of those reporting severe GORS at baseline, alcohol consumption was more frequent among those with loss or reduction of GORS compared to those with stable GORS, and physical exercise was more frequent among those with loss or reduction of GORS (table 1).

Table 1 Characteristics of participants in paper II

	Stable any GORS	Loss of any GORS*	Stable severe GORS	Reduction of severe GORS*	Loss of severe GORS*
Number (%)	6901 (74.2)	2398 (25.8)	540 (34.8)	1013 (65.2)	284 (18.3)
BMI†, HUNT 2					
Mean (sd)	27.3 (4.0)	27.2 (4.3)	27.7 (4.2)	28.1 (4.3)	27.9 (4.3)
Missing, no. (%)	23 (0.3)	21 (0.9)	2 (0.4)	5 (0.5)	2 (0.7)
BMI change‡					
Mean (sd)	1.3 (2.4)	0.5 (2.7)	1.3 (2.4)	0.9 (2.7)	0.6 (2.8)
Missing, no. (%)	78 (1.1)	46 (1.9)	7 (1.3)	19 (1.9)	7 (2.5)
Sex					
Women, no. (%)	3415 (49)	1271 (53)	277 (51)	521 (51)	143 (50)
Age (years), HUNT 3/Mini-Q					
Mean (sd)	59.8 (12.6)	57.4 (14.1)	60.8 (12.7)	60.2 (13.6)	58.7 (14.5)
Tobacco smoking, HUNT 3/Mini-Q					
Never, no. (%)	2428 (35.2)	921 (38.4)	188 (34.8)	304 (30.0)	79 (27.8)
Previous, no. (%)	2332 (33.8)	737 (30.7)	182 (33.7)	383 (37.8)	120 (42.3)
Current, no. (%)	1822 (26.4)	631 (26.3)	141 (26.1)	279 (27.5)	73 (25.7)
Missing, no. (%)	319 (4.6)	109 (4.5)	29 (5.4)	47 (4.6)	12 (4.2)

Table 1 Continued

Alcohol consumption, HUNT 3/Mini-Q					
< Weekly, no. (%)	4292 (62.2)	1498 (62.5)	363 (67.2)	649 (64.1)	173 (60.9)
≥ Weekly, no. (%)	2377 (34.4)	816 (34.0)	153 (28.3)	327 (32.3)	103 (36.3)
Missing, no. (%)	232 (3.4)	84 (3.5)	24 (4.4)	37 (3.7)	8 (2.8)
Education, HUNT 2					
≤ 12 years, no. (%)	5602 (81.2)	1837 (76.6)	469 (86.9)	842 (83.1)	233 (82.0)
> 12 years, no. (%)	1162 (16.8)	511 (21.3)	56 (10.4)	146 (14.4)	41 (14.4)
Missing, no. (%)	137 (2.0)	50 (2.1)	15 (2.8)	25 (2.5)	10 (3.5)
Physical exercise, HUNT 3/Mini-Q					
< Weekly, no. (%)	1672 (24.2)	576 (24.0)	156 (28.9)	272 (26.9)	71 (25.0)
≥ Weekly, no. (%)	5047 (73.1)	1754 (73.1)	363 (67.2)	721 (71.2)	210 (73.9)
Missing, no. (%)	182 (2.6)	68 (2.8)	21 (3.9)	20 (2.0)	3 (1.1)
Antireflux medication§, HUNT 3					
Never or < weekly, no. (%)	3742 (54.2)	2112 (88.1)	87 (16.1)	505 (49.9)	195 (68.7)
≥ Weekly, no. (%)	3159 (45.8)	286 (11.9)	453 (83.9)	508 (50.1)	89 (31.3)

Table 1 Continued

* Loss of any GORS: any GORS at baseline, no GORS at follow-up; Reduction of severe GORS: severe GORS at baseline, no or minor GORS at follow-up; Loss of severe GORS: severe GORS at baseline, no GORS at follow-up

† BMI: body mass index (kg/m2)

‡ BMI change: BMI HUNT 3/Mini-Q - BMI HUNT 2

§ Antireflux medication: proton pump inhibitors, histamine-2-receptor antagonists, and antacids

Participants with no information on antireflux medication were included in never or < weekly category

4.2.3 Paper III

In paper III we studied the association between tobacco smoking cessation and improvement in GORS. In this paper we focused on the participants reporting severe GORS at baseline in HUNT 2 due to the heterogenetic nature of individuals reporting minor GORS (see section 5.3.3 below). Among the 1553 participants with severe GORS in HUNT 2, 486 (31%) were daily tobacco smokers and were included in the study. Of these participants, 182 quitted smoking and 31 reduced to occasional smoking in HUNT 3/Mini-Q. In total, 213 (44%) were previous daily smokers while 251 (52%) were persistent daily smokers in HUNT 3/Mini-Q. In both these groups, about 60% were using antireflux medication at least weekly (figure 3). The mean BMI was similar between the groups, but obesity was less common among the persistent daily smokers. Compared to the previous daily smokers, the persistent daily smokers were characterized by higher female representation, lower mean age, lower education, lower level of physical exercise, and lower alcohol consumption (table 2).

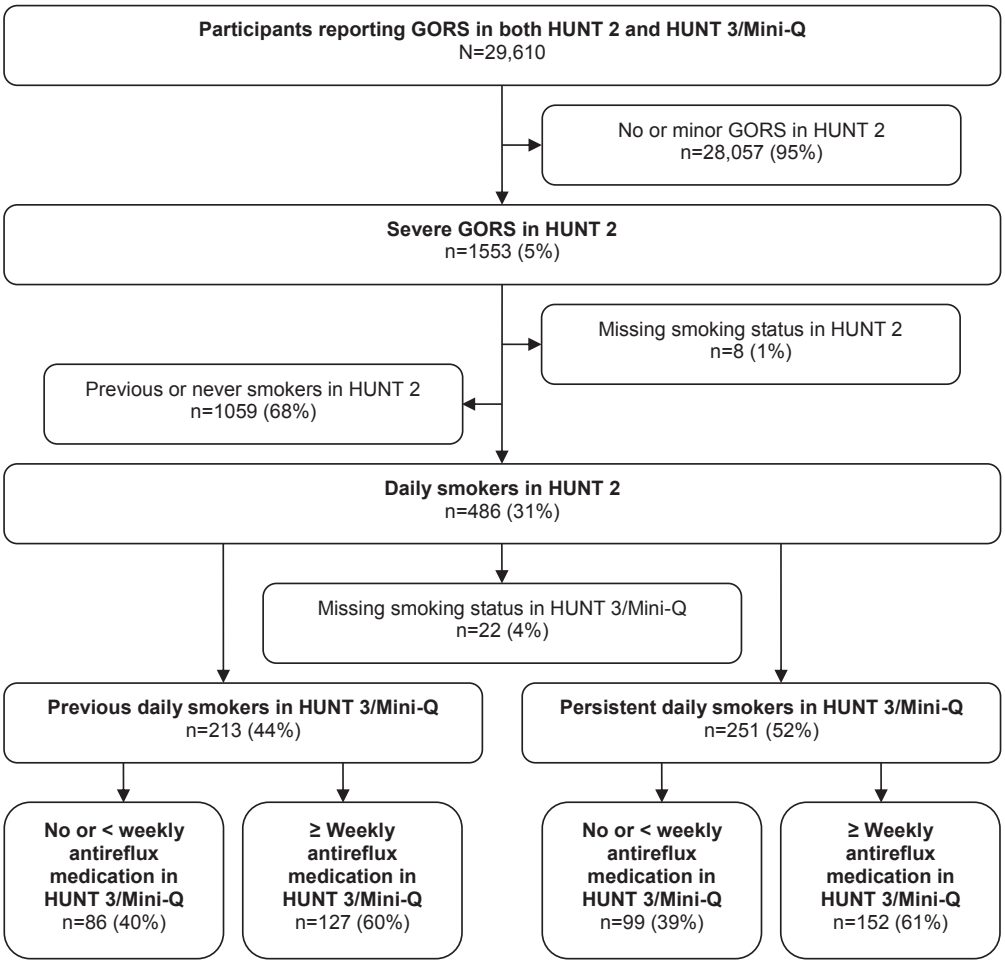

Figure 3 Flowchart of participants in paper III

Table 2 Characteristics of participants in paper III

Tobacco smoking status	**Previous daily smokers** (n=213)		**Persistent daily smokers** (n=251)	
Antireflux medication*	**No or < weekly** (n=86)	**≥ Weekly** (n=127)	**No or < weekly** (n=99)	**≥ Weekly** (n=152)
BMI†				
Mean (sd)	28.5 (4.7)	29.2 (4.5)	28.1 (5.0)	28.9 (5.1)
Median (range)	28.1 (18.7-47.2)	29.0 (19.0-44.1)	27.8 (18.9-49.3)	28.0 (15.2-47.5)
< 18.5, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)
18.5-24.9, no. (%)	22 (25.6)	20 (15.7)	28 (28.3)	30 (19.7)
25.0-29.9, no. (%)	35 (40.7)	55 (43.3)	42 (42.4)	69 (45.4)
≥ 30.0, no. (%)	29 (33.7)	49 (38.6)	28 (28.3)	51 (33.6)
Missing, no. (%)	0 (0.0)	3 (2.4)	1 (1.0)	0 (0.0)
Sex, no. (%)				
Women	37 (43)	54 (43)	52 (53)	92 (61)
Age, years				
Mean (sd)	55.7 (11.7)	58.9 (9.9)	51.8 (10.3)	57.5 (10.3)
Median (range)	55.3 (32.8-84.9)	58.6 (34.3-84.7)	51.3 (34.1-84.4)	56.7 (31.9-87.8)
Alcohol consumption, no. (%)				
< Weekly	51 (59.3)	82 (64.6)	65 (65.7)	107 (70.4)
≥ Weekly	34 (39.5)	44 (34.6)	34 (34.3)	44 (28.9)
Missing	1 (1.2)	1 (0.8)	0 (0.0)	1 (0.7)

Table 2 Continued

Education, no. (%)				
≤ 12 years	67 (77.9)	112 (88.2)	91 (91.9)	135 (88.8)
> 12 years	17 (19.8)	13 (10.2)	7 (7.1)	14 (9.2)
Missing	2 (2.3)	2 (1.6)	1 (1.0)	3 (2.0)
Physical exercise, no. (%)				
< Weekly	28 (32.6)	33 (26.0)	38 (38.4)	56 (36.8)
≥ Weekly	58 (67.4)	92 (72.4)	61 (61.6)	94 (61.8)
Missing	0 (0.0)	2 (1.6)	0 (0.0)	2 (1.3)

* Antireflux medication: proton pump inhibitors, histamine-2-receptor antagonists, and antacids

Participants with no information on antireflux medication were included in never or < weekly category

† BMI: body mass index (kg/m2)

4.3 Occurrence of gastro oesophageal reflux (paper I)

4.3.1 Changes in prevalence

The changes in prevalence of GORS over time in the same population were assessed. During the average 11-year period between HUNT 2 (1995 to 1997) and HUNT 3/Mini-Q (2006 to 2009) the prevalence of any GORS increased by 30%, from 31.4% (95% CI 31.0% to 31.7%) to 40.9% (95% CI 40.4% to 41.3%), and the prevalence of severe GORS increased by 24%, from 5.4% (95% CI 5.2% to 5.6%) to 6.7% (95% CI 6.4% to 6.9%). The OR of any and severe GORS in 2006 to 2009 was 1.46 (95% CI 1.43 to 1.49) and 1.20 (95% CI 1.15 to 1.26), respectively, compared with 1995 to 1997 after adjustment for sex and age. The prevalence increased for both sexes and all age groups (table 3, figure 4-5). In the validation study after HUNT 2, at least weekly GORS were reported by 25% of those participants with minor GORS and by 95% of those with severe GORS. In Mini-Q, the corresponding rates were 31% and 98%. The estimated prevalence of at least weekly GORS increased by 47% between 1995 to 1997 and 2006 to 2009, from 11.6% (95% CI 11.4% to 11.9%) to 17.1% (95% CI 16.7% to 17.4%) (table 4, figure 6).

Table 3 Prevalence of GORS in the HUNT study, stratified by degree of GORS, time point, sex, and age groups

	Prevalence of any GORS*													
	1995-1997 (HUNT 2)						**2006-2009 (HUNT 3/Mini-Q)**						**Relative change†**	
	Total N=58 869						**Total N=44 997‡**						**Total**	
	Number		%		95% CI		Number		%		95% CI		%	
	18 460		31.4		31.0-31.7		18 389		40.9		40.4-41.3		30.3	
	Women N=30 608			**Men N=28 261**			**Women N=24 550**			**Men N=20 440**			**Women**	**Men**
Age (years)§	Number	%	95% CI	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

Table 3 Continued

Prevalence of severe GORS*

	1995-1997 (HUNT 2)						2006-2009 (HUNT 3/Mini-Q)						Relative change†	
	Total N=58 869						Total N=44 997‡						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=30 608			Men N=28 261			Women N=24 550			Men N=20 440			Women	Men
Age (years)§	Number	%	95% CI	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 GORS: minor or severe complaints with heartburn or acid regurgitation; Severe GORS: 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 GORS assessment (HUNT 2 and HUNT 3/Mini-Q, respectively)

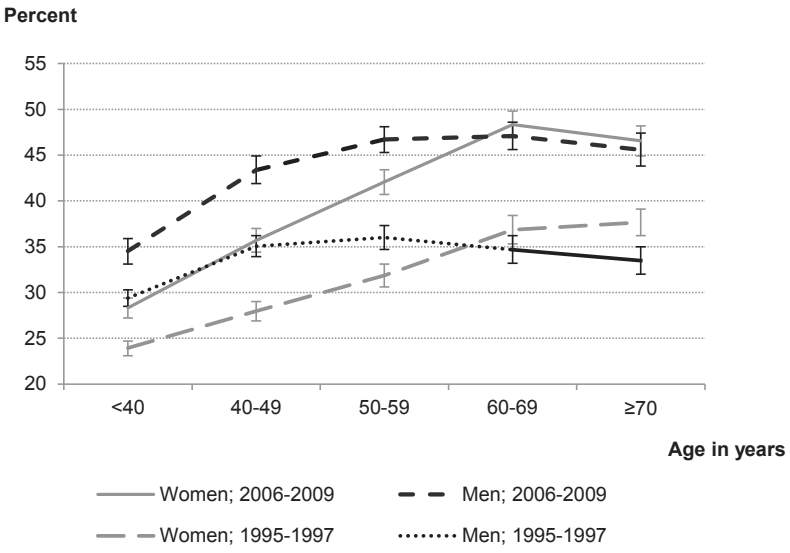

Figure 4 Prevalence of any GORS for each sex and age groups in 1995-1997 (HUNT 2) and 2006-2009 (HUNT 3/Mini-Q) with 95% CI (vertical lines)

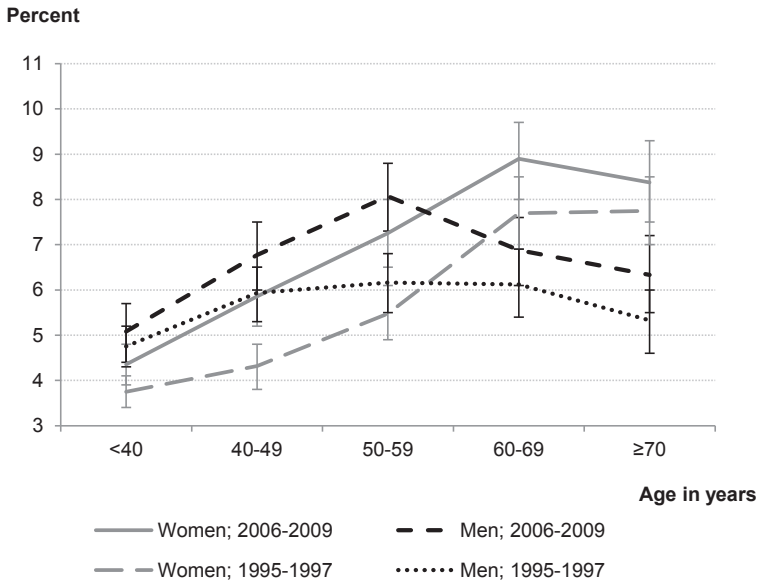

Figure 5 Prevalence of severe GORS for each sex and age groups in 1995-1997 (HUNT 2) and 2006-2009 (HUNT 3/Mini-Q) with 95% CI (vertical lines)

Table 4 Prevalence of at least weekly GORS in the HUNT study, stratified by time point, sex, and age groups

	Prevalence of at least weekly GORS*													
	1995-1997 (HUNT 2)						2006-2009 (HUNT 3/Mini-Q)						Relative change†	
	Total N=58 869						Total N=44 997‡						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=30 608			Men N=28 261			Women N=24 550			Men N=20 440			Women	Men
Age (years)§	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 GORS: 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 GORS assessment (HUNT 2 and HUNT 3/Mini-Q, respectively)

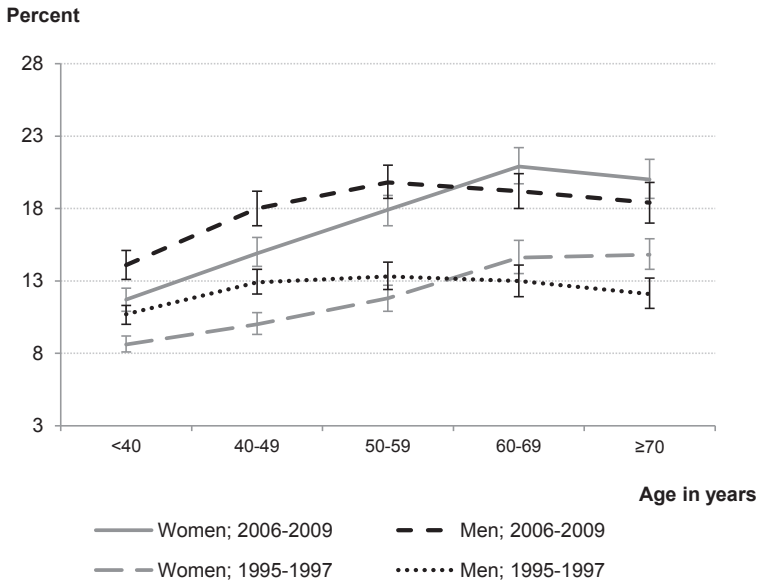

Figure 6 Prevalence of estimated at least weekly GORS for each sex and age groups in 1995-1997 (HUNT 2) and 2006-2009 (HUNT 3/Mini-Q) with 95% CI (vertical lines)

4.3.2 Incidence

Between HUNT 2 (1995 to 1997) and HUNT 3/Mini-Q (2006 to 2009), the cumulative incidence of any GORS was 29.1% (95% CI 28.4% to 29.7%), which corresponded to an average annual incidence of 3.07% (95% CI 2.99% to 3.14%). The incidence increased with increasing age for women, while it was stable with age for men. Women younger than 40 years of age had the lowest incidence of any GORS, but in older age groups there was no difference in the incidence of any GORS between the sexes (table 5, figure 7). The cumulative incidence of severe GORS was 2.5% (95% CI 2.3 to 2.7%), which corresponded to an average annual incidence of 0.23% (95% CI 0.21 to 0.25%).There was a slightly increased incidence of severe GORS 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 GORS (table 5, figure 7).

Table 5 Cumulative incidence of GORS from 1995-1997 (HUNT 2) to 2006-2009 (HUNT3/Mini-Q), stratified by degree of GORS, sex, and age groups*

	Any GORS†									
	Cumulative incidence						**OR and 95% CI‡**			
	Total N=20 311									
	Number		%		95% CI					
	5904		29.1		28.4-29.7					
	Women N=11 394			**Men N=8917**			**Women**		**Men**	
Age(years)§	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

Table 5 Continued

	Severe GORS†									
	Cumulative incidence						OR and 95% CI‡			
	Total N=20 311									
	Number		%		95% CI					
	510		2.5		2.3-2.7					
	Women N=11 394			Men N=8917			Women		Men	
Age(years)§	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 GORS in HUNT 2 to any or severe GORS in HUNT 3/Mini-Q, respectively

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

Severe GORS: severe complaints with heartburn or acid regurgitation

‡ OR and 95% CI of incident GORS for each sex and age group

§ Age at follow-up in HUNT 3/Mini-Q

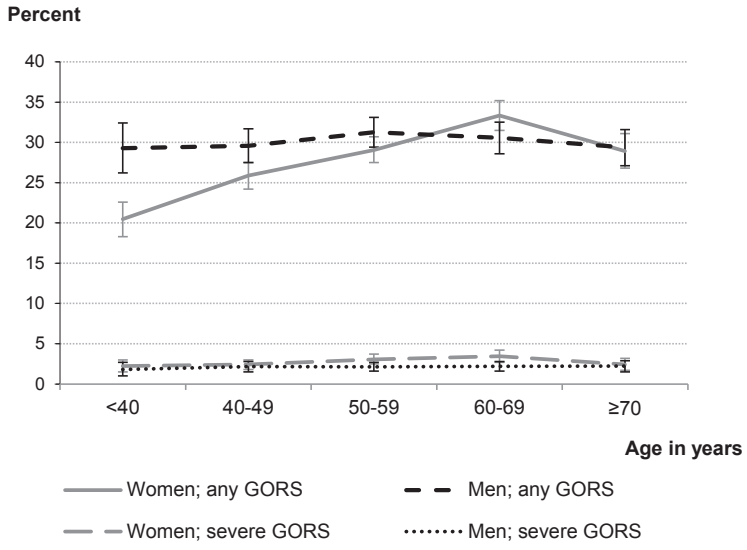

Figure 7 Cumulative incidence of any and severe GORS for each sex and age groups (age at follow-up) between 1995-1997 (HUNT 2) and 2006-2009 (HUNT 3/Mini-Q) with 95% CI (vertical lines)

4.3.3 Spontaneous loss

Between HUNT 2 (1995 to 1997) and HUNT 3/Mini-Q (2006 to 2009), the cumulative loss of any GORS was 22.7% (95% CI 21.9% to 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% to 2.42%). Women younger than 40 years of age had the highest spontaneous loss of any GORS. 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 GORS between the sexes in older age groups (table 6, figure 8). The cumulative loss of severe GORS was 12.6% (95% CI 10.9% to 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% to 1.40%). The spontaneous loss decreased with increasing age for both sexes, but this was particularly evident among women (table 6, figure 8).

Table 6 Cumulative spontaneous loss of GORS from 1995-1997 (HUNT 2) to 2006-2009 (HUNT3/Mini-Q), stratified by degree of GORS, sex, and age groups*

	Any GORS†									
	Cumulative spontaneous loss						**OR and 95% CI‡**			
	Total N=9299									
	Number		%		95% CI					
	2112		22.7		21.9-23.6					
	Women N=4686			**Men N=4613**			**Women**		**Men**	
Age(years)§	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

Table 6 Continued

	Severe GORS†									
	Cumulative spontaneous loss						OR and 95% CI‡			
	Total N=1553									
	Number		%		95% CI					
	195		12.6		10.9-14.2					
	Women N=798			Men N=755			Women		Men	
Age(years)§	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 GORS in HUNT 2, respectively, to no GORS in HUNT 3/Mini-Q, excluding those using antireflux medication at least weekly

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

Severe GORS: severe complaints with heartburn or acid regurgitation

‡ OR and 95% CI of losing GORS for each sex and age group

§ Age at follow-up in HUNT 3/Mini-Q

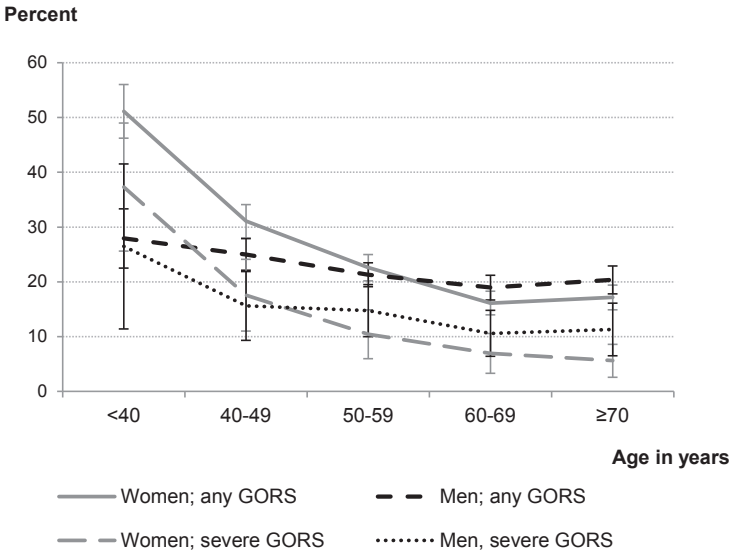

Figure 8 Cumulative spontaneous loss of any and severe GORS for each sex and age groups (age at follow-up) between 1995-1997 (HUNT 2) and 2006-2009 (HUNT 3/Mini-Q) with 95% CI (vertical lines)

4.4 Associations with lifestyle and gastro-oesophageal reflux (papers II-III)

4.4.1 Weight loss and gastro-oesophageal reflux (paper II)

Weight loss was dose-dependently associated with loss or reduction of GORS. When antireflux medication was used at least weekly, weight loss was associated with a particular increased treatment success. Among participants with no or less than weekly use of antireflux medication, the adjusted OR of loss of any GORS among participants with >3.5 units decrease in BMI was 1.98 (95% CI 1.45 to 2.72) compared to participants with <0.5 units change in BMI (table 7, figure 9). Among participants with at least weekly antireflux medication, the corresponding OR was 3.95 (95% CI 2.03 to 7.65) (table 7, figure 10). In the severe GORS cohort, there was no association between weight loss and GORS among participants with no or less than weekly antireflux medication (table 7, figure 11-12). However, among participants using antireflux medication at least weekly, the adjusted OR of reduction of severe GORS was 2.12 (95% CI 0.89 to 5.02) (table 7, figure 13) and the adjusted OR of loss of severe GORS was 3.11 (95% CI 1.13 to 8.58) (table 7, figure 14).

Table 7 OR with 95% CI for loss or reduction of GORS* compared with stable GORS by change in BMI† and use of antireflux medication‡

		Loss of any GORS§			Reduction of severe GORS§			Loss of severe GORS§		
Crude	**Change in BMI (kg/m^2)**	**No.**	**OR**	**95% CI**	**No.**	**OR**	**95% CI**	**No.**	**OR**	**95% CI**
	≥ 0.5 increase	5542	0.72	0.63 - 0.82	897	0.83	0.63 - 1.10	897	0.77	0.55 - 1.09
	< 0.5 change	1589	1.00	Reference	278	1.00	Reference	278	1.00	Reference
	0.5-1.5 decrease	970	1.22	1.03 - 1.46	157	0.88	0.59 - 1.33	157	0.90	0.55 - 1.48
	> 1.5-3.5 decrease	770	1.38	1.15 - 1.66	137	1.87	1.16 - 3.02	137	1.11	0.67 - 1.83
	> 3.5 decrease	304	2.42	1.88 - 3.11	58	1.32	0.70 - 2.47	58	1.51	0.79 - 2.88
	p-value for trend‖		< 0.001			0.001			0.012	
	Missing (%)	124	(1.3)		26	(1.7)		26	(1.7)	
No or less than weekly antireflux medication										
	Change in BMI (kg/m^2)	**No.**	**OR¶**	**95% CI**	**No.**	**OR¶**	**95% CI**	**No.**	**OR¶**	**95% CI**
	≥ 0.5 increase	3100	0.67	0.57 - 0.78	304	0.74	0.36 - 1.51	304	0.72	0.43 - 1.19
	< 0.5 change	939	1.00	Reference	95	1.00	Reference	95	1.00	Reference
	0.5-1.5 decrease	616	1.14	0.92 - 1.40	65	0.50	0.20 - 1.22	65	0.83	0.41 - 1.67
	> 1.5-3.5 decrease	485	1.25	0.99 - 1.56	54	1.64	0.49 - 5.48	54	1.13	0.56 - 2.31
	> 3.5 decrease	198	1.98	1.45 - 2.72	22	0.58	0.16 - 2.10	22	0.90	0.32 - 2.55
	p-value for trend‖		< 0.001			0.804			0.189	
	Missing (%)	516	(8.8)		52	(8.8)		52	(8.8)	

Table 7 Continued

At least weekly antireflux medication

Change in BMI (kg/m^2)	**No.**	**OR¶**	**95% CI**	**No.**	**OR¶**	**95% CI**	**No.**	**OR¶**	**95% CI**
≥ 0.5 increase	2022	0.99	0.67 - 1.45	518	1.04	0.71 - 1.51	518	0.81	0.42 - 1.56
< 0.5 change	507	1.00	Reference	145	1.00	Reference	145	1.00	Reference
0.5-1.5 decrease	267	1.29	0.75 - 2.19	78	1.16	0.66 - 2.03	78	0.94	0.36 - 2.48
> 1.5-3.5 decrease	213	1.79	1.05 - 3.05	67	2.24	1.19 - 4.21	67	0.91	0.32 - 2.55
> 3.5 decrease	66	3.95	2.03 - 7.65	30	2.12	0.89 - 5.02	30	3.11	1.13 - 8.58
p-value for trend‖		< 0.001			0.008			0.047	
Missing (%)	370	(10.7)		123	(12.8)		123	(12.8)	

* GORS: self-reported degree of complaints with heartburn or acid regurgitation during the previous 12 months

† Change in BMI: BMI HUNT 3/Mini-Q - BMI HUNT 2

‡ Antireflux medication: proton pump inhibitors, histamin-2-receptor antagonists, and antacids

§ Loss of any GORS: any GORS at baseline, no GORS at follow-up; Reduction of severe GORS: severe GORS at baseline, no or minor GORS at follow-up; Loss of severe GORS: severe GORS at baseline, no GORS at follow-up. The severe GORS group is a subset of the any GORS group

‖ p-value for trend: Wald test for linear trend

¶ Adjusted for sex, age, cigarette smoking, alcohol consumption, education, and physical exercise

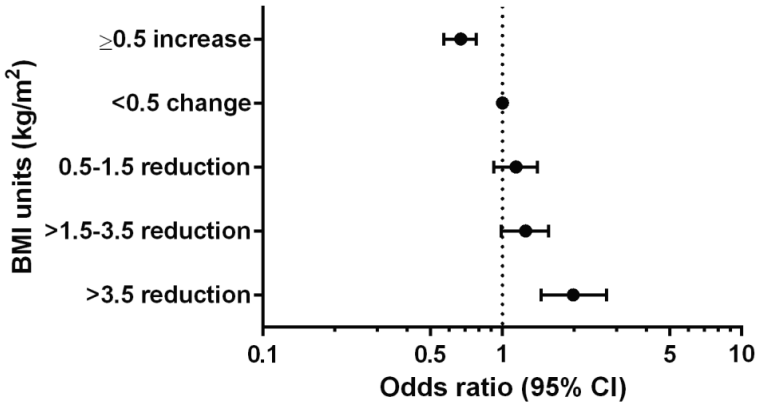

Figure 9 Adjusted OR with 95% CI for *loss of any GORS* by change in BMI when using *no or less than weekly* antireflux medication

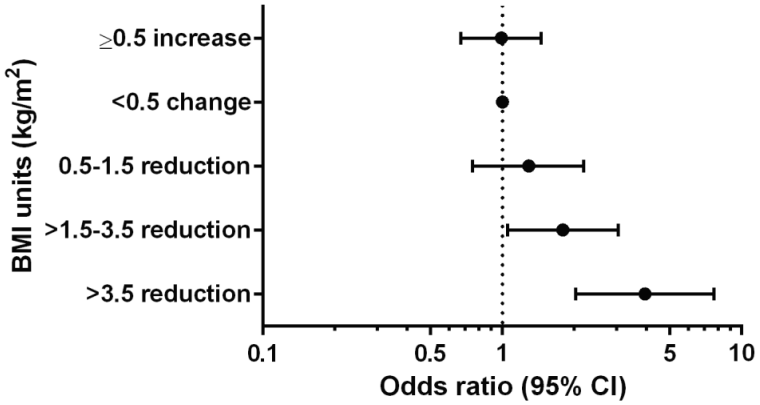

Figure 10 Adjusted OR with 95% CI for *loss of any GORS* by change in BMI when using *at least weekly* antireflux medication

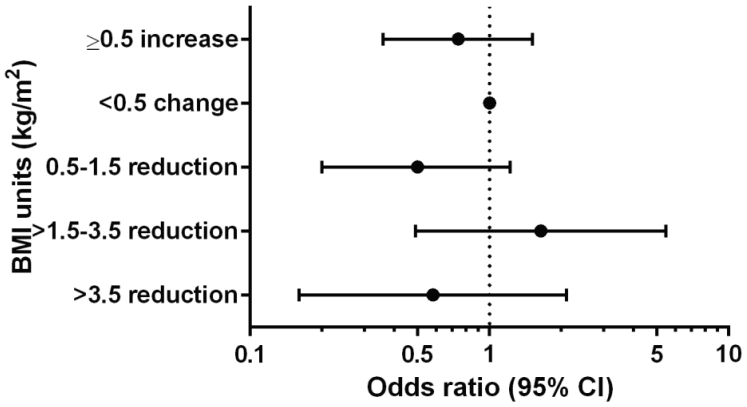

Figure 11 Adjusted OR with 95% CI for *reduction of severe GORS* by change in BMI when using *no or less than weekly* antireflux medication

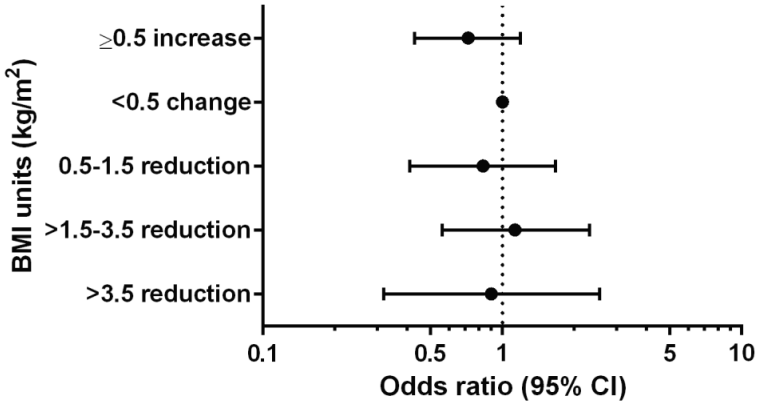

Figure 12 Adjusted OR with 95% CI for *loss of severe GORS* by change in BMI when using *no or less than weekly* antireflux medication

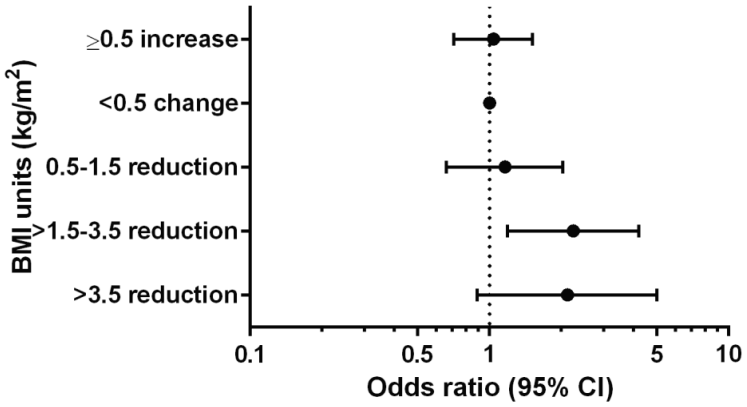

Figure 13 Adjusted OR with 95% CI for *reduction of severe GORS* by change in BMI when using *at least weekly* antireflux medication

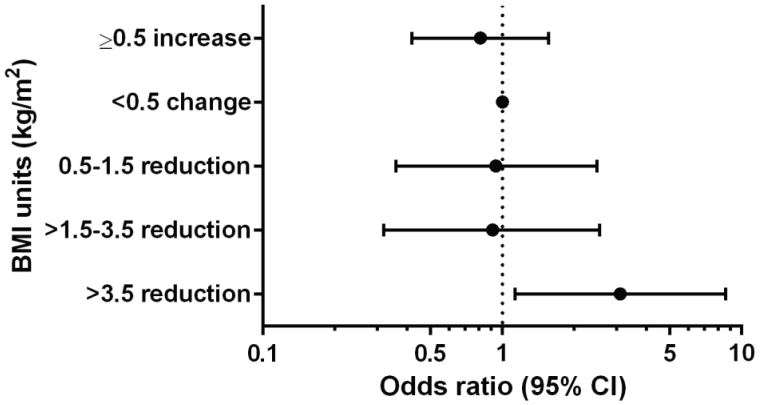

Figure 14 Adjusted OR with 95% CI for *loss of severe GORS* by change in BMI when using *at least weekly* antireflux medication

4.4.2 Tobacco smoking cessation and gastro-oesophageal reflux (paper III)

Among daily tobacco smokers with severe GORS in HUNT 2 using no or less than weekly antireflux medication, there was no statistically significant association between tobacco smoking cessation and GORS status in HUNT 3/Mini-Q (adjusted OR 0.95, 95% CI 0.39 to 2.30), compared with persistent daily smoking (table 8 and figure 15). However, among daily tobacco smokers with severe GORS in HUNT 2 using at least weekly antireflux medication, tobacco smoking cessation was associated with an improvement in GORS status from severe to no or minor complaints in HUNT 3/Mini-Q (adjusted OR 1.78, 95% CI 1.07 to 2.97), compared with persistent daily smoking (table 8 and figure 15). This association was stronger among individuals within the normal weight range (adjusted OR 5.67, 95% CI 1.36 to 23.64), but disappeared among overweight individuals (table 8 and figure 16). There was no association between tobacco smoking cessation and GORS status among individuals with minor GORS in HUNT 2.

Table 8 OR with 95% CI of improvement in severe GORS by tobacco smoking cessation, stratified by use of antireflux medication and BMI*

		Unadjusted			Adjusted for sex and age			Fully adjusted†		
Antireflux medication‡	**BMI§**	**No.**	**OR**	**95% CI**	**No.**	**OR**	**95% CI**	**No.**	**OR**	**95% CI**
No or < weekly	**All**	185	1.12	0.48 - 2.62	185	1.06	0.45 - 2.52	181	0.95	0.39 - 2.30
	18.5-24.9	50	1.06	0.21 - 5.30	50	0.89	0.17 - 4.65	49	0.80	0.13 - 5.08
	25.0-29.9	77	1.29	0.33 - 5.00	77	1.32	0.33 - 5.27	63	1.13	0.27 - 4.75
	≥ 30.0	57	1.04	0.23 - 4.64	57	0.74	0.14 - 3.89	57	0.90	0.16 - 5.17
≥ Weekly	**All**	279	1.44	0.90 - 2.32	279	1.62	0.99 - 2.65	268	1.78	1.07 - 2.97
	18.5-24.9	50	3.92	1.13 - 13.60	50	4.70	1.22 - 18.18	49	5.67	1.36 - 23.64
	25.0-29.9	124	1.25	0.62 - 2.56	124	1.20	0.57 - 2.53	121	1.24	0.57 - 2.71
	≥ 30.0	100	1.01	0.46 - 2.22	100	1.28	0.55 - 2.99	93	1.29	0.53 - 3.17

* From severe heartburn or acid regurgitation (GORS) in HUNT 2, to no or minor GORS in HUNT 3/Mini-Q

Comparing previous daily smokers with persistent daily smokers as reference

† Adjusted for sex, age, alcohol consumption, years of education, and physical exercise

‡ Antireflux medication: proton pump inhibitors, histamine-2-receptor antagonists, and antacids

§ BMI: Body mass index (kg/m2)

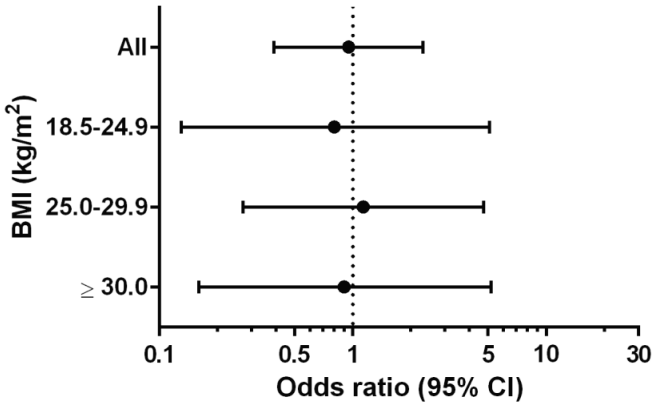

Figure 15 Adjusted OR with 95% CI of improvement in severe GORS by tobacco smoking cessation, comparing previous daily tobacco smokers with persistent daily tobacco smokers as reference. Restricted to those using *no or less than weekly* antireflux medication and stratified by BMI. Model adjusted for sex, age, alcohol consumption, education, and physical exercise.

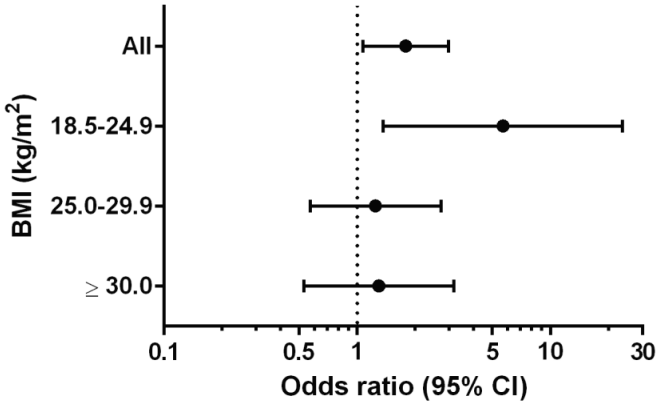

Figure 16 Adjusted OR with 95% CI of improvement in severe GORS by tobacco smoking cessation, comparing previous daily tobacco smokers with persistent daily tobacco smokers as reference. Restricted to those using *at least weekly* antireflux medication and stratified by BMI. Model adjusted for sex, age, alcohol consumption, education, and physical exercise.

5 Discussion

5.1 Materials and methods

5.1.1 Study design

The thesis was based on two repeated population-based cross-sectional surveys conducted approximately 11 years apart, where the entire adult population in a geographically determined area were invited. The population-based design reduces selection bias compared with hospital or clinic based studies (see section 5.1.2.1 1) below). The two separate surveys assessed a wide range of health related variables, including exposures, complaints, and diseases, collected through self-administered questionnaires, clinical measurements, and blood samples, so there was no selection based on specific exposures or diseases. In paper I, the prevalence of GORS was estimated among all the participants at the two time points. In addition, the prospective cohort design, nested within the two surveys, was used to follow the individuals participating at both times. This design made it possible to identify incident cases, i.e. individuals with no GORS at baseline and present GORS at follow-up, and cases with loss or reduction of GORS, i.e. individuals with present GORS at baseline and no or reduced GORS at follow-up. The prospective design also reduces recall bias of the variables that were studied (see section 5.1.2.1 2) below). However, as the follow-up was at one time point and not a continuous registration of each new case, only cumulative incidence/loss was possible to assess and not incidence/loss rates. On the

other hand, a cohort study with continuous registration of new cases would be much more time and resource consuming and probably not a feasible design with a chronic and relapsing disease as GORD. In papers II and III, the cohort was studied prospectively with a case-control design to assess the association between loss/reduction of GORS as outcome and weight loss or tobacco smoking cessation as exposure, respectively. Specifically, the cases were those participants who reported present GORS at baseline and no or reduced GORS at follow-up and the controls were those with stable GORS at both time points. The controls were selected from the same source population as the cases and independent of exposure status. This reduces the risk of selection bias (see section 5.1.2.1 1) below). The main exposures in papers II and III were defined as change in BMI and tobacco smoking status between the two surveys, respectively. In addition, the design used in this thesis allowed simultaneous assessment of a number of other variables than the ones under direct study to adjust for confounding (see section 5.1.2.1 3) below).

5.1.2 Internal validity and precision

There are two main types of error in observational research, systematic error and random error, affecting internal validity and precision, respectively. Internal validity relates to the inference among the source population, as opposed to external validity or generalisability, which relates to the inference to populations outside the source population (see section 5.1.3 below).

5.1.2.1 Systematic error

Systematic error, often termed bias, affects the internal validity of the results. High internal validity, i.e. low level of systematic error, means that the results actually reflect what the study aimed to measure. Systematic error can be divided into: 1) selection bias, 2) information bias, and 3) confounding (and reversed causality).

1) Selection bias

Selection bias occurs when the selection of study participants influence the relationship under study, i.e. when the relationship is different among the actual participants than among those theoretically eligible to participate. In a case-control study, it is essential that the controls are selected from the same source population as the cases and independently of exposure to avoid selection bias. The population-based design, where all controls are sampled directly from the same source population as the cases, protects against selection bias compared to hospital- or clinic-based populations. In hospital- or clinic-based studies, the source population of a specific hospital or clinic is often not well defined and controls from the hospital or clinic are often not selected independently of exposure in the source population. Selection bias might also occur if participants in a study are not a random sample of the source population or the participation rate is low. In such cases, the exposure of those participating might be different from the source population and this might affect the association under study.

In HUNT 2, participation was lower among men, the youngest (20 to 29 years), and the oldest (≥90 years). Among invited, 67% of the men versus 76% of the women, 49% of the youngest, and 53% of the oldest participated, respectively. However, a non-

participation study shortly after HUNT 2 found that the main reasons for non-participation among the young (20 to 44 years) were that they had moved or were absent from the county for a long time, were busy in job, or had forgot to participate or had no specific reason for non-participation.(143) Thus, non-participation among the young was probably not related to exposure or disease and should not influence the results. Among the older (≥70 years), the main reasons for non-participation were regular follow-up by a physician or hospital, immobilisation by disease, or that they had moved or were absent from the county for a long time.(143) So, non-participation among the older was related to disease and the results should be interpreted with caution in this group. The response rate in our study dropped from 64% in HUNT 2 to 49% in HUNT 3/Mini-Q. An important reason for this drop in participation rate was that the GORS question was moved from the mailed screening questionnaire following the invitation in HUNT 2 to the follow-up questionnaire received at the examination sites in HUNT 3. In addition, many participants in HUNT 2 (n=10 535) had moved out of the county or had died before HUNT 3. Again, the participation was lower among men, the youngest (20 to 29 years), and the oldest (≥90 years). Among invited, 49% of the men versus 59% of the women, 31% of the youngest, and 18% of the oldest participated, respectively. The main reason for non-participation in HUNT 3 was lack of time or inconvenient session (57% men and 51% women).(144) In addition, a non-participant study after HUNT 3 found that participation was dependent on socioeconomic status, type of symptoms, and diseases, including cardiovascular diseases and diabetes.(146) So, this should be taken into consideration when interpreting the results. The response rates in our study opens up for the possibility of some level of selection bias. On the other hand, as 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, non-participation due to GORS is unlikely. In Mini-Q and HUNT 3, respectively, 29.9% and 43.1% reported any GORS; 4.3% and 7.1% reported severe GORS; and 5.7% and 8.2% used at least weekly antireflux medication. These differences were retained also after stratification by sex and age. The distribution of the key variables associated with GORS was 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 BMI was 26.1 and 27.2; there were no major 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. The lower prevalence of GORS in Mini-Q compared to HUNT 3 may indicate a selection of individuals with more complaints in the study population than in the source population. This may overestimate the occurrence of GORS. However, this bias is reduced with the inclusion of the participants in Mini-Q in the study population. The lower prevalence of GORS in Mini-Q may also in part be explained by the lower age and lower BMI of this population. In the cohort followed up from HUNT 2 to HUNT 3/Mini-Q, the response rate was 61%. Selection bias due to loss to follow-up is probably small since there were only minor differences in the distribution of the study variables among all the HUNT 2 participants (N=58 869) compared with the cohort which was followed up (N=29 610): there was no difference in the mean BMI (26 kg/m^2) or mean alcohol consumption (2.5 times/month); the proportion of women was 52% and 54%; the mean age was 48.5 years and 45.8 years; the proportion of never smokers was 47% and 48% and of daily smokers 30% and 27%; the proportion with >12 years of education was 21% and 24%; and the proportion who did no exercise weekly was 9% and 6%, respectively. Among the participants who participated at both

HUNT 2 and HUNT 3/Mini-Q, missing values on the included variables were generally low. In paper I, only 7 of the 44 997 participants in HUNT 3/Mini-Q had missing values on sex. In papers II-III, the amount of missing values was higher due to the inclusion of more variables in the analyses. In paper II, less than 2% of the participants had missing values in the crude analyses. When including all co-variables, the rate of participants with missing values reached 12.8%. However, the estimated ORs did not differ substantially between the crude analyses and the fully adjusted analyses. In paper III, the maximum rate of participants with missing values in the analyses reached 4.5%. We did no further corrections due to missing values because the amount of participants with missing values was low and probably without substantial influence on the results. As all Norwegian pharmacies are obligated by Norwegian regulations to send information on every handled prescription to the NorPD, the information on prescriptions from the NorPD should be complete.

2) Information bias

Information bias occurs by misclassification of the variables under study, i.e. the variables in the study do not measure correctly what they are supposed to measure. Misclassification may be differential or non-differential. Misclassification of exposure is differential if it is different for those with and without the outcome under study and non-differential if it is not related to the outcome. Misclassification of disease is likewise differential if it is related to the exposure status of the participants and non-differential if it is not related to the exposure. Differential misclassification may either overestimate or underestimate the association studied and lead to serious error. Non-

differential misclassification usually only dilutes the association studied, a less serious error which does not generate spurious effects. Misclassification can occur due to recall bias. This might happen in a case-control study if the exposure information has to be recalled retrospectively by the participants. Often this type of recall bias is differential, because individuals with disease tend to recall exposure differently than individuals without disease. The prospective design used in this thesis protects against recall bias, as exposure information was assessed at both time points. Moreover, if recall bias is present, it will most likely be non-differential as the participants were unaware of the outcome under study.

The recall period of 12 months might introduce information bias, but individuals with severe or frequent GORS are likely to report this correctly due to the impact on quality of life. The average 11 year time period between the two assessments makes short term fluctuations in GORS impossible to evaluate. In paper I, the analysis of incident GORS may then also have included recurrent symptoms and not only genuinely new cases, and loss of GORS may not necessarily mean a true recovery, but rather a temporary relief of symptoms. However, the 12 months recall period most likely reduced the problem with fluctuating symptoms. The outcome in this thesis is GORS, classified by the response to a written questionnaire on complaints with heartburn and acid regurgitation. In English, “heartburn” and “regurgitation” are known to be words that the general public not understands adequately. However, in Norwegian this is much less of a problem. The Norwegian words “brystbrann”/”halsbrann” and “sure oppstøt” used in this thesis are frequently used in the common language and are readily understood by the general public in the same way as health care professionals and researchers do. Moreover, any

misclassification is likely to be non-differential, as exposure status should not affect the understanding of the questionnaire. There is no uniform, perfect definition of GORD, but the Montreal definition acknowledges that moderate/severe symptoms occurring more than 1 day a week in population-based studies often are considered troublesome by patients and could be used as a definition of GORD. As the HUNT 2 validation and Mini-Q showed that 95% to 97% of the participants reporting severe GORS had at least weekly complaints, respectively, severe GORS have a high specificity for true GORD.

The main exposure in paper II is weight loss, defined by reduction in BMI between HUNT 2 and HUNT 3/Mini-Q. In HUNT 2 and HUNT 3, height and weight were objectively measured under standardised conditions and by trained personnel at examination sites. This makes misclassification unlikely and if present non-differential because neither the participants nor the personnel where aware of GORS as a study outcome. In Mini-Q, height and weight were self-reported, possibly introducing some misclassification of BMI in this limited subpopulation. The mean BMI was lower among the participants in Mini-Q than in HUNT 3 (26.1 and 27.2, respectively), probably because self-reported weight is an underestimation of the actual weight. However, the number of individuals from Mini-Q was limited to n=938 (10.1%) and n=190 (12.2%) in the any GORS cohort and the severe GORS cohort, respectively. Again, misclassification is likely to be non-differential. In addition, assuming that self-reported weight is an underestimate of the actual weight, this would overestimate any weight loss from baseline in the study, and dilute the effect of weight loss on loss or reduction of GORS, make the presented ORs closer to the null.

In paper III, the main exposure was tobacco smoking cessation between HUNT 2 and HUNT 3/Mini-Q. Tobacco smoking was assessed by the participants through questionnaires and again potential misclassification is likely to be non-differential as the participants were not aware of GORS as an outcome. The categorisation of tobacco smoking used in the study is crude and do not reflect duration or amount of smoking, besides daily smoking. However, pathophysiological data suggests that the effect of tobacco smoking is very short lived, so duration or amount of smoking should be of less importance. In addition, daily smoking is a common cut-off level in observational study, making comparisons with other studies easier. The co-variables alcohol consumption, education, and physical exercise were all dichotomised. This is a simplification, but the cut-offs are chosen to reflect common and sensible differences in the value of the variables. On the other hand, higher levels of categorisation would reduce the statistical power and increase the risk of type II errors, i.e. not able to show an actual association. The NorPD uses the ATC classification system and the records include dosage, package size, and number of packages for each single prescription. So, the information is systematic and detailed with easy access. However, drugs purchased without prescription are not included in the NorPD. Instead, the participants in HUNT 3 reported OTC use of antireflux medication through questionnaires and these data are more prone to bias than the systematic collection of data in the NorPD. On the other hand, the information on the most potent and frequently used drugs, the PPIs and H2RAs, were collected from the NorPD.

3) Confounding and reversed causality

Confounding may be thought of as confusion or mixing of effects. The apparent effect of the exposure under study on the outcome is distorted because the effect of extraneous factors is mistaken for the effect of the exposure. A confounding factor must in general be associated with both the outcome and exposure under study, but not an effect of the exposure or outcome.(147) In observational research, confounding is often controlled for by study design, stratification, restriction, matching, or multivariable regression analyses. The latter method is preferred if several potential confounders are present, as in papers II and III.

In papers II and III, we restricted the choice of co-variables to those variables that were most consistently associated with GORS in population-based studies from Western populations: sex,(5, 9, 66, 70, 75, 76) age,(5, 6, 66, 70, 75) alcohol consumption,(9, 63, 69) socioeconomic status represented by years of education,(8, 74, 75) and physical exercise.(69, 73) One could argue that other variables should be included as well, as variables reflecting dietary patterns and genetic variables, but such data were not available. Moreover, if the model is busy with too many variables it does not allow proper adjustment. Residual confounding by known and unknown factors can never be excluded in observational research due to information bias. Sex and age were included as possible confounders because they were associated with the prevalence of GORS in paper I. In addition, sex and age are typical proxy variables or surrogates of unmeasured confounders, e.g. diseases have often different occurrence between women and men and increasing age is associated with increasing rate of disease. Education was chosen to reflect socioeconomic status. Socioeconomic status is known to effect general health

and education is used as a valid proxy variable of the possible unmeasured confounders related to socioeconomic status. Alcohol consumption and physical exercise have both been related to GORD in pathophysiological and epidemiological studies and they are also associated with the main exposures under study. None of the included potential confounding variables are likely to be an effect of the exposures or outcome. Other variables could perhaps also have been included as confounders, but we restricted the number of confounders to those considered most relevant by pathophysiological and epidemiological studies to avoid spurious effects by the adjustments. Antireflux medication was not considered a confounder according to the definition above. However, to account for the use of antireflux medication, the analyses were stratified by antireflux medication and the results presented for each strata. In paper III, stratification by BMI was used to show the effect modification of BMI on tobacco smoking cessation. As we were interested in the association between weight loss and tobacco smoking cessation on GORS status at follow-up, we used the values of the possible confounders at follow-up and not at baseline. The value of a confounder at the time of the outcome assessment is probably more relevant than the value of the confounder 11 years before. The only exception was education, where we used the value recorded in HUNT 2. Education was not assessed in Mini-Q, so to reduce the amount of missing values the baseline value was used. Moreover, due to the study design, all participants were above 20 years of age at participation and the level of education was probably determined already at baseline for the vast majority of participants. An alternative approach considered, was to include variables reflecting the change in the confounders as well. However, the interpretation of changing co-variables in observational research is complex and difficult to interpret. The changing co-variables might interact in

complex manners and they might act as both intermediates and confounders depending on the sequence and timing of the changes. In addition, this would heavily reduce the statistical power due to more subgroup analyses. Moreover, the number participants with missing values would also increase, opening for selection bias. Residual confounding due to simplification and inaccurate information on the confounding variables or due to other unknown factors cannot be ruled out. The co-variables were dichotomised, except for age, and this is probably an oversimplification of the information within each variable, making residual confounding possible. However, dichotomisation improves the statistical power and the robustness of the full model.

In observational research causality cannot be implied due to the lack of control of extraneous factors, as opposed to large and well-done randomised trials. Even the opposite conclusions of effect may be drawn due to reverse causality in non-experimental studies. Cross-sectional studies are especially prone to this as the exposure and outcome are assessed at the same time. Reversed causality may appear if the outcome under study affects the exposure. An example from the HUNT study is the reduced risk of severe GORS found among frequent coffee drinkers in HUNT 2.(73) In this analysis coffee seems to protect against severe GORS. However, coffee is known to be a trigger of reflux by reducing the LOS pressure and individuals with severe GORS probably abstain from frequent coffee drinking. As that probably is the case, individuals without GORS drink more coffee than those with severe GORS and coffee drinking is associated with reduced risk of severe GORS, i.e. reversed causality. In papers II and III, the use of longitudinal data with assessment of change in the main exposures and outcome over time protect against reversed causality. In addition, the

pathophysiological and epidemiological evidence makes it unlikely that weight loss and tobacco smoking cessation should increase the risk of GORS. Although a randomised trial is the most reliable method to establish disease causality in humans, such a trial of tobacco smoking cessation would be unethical to perform, leaving observational studies the best alternative. Moreover, comparisons of results from randomised trails and cohort studies have yielded very similar findings.

5.1.2.2 Random error

Random error affects the precision of the results. Random error is determined by the variability within the measured variables, the sample size, and variability related to the sampling of the specific study participants. Random error is reduced with low measurement variability and with large sample size. There will always be some degree of variability related to the specific study participants compared with the broader population of interest.

One of the main strengths of the HUNT study is the large sample size, reducing random error and increasing the precision of the results. This is shown in paper I with the narrow CIs around the estimated prevalence rates. The large sample size also makes extensive subgroup analyses possible. However, high precision provides no assurance against systematic error. Even if the precision is high, we cannot know if the exposure is responsible for the observed effect or whether differences in effect are important for the outcome under study.

5.1.3 Generalisability

Generalisability or external validity of the results in a study means how well the results can be transferred to other populations than the source population. Generalisability also heavily depends on a high internal validity. With some exceptions, the population of Nord-Trøndelag is considered to be representative of the Norwegian population at large. The residents of Nord-Trøndelag have slightly lower average income and education than the Norwegian average and Nord-Trøndelag County lacks a large city (>25 000 inhabitants). On the other hand, the population of Nord-Trøndelag is stable and homogenous with the large majority being Caucasians.(144, 148) So, the results should be generalisable internationally to similar populations.

5.2 Ethical considerations

The HUNT study has been approved by the Regional Committee for Medical and Health Research Ethics, Central Norway, and has obtained consent to handle personal information by the Data Inspectorate. All participants in the HUNT study received written information about the study and signed a consent form when they participated. As part of the consent, information on research projects using the HUNT material is published on the official HUNT internet pages.

Our study has been approved by the Regional Committee for Medical and Health Research Ethics, Central Norway. In HUNT 3, the consent included approval of linkage with other registries, including the NorPD. However, at the time of HUNT 2 the NorPD

was not established and the consent did not include this registry. To allow linkage of data between HUNT 2 and the NorPD, we have obtained exemption from the confidentiality by the Norwegian Directorate of Health and consent to handle personal information by the Data Inspectorate.

5.3 Main results and implications

5.3.1 Occurrence of gastro-oesophageal reflux (paper I)

The prevalence of GORS increased substantially between 1995 to 1997 and 2006 to 2009. This will affect the quality of life for a considerable amount of people. In addition, it will have implications for the society with increased demands on the health care system and lost work productivity. Even if the risk is low for each individual suffering from GORS, the increasing prevalence of GORS will most likely contribute to an increasing incidence of oesophageal adenocarcinoma. GORS are usually of a chronic and persistent nature, but we found that some lost their symptoms without medication. To understand why and how these individuals spontaneously lost their symptoms might have implications for preventive and management strategies in GORD.

5.3.2 Weight loss and gastro-oesophageal reflux (paper II)

Both patients and clinicians often report that weight loss improves the occurrence and severity of GORS, but the scientific evidence has not been convincing. However, in this study weight loss was dose-dependently associated with reduction in GORS. Weight

loss was also associated with an increased treatment success with antireflux medication. Due to the observational design of the study, strict causality cannot be implied. However, the pathophysiology, the consistent and dose related association between weight loss and reduction in GORS, and the preserved association after adjustment for possibly important confounders argues for a valid, biological relation which is not due to bias. As the validation study after HUNT 2 and Mini-Q showed that 95% and 98% of those reporting severe GORS had at least weekly complaints, respectively, the study suggests that weight loss also could benefit patients with GORD according to the Montreal definition. However, weight loss was not sufficient to reduce severe GORS without regular use of antireflux medication. This probably reflects an advanced stage of GORD in these participants, as oesophagitis and symptoms related to the presence of a hiatal hernia, which do not resolve only with weight loss. Weight loss probably reduces the frequency of TLOSRs and the association of TLOSRs with reflux episodes, which are not the main pathophysiologic mechanisms of hiatal hernia. A fairly modest weight loss seems to reduce GORS and the data also indicates that greater benefits might be seen with even larger weight loss. Moreover, weight loss was associated with a better treatment success with antireflux medication. This might be especially useful in patients with refractory GORS despite regular use of antireflux medication to improve the response to medical therapy.

5.3.3 Tobacco smoking cessation and gastro-oesophageal reflux (paper III)

Tobacco smoking cessation was associated with an improvement in GORS only among normal weight individuals using antireflux medication at least weekly. There was no

such pattern in individuals with minor GORS, overweight, or those using antireflux medication less than weekly. The results are consistent with the pathophysiology (136-140) and a randomised controlled trial of smoking cessation would be unethical to perform. Due to the low absolute number of individuals who totally quit smoking (n=182), we defined the 'exposure' in this study to be a combination of those quitting smoking and those only reducing daily smoking to occasional smoking (n=31). Even so, we found an association between the 'exposure', i.e. reduced tobacco smoking, and the outcome, i.e. improved GORS. This suggests that total smoking cessation would increase the chance of success even more than apparent from our study. We found no association between tobacco smoking cessation and improvement in minor GORS. This probably reflects the heterogenetic nature of individuals reporting minor GORS, including individuals with functional syndromes. These syndromes have other pathophysiological mechanisms which at least in part are not related to gastroesophageal reflux or tobacco smoking. The lack of improvement in overweight individuals might be explained by overweight being a stronger contributor to GORS than tobacco smoking. The pathophysiology of GORS is probably driven by the weight in overweight and obese individuals and smoking has a minor role, but in individuals of normal weight smoking has a more important role in the pathophysiology. The lack of improvement among those using no or less than weekly antireflux medication, suggests that the individuals with severe GORS have a more advanced stage of GORD, i.e. oesophagitis or symptoms related to the presence of hiatal hernia, which does not resolve only with tobacco smoking cessation. However, weight loss and tobacco smoking cessation might reduce the need for antireflux medication over time. In addition, these lifestyle measures are also advisable due to the effects on general health.

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As tobacco smoking as well as GORS is associated with adenocarcinoma of the oesophagus and gastric cardia, persons with GORS should be advised to refrain from smoking.(149-152)

5.4 Comparison with previous research

5.4.1 Occurrence of gastro-oesophageal reflux (paper I)

Comparison with previous research on the occurrence of GORS is inherently difficult because the definitions and settings used vary between studies. We have restricted our comparisons to population-based studies conducted in Western populations. Only few previous studies have assessed the prevalence of GORS in the same population at two different time points or followed-up a cohort over time and addressed the cumulative incidence and loss of GORS. Due to low number of participants, most of these studies have not been able to investigate the occurrence of GORS by sex and age groups.

5.4.1.1 Changes in prevalence

Two studies conducted in Olmsted County, Minnesota, USA, found that the prevalence of at least weekly heartburn had increased from 13.2% (n=835; aged 30 to 64 years) to 17.8% (n=1511; aged 25 to 74 years) from the 1980s to the 1990s.(4, 11) A study from Göteborg Municipality in the western part of Sweden, found that the prevalence of any GORS had increased from 20% to 21% (n=337; aged 20 to 79 years) in 1986 to 22% to 25% (n=197) at follow-up 10 years later.(65, 153) Another Swedish study from

Östhammar Municipality in the eastern part of Sweden, found that the prevalence of any GORS had increased from 18.9% (n=1156; aged 20 to 79 years) to 19.4% (n=877) between 1988 and 1995.(154) Finally, a study from Fyn County, Denmark, found a stable prevalence of at least mild GORS of 22% (n=6781; aged 40 to 65 years) in 1998 to 1999 and 5 years later (n=5578).(155) All these studies had considerably lower number of participants (range 197 to 5578 participants) than the HUNT study, but over all they confirm the conclusion that the prevalence of GORS seems to be increasing.

5.4.1.2 Incidence

A study from the western part of København County, Denmark, including 2987 participants from 30 to 60 years of age reported an annual incidence of any GORS of 13% to 19% and of frequent GORS of 1% to 3% between 1982 to1984 and 1987 to 1988.(156) In a study from Östhammar Municipality, Sweden, including 1059 participants from 20 to 79 years of age the annual incidence of predominant GORS was 0.05% and of GORS with other concurrent gastrointestinal symptoms of 0.75% between 1988 and 1989. In a study from Olmsted County, Minnesota, including 690 participants from 30 to 64 years of age the cumulative onset rate of heartburn several times a weekly or daily was 2.7% after 12 to 20 months follow-up in 1988 to 1991, corresponding to an average annual incidence of 1.6% to 2.7%.(16) In a study from Göteborg Municipality, Sweden, including 197 participants from 20 to 79 years of age the annual incidence of any GORS was 1.2% to 1.8% between 1986 and 1996.(153) Finally, in a study from Fyn County, Denmark, including 5578 participants from 40 to 65 years of age the annual incidence of at least mild GORS was 2.2% between 1998 to 1999 and

2004.(155) Except for the study from København, these studies comply with our results (average annual incidence of any and severe GORS of 3.07% and 0.23%, respectively) and the incidence has been stable or possibly increasing over the last two decades.

5.4.1.3 Spontaneous loss

In København County, Denmark, the cumulative loss of any GORS was 27% to 37% between 1982 to 1984 and 1987 to 1988, corresponding to an average annual loss of 6.2% to 9.0% and the cumulative loss of frequent GORS was 59% to 77%, corresponding to an average annual loss of 16.1% to 23.2%.(156) In Olmsted County, Minnesota, the cumulative loss of heartburn several times a week or daily was 47.8% in 1988 to 1991, corresponding to an average annual loss of 36.9% to 61.3%.(16) In Göteborg Municipality, Sweden, the annual loss of any GORS was 1.1% to 1.3% between 1986 and 1996.(153) Finally, in Fyn County, Denmark, the annual loss of at least mild GORS was 8.6% between 1998 to 1999 and 2004.(155) Except for Göteborg Municipality, Sweden, these figures deviate from our results (average annual spontaneous loss of any and severe GORS of 2.32% and 1.22%, respectively). However, the large number of participants in the HUNT study, the long follow-up time, and ability to adjust for antireflux medication argues for validity. In addition, we found a substantial association between spontaneous loss of GORS and age.

5.4.2 Weight loss and gastro-oesophageal reflux (paper II)

There has only been one previous population-based study assessing the association between weight loss and GORS. In this study from Olmsted County, Minnesota, 637 individuals were followed over a median of 10.5 years and no association between weight loss of >10 lb (>4.5 kg) and GORS was found. The mean age was 61 years at follow-up and 54.8% were females. Major limitations of this study were the use of self-reported height and weight and a large loss to follow-up from the initial 4793 participants. The mean BMI of the initial participants was 26.5, but the mean BMI at baseline of the actual 637 participants followed-up was not reported.(157) However, in the Nurses' Health Study the OR of at least weekly GORS was 0.64 (95% CI 0.42 to 0.97) among participants with at least 3.5 decrease in BMI compared with participants with no change in BMI.(129) Two randomised, double-blind, sham controlled trials of gastric balloon distension on extremely obese patients with pH-verified GORD also found an effect of weight loss on oesophageal pH. In these studies, individuals with high grade oesophagitis (Los Angeles classification grade C or D (82, 83)) or large (>3 cm) hiatus hernia on endoscopy were excluded. Weight loss was achieved by a weight reducing program using dietary guidance, physical exercise, and behavioural therapy.(158, 159) The first trial of 42 patients with mean BMI 43.4 found improvement in total time of pH <4 from 5.60% to 3.72% ($p<0.05$) after a decrease in mean BMI of 3.8 after 13 weeks of treatment.(158) The second trial of 28 patients with mean BMI 43.3 found improvement in upright time of pH <4 from 8.0% to 5.5% ($p<0.05$) and decreased number of meal and postprandial reflux episodes from 49.0 to 32.1 ($p<0.05$) after a decrease in body weight of 12.4 kg after 13 weeks of treatment.(159) An uncontrolled prospective study of 34 patients with mean BMI 23.5 and troublesome

GORS also found improvement in a modified DeMeester questionnaire symptom score after 6 weeks with dietary advice. These individuals had either normal endoscopy or low grade oesophagitis (grade I in the Savary-Miller classification (160)) and a decrease in mean BMI of 1.7.(161) Another uncontrolled prospective study of 18 volunteers with mean BMI 43.5 and GORS, found an improvement in the distress subscale of the gastroesophageal reflux disease symptom assessment scale (162, 163) from a mean of 1.28 to 0.72 ($p=0.0004$) and reduction in the Johnson-DeMeester score (54, 164) from a mean of 34.7 to 14.0 ($p=0.023$) after a mean of 4 days on a very low-carbohydrate diet and an average weight loss of 1.7 kg.(165) However, a randomized trial of 20 obese patients with mean BMI 31.4 at inclusion with pH-verified reflux, erosive oesophagitis, and daily GORS, did not find any effect of a very low-calorie diet after 6 months on measures of pH, oesophagitis, or GORS despite decrease in mean BMI of 2.6 to 4.8.(166) This study included participants with hiatus hernia, which contributes to the occurrence of GORD and is irreversible with weight loss.

5.4.3 Tobacco smoking cessation and gastro-oesophageal reflux (paper III)

Three previous studies have addressed smoking cessation and GORD but found conflicting results. One study found no influence of 24 hours refrainment from smoking on 24-hour pH-measurements of the distal oesophagus in 10 smokers with GORS who regularly smoked about 20 cigarettes a day.(167) Another study found no immediate effect of smoking cessation on total oesophageal acid exposure in 8 smoking men with moderate to severe endoscopic evidence of GORD who smoked at least one pack of cigarettes a day.(168) The third study, however, found a reduced distal oesophageal acid

exposure in 14 smokers with daily heartburn for at least 6 months and endoscopy or biopsy evidence of reflux oesophagitis who smoked at least 20 cigarettes a day who abstained from smoking for 48 hours.(169) Our study is the first epidemiological investigation testing whether tobacco smoking cessation improves GORS and the first study that evaluates such cessation in a long-term perspective.

6 Conclusions

GORD is a disease which affects a large proportion of our population and the occurrence of GORD seems to be increasing for both sexes and in all age groups. There is an association between weight loss and tobacco smoking cessation and improvement in GORS. Moreover, weight loss and tobacco smoking cessation are associated with an increased chance of treatment success with antireflux medication. Thus, weight loss and tobacco smoking cessation could be important measures to prevent and treat GORD.

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Paper I

Is not included due to copyright

Paper II

see related editorial on page 383

ESOPHAGUS

Weight Loss and Reduction in Gastroesophageal Reflux. A Prospective Population-Based Cohort Study: The HUNT Study

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OBJECTIVES: **High body mass index (BMI) is an established risk factor of gastroesophageal reflux symptoms (GERS). The aim of this study was to clarify if weight loss reduces GERS.**

METHODS: **The study was part of the Nord-Trøndelag health study (the HUNT study), a prospective population-based cohort study conducted in Nord-Trøndelag County, Norway. All residents of the county from 20 years of age were invited. In 1995–1997 (HUNT 2) and 2006–2009 (HUNT 3), 58,869 and 44,997 individuals, respectively, responded to a questionnaire on heartburn and acid regurgitation. Among these, 29,610 individuals (61% response rate) participated at both times and were included in the present study. The association between weight loss and reduction of GERS was calculated using logistic regression. The analyses were stratified by antireflux medication and the results adjusted for sex, age, cigarette smoking, alcohol consumption, education, and physical exercise.**

RESULTS: **Weight loss was dose-dependently associated with a reduction of GERS and an increased treatment success with antireflux medication. Among individuals with >3.5 units decrease in BMI, the adjusted odds ratio (OR) of loss of any (minor or severe) GERS was 1.98 (95% confidence interval (CI) 1.45–2.72) when using no or less than weekly antireflux medication, and 3.95 (95% CI 2.03–7.65) when using at least weekly antireflux medication. The corresponding ORs of loss of severe GERS was 0.90 (95% CI 0.32–2.55) and 3.11 (95% CI 1.13–8.58).**

CONCLUSIONS: **Weight loss was dose-dependently associated with both a reduction of GERS and an increased treatment success with antireflux medication in the general population.**

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a highly prevalent disease in Western populations (1,2), associated with a decreased health-related quality of life (3,4) and an increased risk of esophageal adenocarcinoma (5,6). The Montreal definition and classification of GERD states that: "GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications" and the definition recognizes that heartburn and acid regurgitation are characteristic symptoms of GERD (7,8). Overweight, defined according to the World Health Organization's classification as body mass index (BMI) of ≥25 kg/m^2 (9), increases the risk of gastroesophageal reflux symptoms (GERS) (10–12) and is independently associated with esophageal adenocarcinoma (11). The increasing weight seen in the general population will have unfortunate effects on the prevalence of GERD (13–15). Weight loss may be of great importance in the prevention and treatment of the many individuals with GERD. The aim of this study was to clarify if weight loss reduces GERS in a large population-based cohort followed prospectively over time.

METHODS

Study population and design

The study was performed as part of a large population-based study, the Nord-Trøndelag health study (the HUNT study). The HUNT study is an on-going prospective cohort study based

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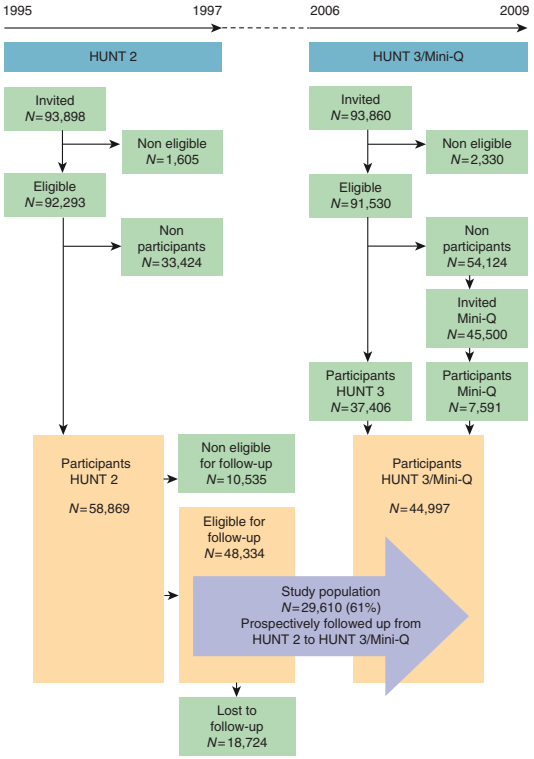

Figure 1. Flowchart of participants. Number of individuals (*N*) at each stage and the response rate (%). The response rate was calculated from those eligible for follow-up, excluding those who were no longer residents in the county or had deceased (non eligible for follow-up).

on repeated health surveys of the entire adult population of Nord-Trøndelag County, Norway. All residents in the county from 20 years of age have been invited to participate in three surveys, entitled HUNT 1 (1984–1986), HUNT 2 (1995–1997), and HUNT 3 (2006–2008). The HUNT study includes data on a wide range of health-related items gathered from written questionnaires answered by the participants, clinical examinations performed by trained personnel, and blood samples taken from the participants (16). GERS were assessed in HUNT 2 and HUNT 3, and these two surveys constituted the base of the present study. In addition, GERS were assessed in a "non responder study" (Mini-Q) after HUNT 3 in 2009, where those who did not participate in HUNT 3 were invited (2,16). The individuals who participated in HUNT 2 and were followed-up in Mini-Q were also eligible for inclusion in the present study (**Figure 1**).

Assessment of GERS

GERS were assessed by a questionnaire in HUNT 2 (1995–1997) and HUNT 3/Mini-Q (2006–2009). The participants replied to the question: "To what degree have you had heartburn or acid regurgitation during the previous 12 months?" with one of three response alternatives: "no complaints," "minor complaints," or "severe complaints." In a validation study after HUNT 2, 25% of those reporting minor complaints and 95% of those reporting severe complaints had at least weekly symptoms (10). In Mini-Q, where frequency of complaints was also assessed, the corresponding proportions were 31% and 98% (2). We defined "any GERS" to include all participants reporting minor or severe complaints and "severe GERS" to include only those reporting severe complaints.

Assessment of BMI

BMI equals weight in kilograms divided by the square height in meters (kg/m^2). Weight and height were objectively measured under standardized conditions and by trained personnel at screening stations in both HUNT 2 and HUNT 3. In Mini-Q, weight and height measurements were self-reported.

Assessment of covariables

Covariables in the analyses were chosen using accepted criteria for a confounding factor i.e., being associated with the outcome (GERS), associated with the exposure (weight loss), and not an effect of the exposure or outcome under study (17). The variables selected as potential confounders were sex, age, cigarette smoking, alcohol consumption, education, and physical exercise. These covariables were assessed through questionnaires in HUNT 3 /Mini-Q, except for education, which was assessed in HUNT 2. The participants reported cigarette smoking status, frequency of alcohol drinking during the previous 12 months, length of education, and average frequency of physical exercise.

Assessment of antireflux medication

Data on antireflux medication, i.e., proton pump inhibitors (PPIs), histamine-2-receptor antagonists (H2RAs), or antacids, were gathered from HUNT 3 and from the Norwegian Prescription Database (NorPD). Until 2010, proton pump inhibitors and H2RAs (except small packages of low-dose H2RAs) have only been available in Norway through a prescription from a physician, and only small packages of low-dose H2RAs and antacids have been available over the counter. In HUNT 3, the frequency of over-the-counter antireflux medication use was assessed through written questionnaires. Since 2004, data on all prescribed medication in Norway have been collected in the NorPD. By linkage of the HUNT study and the NorPD, data on all prescribed antireflux medication among the study participants were gathered. Using number of prescriptions and number of tablets in each prescription, average frequency of antireflux medication was estimated during the HUNT 3 study period. Thus, all antireflux medication should be accounted for in HUNT 3: over-the-counter use through the HUNT 3 questionnaires and prescribed use through the NorPD. Only those who were actually prescribed an antireflux medication were included in the data from the NorPD, and therefore it was not possible to distinguish between never users and participants with missing information on medication use. All participants with missing data on antireflux medication were therefore regarded as never users.

Statistical methods

Logistic regression was used to analyze the association between weight loss and reduction of GERS, providing odds ratios (ORs) with 95% confidence intervals (CIs). The participants who had any GERS at baseline (HUNT 2) and no GERS at follow-up (HUNT 3/Mini-Q), defined as "loss of any GERS," were compared with those who had any GERS at both time points, i.e., "stable any GERS." The participants who had severe GERS at baseline and no or minor GERS at follow-up, defined as "reduction of severe GERS," were compared with those who had severe GERS at both time points, i.e., "stable severe GERS." Finally, those who had severe GERS at baseline and no GERS at follow-up, defined as "loss of severe GERS," were compared with those who had severe GERS at both time points, i.e., "stable severe GERS." The absolute change in BMI units between the two time points was calculated and five categories reflecting this change were used in the analyses: <0.5 units change (reference category), 0.5–1.5 units decrease, >1.5–3.5 units decrease, >3.5 units decrease, and ≥0.5 units increase. In the statistical model, adjustments were made by categorization of age (<40, 40–49, 50–59, 60–69, or ≥70 years), cigarette smoking status (never smoker, previous smoker, or current smoker), frequency of alcohol consumption (less than weekly or at least weekly), years of education (≤12 years or >12 years), and frequency of physical exercise (less than weekly or at least weekly). Antireflux medication was not considered a confounder according to the definition above. Instead, the analyses were stratified into two groups of antireflux medication use at follow-up: no or less than weekly or at least weekly. The analyses were performed with the statistics and data analysis software Stata, version 11.2 (StataCorp LP, College Station, TX).

Study approval

The study was approved by the Regional Committee for Medical and Health Research Ethics, Central-Norway (ID 4.2009.328). All participants in the HUNT study signed a written consent form before participating, which stated the purpose of the study and the possibility of future research and linkage to other registries.

RESULTS

Participants

In HUNT 2 (1995–1997) and HUNT 3/Mini-Q (2006–2009), 58,869 individuals (64% response rate) and 44,997 individuals (49% response rate) reported their complaints with GERS, respectively. Among these, 29,610 individuals participated in both surveys and were included in the present study. This corresponds to a response rate of 61% at follow-up, after excluding the 10,535 participants in HUNT 2 who were no longer residents in the county at the time of HUNT 3/Mini-Q or had deceased before HUNT 3/Mini-Q (non eligible for follow-up; **Figure 1**).

Characteristics

At baseline (HUNT 2), 9,299 individuals (31.4%) reported any GERS (any GERS cohort) and 1,553 individuals (5.2%) reported severe GERS (severe GERS cohort). Of the any GERS cohort, 2,398 individuals (25.8%) reported no GERS at follow-up in HUNT 3/Mini-Q, i.e., "loss of any GERS" (**Table 1**). Of the severe GERS cohort, 284 individuals (18.3%) reported no GERS at follow-up in HUNT 3/Mini-Q, i.e., "loss of severe GERS" (**Table 1**), 729 individuals (46.9%) reported minor GERS, and 1,013 (65.2%) reported no or minor GERS, i.e., "reduction of severe GERS" (**Table 1**).

The mean BMI among all the participants increased between the two time points. The participants with loss or reduction of GERS had a lower increase in BMI than those with stable GERS (**Table 1**). Those with loss or reduction of GERS were younger, had higher education, and used less antireflux medication than those with stable GERS for both cohorts (**Table 1**). There was no difference in the proportion of current cigarette smokers among the subgroups (**Table 1**). In the any GERS cohort, the proportion of women was higher among those with loss of GERS compared with those with stable GERS (**Table 1**). In the severe GERS cohort, alcohol consumption was more frequent among those with loss or reduction of GERS compared with those with stable GERS, and physical exercise was more frequent among those with loss or reduction of GERS (**Table 1**).

Association between weight loss and GERS

In the crude analyses, without considering antireflux medication or any potential confounder, weight loss was dose-dependently associated with loss or reduction of GERS (*P* value for trend ≤0.012; **Table 2**). When stratified by antireflux medication, weight loss was associated with an increased treatment success with antireflux medication when used at least weekly (**Table 2**). Among participants with no or less than weekly antireflux medication, there was a twofold increase in the adjusted odds of loss of any GERS among participants with >3.5 units decrease in BMI compared with participants with <0.5 units change in BMI (OR 1.98, 95% CI 1.45–2.72; **Table 2**). Among participants with at least weekly antireflux medication, the corresponding odds increased fourfold (OR 3.95, 95% CI 2.03–7.65; **Table 2**). The association between weight loss and any GERS was dose dependent, regardless of antireflux medication (*P* value for trend <0.001; **Table 2**). In the severe GERS cohort, there was no association between weight loss and GERS among participants with no or less than weekly antireflux medication. The adjusted ORs of reduction and loss of severe GERS among those with >3.5 units decrease in BMI compared with those with <0.5 units change in BMI was 0.58 (95% CI 0.16–2.10; **Table 2**) and 0.90 (95% CI 0.32–2.55; **Table 2**), respectively, and there was no dose-response association (*P* value for trend 0.804 and 0.189, respectively; **Table 2**). However, among those with at least weekly antireflux medication, the corresponding OR was 2.12 (95% CI 0.89–5.02; **Table 2** and **Figure 2**) and 3.11 (95% CI 1.13–8.58; **Table 2** and **Figure 3**), respectively, and there was a dose-response association (*P* value for trend 0.008 and 0.047, respectively; **Table 2**). As the crude and adjusted ORs were similar when stratified by antireflux medication, only the adjusted data are presented in **Table 2**.

Table 1. Characteristics of cohort reporting gastroesophageal reflux symptoms (GERS)[a] in HUNT 2 and HUNT 3/Mini-Q (*N*=29,610)

	Stable any GERS	Loss of any GERS[b]	Stable severe GERS	Reduction of severe GERS[b]	Loss of severe GERS[b]
Number (%)	6,901 (74.2)	2,398 (25.8)	540 (34.8)	1,013 (65.2)	284 (18.3)
BMI (kg/m²), HUNT 2					
Mean (s.d.)	27.3 (4.0)	27.2 (4.3)	27.7 (4.2)	28.1 (4.3)	27.9 (4.3)
Missing, no. (%)	23 (0.3)	21 (0.9)	2 (0.4)	5 (0.5)	2 (0.7)
BMI (kg/m²) change[c]					
Mean (s.d.)	1.3 (2.4)	0.5 (2.7)	1.3 (2.4)	0.9 (2.7)	0.6 (2.8)
Missing, no. (%)	78 (1.1)	46 (1.9)	7 (1.3)	19 (1.9)	7 (2.5)
Sex					
Women, no. (%)	3,415 (49)	1,271 (53)	277 (51)	521 (51)	143 (50)
Age (years), HUNT 3/Mini-Q					
Mean (s.d.)	59.8 (12.6)	57.4 (14.1)	60.8 (12.7)	60.2 (13.6)	58.7 (14.5)
Cigarette smoking, HUNT 3/Mini-Q					
Never, no. (%)	2,428 (35.2)	921 (38.4)	188 (34.8)	304 (30.0)	79 (27.8)
Previous, no. (%)	2,332 (33.8)	737 (30.7)	182 (33.7)	383 (37.8)	120 (42.3)
Current, no. (%)	1,822 (26.4)	631 (26.3)	141 (26.1)	279 (27.5)	73 (25.7)
Missing, no. (%)	319 (4.6)	109 (4.5)	29 (5.4)	47 (4.6)	12 (4.2)
Alcohol consumption, HUNT 3/Mini-Q					
<Weekly, no. (%)	4,292 (62.2)	1,498 (62.5)	363 (67.2)	649 (64.1)	173 (60.9)
≥Weekly, no. (%)	2,377 (34.4)	816 (34.0)	153 (28.3)	327 (32.3)	103 (36.3)
Missing, no. (%)	232 (3.4)	84 (3.5)	24 (4.4)	37 (3.7)	8 (2.8)
Education, HUNT 2					
≤12 Years, no. (%)	5,602 (81.2)	1,837 (76.6)	469 (86.9)	842 (83.1)	233 (82.0)
>12 Years, no. (%)	1,162 (16.8)	511 (21.3)	56 (10.4)	146 (14.4)	41 (14.4)
Missing, no. (%)	137 (2.0)	50 (2.1)	15 (2.8)	25 (2.5)	10 (3.5)
Physical exercise, HUNT 3/Mini-Q					
<Weekly, no. (%)	1,672 (24.2)	576 (24.0)	156 (28.9)	272 (26.9)	71 (25.0)
≥Weekly, no. (%)	5,047 (73.1)	1,754 (73.1)	363 (67.2)	721 (71.2)	210 (73.9)
Missing, no. (%)	182 (2.6)	68 (2.8)	21 (3.9)	20 (2.0)	3 (1.1)
Antireflux medication[d], HUNT 3					
Never or <weekly, no. (%)[e]	3,742 (54.2)	2,112 (88.1)	87 (16.1)	505 (49.9)	195 (68.7)
≥Weekly, no. (%)	3,159 (45.8)	286 (11.9)	453 (83.9)	508 (50.1)	89 (31.3)

[a]GERS: self-reported degree of complaints with heartburn or acid regurgitation during the previous 12 months.

[b]Loss of any GERS: any GERS at baseline, no GERS at follow-up; Reduction of severe GERS: severe GERS at baseline, no or minor GERS at follow-up; loss of severe GERS: severe GERS at baseline, no GERS at follow-up. The severe GERS group is a subset of the any GERS group.

[c]Body mass index (BMI) change: BMI HUNT 3/Mini-Q – BMI HUNT 2.

[d]Antireflux medication: proton pump inhibitors, histamine-2-receptor antagonists, and antacids.

[e]Participants with no information on antireflux medication were included in never or <weekly category.

DISCUSSION

In this study, weight loss was dose-dependently associated with a reduction of GERS, especially among those with the highest decrease in BMI. Weight loss was also associated with an increased treatment success with antireflux medication.

The major strengths of this study are (i) the population-based design, reducing selection bias; (ii) the large sample size, reducing the risk of chance findings and making subgroup analyses possible; (iii) the prospective design, minimizing recall bias; (iv) the large selection of variables assessed in the HUNT study, making adjustments for potential confounders possible; and (v) the linkage with the NorPD, complementing the data on antireflux medication. The limitations are (i) the loss to follow-up between the two time points, making selection bias possible;

Table 2. Odds ratio (OR) with 95% confidence interval (95% CI) for loss or reduction of gastroesophageal reflux symptoms (GERS)[a] compared with stable GERS by change in body mass index (BMI)[b] and antireflux medication[c]

	Loss of any GERS[d]			Reduction of severe GERS[d]			Loss of severe GERS[d]		
Change in BMI (kg/m²)	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI
Crude									
≥0.5 increase	5,542	0.72	0.63–0.82	897	0.83	0.63–1.10	897	0.77	0.55–1.09
<0.5 change	1,589	1.00	Reference	278	1.00	Reference	278	1.00	Reference
0.5–1.5 decrease	970	1.22	1.03–1.46	157	0.88	0.59–1.33	157	0.90	0.55–1.48
>1.5–3.5 decrease	770	1.38	1.15–1.66	137	1.87	1.16–3.02	137	1.11	0.67–1.83
>3.5 decrease	304	2.42	1.88–3.11	58	1.32	0.70–2.47	58	1.51	0.79–2.88
P value for trend[f]		<0.001			0.001			0.012	
Missing (%)	124	(1.3)		26	(1.7)		26	(1.7)	
No or less than weekly antireflux medication[e]									
≥0.5 increase	3,100	0.67	0.57–0.78	304	0.74	0.36–1.51	304	0.72	0.43–1.19
<0.5 change	939	1.00	Reference	95	1.00	Reference	95	1.00	Reference
0.5–1.5 decrease	616	1.14	0.92–1.40	65	0.50	0.20–1.22	65	0.83	0.41–1.67
>1.5–3.5 decrease	485	1.25	0.99–1.56	54	1.64	0.49–5.48	54	1.13	0.56–2.31
>3.5 decrease	198	1.98	1.45–2.72	22	0.58	0.16–2.10	22	0.90	0.32–2.55
P value for trend[f]		<0.001			0.804			0.189	
Missing (%)	516	(8.8)		52	(8.8)		52	(8.8)	
At least weekly antireflux medication[e]									
≥0.5 increase	2,022	0.99	0.67–1.45	518	1.04	0.71–1.51	518	0.81	0.42–1.56
<0.5 change	507	1.00	Reference	145	1.00	Reference	145	1.00	Reference
0.5–1.5 decrease	267	1.29	0.75–2.19	78	1.16	0.66–2.03	78	0.94	0.36–2.48
>1.5–3.5 decrease	213	1.79	1.05–3.05	67	2.24	1.19–4.21	67	0.91	0.32–2.55
>3.5 decrease	66	3.95	2.03–7.65	30	2.12	0.89–5.02	30	3.11	1.13–8.58
P value for trend[f]		<0.001			0.008			0.047	
Missing (%)	370	(10.7)		123	(12.8)		123	(12.8)	

[a]GERS: self-reported degree of complaints with heartburn or acid regurgitation during the previous 12 months.
[b]Change in BMI: BMI HUNT 3/Mini-Q – BMI HUNT 2.
[c]Antireflux medication: proton pump inhibitors, histamin-2-receptor antagonists, and antacids.
[d]Loss of any GERS: any GERS at baseline, no GERS at follow-up; Reduction of severe GERS: severe GERS at baseline, no or minor GERS at follow-up; loss of severe GERS: severe GERS at baseline, no GERS at follow-up. The severe GERS group is a subset of the any GERS group.
[e]Adjusted for sex, age, cigarette smoking, alcohol consumption, education, and physical exercise.
[f]*P* value for trend: Wald test for linear trend.

(ii) the 12-month recall period used in the questionnaire, making recall bias possible; (iii) the long time period between the assessments of GERS, making short-term fluctuations in GERS impossible to evaluate; (iv) residual confounding, which cannot be excluded in observational research, although the choice of covariables was restrictive to avoid spurious effects; and (v) self-reported height and weight in Mini-Q, reducing the measurement accuracy of BMI.

The Nord-Trøndelag County is representative of the Norwegian population at large, making the findings generalizable (18). Selection bias due to loss of follow-up is probably small as there were only minor differences in the distribution of the study variables among all the HUNT 2 participants ($N=58,869$) compared with the cohort that was followed-up ($N=29,610$): there was no difference in the mean BMI (26 kg/m²) or mean alcohol consumption (2.5 times/month); the proportion of women was 52 and 54%; the mean age was 48.5 years and 45.8 years; the proportion of never smokers was 47 and 48% and of daily smokers 30 and 27%; the proportion with >12 years of education was 21 and 24%; and the proportion who did no exercise weekly was 9 and 6%, respectively. The 12-month recall period used in the questionnaire is a suboptimal long period to recall GERS. However, this should not be a major threat to the validity of the study, as most people with GERS, at least of a more severe type, are likely to be able to report their symptoms. The passage of 11 to 12 years between the surveys does not capture the short-term fluctuations in symptoms in the individual subject. Moreover, some people with GERS might have

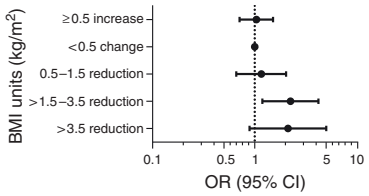

Figure 2. Adjusted odds ratio (OR) with 95% confidence interval (95% CI) for *reduction of severe* gastroesophageal reflux symptoms (GERS) by change in body mass index (BMI) when using *at least weekly* antireflux medication.

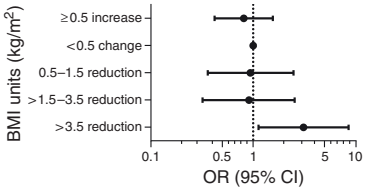

Figure 3. Adjusted odds ratio (OR) with 95% confidence interval (95% CI) for *loss of severe* gastroesophageal reflux symptoms (GERS) by change in body mass index (BMI) when using *at least weekly* antireflux medication.

developed Barrett's esophagus between the surveys, which might reduce symptoms, although the reflux disease remains. However, this should be limited to only a few people in the study. In Mini-Q, height and weight were self-reported, reducing measurement accuracy of BMI in this subpopulation. However, the number of individuals from Mini-Q was limited to $n=938$ (10.1%) and $n=190$ (12.2%) in the any GERS cohort and the severe GERS cohort, respectively. Assuming that self-reported weight is an underestimate of the actual weight, this would overestimate any weight loss from baseline in the study, and dilute the effect of weight loss on loss or reduction of GERS, make the presented ORs closer to the null. In English, "heartburn" and "regurgitation" are known to be words that the general public not understands adequately. However, in Norwegian language, this is much less a problem. The Norwegian words "brystbrann"/"halsbrann" and "sure oppstøt" used in this study are frequently used in the common language and are understood by the general public in the same way as healthcare professionals and researchers do.

Previous research on the effect of weight loss on GERS is limited, conflicting, and suffers from varying definitions of GERD. Two randomized, double-blind, sham-controlled trials of gastric balloon distension on 42 and 28 extremely obese patients with pH-verified reflux, but without grade C or D esophagitis (Los Angeles classification (19)) or large (>3 cm) hiatus hernia on endoscopy, found that weight loss was followed by reduced reflux (20,21). An uncontrolled prospective study of 34 patients (mean BMI 23.5 kg/m^2) with troublesome GERS, and either normal endoscopy or grade I esophagitis (Savary–Miller classification (22)), found improvement in reflux symptom score after 6 weeks with a decrease of mean BMI of 1.7 units (23). Another uncontrolled prospective study of 18 volunteers (mean BMI 43.5 kg/m^2) with GERS found improvement in symptom score after a mean of 4 days with an average weight loss of 1.7 kg (24). In the Nurses' Health Study from the United States, there was a 36% reduction in the risk of at least weekly GERS among women with at least a 3.5 decrease in BMI compared with those with no change in BMI (OR 0.64, 95% CI 0.42–0.97) (25). However, a randomized trial of 20 obese patients (mean BMI 31.4 kg/m^2 at inclusion) with pH-verified reflux, erosive esophagitis, and daily GERS did not find any effect on GERS with a mean decrease in BMI of 2.6 to 4.8 units (26). This study included participants with hiatus hernia, which contributes to the occurrence of GERD and is irreversible with weight loss. The only previous population-based study of the effect of weight change on GERS was from the United States and followed 637 individuals over a median of 10.5 years (mean age 62 years and 53% females at follow-up) and found no relation between weight change and change in reported GERD symptoms (27). However, a major limitation of that study was the use of self-reported height and weight.

Our results favor the hypothesis that weight loss improves GERS. Because of the observational design of the study, strict causality cannot be implied. However, the consistent and dose-related association between weight loss and reduction of GERS, which is preserved after adjustment for possible important confounders, argues for a valid conclusion. The data also indicate that even greater benefits might be seen in overweight individuals who achieve a larger weight loss. According to the Montreal definition and classification, "GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications" and it further states that "In population-based studies, mild symptoms occurring 2 or more days a week, or moderate/severe symptoms occurring more than 1 day a week, are often considered troublesome by patients" (8). As the validation studies of our questionnaire showed that 95–98% of the participants who reported severe GERS had at least weekly complaints, those reporting severe GERS in our study can be regarded as having GERD according to the Montreal definition. It seems that the weight loss needs to be substantial to improve severe GERS. This is probably because of the strong association between BMI and GERS. Even BMI in the upper normal range has been shown to be associated with GERS compared with BMI in the lower normal range (25). In addition, weight loss without regular use of antireflux medication does not seem to be sufficient. This probably reflects an advanced stage of disease in these subjects, i.e., esophagitis or symptoms related to the presence of hiatal hernia, which does not resolve only with weight loss. However, weight loss was associated with an increased chance of treatment success with antireflux medication.

CONCLUSION

In this large prospective population-based cohort study, weight loss was dose-dependently associated with reduction of GERS and increased chance of treatment success with antireflux medication. The study also suggests that patients with GERD using regular antireflux medication might benefit from weight reduction.

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CONFLICT OF INTEREST

Guarantor of the article: Eivind Ness-Jensen, MD.

Specific author contributions: E.N.-J., A.L., and J.L. have provided substantial contributions in planning and conducting the study, interpreting data, drafting the manuscript, and have approved the final draft submitted; K.H. has provided substantial contributions in planning and conducting the study, collecting and interpreting data, drafting the manuscript, and he has approved the final draft submitted.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The prevalence of gastroesophageal reflux symptoms (GERS) is high and increasing in Western populations.
- ✓ High body mass index is a risk factor of GERS.
- ✓ The effect of weight loss on GERS is not clear.

WHAT IS NEW HERE

- ✓ Weight loss was associated with a reduction of GERS in the general population.
- ✓ There was a dose-response relationship between weight loss and reduction of GERS.
- ✓ Weight loss was associated with an increased treatment success with antireflux medication.

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Paper III

Tobacco Smoking Cessation and Improved Gastroesophageal Reflux: A Prospective Population-Based Cohort Study: The HUNT Study

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OBJECTIVES: **Tobacco smoking increases the risk of gastroesophageal reflux symptoms (GERS), but whether tobacco smoking cessation improves GERS is unclear. The aim of this study was to clarify if tobacco smoking cessation improves GERS.**

METHODS: **The study was based on the Nord-Trøndelag health study (the HUNT study), a prospective population-based cohort study conducted from 1995–1997 to 2006–2009 in Nord-Trøndelag County, Norway. All residents of the county from 20 years of age were invited. The study included 29,610 individuals (61% response rate) who reported whether they had heartburn or acid regurgitation. The association between tobacco smoking cessation and improvement in GERS was assessed by logistic regression, providing odds ratios (ORs) with 95% confidence intervals (CIs). The analyses were stratified by antireflux medication, and the results were adjusted for sex, age, body mass index (BMI), alcohol consumption, education, and physical exercise. Subgroup analyses were also stratified by BMI.**

RESULTS: **Among individuals using antireflux medication at least weekly, cessation of daily tobacco smoking was associated with improvement in GERS from severe to no or minor complaints (adjusted OR 1.78; 95% CI: 1.07–2.97), compared with persistent daily smoking. This association was present among individuals within the normal range of BMI (OR 5.67; 95% CI: 1.36–23.64), but not among overweight individuals. There was no association between tobacco smoking cessation and GERS status among individuals with minor GERS or individuals using antireflux medication less than weekly.**

CONCLUSIONS: **Tobacco smoking cessation was associated with improvement in severe GERS only in individuals of normal BMI using antireflux medication at least weekly, but not in other individual with GERS.**

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INTRODUCTION

Tobacco smoking is associated with an increased risk of gastroesophageal reflux symptoms (GERS) according to several population-based studies from Western countries (1–9). The odds ratios (ORs) of GERS among smokers compared with non-smokers have been in the range of 1.3–2.5. Tobacco smoking increases the risk of GERS by reducing the lower esophageal sphincter pressure, facilitating gastric acid to reach the esophagus (10–12), and reducing the salivary bicarbonate secretion, which neutralizes the acidity of the gastric contents (13,14). In addition, both GERS and tobacco smoking are independently associated with an increased risk of adenocarcinoma of the esophagus and esophagogastric junction (15–19). Two recent reviews on the effect of lifestyle changes on gastroesophageal reflux disease (GERD) concluded that the evidence to date does not support an improvement in GERD after cessation of tobacco use (20,21). However, in the available studies, only the very short-term effect of smoking cessation on GERD outcomes was evaluated (22–24). Our hypothesis states that tobacco smoking cessation improves GERS. The aim of this study was to clarify if there is

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an association between tobacco smoking cessation and improvement in GERS in a large and population-based study with long follow-up.

METHODS

Study design, setting, and participants

The study was based on a large population-based health study, the Nord-Trøndelag health study (the HUNT study), which we have used previously for epidemiological studies of GERS (6,25–27). The HUNT study is based on a series of health surveys where the entire population of Nord-Trøndelag County, Norway, from 20 years of age has been invited to participate. The first survey was conducted in 1984–1986 (HUNT 1), the second survey in 1995–1997 (HUNT 2), and the third survey in 2006–2008 (HUNT 3). In all surveys a basic questionnaire was accompanying the invitation letter and the participants were asked to meet at screening stations for clinical and laboratory examinations. A short questionnaire (Mini-Q) was sent to non-participants after HUNT 3 in 2009 and those who responded to the Mini-Q were also included in our study. The questionnaires and examinations included a wide range of health-related topics (28).

Assessment of the outcome GERS

In HUNT 2 and HUNT 3/Mini-Q, GERS status of the participants was defined based on the participants' response to the following question: "To what degree have you had heartburn or acid regurgitation during the previous 12 months?" The question had three response alternatives: "No complaints," "Minor complaints," or "Severe complaints." Improvement in GERS status from severe GERS in HUNT 2 to no or minor GERS in HUNT 3/Mini-Q was defined as the study outcome, whereas severe GERS at both time points (stable GERS) were defined as reference. We have previously validated this GERS question and found that 25–31% of those reporting minor GERS and 95–98% of those reporting severe GERS had at least weekly complaints (25). This suggests that the majority of those reporting severe GERS actually have GERD according to the Montreal definition and classification of GERD (25,26,29).

Assessment of the exposure tobacco smoking

In HUNT 2, the participants were asked about their tobacco smoking status by answering yes or no to these questions: "Have you ever smoked daily?," "Do you smoke cigarettes daily?," "Do you smoke cigars or cigarillos daily?," and "Do you smoke pipe daily?" In HUNT 3/Mini-Q, the participants were asked: "Do you smoke?" The response alternatives to this question were: "No, I have never smoked," "No, I have quit smoking," "Yes, cigarettes occasionally (parties/vacation, not daily)," or "Yes, cigarettes daily." Those who quitted daily tobacco smoking or reduced daily smoking to only occasional smoking between HUNT 2 and HUNT 3/Mini-Q were defined as "exposed" to tobacco smoking cessation, and those who were persistent daily tobacco smokers at both time points were regarded as "unexposed" to such cessation.

Assessment of covariables

Covariables were selected based on their known association with GERS: sex, age, alcohol consumption, education, physical exercise, body mass index (BMI), and antireflux medication. Data on sex and age at participation were recorded at each survey. Average frequency of alcohol consumption and physical exercise was reported through questionnaires in HUNT 3/Mini-Q. Years of education were reported through questionnaires in HUNT 2. BMI was assessed by objectively measuring height and body weight under standardized conditions and by trained personnel at the screening stations in HUNT 2 and HUNT 3, whereas in Mini-Q height and weight were reported by the responders. BMI was calculated as body weight in kilograms divided by the square height in meters (kg/m^2). Antireflux medication included proton pump inhibitors, histamine-2-receptor antagonists, and antacids. In Norway, the prescription rules have until 2010 demanded a prescription from a physician to get proton pump inhibitors or histamine-2-receptor antagonists, except small packages of low-dose histamine-2-receptor antagonists that have been available over the counter. In this study, information was gathered on the participants' use of prescribed antireflux medication through the Norwegian Prescription Database (NorPD). The NorPD was established in 2004, and all prescribed medications from all Norwegian pharmacies were by legislation reported to the NorPD. From the NorPD data, the average use of prescribed antireflux medication was estimated based on the number of tablets prescribed during the HUNT 3 data collection period (2006–2008). In addition, the questionnaires in HUNT 3 included an assessment of over the counter medication use against several complaints, including heartburn or acid regurgitation. The question was: "How often have you used over the counter medication against the following complaints during the last month?" The participants responded with one of four alternatives to this question: "Rare/never," "1–3 times/week," "4–6 times/week," or "Daily." Thus, the two data sources were complementary with regard to the use of antireflux medication. There was no information on antireflux medication available during the HUNT 2 period.

Statistical analysis

Response rates were calculated from those eligible to participate at each survey, excluding those who were no longer residents in the county or had died. The association between tobacco smoking cessation (exposure) and GERS status (outcome) was assessed by multivariable logistic regression. Based on acknowledged criteria of a confounding factor, antireflux medication should not be included in the regression model, but instead be assessed as an effect modifier (30). To account for the effect of antireflux medication on GERS, the analyses were stratified by the use of antireflux medication, no or less than weekly use or at least weekly use, and the results were reported for each stratum separately. Participants with missing information on antireflux medication were analyzed as using no or less than weekly antireflux medication, because in the NorPD data it was not possible to distinguish between those with truly missing data and those who did not receive a prescription. Secondary analyses were also stratified by BMI using

the categories defined by the World Health Organization: <18.5 (underweight), 18.5–24.9 (normal weight), 25.0–29.9 (preobese), and ≥30.0 (obese) (31). To account for other potential confounders of the association between tobacco smoking and GERS, a continuous variable for age and categorical variables for sex, alcohol consumption (<weekly or ≥weekly), education (≤12 years or >12 years), and physical exercise (<weekly or ≥weekly) were included in the regression model. The statistical analyses were performed using Stata/IC 12.1 by StataCorp LP (College Station, TX).

Study approval

The study was approved by the Regional Committee for Medical and Health Research Ethics, Central-Norway (ID 4.2009.328).

RESULTS

Participants

We have previously published a complete flowchart of the participants (26). In HUNT 2 and HUNT 3/Mini-Q, 58,869 individuals (64% response rate) and 44,997 individuals (49%) reported GERS status, respectively. Among these, the 29,610 individuals (61%) who reported GERS status at both time points were eligible. The average follow-up time was approximately 11 years. Among the 1553 participants with severe GERS (5%) in HUNT 2, the 486 (31%) who were daily tobacco smokers were included in the present study. Of these participants, 182 quitted smoking and 31 reduced to occasional smoking. In total, 213 (44%) were previous daily smokers, whereas 251 (52%) were persistent daily smokers in HUNT 3/Mini-Q. In both these groups, about 60% were using antireflux medication at least weekly (**Figure 1**). The mean BMI was similar between the groups, but obesity was less common among the persistent daily smokers. Compared with the previous daily smokers, the persistent daily smokers were characterized by higher female representation, lower mean age, lower education, lower level of physical exercise, and lower alcohol consumption (**Table 1**).

Associations

Among the daily tobacco smokers with severe GERS in HUNT 2 using no or less than weekly antireflux medication, there was no statistically significant association between tobacco smoking cessation and GERS status (adjusted OR 0.95; 95% CI: 0.39–2.30) compared with persistent daily smoking (**Table 2**). However, among the daily tobacco smokers with severe GERS in HUNT 2 using at least weekly antireflux medication, tobacco smoking cessation was associated with an improvement in GERS status from severe to no or minor complaints (adjusted OR 1.78; 95% CI: 1.07–2.97) compared with persistent daily smoking (**Table 2**). Secondary, subgroup analyses found that the association only was present among individuals within the normal weight range

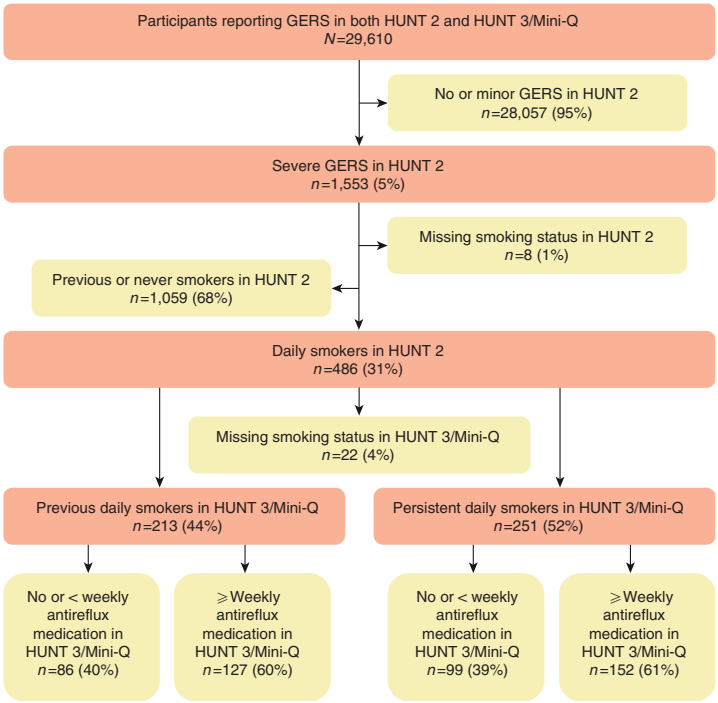

Figure 1. Flow chart of study participants. GERS, gastroesophageal reflux symptoms; HUNT, Nord-Trøndelag health study.

Table 1. Characteristics of study participants

	Tobacco smoking status			
	Previous daily smokers (*n*=213)		Persistent daily smokers (*n*=251)	
Antireflux medication[a]	No or < weekly (*n*=86)	≥ Weekly (*n*=127)	No or < weekly (*n*=99)	≥ Weekly (*n*=152)
BMI[b]				
Mean (s.d.)	28.5 (4.7)	29.2 (4.5)	28.1 (5.0)	28.9 (5.1)
Median (range)	28.1 (18.7–47.2)	29.0 (19.0–44.1)	27.8 (18.9–49.3)	28.0 (15.2–47.5)
<18.5, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)
18.5–24.9, no. (%)	22 (25.6)	20 (15.7)	28 (28.3)	30 (19.7)
25.0–29.9, no. (%)	35 (40.7)	55 (43.3)	42 (42.4)	69 (45.4)
≥ 30.0, no. (%)	29 (33.7)	49 (38.6)	28 (28.3)	51 (33.6)
Missing, no. (%)	0 (0.0)	3 (2.4)	1 (1.0)	0 (0.0)
Sex, no. (%)				
Women	37 (43)	54 (43)	52 (53)	92 (61)
Age (years)				
Mean (s.d.)	55.7 (11.7)	58.9 (9.9)	51.8 (10.3)	57.5 (10.3)
Median (range)	55.3 (32.8–84.9)	58.6 (34.3–84.7)	51.3 (34.1–84.4)	56.7 (31.9–87.8)
Alcohol consumption, no. (%)				
< Weekly	51 (59.3)	82 (64.6)	65 (65.7)	107 (70.4)
≥ Weekly	34 (39.5)	44 (34.6)	34 (34.3)	44 (28.9)
Missing	1 (1.2)	1 (0.8)	0 (0.0)	1 (0.7)
Education, no. (%)				
≤12 years	67 (77.9)	112 (88.2)	91 (91.9)	135 (88.8)
>12 years	17 (19.8)	13 (10.2)	7 (7.1)	14 (9.2)
Missing	2 (2.3)	2 (1.6)	1 (1.0)	3 (2.0)
Physical exercise, no. (%)				
<Weekly	28 (32.6)	33 (26.0)	38 (38.4)	56 (36.8)
≥Weekly	58 (67.4)	92 (72.4)	61 (61.6)	94 (61.8)
Missing	0 (0.0)	2 (1.6)	0 (0.0)	2 (1.3)

Participants with no information on antireflux medication were included in never or less than weekly category.

[a]Antireflux medication: proton pump inhibitors, histamine-2-receptor antagonists, and antacids; participants with no information on antireflux medication were included in never or < weekly category.

[b]BMI: body mass index (kg/m^2).

(adjusted OR 5.67; 95% CI: 1.36–23.64), but not among overweight individuals (**Table 3** and **Figure 2**). There was no association between tobacco smoking cessation and GERS status among individuals with minor GERS in HUNT 2 (data not shown).

DISCUSSION

This study found that tobacco smoking cessation was associated with an improvement in severe GERS among normal weight individuals using antireflux medication at least weekly. There was, however, no such pattern in individuals with minor GERS, overweight, or those using antireflux medication less than weekly.

Strengths of this study include the population-based design, reducing selection bias, and increasing generalizability compared with clinic-based studies. Except for slightly lower average income and education and lack of a large city, the population of Nord-Trøndelag County is representative of the Norwegian population at large (28,32). In addition, the prospective design circumvents recall bias and the wide range of variables assessed, including antireflux medication, makes adjustments for relevant confounders possible. Limitations include the inherent arbitrary definition of GERD, reducing the accuracy of identifying individuals with true GERD, probably leading to some misclassification. Misclassification is also possible among the exposure and covariables, as the variables were dichotomized. In addition, the associations found were only modest and residual confounding can never be totally excluded in observational research. Loss to follow-up may introduce selection and survival bias, but such potential biases are probably small as

Table 2. OR with 95% CI of improvement in severe GERS by tobacco smoking cessation, stratified by use of antireflux medication[a]

	Unadjusted			Adjusted for sex and age			Fully adjusted[b]		
Antireflux medication[c]	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI
No or < weekly	185	1.12	0.48–2.62	185	1.06	0.45–2.52	181	0.95	0.39–2.30
≥Weekly	279	1.44	0.90–2.32	279	1.62	0.99–2.65	268	1.78	1.07–2.97

CI, confidence interval; GERS, gastroesophageal reflux symptoms; HUNT, Nord-Trøndelag health study; OR, odds ratio.
Comparing previous daily smokers with persistent daily smokers as reference.
[a]From severe heartburn or acid regurgitation (GERS) in HUNT 2, to no or minor GERS in HUNT 3/Mini-Q; comparing previous daily smokers with persistent daily smokers as reference.
[b]Adjusted for sex, age, body mass index, alcohol consumption, years of education, and physical exercise.
[c]Antireflux medication: proton pump inhibitors, histamine-2-receptor antagonists, and antacids.

Table 3. OR with 95% CI of improvement in severe GERS by tobacco smoking cessation, stratified by the use of antireflux medication and BMI[a]

		Unadjusted			Adjusted for sex and age			Fully adjusted[b]		
Antireflux medication[c]	BMI (kg/m²)	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI
No or < weekly	All	185	1.12	0.48–2.62	185	1.06	0.45–2.52	181	0.95	0.39–2.30
	18.5–24.9	50	1.06	0.21–5.30	50	0.89	0.17–4.65	49	0.80	0.13–5.08
	25.0–29.9	77	1.29	0.33–5.00	77	1.32	0.33–5.27	63	1.13	0.27–4.75
	≥30.0	57	1.04	0.23–4.64	57	0.74	0.14–3.89	57	0.90	0.16–5.17
≥ Weekly	All	279	1.44	0.90–2.32	279	1.62	0.99–2.65	268	1.78	1.07–2.97
	18.5–24.9	50	3.92	1.13–13.60	50	4.70	1.22–18.18	49	5.67	1.36–23.64
	25.0–29.9	124	1.25	0.62–2.56	124	1.20	0.57–2.53	121	1.24	0.57–2.71
	≥30.0	100	1.01	0.46–2.22	100	1.28	0.55–2.99	93	1.29	0.53–3.17

BMI, body mass index; CI, confidence interval; GERS, gastroesophageal reflux symptoms; HUNT, Nord-Trøndelag health study; OR, odds ratio.
[a]From severe heartburn or acid regurgitation (GERS) in HUNT 2, to no or minor GERS in HUNT 3/Mini-Q; comparing previous daily smokers with persistent daily smokers as reference.
[b]Adjusted for sex, age, body mass index, alcohol consumption, years of education, and physical exercise.
[c]Antireflux medication: proton pump inhibitors, histamine-2-receptor antagonists, and antacids.

a previous publication has shown that there was virtually no difference in the distribution of the study variables between all the HUNT 2 participants ($N=58,869$) and the cohort who was followed up from HUNT 2 to HUNT 3/Mini-Q ($N=29,610$) (27). Owing to the observational design, causal relationships cannot be claimed. As there were low numbers of missing data among the participants (**Table 1**), complete case analyses were performed.

The three previous studies addressing smoking cessation and GERD found conflicting results. One study found no influence of 24 h refrainment from smoking on 24-h pH measurements of the distal esophagus in 10 smokers with GERS (22). Another study found no immediate effect of smoking cessation on total esophageal acid exposure in eight smoking men with moderate-to-severe endoscopic evidence of GERD (23). The third study, however, found a reduced distal esophageal acid exposure in 14 smokers with reflux esophagitis who abstained from smoking for 48 h (24). Our study is the first epidemiological investigation testing whether tobacco smoking cessation improves GERS and the first study that evaluates such cessation in a long-term perspective.

The results of our study suggest that tobacco smoking cessation may improve severe GERS among normal weight individuals in the general population. As this is an observational study, a causal relationship cannot be claimed, and we do not know if smoking cessation occurred before improvement of GERS or the other way around. However, the results are consistent with the pathophysiology (10–14) and a randomized controlled trial of smoking cessation would be very hard and unethical to perform. The study only considered frequency of tobacco smoking, not dose or time since cessation. However, pathophysiologic data suggests that the effect of tobacco smoking is very short lived, and thus dose and time since cessation should be of less importance. In addition, daily smoking is a common cutoff level in observational study, making comparisons with other studies easier. We found no association between tobacco smoking cessation and improvement in minor GERS. This probably reflects the heterogenetic nature of individuals reporting minor GERS, including individuals with functional syndromes. These syndromes have other pathophysiological mechanisms, at least partly not related to gastroesophageal reflux or tobacco smoking. Owing to the low absolute number of individuals, we defined the "exposure" in this study to be a combination of those quitting smoking and those only reducing daily smoking to occasional smoking. Even so, we found an association between the "exposure," i.e., reduced

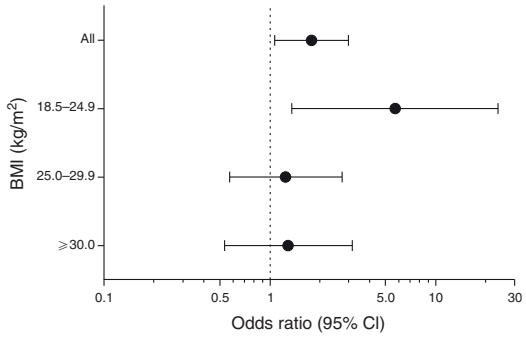

Figure 2. Odds ratio and 95% confidence interval (CI) of improvement in severe gastroesophageal reflux symptoms by tobacco smoking cessation, comparing previous daily tobacco smokers with persistent daily tobacco smokers as reference. Restricted to those using *at least weekly* antireflux medication and stratified by body mass index (BMI). Model adjusted for sex, age, alcohol consumption, education, and physical exercise.

tobacco smoking, and the outcome, i.e., improved GERS. This suggests that total smoking cessation would increase the chance of success even more than apparent from our study. The improvement in GERS was limited to persons of normal weight using at least weekly antireflux medication. The lack of improvement in overweight individuals might be explained by the strong association between BMI and GERS, which might dominate compared with the effect of tobacco smoking on GERS in overweight individuals. Thus, the pathophysiology of GERS is probably driven by the weight in overweight and obese individuals and smoking has a minor role, but in individuals of normal weight smoking has a more important role in the pathophysiology. The lack of improvement among those using no or less than weekly antireflux medication suggests that the individuals with severe GERS have an advanced stage of GERD, i.e., esophagitis or symptoms related to the presence of hiatal hernia, which does not resolve only with tobacco smoking cessation. However, weight loss and tobacco smoking cessation might reduce the need for antireflux medication over time. In addition, these lifestyle measures are also advisable owing to the effects on general health. As tobacco smoking as well as GERS is associated with adenocarcinoma of the distal esophagus and gastric cardia, persons with GERS should be advised to refrain from smoking (16–19). The population-based design argues for generalizability to the general Norwegian population and other Western populations of mainly Caucasians.

In conclusion, although tobacco smoking cessation was not associated with any decrease in GERS among individuals with minor GERS, overweight, or those using antireflux medication less than weekly, an improvement in severe GERS was identified among normal weight individuals using regular antireflux medication. Tobacco smoking cessation might be beneficial in this latter group of patients suffering from gastroesophageal reflux.

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CONFLICT OF INTEREST

Guarantor of the article: Eivind Ness-Jensen, MD.

Specific author contributions: Eivind Ness-Jensen has provided substantial contributions in planning and conducting the study, interpreting data, drafting the manuscript, and approved the final draft submitted. Anna Lindam has provided substantial contributions in planning and conducting the study, interpreting data, drafting the manuscript, and approved the final draft submitted. Jesper Lagergren has provided substantial contributions in planning and conducting the study, interpreting data, drafting the manuscript, and approved the final draft submitted. Kristian Hveem has provided substantial contributions in planning and conducting the study, collecting and interpreting data, drafting the manuscript, and approved the final draft submitted.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Gastroesophageal reflux symptoms (GERS) are prevalent in Western populations and associated with reduced health-related quality of life and increased risk of esophageal adenocarcinoma.
- ✓ Tobacco smoking is associated with an increased the risk of GERS.
- ✓ The effect of tobacco smoking cessation on GERS is not clear.

WHAT IS NEW HERE

- ✓ This study did not find any association between tobacco smoking cessation and improvement in GERS in individuals not using regular antireflux medication.
- ✓ Tobacco smoking cessation was associated with an improvement in severe GERS in individuals of normal weight using regular antireflux medication.
- ✓ Tobacco smoking cessation was associated with an increased chance of treatment success with regular use of antireflux medication in severe GERS.
- ✓ This study suggests that tobacco smoking cessation might be beneficial in normal weight patients suffering from gastroesophageal reflux.

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