From DEPARTMENT OF MOLECULAR MEDICINE AND SURGERY
Karolinska Institutet, Stockholm, Sweden

GASTROESOPHAGEAL REFLUX AND SLEEP PROBLEMS

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Stockholm 2014

Published by Karolinska Institutet.

Illustration by Mats Ceder, Koboltart.se

ISBN 978-91-7549-613-9

Printed by
REPROPRINT AB
Stockholm 2014
www.reproprint.se
Gårdsvägen 4, 169 70 Solna

Karolinska Institutet

Institutionen för molekylärmedicin och kirurgi

Gastroesophageal reflux and sleep problems

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i **Nanna Schwartz auditorium, Karolinska Universitetssjukhusets huvudbyggnad, Solna**

Fredagen den 12 september 2014, kl. 10.00

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“Go ahead, be cynical and let fear rule your life. I've got (stuff) to do, worlds to change, and it's fun, so I’ll see you later.”

Nicco Miele

ABSTRACT

Gastroesophageal reflux disease (GERD) and sleep problems are common health problems in the Western world affecting up to 30% and 33% of the population respectively. GERD is associated with decreased quality of life, medication, increased use of health care facilities and increased risk of esophageal adenocarcinoma. Sleep problems are linked to mental disorders, pain disorders, coronary heart disease, impaired work productivity and increased risks of traffic accidents. These two disorders have been shown to be associated and a bidirectional association has been suggested. The main focus of this thesis is the link between sleep problems and gastroesophageal reflux symptoms (GERS), while also including one study of the related potential association of obstructive sleep apnea and Barrett´s esophagus.

In study I we explored prevalence changes, incidence and spontaneous loss of GERS in a longitudinal population-based setting using the Nord-Trøndelag health study (HUNT). Included in the study were all residents of the county of Nord-Trøndelag, Norway and who reported any degree of GERS in 1995-1997 (n=58,869) and in 2006-2009 (n=44,997). Of these, 29,610 (61%) responded at both time points with an average of 11 year follow-up. Between 1995-1997 and 2006-2009 we found a 30% increase in the prevalence of any GERS, a 24% increase in severe GERS and a 49% increase in the prevalence of at least weekly GERS. The average annual incidence was 3.07% for any GERS and 0.23% for severe GERS, while the annual average spontaneous loss of any GERS were 2.32% and 1.22% respectively.

In study II we used a cross-sectional co-twin control design to analyze the association between sleep problems and GERD while controlling for hereditary factors. Included in the study were 8,014 same-sexed twins of at least 65 years of age born 1886-1958 identified from the Swedish Twin Register. There was a dose-dependent association between sleep problems and GERD which remained when only discordant dizygotic twins (one twin has GERD the other not) were included in the analysis but this was not seen for monozygotic twins. The association between sleep problems and GERD does not seem to be confounded by hereditary factors.

In study III we explored the association between symptoms of obstructive sleep apnea, GERS and Barrett's esophagus in a population-based case-control study from Brisbane, Australia. Included in the study were 237 cases of histological confirmed Barrett´s esophagus and 247 population-controls. No statistically significant association between obstructive sleep apnea symptoms and Barrett´s esophagus was observed.

In study IV we investigated the direction of association between sleep problems and GERS, based on the same two previously describe data collections from HUNT (see study I). We found that the association between sleep problems and GERS seems to be bidirectional, but contrary to what was expected we found a stronger association sleep problems and incident GERS than between GERS and incident sleep problems.

LIST OF SCIENTIFIC 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

II. Lindam A, Jansson C, Nordenstedt H, Pedersen NL, Lagergren J.
A population-based study of gastroesophageal reflux disease and sleep problems in elderly twins
PLoS One 2012; 7(10):e48602.

III. Lindam A, Kendall BJ, Thrift AP, Macdonald GA, O'Brien S, Lagergren J, Whiteman DC.
Obstructive sleep apnoea, gastro-oesophageal reflux and the risk of Barrett´s oesophagus in a case-control study
Submitted

IV. Lindam A, Ness-Jensen E, Jansson C, Nordenstedt H, Hveem K, Lagergren J.
Gastroesophageal reflux and sleep problems: direction of association in a population-based longitudinal cohort study, the HUNT study
Submitted

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LIST OF ABBREVIATIONS

BMI	Body mass index
BOMS	Barrett´s Oesophagus Metabolic Study
CI	Confidence interval
DZ	Dizygotic
GERD	Gastroesophageal reflux disease
GERS	Gastrosesophageal reflux symptoms
H2RA	Histamine receptor antagonist
HUNT	Nord-Trøndelag Health Study
LES	Lower esophageal sphincter
MZ	Monozygotic
NorPD	Norwegian Prescription Database
OR	Odds ratio
OSA	Obstructive sleep apnea
PPI	Proton pump inhibitor
SALT	Screening Across the Lifespan Twin Study
SDH	Study of digestive health
TLESRs	Transient lower esophageal sphincter relaxations

1 INTRODUCTION

Gastroesophageal reflux disease (GERD) and sleep problems are major health problems, and the association between them has attracted a great deal of attention over the last decade. GERD, commonly presenting as acid regurgitations and heartburn, affects 10-30% of the adults in the Western world and is a rising health problem in Asia.[1] It has been shown that frequent GERD is associated with adverse quality of life,[2] sickness absence,[3] disturbed sleep, increased medication use, increased burden for the health care system, all with high costs to society.[4] Sleep problems are also a common health problem and affect up to 33% of the population.[5] An association between sleep problems and GERD has been observed, and it has been suggested, but not thoroughly studied, that the association is bidirectional.[6] The following questions then arise: How are these common disorders related? Do sleep problems cause GERD or does GERD cause sleep problems? Or is the association bidirectional? This thesis aims to increase the knowledge regarding the relationship between sleep problems and reflux by providing valid measures of changes in prevalence, incidence and loss of gastroesophageal reflux symptoms (GERS), studying hereditary factors, investigating the wider association between obstructive sleep apnea and Barrett´s esophagus (a precursor for adenocarcinoma of the esophagus and for which GERD is the main risk factor)[7,8] and the direction of the association between sleep problems and GERS.

2 BACKGROUND

2.1 GASTROESOPHAGEAL REFLUX

2.1.1 Definitions

2.1.1.1 The Montreal definition

According to the Montreal definition gastroesophageal reflux disease (GERD) is the recurrent regurgitation of stomach contents into the esophagus which causes troublesome symptoms and/or complications.[9] The definition further states that characteristic symptoms of GERD are heartburn (defined as a burning sensation in the retrosternal area behind the breastbone) and regurgitation (defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx) and that in clinical practice the patients themselves should determine if their symptoms are troublesome. Reflux symptoms that are not perceived as troublesome by the patients should not be diagnosed as GERD. The definition further distinguishes between manifestations of GERD as symptomatic syndromes and syndromes with esophageal injury. The first describes patients with symptoms of GERD (not examined with endoscopy) or patients with symptoms where no mucosal damage was found during endoscopy. The second group of syndromes includes disorders where mucosal injury has been seen during endoscopy and includes manifestations of esophagitis, reflux stricture, Barrett´s esophagus and esophageal adenocarcinoma. The reason for this distinction is that, in clinical practice, a clinician should be able to diagnose GERD with varying amounts of information.[9]

The Montreal definition came about as a result of a Delphi process in 2006, i.e. a consensus-seeking model, including a group of 44 experts from 18 countries with relevant expertise in GERD. A working group made a draft of statements which constitute the definition, conducted systematic literature reviews and graded the level of evidence to support the statements. The larger consensus group voted and statements were altered during a number of iterations until consensus was reached. A non-voting chairman led the discussions and the voting processes were anonymous, allowing for changes of opinion during the process and in order to minimize the influence of the most well-known experts upon the others.[9]

The Montreal definition has been challenged and the subjective nature of the patient's perception in the decision making process in clinical settings are questioned. It has been proposed that the response of patients to proton pump inhibitors (PPIs) should be used as a verification of gastroesophageal reflux symptoms (GERS).[10] It has also been shown in a group of patients with esophagitis verified by upper endoscopy that up to 37% of the patients did not suffer from heartburn or acid regurgitation, which may indicate that the definition might lead to under or over-reporting of GERD.[11]

In the studies included in this thesis we have used the term gastroesophageal reflux symptoms (GERS) when reflux was assessed by 1-2 questions asking about the intensity or frequency of symptoms (studies I, III and IV), and gastroesophageal reflux disease (GERD) when it was assessed by a battery of 10 reflux questions asking both about the intensity and frequency of symptoms (study II).

2.1.1.2 pH-monitoring

In clinical practice, pH-monitoring is also used to objectively detect acidic GERD. A small catheter or wireless pH-capsules are inserted and left in the esophagus, approximately 5 cm above the proximal lower esophageal sphincter (LES) for a catheter electrode and 6 cm above the squamocolumnar junction for wireless pH-capsules, and the pH-level is usually measured during 24 or 48 hour surveillance.[12] The percentage of time the pH is <4 is measured and a cutoff point of 4.2% is suggested to indicate pathological acid reflux.[13] But a lower exposure time, 3.5% has also shown to correlate well with acidic reflux.[14] However, many patients with GERS do not show a pH <4 for longer periods, so this method has low sensitivity, and should be used together with assessment of symptoms and upper endoscopic investigation.

2.1.1.3 Nocturnal reflux

Nocturnal reflux is GERD that occurs during sleep. It has been suggested that nocturnal reflux is a different disease from GERD,[15] and that nocturnal reflux is more severe and has a larger impact on the esophageal mucosa.[16,17] In our studies we did not have the ability to differentiate between GERD/ GERS and nocturnal reflux.

2.1.2 Pathophysiology

In order to study the link between sleep problems and GERD an understanding of the functions of the esophagogastric junction is needed. There is a natural intricate barrier in the esophagogastric junction that prevents backflow of gastric contents into the esophagus. The barrier has three components: the lower esophageal sphincter (LES), the hiatus in the crural diaphragm, and the flap valve mechanism which forms a sharp angle between the esophagus and the cardia of the stomach, also called the angle of His.[18,19] The LES consists of a segment of approximately 4 cm of smooth muscles in the distal esophagus. These muscles constitute the internal part of the pressure mechanism while the crural diaphragm constitutes the external part of the pressure mechanism. It is the constant high pressure which prevents backflow of gastric contents. The normal resting pressure of LES is 10 to 35 mm Hg. In a normal case, hiatus of the crural diaphragm encircles the distal esophagus and the hiatus is approximately 2 cm long.[19]

Gastroesophageal reflux occurs when the reflux barrier is intimidated which most commonly happens by: 1) transient lower esophageal sphincter relaxations (TLESRs), 2) anatomic

disruption of the reflux barrier, and 3) low resting pressure of the LES.[16,19]
1) TLESRs are defined as an abrupt decrease in LES pressure compared to the intragastric pressure that is not associated with swallowing. The duration of the TLESRs is considered to be longer than swallow-induced LES relaxations.[20] These relaxations allow us to belch, but are also responsible for the majority of reflux episodes both in GERD patients and in healthy subjects.[20,21]
2) Hiatal hernia is an anatomic disruption of the anti-reflux barrier. Typically a hiatal hernia occurs when a part of the stomach herniates through the diaphragm, and the pressure mechanism between the LES and the surrounding diaphragm is disrupted. When the LES relaxes to allow swallowing, acid that has been caught in the hernia sack can flow back into the esophagus.[19] Hiatal hernias are very common among patients with moderate to severe reflux and hernia size correlates with severity of esophageal esophagitis.[22] However, many patients with verified hiatal hernia do not have any reflux symptoms at all.[23]
3) Low resting pressure of LES was previously believed to be the main factor involved in GERD episodes, before the discovery of TLESRs.[16] High abdominal pressure can, however, in combination with lower resting LES pressure, lead to reflux episodes or very low LES pressure (0-4 mm Hg) increasing the risk of spontaneous reflux episodes.[16,24]

2.1.3 Occurrence

GERD is a common disorder which is prevalent worldwide and the prevalence seems to have increased over time.[25] In 2005 a systematic review of 15 studies concluded that the prevalence of GERD was 10-20% in Europe and the USA, and less than 5% in Asia. The incidence was 5 per 1000 person years in the populations of UK and USA.[26] An update of the previous systematic review concluded that the prevalence of GERD was 18.1-27.8% in North America, 23.0% in South America, 8.8-25.9% in Europe, 2.5-7.8% in East Asia, 8.7-33.1% in the Middle East and 11.6% in Australia.[1] In these studies GERD was defined as at least weekly symptoms of acid regurgitation or heartburn and assessed by questionnaires or by a physician.

2.1.4 Etiology

2.1.4.1 Heredity

As early as in the 1930s there were reports of familial aggregation of GERS.[27] Later studies of family members of patients with GERD found a familial aggregation of both GERD and Barrett´s esophagus.[28,29] Even though these studies controlled for potential confounding factors, they could not differ between genetic and environmental factors. Later this was accomplished in two large twin studies which used monozygotic and dizygotic twin-pairs to show that the liability of GERD was 31% in a large Swedish twin study,[30] and 43% in a large twin study from the UK.[31] The gene collagen type III alpha 1 has been associated with GERD in both men and women, and for men a hereditary association has also been seen with hiatal

hernia.[32]

2.1.4.2 Lifestyle factors

Associations between high body mass index (BMI) and GERD have been observed repeatedly,[33-37] and obesity is seen as one of the strongest risk factors for GERD. Tobacco smoking has also been associated with an increased risk of GERD,[37,38] while high dietary fiber intake and physical exercise seem to be protective.[39] The results for alcohol consumption and GERD are diverse. Some studies reported that excessive drinking[37] or drinking spirits was associated with GERD,[40] but in other studies no association, regardless of type of alcohol were found. [35,39] Low socioeconomic status and low education has also been associated with GERS.[41,42]

2.1.5 Treatment

GERD is mainly treated with medical therapy or surgery, and lifestyle changes are also recommended as a first step to decrease symptoms. These changes include smoking cessation, weight loss, avoiding food that may trigger reflux episodes such as coffee, chocolate, alcohol, citrus fruits, peppermint, carbonated drinks and to sleep with one's head raised off the bed.[43] Of these factors, a systematic review found improved pH-profiles or symptom decrease only for head off bed elevation and weight loss.[44] A recent study from our group also found a decrease in GERS after weight-loss and a more efficient effect of reflux medication after weight loss.[45]

2.1.5.1 Medical treatment

The most commonly used drugs for treatment of GERD are proton pump inhibitors (PPI), H2-receptor antagonists (H2RA) and antacids. While PPIs and H2RAs decrease the production of acid secretion by shutting down the cell pump (PPI) and blocking the signal generated by histamine receptors substance (H2RA), antacids neutralize the acid. PPIs have been reported to be more effective than H2RA in relieving more severe GERS and to be more effective at healing esophagitis.[43] Low dose PPI, H2RA and antacids can be bought without prescription over the counter while a prescription is needed for higher doses.

2.1.5.2 Anti-reflux surgery

Another treatment for severe GERD is anti-reflux surgery where the reflux barrier is partly reconstructed by removing any hiatal hernia and wrapping the fundus of the stomach around the distal esophagus by means of total fundoplication 360 (e.g. Nissen) or partial fundoplication (e.g. Toupét).[46-48] Both open and laparoscopic approaches have been shown to be equally effective at decreasing recurrence of esophagitis and heartburn as treatment with PPI, and better at treating regurgitations.[49,50] The adverse effects of surgery compared to PPI use include, apart from risk of surgical complications, higher rates of dysphagia, bloating and flatulence, since the patient is unable to belch and vomit.[49,50] PPIs are therefore recommended as initial therapy because of the superior safety but in selected severe cases, if patients are at

least partly responsive to medical treatment but intolerant, anti-reflux surgery should be considered.[43]

2.1.6 Complications of GERD

Complications of GERD includes esophagitis, strictures, Barrett´s esophagus and adenocarcinoma of the esophagus,[8,9] but progression of GERD is only seen in a small proportion of cases.[51] Esophagitis is defined endoscopically by visible breaks of the distal esophageal mucosa and is seen in less than 50% of patients with typical GERD symptoms.[9] Strictures are caused by acidic damage and scarring, and can result in dysphagia. Barrett´s esophagus is described in more detail below. Adenocarcinoma of the esophagus is a cancer with poor prognosis, with an increasing incidence since the 1970, particularly in white men.[52] The ratio between men and women in this cancer is up to 9:1,[53,54] and cannot be explained by the relatively small differences in prevalence between men and women in GERD.

2.2 BARRETT'S ESOPHAGUS

2.2.1 Definition

Barrett´s esophagus is defined as the presence of a specialized intestinal metaplasia (columnar epithelium with goblet cells) replacing the native squamous cell epithelium. Barrett's esophagus is typically occurring in the distal esophagus, but the extent could be high.[55] The diagnosis is confirmed by biopsies taken from the esophagus by upper gastrointestinal endoscopy.

2.2.2 Occurrence

The population prevalence of Barrett´s esophagus is difficult to assess as the condition does not usually cause any specific symptoms and upper endoscopy is needed for a diagnosis. A prevalence study based on endoscopies a random sample of adults living in northern Sweden revealed a population prevalence of Barrett´s esophagus as high as 1.6%, although this might still be an overestimation due to selection bias.[56]

2.2.3 Etiology

GERD is the strongest known risk factor for Barrett's esophagus,[57] but high BMI,[58] particularly abdominal obesity typically seen in men with high BMI, is also a strong risk factor.[59] Tobacco smoking has been shown to be associated with increased risk of Barrett's esophagus and the risk increases with number of pack-years (estimated value of life consumption of cigarettes).[60] Interaction effects between GERD, obesity, smoking and increased risks of Barrett´s esophagus have been seen.[61]

2.3 SLEEP DISTURBANCES

Sleep disturbances are associated with mental disorders, generally poor health, moderately increased risk of myocardial infarction and decreased health related quality of life.[62,63 64]

There are etiological differences for sleep problem/insomnia and obstructive sleep apnea, but as they are both sleep disturbances they will be described jointly.

2.3.1 Definitions

2.3.1.1 Sleep problems

"Sleep problems" is a widely used term which can cover a number of different disorders and is often used differently across studies. In general, sleep problems are often defined as having trouble falling asleep, maintaining or experiencing non-restorative sleep. Usually it is differentiated from a clinical diagnosis of sleep problems such as primary insomnia and symptoms of sleep problems. In this thesis, sleep problems is used as a general term for participants reporting trouble falling asleep, having difficulty maintaining sleep (waking up too early) or experiencing non-restorative sleep.

2.3.1.2 Insomnia

According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV),[65] the criteria for primary insomnia includes having difficulty initiating or maintaining sleep or experiencing non-restorative sleep for at least one month. In addition it is also a prerequisite that the sleep disturbance has a clinically significant adverse impact on social, occupational or other important areas of functioning. In order to give a patient the diagnosis primary insomnia, the symptoms may not occur exclusively during the course of another sleep disorder, exclusively during the course of a mental disorder, or exclusively due to direct physiological effects of a substance or a general mental condition.[65] In epidemiological studies it is often not possible to use the strict diagnoses of insomnia and instead insomnia symptoms (usually a combination of symptoms of trouble falling asleep, maintaining or experiencing non-restorative sleep and signs of effects on daily life) is often used. In study IV we use a proxy for primary insomnia based on insomnia symptoms.

2.3.1.3 Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a chronic condition characterized by recurrent complete or partial airway collapse during sleep which often results in disturbed sleep and excessive daytime sleepiness.[66,67] For a clinical diagnosis of OSA a test with polysomnography (a sleep test usually performed in a sleep lab which can measure different activities including brain activity, eye movement and breathing patterns during sleep) should be performed. The number of complete (apneas) or incomplete (hypneas) breathing stops per hour of sleep is then counted and a mean apnea-hypnea score (AHI) number of breathing stops per hour of sleep is calculated. A score of ≥5 to <15 is considered mild OSA, a score of ≥15 to <30 moderate and a score of ≥30/h as severe OSA.[66,68]

2.3.1.4 Obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome (OSAS) has a stricter definition than OSA. As well as fulfilling an AHI score of ≥5, symptoms of daytime sleepiness should also be present.[66]

2.3.1.5 Symptoms of obstructive sleep apnea

Symptoms of obstructive sleep apnea are clinical symptoms which are often present in patients with sleep apnea, such as daytime sleepiness, snorting or gasping, loud snoring or breathing stops, choking or struggling for breath. In study III we use symptoms of obstructive sleep apnea as a proxy for OSA.

2.3.2 Occurrence

2.3.2.1 Sleep problems and insomnia

The prevalence of sleep problems and insomnia varies across studies, often due to the fact that sleep problems and insomnia are defined and assessed differently. In a large review the prevalence of sleep problems defined as having trouble falling asleep, maintaining or experiencing non-restorative sleep was 33%. This figure was 9-15% when the criterion of daytime impairment was added, and about 6% when only clinical diagnoses where included; results were mainly from studies performed in Europe or the US.[5] In a recent population-based Swedish study, the prevalence of sleep problems (defined as having trouble falling asleep at least 3-4 times a week or waking up at least 3-4 times per night) was 24.6% and the prevalence for insomnia symptoms (defined as having sleep problems and at least moderate inference with daytime functioning) was 10.5%. [69] In a Chinese study using a similar definition, the prevalence of sleep problems was 6.8%, insomnia symptoms 4.8%, and the cumulative incidence of insomnia symptoms was 5.9%.[70] In a recent Norwegian study using the HUNT data, the prevalence of insomnia symptoms (defined as having difficulty falling asleep, waking up repeatedly during the night or waking up too early and unable to go back to sleep several times a week, in combination with feeling sleepy during the day several times a week) was 7.1% .[71]

2.3.2.2 Obstructive sleep apnea

The prevalence of mild to moderate OSA (apnea-hypnea score of ≥5 only) is as common as 27% and 16% in middle aged men and women, respectively. The prevalence of OSAS (OSA with apnea-hypnea score of ≥5 in combination with symptoms of daytime sleepiness) is estimated to be 2-4% in men and 2-3% in women.[66]

2.3.3 Etiology

2.3.3.1 Sleep problems and insomnia

Heritability has been shown to account for about 33-44% of the variation in sleep quality and length of sleep in studies of Finnish and Australian monozygotic and dizygotic twins.[72,73] Sleep problems seem to increase with age and affect more women than men.[5,74] A number of studies report an association between mental disorders such a as depression,[75] anxiety,[71] stress,[75,76] and sleep problems. The direction of the associations is not easily determined, and as insomnia is included as a symptom of depression, a bidirectional association has also been found regarding depression and insomnia.[76]

Sleep problems are also often associated with adverse general health ,[71] cardiovascular disease, lung disorders, infectious diseases, gastrointestinal disorders including GERD, disorders associated with chronic pain such as fibromyalgia or back pain.[75,77] An increased risk of sickness absence, both all cause and due to mental diagnoses, have also been seen in patients with at least one admission or visit to inpatient or specialist outpatient care with an insomnia diagnosis.[78] Tobacco smoking and excessive alcohol consumption are associated with sleep problems,[5,75] while some studies have found an association between sleep problems and obesity and others not.[71,75]

2.3.3.2 Obstructive sleep apnea

Familial aggregation has also been seen in OSA but it has generally been believed that there are factors involved in the pathophysiology of OSA that are responsible for the aggregation.[79] Obesity, male gender, higher age and certain cranial malformations are risk factors for OSA,[80 81-83] and OSA has also been associated with cardiovascular disease, hypertension, stroke, and GERD.[66] As sleep quality usually decreases in people with OSA, non-qualitative sleep and daytime sleepiness are also strongly linked to the disorder.

2.3.3.3 Treatment

The standard treatment for insomnia and persistent insomnia symptoms are medication, cognitive behavioral therapy (CBT) and general sleep advice from a primary physician. The most commonly used sleep medication in Sweden is non-benzodiazepine hypnotics, such as zolpidem and zopiclon.[84]

The standard management of OSA is treatment with continuous positive airway pressure (CPAP) during sleep, which prevents the airways from collapsing or being blocked.[85] The standard CPAP consists of a mask that covers the nose and mouth that is connected to a small machine that continuously blows in air. As OSA is also strongly associated with cardiovascular disease it has been suggested that untreated OSA may contribute to high costs for society for these patients due to a higher demand for health care ensuing.[86]

2.4 SLEEP PROBLEMS AND GERD

In a number of studies, an association between sleep problems and GERD or GERS has been noted.[6,87] These are both population-based epidemiological studies[88,89] and in-hospital or open clinic patient studies of patients with sleep problems, and GERD patients. [90] In clinical trials, treatment with reflux medication have been noted to also decrease sleep problems.[91,92]

There are several physiological gastrointestinal differences between being asleep and being awake, including delayed gastric emptying, decreased TLESR, decreased basal LES pressure, and decreased primary and secondary esophageal peristalsis during sleep.[87] Indications for sleep problems causing or aggregating GERD include findings of sleep deprivation leading to esophageal hyperalgesia, i.e. patients with GERD are more pain sensitive to their reflux symptoms when deprived of sleep.[93] Sleep medication has also been proposed as a factor for provoking GERD by causing LES relaxations.[94] Reflux events, on the other hand, are

assumed to cause more arousals, both conscious and unconscious, compared with individuals without GERD,[90] and arousals from sleep lead to impaired sleep quality.

Regarding OSA and GERD, an improvement in GERD after treatment with continuous positive airway pressure (the standard treatment for OSA) has been noted,[95] although the results are conflicting.[96,97] It has been suggested that OSA increases nocturnal GERD by lowering the pressure of the lower esophageal sphincter.[6] Increased GERD could in turn lead to increased risk of Barrett´s esophagus.

3 AIMS

The overall aim of this thesis is to increase the knowledge of the etiology and consequences of GERD, and focus on the association between sleep problems and GERD.

Specific aims

- To provide a valid measure of changes in the prevalence with calendar time, incidence and spontaneous loss of GERD, in a large population-based study.

- To clarify the relation between sleep problems and GERD while adjusting for hereditary factors in a large population-based twin study.

- To assess the association between sleep apnea symptoms and Barrett's esophagus.

- To address the direction of the association between GERS and sleep problems by performing a large, prospective, and longitudinal cohort study.

4 MATERIAL AND METHODS

Table 1. An overview of the design and methods of the four studies included in the thesis

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Design	Population-based cohort study	Population-based cross-sectional nested case-control twin study	Population-based case-control study	Population-based cohort study
Data source, country	HUNT and NorPD, Norway	The Swedish Twin Registry, Sweden	SDH and BOMS, Australia	HUNT, Norway
Collection years	1995-1997, 2006-2009	1998-2002	2003-2006, 2007-2009	1995-1997, 2006-2009
Study exposure	Age and sex	Sleep problems	Symptoms of obstructive sleep apnea and daytime sleepiness	Sleep problems, insomnia symptoms and gastroesophageal reflux symptoms
Outcome	Incidence, prevalence and loss of gastroesophageal reflux	Frequent gastroesophageal reflux	Barrett´s esophagus	Sleep problems, insomnia symptoms and gastroesophageal reflux symptoms
Statistical analysis	Proportions and unconditional logistic regression	Unconditional and conditional logistic regression	Unconditional logistic regression	Unconditional logistical regression
Estimate	% and Odds ratio	Odds ratio	Odds ratio	Odds ratio
Matching criteria	-	Co-twin and reflux status	Age and sex	-
Confounders	-	Age, sex, education, BMI, and tobacco smoking	Age, sex, BMI and gastroesophageal reflux symptoms	Age, sex, BMI, tobacco smoking and education

4.1 MATERIAL

4.1.1 The Nord-Trøndelag Health Study

The Nord-Trøndelag Health Study (HUNT) is a large longitudinal population-based collection of data, consisting of three public health surveys conducted in the county of Nord-Trøndelag, Norway. HUNT1 data were collected in 1984-1986, HUNT2 in 1995-1997 and HUNT3 in 2006-2008. All residents aged 20 years or older (or if they turned 20 that year) were invited to answer questionnaires regarding self-reported health, quality of life and diseases. Participants were also invited to attend screening stations, where anthropometric measures such as height and weight, blood pressure and heart rate were measured.[98] In 2009,

a condensed questionnaire called MINI-Q was sent out to non-participants in HUNT3. Data from HUNT2 and HUNT3 and MINI-Q were used in study I and IV. HUNT1 does not include questions regarding GERS and therefore could not be included.
For HUNT2, 93,898 residents were invited and 65,237 (69%) participated. For HUNT3, 93,860 residents were invited and 50,807 (54%) participated.[98] The MINI-Q was sent out to 45,000 of the non-participants in HUNT3 and 7,591 (17%) responded.

4.1.2 The Norwegian Prescription Database

The Norwegian Prescription Database (NorPD) includes data on all drugs dispensed by prescription in Norway since the 1 January 2004. All Norwegian pharmacies are required by law to report all sold prescribed medications. Drugs sold over the counter without prescription are not covered by the database. NorPD includes information about dosage, package size and number of packages sold for each prescription. The database also includes the national identity number which is assigned to all Norwegian residents, of the recipient of the drug prescription. The national identity number made it possible to link the NorDP to the HUNT database. Information on use of the reflux medications with PPI and H2RA were used in study I.

4.1.3 The Swedish Twin Register

The Swedish Twin Register was established in the late 1950s to measure the effect of tobacco smoking and alcohol consumption on cardiovascular disease and cancer while controlling for genetic liability of disease.[99] The register includes more than 170,000 twins and approximately 85,000 complete twin pairs, and includes, in principle, all twins born in Sweden since 1886. Briefly, the register can be divided into three cohorts: the old cohort with twins born 1886-1925, the middle cohort with twins born 1926-1958, and the young cohort with twins born 1959 and later. Data on the old cohort were collected with postal questionnaires in 1961, 1963, 1967 and 1970 and included questions regarding smoking, alcohol consumption, diet, stress and selected diseases. The middle cohort were contacted by postal questionnaires in1972-1973 which included similar questions as for the older cohort, but also included questions on personality traits and more demographic environmental questions including exposure to pollution.[99]

In 1998-2002 all twins from the old and middle cohorts were contacted again and asked to participate in the Screening Across the Lifespan Twin Study (SALT); a comprehensive study on health, disorders, diseases, family situation and socioeconomic factors. The study was conducted with computer assisted structured phone interviews and a total of 45,800 twins responded with a response rate of 65% for the old cohort and 74% for the middle cohort.[100] In study II we used twins from SALT to study the association of sleep problems and GERD.

4.1.4 The Study of Digestive Health and Barrett´s Oesophagus Metabolic Study

Study III uses data from the Barrett´s Oesophagus Metabolic Study (BOMS), which is nested within the study of digestive health (SDH), and cases of Barrett's esophagus and population controls are defined in SDH. The SDH is a population-based case-control study that included newly diagnosed cases of Barrett's esophagus aged 18-79 years in Brisbane, Australia from February 2003 to June 2006.[101] The aim of the data collection was to identify environmental and genetic determinants of Barrett's esophagus. Information about new cases was attained from the two major private pathology laboratories and the single public pathology laboratory. All patients were contacted and gave their written permission before information was released to the researchers. In total, 1,714 patients were diagnosed with Barrett´s esophagus by the laboratories. Of those, 410 (24%) did not respond, 200 (12%) declined participation and 1,096 (64%) agreed to be contacted by the study investigators. Of these, 487 patients were excluded due to a previous diagnosis of Barrett's esophagus, and 130 patients did not meet the inclusion criteria, i.e. primary residence out of the study area, too ill, did not speak English or unwilling to give a blood sample, and were excluded. An additional criterion for inclusion, to ensure that the index biopsy came from the tubular esophagus, was that the pathology report, the pathology request form and endoscopy report relating to the index biopsy were reviewed by two investigators. An additional 86 patients were excluded because they had only intestinal metaplasia of the gastroesophageal junction. After exclusions, 393 patients met the inclusion criteria and were included in the study. The population controls from the same geographical region were randomly selected from the Australian Electoral Roll (enrolment is compulsory by law in Australia) and matched to the cases by age (in five year age groups) and sex. Out of the 1,554 potentially eligible controls, 748 accepted the invitation (48% of all the potential controls selected from the election roll and 67% of those able to be contacted) and 646 of those returned a completed questionnaire. The data were collected through structured self-completion questionnaires and by standard telephone interviews by trained nurses. The data included information on height, weight, current and historical gastroesophageal reflux status, medication use, smoking and alcohol intake.[101]

Since BOMS was nested within the SDH study and the same cases and controls which were enrolled in the SDH study were invited to take part in this anthropometric study. The data were gathered between 2007 and 2009 and patients and controls were contacted via letters and telephone calls. Of the 359 patients from SDH who were approached, 237 (66%) completed the study, 69 (19%) declined to participate and 53(15%) were found to be ineligible. Out of the 419 age- (5-year groups) and sex-matched population controls, 247 (59%) completed the study, 108 (26%) declined to participate and 64 (15%) were found to be ineligible. Participants from SDH were ineligible for BOMS if they had developed esophageal adenocarcinoma since SDH, died, become too ill or mentally incompetent, had moved out of the study area, or were uncontactable. The data were collected through self-completed questionnaires, followed by a standardized interview by a trained research nurse who also used anthropometric measures. The questionnaire included questions regarding

general health, tobacco smoking habits, sleep apnea symptoms, and the Epworth sleepiness scale. Information regarding gastroesophageal reflux symptoms, medications and previous endoscopies were attained during the interview. The anthropometric measures were collected using a standardized protocol and consisted of height, weight, waist circumference, hip circumference, neck circumference and sagittal abdominal diameter.[59]

4.2 MEASURES

4.2.1 Assessment of gastroesophageal reflux

According to the Montreal definition, a GERD diagnosis can be given without endoscopy or pH measurement.[9] In all four studies GERS/GERD was self-assessed, i.e. the participants answered a questionnaire or participated in an interview either face-to-face or by telephone.

In studies I and IV (HUNT study), GERS was assessed with the question "To what degree have you had heartburn or acid regurgitation during the previous 12 months?" The response alternatives were "no complaints", "minor complaints" or "severe complaints". Participants answering "minor complaints" or "severe complaints" were categorized as having *any* GERS, and those who reported "severe complaints" were categorized as having *severe* GERS. The same reflux question was used in HUNT2, HUNT3 and Mini-Q and has been validated in a previous study from our group.[34]

In study I the question "If you have had heartburn or acid regurgitation during the previous 12 months, how often do you have complaints?", which was asked only in Mini-Q, was also used. The response alternatives for this question were "daily", "weekly" or "less frequent". If a participant had answered "daily" or "weekly" it was categorized as having "*at least weekly GERS"*. This question had also been used in the previously mentioned validation study of HUNT2 data. That validation study found that 95% of participants reporting severe GERS at HUNT2 reported more than weekly symptoms or reported daily anti-reflux medication use, and 25% of those who reported minor symptoms in HUNT2 also reported more than weekly symptoms or daily medication use.[34] These numbers were used as weights to estimate more than weekly symptoms in HUNT2 and the corresponding numbers from Mini-Q were used as weights to estimate more than weekly symptoms in HUNT3.

In study II we used a battery of 10 validated questions to assess GERD. The participants were asked they had heartburn, pain behind the breastbone, or regurgitation of bitter fluid or acidic fluids into the mouth. If a positive response was given to any of these questions, seven additional questions were asked regarding duration and frequency of symptoms, radiation of pain towards the neck, antacid relief, and use of histamine-receptor antagonists or proton pump inhibitors. GERD was defined by at least weekly occurrence of pain behind the breast bone, regurgitation of bitter or acidic fluids, or heartburn. Participants who reported having pain behind the breast bone 1-3 times a month in combination with i) waking up at night due

to the pain, ii) use of medications to prevent the pain, iii) pain radiating towards the neck, or iv) antacids not reducing the pain, were also classified as having GERD.

In study III GERD was used as a potential confounding factor and the participants were asked "Have you ever had acid reflux (not including acid reflux during pregnancy)?" If the participant answered "yes" he/she was asked "Thinking about the time when your acid reflux happened most frequently, how often did you have it?" Symptoms were then categorized as "at least weekly symptoms" or "less than weekly symptoms". People with no GERS were categorized into the group "less than weekly symptoms".

4.2.2 Assessment of Barrett´s esophagus

Barrett's esophagus was assessed only in study III by analyzing the presence of intestinal metaplasia (columnar epithelium with goblet cells) in biopsies taken from the esophagus by upper gastrointestinal endoscopy. An additional criterion for receiving the Barrett´s diagnosis and to ensure that the index biopsy came from the tubular esophagus, was that the pathology report, the pathology request form and endoscopy report relating to the index biopsy was reviewed by two investigators.

4.2.3 Assessment of sleep problems, insomnia symptoms and symptoms of obstructive sleep apnea

Sleep problems were assessed in studies II and IV, insomnia symptoms in study IV and symptoms of obstructive sleep apnea in study III.

In study II, sleep problems were assessed with three questions from the Karolinska sleep questionnaire.[102,103] Participants were asked how often during the last six months they had experienced feeling "not rested when waking up", "disturbed sleep" and "waking up too early and not able to go back to sleep". Each item had 5 response alternatives and the responses "never" and "seldom" were categorized as "seldom", "sometimes" was kept and "mostly" and "always" grouped together as "often". An insomnia index was also constructed based on the responses of the 3 items, and 0 points were given for "seldom", 1 point for "sometimes" and 2 points for "often". The scores were summed and a score of 4-6 points or a response of "often" was classified as "often having sleep problems", 1-3 points as "sometimes having sleep problems" and 0 points as "seldom having sleep problems".

In study III, symptoms of OSA were measured by daytime sleepiness and with a sleep apnea symptom index. The Epworth Sleepiness Scale (ESS), which consists of 8 items which measures the participants' likelihood to "doze off" in different everyday situations, was used to measure daytime sleepiness. Each item had 4 response alternatives: "would never doze", "slight chance of dozing", "moderate chance of dozing", and "high chance of dozing". Scores for each item were given; 0 for never, up to 3 for "high chance of dozing" and when added together a score of 10 or higher was defined as having excessive daytime sleepiness. The scale has been constructed as a proxy for OSA with which it has been shown to correlate

well.[104] Symptoms of sleep apnea were assessed with a sleep apnea symptom index, which consists of 3 questions. Participants were asked how often during the last month they had (or had been told they have) the sleep related symptoms: "snorting or gasping", "load snoring" and "breathing stops, choking or struggle for breath". For each item the participant could answer "never", "rarely, "less than once a week", "1-2 times a week", "3-4 times a week", "5-7 times a week" or "don´t know" and the answers were coded as 0-4, with the answer "don´t know" set to missing. The items where then summarized and the mean values calculated. A mean score of <1 was defined as "never" having sleep apnea symptoms, 1-<2 as "rarely" having sleep apnea symptoms and 2 or higher as "often" having sleep apnea symptoms.

In study IV, *sleep problems* were assessed with the question "Have you had difficulty falling asleep during the last month?" in HUNT2, with response alternatives "almost every night", "often", "now and again", or "never". The answers "almost every night" or "often" were classified as having sleep problems. In HUNT3/Mini-Q sleep problems were assessed with a similar question: "How often during the last 3 months have you had difficulty falling asleep at night?", with response alternatives "never/seldom", "sometimes", or "several times a week". Participants who answered "several times a week" were classified as having sleep problems. *Insomnia symptoms* were assessed with 3 questions in HUNT2: "Have you had difficulty falling asleep during the last month?", "During the last month, have you woken too early and not been able to go get back to sleep?" and "During the last year, have you been troubled by insomnia to such a degree that it affected your work?". A participant was defined as suffering from insomnia symptoms if responding "almost every night" or "often" to initiating or maintaining sleep, in combination with experiencing impaired work performance due to insomnia during the last year. In HUNT3, insomnia symptoms were assessed by the questions: "How often during the last 3 months have you had difficulty falling asleep at night?", "How often during the last 3 months have you woken up too early and couldn´t go back to sleep?", and "How often during the last 3 months have you felt sleepy during the day?". If a participant answered "several times a week" on initiating or maintaining sleep, and "feeling sleepy during the day" that participant was considered as suffering from insomnia symptoms. Since there was no question to assess any influence of sleep disturbance on daily life in Mini-Q, the assessment of insomnia symptoms was restricted to HUNT2 and HUNT3.

4.2.4 Assessment of zygosity

To assess zygosity in the twin pairs in study II, each twin independently answered the question: "During childhood, were you and your twin partner as alike as 'two peas in a pod' or 'not more alike than siblings in general?' If both twins in the pair answered that they were "alike as two peas in a pod" they were classified as monozygotic (MZ), and if both answered that they "were not more alike than siblings" they were classified as dizygotic (DZ). If the twins answered differently they were categorized as "not determined". This method of determining zygosity has been shown to be 98% accurate compared to DNA-testing.[99]

4.2.5 Assessment of additional potential confounders

All studies controlled for potential confounding by age and sex. In studies II, III and IV we also assessed obesity, tobacco smoking and education in the main analyses while we used obesity and GERS in study III. Obesity was measured by body mass index (BMI), the weight in kilograms divided by the square of the height (kg/m^2). BMI was analyzed in categories; BMI <25 was classified as normal weight, BMI 25-29.9 as overweight and BMI ≥30.0 as obese, all according to the WHO classification. WHO does further distinguish between underweight (BMI<18.5) and normal weight (BMI 18.5-24.9) but these categories were collapsed and labelled "normal weight" in these studies. Height and weight were measures by trained personnel in study III and study IV (HUNT2 and HUNT3) and self–reported in study II and study IV (Mini-Q). Tobacco smoking was self-assessed and smoking habits categorized as "current smoker", "previous smoker", or "never smoker", in all three studies. Education was used as a proxy for socio-economic status in all three studies, and number of years of education grouped in three categories (0-9, 9-12, >12) in study II and two in study IV (≤12, < 12). In study III, highest type of education was used instead (divided into high school, tech/trade collage, or university). In study III we also assessed neck circumference which was measured by a trained research nurse. Neck circumference was divided into tertiles [t] with sex specific thresholds from the population controls (males t1: 0-39.05, t2 39.05-41.40, or t3: >41.40; females t1: 0-33.45, t2: 33.45-35.55, or t3: >35.55).

4.3 METHODS

4.3.1 Study I

4.3.1.1 Design

A population-based cohort study including residents of at least 20 years of age in the county of Nord-Trøndelag, who reported GERS status in the health surveys HUNT2 (1995-1997) and HUNT3/Mini-Q (2006-2009).

4.3.1.2 Statistical analysis

Prevalence of GERS was calculated as the proportion of persons in HUNT2 and HUNT3/Mini-Q who reported any (minor or severe) GERS or severe GERS, respectively. Prevalence of at least weekly GERS was calculated by multiplying the proportions from the validation study in HUNT2[34] with severe and minor GERS in HUNT2, and by proportions from Mini-Q in HUNT3.

The cumulative incidence of GERS was calculated from participants who reported no GERS in HUNT2 and then reported any or severe GERS in HUNT3/Mini-Q. The spontaneous cumulative loss of GERS was calculated from participants who reported any or severe GERS in HUNT2 and later reported no GERS at HUNT3/Mini-Q. In order to measure only spontaneous loss of GERS, participants using prescribed reflux medications at least weekly were excluded. Information on medication usage was obtained from the NorPD and matched to the participants by their national identity number. Average annual cumulative incidence

(average annual percentage change) were calculated by the formula (exp (cumulative proportion)-1)/11 years. The same formulae were used to calculate annual cumulative spontaneous loss of GERS. We also stratified the incidence, prevalence and spontaneous loss of GERS by age (<40, 40-49, 50-59, 60-69, and ≥70 years) and sex, and calculated 95% confidence intervals.

To measure differences in incidence and spontaneous loss of GERS between age groups in men and women, we calculated odds ratios (OR) with logistic regression. An interaction term was included in the model to measure the joint age and sex effect. The statistical analyses where performed with the software Stata/IC 11.1 for Windows by StataCorp LP.

4.3.2 Study II

4.3.2.1 Design

A population-based cross-sectional nested case-control twin design including twins 65 years of age or older who had answered GERD and sleep problem items in the Screening across the lifespan in study, in the Swedish Twin Registry.

4.3.2.2 Statistical analysis

The co-twin control method was used to adjust for genetic and early environmental factors between sleep problems and GERD and the analyses were performed in three steps. First, the association between sleep problems and GERD was analyzed with unconditional logistic regression using the whole cohort in the analyses. Because of the within-pair dependency, the cohort included both pairs and single twins, so generalized estimated estimations (GEE) models were used in order to avoid underestimation of the variance. In the second step, within-pair co-twin analyses with dizygotic (DZ) twins only were performed with conditional logistic regression. Only complete twin pairs discordant for GERD (one twin had GERD the other not), were included in this analysis. In the third step, within-pair co-twin analyses with monozygotic (MZ) twins discordant for GERD were analyzed with conditional logistic regression. In all analyses crude models and models which adjusted for education level, BMI and tobacco smoking were calculated. In the models including the whole cohort we also adjusted for age and sex. By including twin pairs discordant for the outcome, and comparing estimates from full-cohort analyses with estimates discordant DZ twins and MZ twins, it is possible to adjust for genetic and early environmental factors. This is due to the fact that MZ twins share 100% of their genes and DZ twins on average 50% of their genes. If an association is found in the external analysis, the analysis with the whole cohort, and the association disappears for the within-pair analyses for both DZ and MZ twins, there is an indication of confounding by early environmental factors. This is because twins usually share the environment in the uterus and are also usually brought up together and this factor does not vary between DZ and MZ twins. If the association instead is seen in the within-pair analysis for DZ twins but disappears for MZ twins there this indicates genetic confounding. Intraclass correlations (correlations within GERD and sleep problems separately) and twin cross-trait correlations (correlations between GERD and sleep problem items) were estimated to further

study the influence of genes. Polychoric correlations were used for these analyses. In a sub-analysis of participants reporting pain behind the breastbone or heartburn, we analyzed if participants reported nocturnal symptoms suffered more often from sleep problems, using Pearson's chi squared test. SAS software 9.2 (SAS Institute, Cary, NC) was used for all analyses.

4.3.3 Study III

4.3.3.1 Design

A population-based case-control study, including histologically confirmed cases of Barrett´s esophagus and matched population controls from Brisbane, Australia.

4.3.3.2 Statistical analysis

In this study, baseline characteristics of Barrett´s esophagus and population controls were first compared. These characteristics included sex, age, BMI, tobacco smoking, education, GERS and neck circumference. Pearson's chi-square test was used to evaluate potential differences between cases and controls. In a second step we studied the same baseline characteristics among population controls only, and compared participants with and without excessive daytime sleepiness, and participants with different frequencies of sleep apnea symptoms. Finally, we used unconditional logistic regression and estimated OR and 95% confidence intervals (95% CI) for associations between excessive daytime sleepiness, sleep apnea symptoms and Barrett's esophagus. The main exposures excessive daytime sleepiness and sleep apnea symptoms were analyzed separately in three models: 1) adjusted for age and sex only 2) adjusted for age, sex and BMI, and 3) adjusted for age, sex, BMI and GERS. Tobacco smoking and education seemed to be associated with Barrett´s esophagus (from the descriptive analyses) but not with excessive daytime sleepiness and were therefore not included in the adjusted models. Statistical analyses were performed with software SAS version 9.2 (SAS institute, Cary, NC).

4.3.4 Study IV

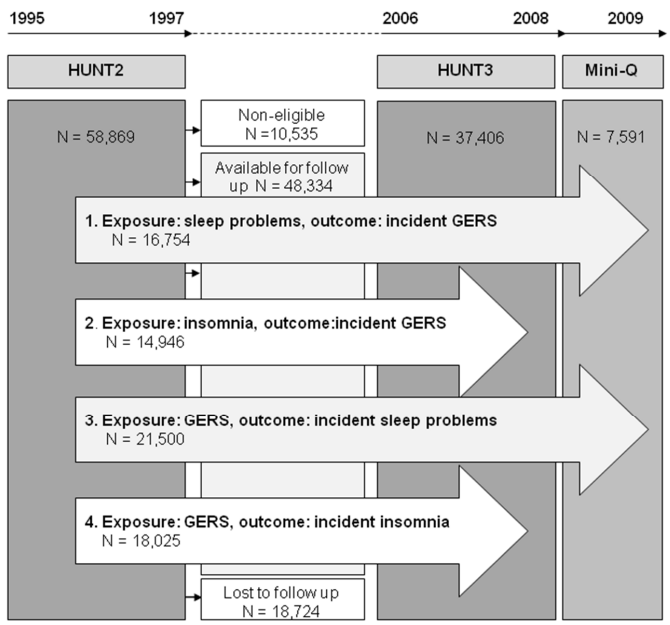
4.3.4.1 Design

A longitudinal population-based cohort study (the HUNT study) conducted in Nord-Trøndelag county, Norway, including HUNT2 (1995-1997) and HUNT3/Mini-Q (2006-2009).

4.3.4.2 Statistical analysis

In the analyses we assessed two levels of GERS, any GERS and severe GERS, and two levels of sleep problems, general sleep problems and insomnia symptoms. As the questions used to assess insomnia symptoms were not included in Mini-Q, analyses of insomnia symptoms either as outcome or exposure, were restricted to HUNT2 and HUNT3. Thus, the analyses were conducted in 4 cohorts (see flowchart below).

Figure 1. Flowchart over the participants in HUNT2, HUNT3 and Mini-Q and the four study sub-cohorts. Cohort 1 measured the cumulative incidence of *any* and *severe* gastroesophageal reflux symptoms (GERS) in HUNT3/Mini-Q among participants without GERS in HUNT2 with sleep problems as exposure. Cohort 2 measured the cumulative incidence of *any* and *severe* GERS in HUNT3 among participants without GERS in HUNT2 and with insomnia symptoms as exposure. Cohort 3 measured the cumulative incidence of sleep problems in HUNT3/Mini-Q among participants without sleep problems in HUNT2 with were *any* and *severe* GERS as exposures. Cohort 4 measured the cumulative incidence of insomnia symptoms in HUNT3 among participants without insomnia symptoms in HUNT2 with *any* and *severe* GERS as exposures.



The four sub-cohorts were analyzed separately. Analyzes were performed with unconditional logistic regression and OR and 95% CI were calculated. The main exposures (sleep problems, insomnia symptoms, *any* GERS and *severe* GERS) were all categorized in the same way: 1) no exposure, 2) exposure in HUNT2, but not in HUNT3/Mini-Q, 3) exposure in HUNT3/Mini-Q, but not in HUNT2, and 4) exposure in both HUNT2 and HUNT3/Mini-Q. In this way we wished to see if prolonged exposure to GERS or sleep problem/insomnia symptoms would lead to increased GERS or sleep problems/insomnia symptoms.

In the multivariable analyses we adjusted for sex, age (< 40, 40-49, 50-59, 60-69, or ≥70 years), BMI (categorized according to WHO classification <25 normal or low weight, 25-30 overweight, or ≥30 obesity), cigarette smoking status (current smoker, previous smoker, or never smoker), and educational level (≤12 years or >12 years). SAS software 9.2 (SAS Institute, Cary, NC) was used for all analyses.

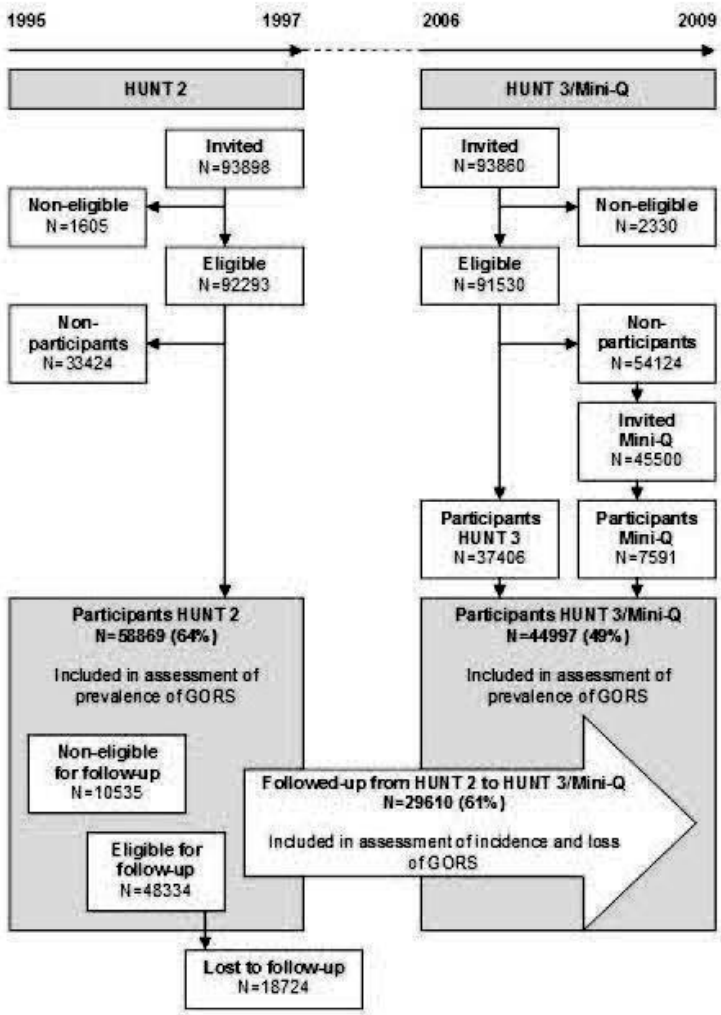
5 RESULTS

5.1 STUDY I

5.1.1 Population and Characteristics

GERS status was reported by 58,869 (64% of the eligible) in HUNT2 and by 44,997 (49%) in HUNT3/MINI-Q. Between HUNT2 and HUNT3/MINI-Q, 10,535 participants either died or moved out of the county and 18,724 choose not to participate, leaving 29,610 who reported GERS-status and answered both HUNT2 and HUNT3/MINI-Q (see the flowchart on the page below).

Figure 2. Flowchart of patients reporting gastroesophageal reflux symptoms (GERS) in HUNT2 and HUNT3/Mini-Q with the number of individuals (N) at each stage and response rates. Response rates were calculated from those eligible, excluding those who had died or were no longer resident in the county (non-eligible). Published in GUT (2012) Oct;61(10):1390-7



5.1.2 Prevalence

Between the surveys in 1995-1997 and 2006-2009, the prevalence of any GERS increased by 30%, from 31.4% to 40.9% and the prevalence of severe GERS increased by 24%, from 5.4% to 6.7%. The estimated prevalence of weekly GERS increased by 47%, from 11.6% to 17.1% (Table 2).

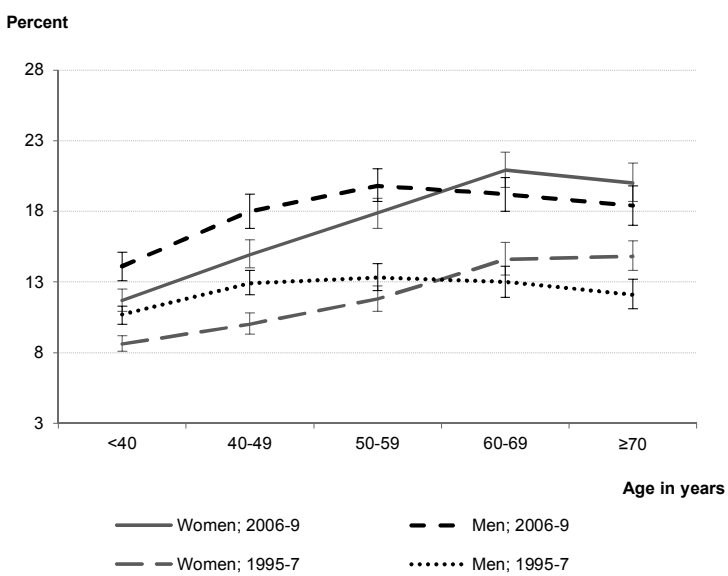
The prevalence of GERS increased for both sexes and all age groups, but for severe GERS the prevalence increased mainly among those in the middle age group (data not shown). The estimated prevalence of at least weekly GERS also increased for all age groups and the largest relative change were seen middle-aged women men above 70 years of age (Figure 3).

Table 2 An overview of the prevalence of any, severe and at least weekly gastroesophageal reflux symptoms (GERS). [1] A complete table can be seen in study I.

	HUNT 2 1996-1997 n = 58869		HUNT3/ Mini-Q 2006-2009 n = 44997		Relative change[2]
Prevalence any GERS[1]	n GERS	%	n GERS	%	%
Total	18460	31.4	18389	40.9	30.3
Women	9104	29.7	9526	38.8	30.5
Men	9356	33.1	8860	43.3	30.9
Prevalence severe GERS					
Total	3167	5.4	2994	6.7	23.7
Women	1603	5.2	1629	6.6	26.7
Men	1564	5.5	1364	6.7	20.6
Prevalence weekly GERS					
Total	6835	11.6	7692	17.1	47.2
Women	3400	11.1	4036	16.4	48.0
Men	3435	12.2	3654	17.9	47.1

[1] *Any* GERS : minor plus severe complaints with heartburn and acid regurgitation. *Severe* GERS: severe complaints only. *Weekly* GERS: at least weekly complaints of heartburn and acid regurgitation.
[2] Relative prevalence change: (prevalence HUNT3/Mini-Q - prevalence HUNT2)/ prevalence HUNT2.

Figure 3 Prevalence of estimated at least weekly GORS for each sex and age groups in 1995-1997 (HUNT2) and 2006-2009 (HUNT3/Mini-Q with 95% CI (vertical lines)



5.1.3 Incidence

During the average 11 years of follow-up from 1995-1997 to 2006-2009, the cumulative incidence of any GERS was 29.1%, which corresponded to an average annual incidence of 3.07%. The cumulative incidence of severe GERS was 2.5% and slightly higher among women (2.8%) than in men (2.1%) (Table 3). The corresponding annual incidence of severe GERS was 0.23%.

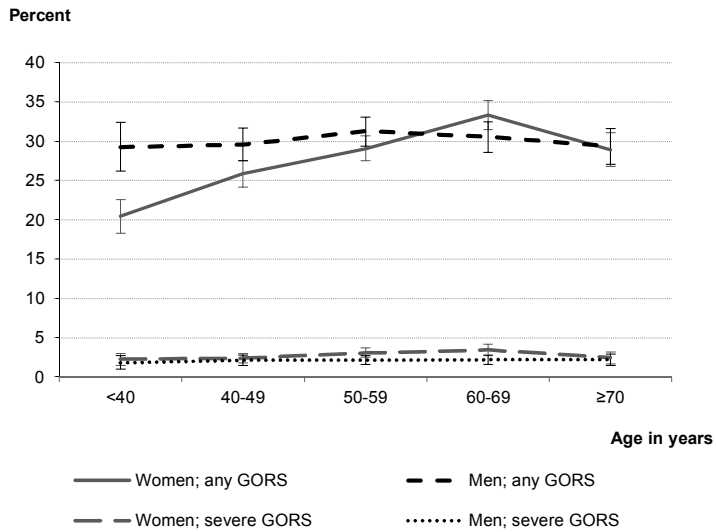
Table 3 Overview of the cumulative incidence and spontaneous loss of gastroesophageal reflux symptoms (GERS).[1] Complete tables can be seen in the appendix in study I.

Cumulative incidence of *any* GERS			**Cumulative spontaneous loss of *any* GERS**		
Incidence any GERS	Number	%		Number	%
Total	5904	29.1	Total	2112	22.7
Women	3209	28.2	Women	1118	23.9
Men	2695	30.2	Men	994	21.5
Cumulative incidence of *severe* GERS			**Cumulative spontaneous loss of *severe* GERS**		
Total	510	2.5	Total	195	12.6
Women	319	2.8	Women	93	11.7
Men	191	2.1	Men	102	13.5

[1]The cumulative incidence was calculated from those with no GERS at HUNT2 (n=2033) and spontaneous loss of any GERS from those with any GERS at HUNT2 (n= 9,299) and spontaneous loss of severe GERS from those with severe GERS at HUNT2 (n= 1,553). Participants using anti-reflux medication at least weekly were excluded.

Women at the age 60-69 had the highest incidence of any GERS (33.3%), while the lowest incidence of any GERS was seen in women below the age of 40 (20.5%). In men the cumulative incidences of any GERS were similar over all age categories (29.3%- 31.3%). The cumulative incidence of severe GERS were similar between age groups but slightly in women 50-69 years of age (Figure 4).

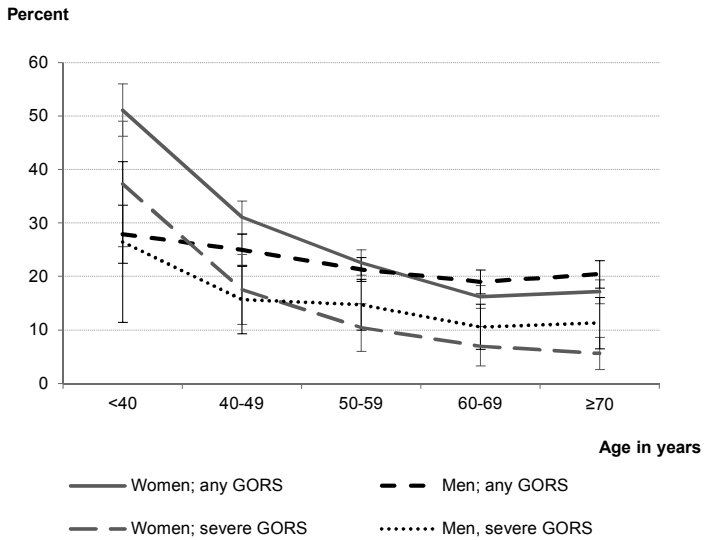
Figure 4. Cumulative incidence of any and severe GERS for each sex and age group (age at follow-up) between 1995-1997 and 2006-2009 (HUNT3/Mini-Q) with 95% CI (vertical lines).



5.1.4 Spontaneous loss of GERS

The cumulative loss of any GERS during the study period was 22.7%, when excluding the 286 participants (12%) using antireflux medication at least weekly. This corresponded to an average annual spontaneous loss of 2.32%. The cumulative loss of severe GERS was 12.6% when excluding the 89 participants (31%) using antireflux medication at least weekly (Table 3). This corresponded to an average annual spontaneous loss of 1.22%.The spontaneous loss decreased with increasing age for both sexes, but this was particularly evident among women (Figure 5).

Figure 5 Cumulative spontaneous loss of any and severe GORS for each sex and age groups (age at –follow-up) between 1995-1997 (HUNT2) and 2006-2009 (HUNT3/Mini-Q with 95% CI (vertical lines).



5.2 STUDY II

5.2.1 Study participants

Of the 8,951 twins that were eligible for inclusion in this study, we excluded 937 (10%) due to missing information about GERD. Of the twins included in the descriptive analysis, 1,327 (17%) had GERD. Participants with GERD were to a greater extent overweight (42%) and obese (9%) than participants without GERD, where 35% were overweight and 7% obese. Previous tobacco smoking was more common among participants with GERD, 36% compared to 31%, while current smoking was as common in both groups, 11% compared to 10%. Of the 7,857 twins included in the final external analyses (157 twins were excluded due to missing information about insomnia), 4,682 twins had a co-twin in the sample (2,341 pairs). Of these, 356 DZ pairs and 210 MZ pairs were discordant for GERD and were used in the within-pair analyses. The age and sex distributions were similar for DZ and MZ twins (Table 4).

Table 4 The distribution of gastroesophageal reflux disease (GERD) in same-sexed dizygotic (DZ) and monozygotic (MZ) twin pairs.

	DZ pairs n (%)	MZ pairs n (%)
Concordant, both twins have GERD	51 (4)	52 (6)
Concordant, neither twin has GERD	1004 (71)	647 (71)
Discordant, one twin has GERD, and not the other	356 (25)	210 (23)
Sex, same-sexed discordant pairs		
Men	137 (38)	80 (38)
Women	231 (61)	130 (62)
Age (in years), discordant pairs		
64-74	259 (73)	149 (71)
≥75	97 (27)	61 (29)

5.2.2 The association between sleep problems and GERD

In the external analyses a dose-dependent association was seen among twins with increasing sleep problems, in all of the sleep problem exposures, and occurrence of GERD (Table 5). Participants who often experienced sleep problems (according to the insomnia index) had a 2-fold increased occurrence of GERD compared with those who seldom experienced sleep problems (OR 2.0; 95% CI 1.8-2.4). Similarly, those who sometimes experienced sleep problems had a 50% increased occurrence compared with those who seldom experienced sleep problems (OR 1.5; 95% CI 1.3-1.7). In the co-twin control analyses with DZ twins, the associations of often having sleep problems compared to seldom having sleep problems remained, while the associations decreased and become non-significant in co-twin analysis with MZ twins. This could be an indication of genetic confounding, but the twin cross-trait correlations between the insomnia index and GERD were low, 0.077 in DZ twin-pairs and 0.043 in MZ twin pairs. If there is a genetic effect, the correlation in MZ pairs should be higher than for DZ pairs and therefore there does not seem to be strong confounding by heredity present. The separate items “not rested when waking up”, “disturbed sleep” and “waking up too early” showed a similar pattern between the external, DZ and MZ analyses as the sleep insomnia index, except for “disturbed sleep” where “sometimes” having disturbed sleep showed higher risk for GERD than “often” among DZ twins (OR 1.9; 95% CI 1.2-1.9 and OR 1.7; 95% CI 1.0 -2.8), and the effect of sometimes having disturbed sleep remained among MZ twins (Table 5). Finally, in a sub-analyses of those reported waking up at night due to pain behind the breastbone or heartburn, 16% “often” had disturbed sleep compared to 11% among those who did not and there was a significant association between nocturnal reflux symptoms and disturbed sleep (χ^2 8.6; p-value 0.01).

Table 5 Associations between sleep problems and gastroesophageal reflux disease (GERD)

		External analysis		Co-twin analysis DZ twins		Co-twin analysis MZ twins	
		n = 7,857		n = 365 pairs		n= 210 pairs	
Exposure	**GERD**[a]	adjusted[a]		adjusted[b]		adjusted[b]	
Insomnia index[d]	n (%)	OR	95% CI	OR	95% CI	OR	95% CI
Seldom	456 (35)	1.0	(reference)	1.0	(reference)	1.0	(reference)
Sometimes	438 (34)	1.5	1.3-1.7	1.5	1.0-2.2	1.3	0.8-2.2
Often	403 (31)	2.0	1.8-2.4	2.2	1.5-3.4	1.5	0.9-2.7
Not rested when waking up							
Seldom	842 (65)	1.0	(reference)	1.0	(reference)	1.0	(reference)
Sometimes	261 (20)	1.5	1.3-1.8	1.5	1.0-2.3	1.6	0.9-2.8
Often	197 (15)	1.7	1.5-2.1	2.1	1.3-3.3	1.9	0.9-3.9
Disturbed sleep							
Seldom	872(67)	1.0	(reference)	1.0	(reference)	1.0	(reference)
Sometimes	269 (21)	1.7	1.4-1.9	1.9	1.2-2.9	1.9	1.0-3.6
Often	162 (12)	2.0	1.6-2.4	1.7	1.0-2.8	1.4	0.7-3.1
Waking up too early							
Seldom	709 (54)	1.0	(reference)	1.0	(reference)	1.0	(reference)
Sometimes	357 (27)	1.3	1.1-1.5	1.1	0.7-1.6	1.5	0.9-2.4
Often	240 (18)	1.9	1.6-2.3	1.7	1.1-2.7	1.5	0.8-2.9

OR, odds ratio; CI, confidence interval; MZ, monozygotic; DZ, dizygotic;

[a]The different numbers of GERD cases for the four sleep exposures are due to different numbers of missing observations in the sleep questions.

[b]ORs adjusted for age, sex, educational level, body mass index, and tobacco smoking.

[c]ORs adjusted for educational level, body mass index, and tobacco smoking. Genetic and early environmental factors, sex and age are adjusted for by the within-pair structure.

5.3 STUDY III

Included in this study were 237 cases of Barrett's esophagus and 247 controls. The characteristics differed regarding obesity (BMI >30) (35% among cases, 23% among controls) neck circumference (44% of cases were in the highest tertile compared with the expected 33% among controls) and smoking habits (14% current and 53% previous smokers among cases versus 9% current smokers and 34% previous smokers among controls). The cases also tended to have lower education (43% had high school as highest education compared with 35% among controls) and a higher proportion of frequent GERS (85% among cases compared with 38% among controls). Of the 247 controls, all answered the Epworth sleepiness scale, while 214 controls reported information about sleep apnea status (the 33 participants who answered "do not know" were set to missing) (Table 6). The distributions of smoking status and education level were similar for those with and without excessive daytime sleepiness. Compared with controls without daytime sleepiness, a higher percentage of

controls with daytime sleepiness had a BMI ≥30 (32% vs. 21%) but otherwise the distribution of BMI was fairly similar between groups. At least weekly GERS was more common among participants with daytime sleepiness (57% vs. 34%). In a multivariable model including at least weekly GERS, BMI, tobacco smoking and education, a more than 2-fold increased occurrence of excessive daytime sleepiness was seen among participants with at least weekly GERS compared to participants with less than at least weekly GERS (OR 2.60; 95% CI 1.28-5.30).

The distribution of smoking and education were similar regardless of frequency of sleep apnea symptoms, while a higher percentage of controls with frequent sleep apnea symptoms had a BMI ≥30 (50%), compared with those who never had sleep apnea symptoms (14%). Large neck circumference was more common among those who "often" had sleep apnea symptoms (64%) compared with those who "never" had (22%) (Table 6). In a multivariable model controls with at least weekly GERS had a 3-fold increased occurrence of high level of sleep apnea symptoms compared to those with less than weekly GERS (OR 3.08; 95% CI 1.69-5.62), after adjusting for BMI, tobacco smoking and education.

Table 6 Characteristics for excessive daytime sleepiness and sleep apnea symptoms among population controls.

	Excessive daytime sleepiness			Sleep apnea symptoms			
	n = 247			**n = 214**[1]			
	present	**absent**		**never**	**rarely**	**often**	
	n (%)	n (%)	p-value	n (%)	n (%)	n (%)	p-value[2]
Body mass index							
< 25 kg/m2	8 (18)	60 (30)		42 (34)	13 (21)	3 (11)	
25-29.99 kg/m2	22 (50)	100 (49)		65 (52)	31 (51)	11 (39)	
≥ 30 kg/m2	14 (32)	43 (21)	0.1759	18 (14)	17 (28)	14 (50)	0.0005
Neck circumference[3]							
Tertile 1	11 (25)	74 (36)		54 (43)	16 (26)	3 (11)	
Tertile 2	15 (34)	66 (33)		44 (35)	19 (31)	7 (25)	
Tertile 3	18 (41)	63 (31)	0.2892	27 (22)	26 (43)	18 (64)	<.0001
Tobacco smoking							
Never smoker	24 (55)	118 (58)		76 (61)	37 (61)	13 (46)	
Ex-smoker	16 (36)	68 (34)		39 (31)	19 (31)	11 (39)	
Current smoker	4 (9)	17 (8)	0.9094	10 (8)	5 (8)	4 (14)	0.6615
Education							
High school or lower	18 (41	66 (33)		38 (31)	25 (42)	9 (35)	
Tech/trade College	16 (36)	80 (40)		49 (40)	19 (32)	13 (50)	
University studies	10 (23)	53 (27)	0.6153	37 (30)	16 (27)	4 (15)	0.3144
Gastroesophageal reflux symptoms[4]							
< weekly	19 (43)	133 (66)		94 (75)	35 (57)	7 (25)	
≥ weekly	25 (57)	68 (34)	0.0044	31 (25)	26 (43)	21 (75)	<.0001

[1]33 patients were missing information about sleep apnea symptoms as the answer "do not know" is coded as "missing".
[2]Pearson's chi-square test
[3]The cut-offs for neck circumference were tertiles (t): males t1 0-39.05; t2 39.05-41.40, t3 > 41.40, females t1 0-33.45; t2 33.45-35.55; t3 > 35.55
[4]The participants were asked how often they had acid regurgitation or heartburn when the symptoms were most frequent.

In the analyses of excessive daytime sleepiness and occurrence of Barrett's esophagus, a 40% increased occurrence was indicated in the minimally adjusted model, but the association did not reach statistical significance (OR 1.42; 95% CI 0.91-2.21) (Table 7). After adjustment for BMI and GERS the increased point estimate disappeared. A similar pattern was seen for sleep apnea symptoms. An initial non-statistical significant association of 58% among those often having sleep apnea symptoms and occurrence for Barrett's esophagus were noted in the first model (OR 1.58; 95% CI 0.91-2.76), but disappeared after adjusting for BMI and GERS. No association was seen among those who rarely experienced sleep apnea symptoms and Barrett´s esophagus.

Table 7 Excessive daytime sleepiness, sleep apnea symptoms and the risk of Barrett's esophagus measured with odds ratio (OR) and 95% confidence interval (CI).

	Barrett's esophagus cases	Controls	Minimally adjusted model[1]	Partially adjusted model[2]	Fully adjusted model[3]
	n (%)	n (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Excessive daytime sleepiness[4]					
Absent	181 (76)	203 (82)	1 (reference)	1 (reference)	1 (reference)
present	56 (24)	44 (18)	1.42 (0.91-2.21)	1.34(0.85-2.10)	0.99(0.60-1.65)
Sleep apnea symptoms[5]					
Never	107 (55)	125 (58)	1 (reference)	1 (reference)	1 (reference)
Rarely	50 (26)	61 (29)	0.94 (0.60-1.49)	0.86 (0.54-1.37)	0.76 (0.44-1.31)
Often	39 (20)	28 (13)	1.58 (0.91 -2.76)	1.33 (0.75-2.35)	0.74 (0.39-1.40)

[1]Adjusted for age and sex
[2]Adjusted for age, sex and body mass index
[3]Adjusted for age, sex, body mass index and gastroesophageal reflux symptoms
[4]Measured with the Epworth sleepiness scale
[5]Measured with the sleep apnea index

5.4 STUDY IV

5.4.1 Characteristics

The characteristics of the 4 sub-cohorts of study IV are presented in Table 8. The mean age of the participants (measured at HUNT2) was similar in all cohorts, but only slightly lower in cohort 1, with mean 43 years compared to 44 in the other cohorts. More women than men were represented in all cohorts and a higher percentage of participants in cohort 3 and 4 were obese (20% compared to 17% in cohort 1 and 2).

Table 8 Characteristics of the 4 cohorts. Cohort 1 measured the cumulative incidence of *any* and *severe* gastroesophageal reflux symptoms (GERS) in HUNT3/Mini-Q among participants without GERS in HUNT2 with sleep problems as exposure. Cohort 2 measured the cumulative incidence of *any* and *severe* GERS in HUNT3 among participants without GERS in HUNT2 and with insomnia symptoms as exposure. Cohort 3 measured the cumulative incidence of sleep problems in HUNT3/Mini-Q among participants without sleep problems in HUNT2 with were *any* and *severe* GERS as exposures. Cohort 4 measured the cumulative incidence of insomnia symptoms in HUNT3 among participants without insomnia symptoms in HUNT2 with *any* and *severe* GERS as exposures.

	Cohort 1 Cumulative incidence of *any* and *severe* GERS. Exposure sleep problems	Cohort 2 Cumulative incidence of *any* and *severe* GERS. Exposure insomnia symptoms	Cohort 3 Cumulative incidence of sleep problems. Exposure *any* and *severe* GERS	Cohort 4 Cumulative incidence of insomnia symptoms. Exposure *any* and *severe* GERS
All, N (%)	16,754 (100)	14,946 (100)	21,500 (100)	18,025 (100)
Women, N (%)	9,602 (57)	8,649 (58)	11,736 (55)	9,872 (55)
Men, N (%)	7,152 (43)	6,297 (42)	9,764 (45)	8,153 (45)
Age in years[1]				
Mean (SD)	43 (12)	44 (11)	44 (11)	44 (11)
Median (range)	44 (19-67)	44 (19-67)	44 (19-67)	44 (19-67)
Body mass index				
<25, N (%)	4,812 (29)	4,270 (29)	5,469 (26)	4,533 (25)
25-30, N (%)	9,036 (54)	8,110 (54)	11,711 (55)	9,927 (55)
≥30, N (%)	2,794 (17)	2,536 (17)	4,187 (20)	3,536 (20)
Cigarette smoking				
Current, N (%)	2,486 (15)	2,151 (15)	3,309 (16)	2,644 (15)
Previous, N (%)	6,474 (40)	5,763 (40)	8,556 (41)	7,124 (41)
Never, N (%)	7,294 (45)	6,556 (45)	9,002 (43)	7,681 (44)
Education4				
≤12 years, N (%)	11,930 (72)	10,624 (72)	15,716 (74)	13,175 (74)
>12 years, N (%)	4,661 (28)	4,186 (28)	5,573 (26)	4,680 (26)

[1]Age was measured in HUNT2.

5.4.2 Sleep problems and insomnia symptoms as risk factors for developing any and severe GERS

In total, 4,850 participants (29%) developed *any* GERS and 396 (2%) developed *severe* GERS between HUNT2 and HUNT3/Mini-Q.

Any GERS was more common among those with sleep problems in both HUNT2 and HUNT3/Mini-Q compared to those without sleep problems (adjusted OR 1.84; 95% CI 1.48-2.30) and this was true also for those with sleep problems in HUNT2 only (1.51; 95% CI 1.23-1.84) (Table 9). The same pattern was seen for the incidence of *severe* GERS among those with sleep problems at both HUNT2 and HUNT3/Mini-Q compared to those without sleep problems (OR 3.53; 95% CI 2.28-5.48) and for those with sleep problems in HUNT2 only compared to non-exposed (OR 2.06; 95% CI 1.26-3.36).

When the exposure was restricted to insomnia symptoms, slightly stronger associations were seen. The OR of *any* GERS was 2.13 (95% CI 1.45-3.13) among individuals exposed in both HUNT2 and HUNT3, and 1.54 (95% CI 1.25-1.90) among those exposed in HUNT2 only, compared to non-exposed. The corresponding ORs of *severe* GERS were 5.39 (95% CI 2.83-10.26) and 2.43 (95% CI 1.53-3.84), respectively. Since the crude ORs were similar to the adjusted ORs, only the adjusted ORs are shown (Table 9).

Table 9 Exposure to sleep problems and insomnia symptoms and risk of *any* and *severe* gastroesophageal reflux symptoms (GERS). Odds ratios (OR) with 95% confidence intervals (CI) were adjusted for sex, age, body mass index (BMI), tobacco smoking and education[1].

Cohort 1 N= 16,754[2]	**Incidence of any GERS**[3]		**Incidence of severe GERS**[4]	
Exposure to sleep problems[5]	OR	95% CI	OR	95% CI
No sleep problems (reference)	1.00	-	1.00	-
Sleep problems in HUNT2 but not at HUNT3/Mini-Q	1.51	1.23-1.84	2.06	1.26-3.36
Sleep problems at HUNT3 /Mini-q but not in HUNT2	1.46	1.28-1.66	2.14	1.57-2.92
Sleep problems at both HUNT2 and HUNT3/Mini-Q	1.84	1.48-2.30	3.53	2.28-5.48
Cohort 2 N= 14,946[6]	**Incidence of any GERS**[3]		**Incidence of severe GERS**[4]	
Exposure to insomnia[7]	OR	95% CI	OR	95% CI
No insomnia (reference)	1.00	-	1.00	-
Insomnia in HUNT2 but not in HUNT3	1.54	1.25-1.90	2.43	1.53-3.84
Insomnia in HUNT3 but not in HUNT2	1.70	1.40-2.08	2.32	1.48-3.63
Insomnia at both HUNT2 and HUNT3	2.13	1.45-3.13	5.39	2.83-10.26

[1]The crude ORs were very similar to the adjusted and are therefore not shown.

[2]The cohort included data from HUNT2, HUNT3/Mini-q without GERS in HUNT2

[3]Any GERS: minor or severe complaints with heartburn or acid regurgitation

[4]Severe GERS: severe complaints with heartburn or acid regurgitation

[5]Sleep problems were defined as having difficulty falling asleep several times a week

[6]The cohort included participants in HUNT2 and HUNT3 without insomnia in HUNT2

[7]Insomnia was defined as having daytime sleepiness/experiencing impaired work performance due to sleep problems and having difficulty falling asleep or waking up to early several times a week.

5.4.3 Any and severe GERS as risk factors for developing sleep problems and insomnia symptoms

Between HUNT 2 and HUNT3/Mini-Q, 1,725 participants (8%) developed sleep problems and 497 participants (3%) developed insomnia symptoms. Participants with *any* GERS in both HUNT2 and HUNT3/Mini-Q had an odds ratio of 1.91 (95% CI 1.68-2.17) compared to those without GERS. For participants exposed to GERS in HUNT2 only there was a 46% increased occurrence sleep problems (OR 1.46; 95% CI 1.20-1.78) compared to non-exposed (Table10).

Similar estimates were observed for individuals exposed to *severe* GERS in HUNT2 and HUNT3 (OR 1.92; 95% CI 1.37-2.69) and in HUNT2 only (OR 2.0; 95% CI 1.56-2.56). The OR of insomnia symptoms was increased among those exposed to any GERS in HUNT2 and HUNT3 (OR 2.15; 95% CI 1.71-2.72) and among those exposed in HUNT2 only (OR 1.51; 95% CI 1.05-2.16), compared to those without GERS. The risk of insomnia symptoms among those exposed to *severe* GERS in HUNT2 only was more than 2-fold increased (OR 2.24; 95% CI 1.49-3.69), while the OR was attenuated (OR 1.75; 95% CI 0.94-3.25) among those exposed to *severe* GERS in HUNT2 and HUNT3. Since the crude ORs were similar to the adjusted ORs, only the adjusted ORs are shown (Table 10).

Table 10. Exposure to *any* and *severe* gastroesophageal reflux symptoms (GERS) and risk of sleep problems and insomnia symptoms. Odds ratios (OR) with 95% confidence intervals (CI) were adjusted for sex, age, BMI, smoking and education[1].

Cohort 3 N= 21,500[2]	**Incident sleep problems**[3]	
Exposure to any GERS[4]	OR	95% CI
No GERS (reference)	1.00	-
Any GERS in HUNT2 but not in HUNT3/Mini-Q	1.46	1.20-1.78
Any GERS in HUNT3 /Mini-Q but not in HUNT2	1.44	1.25-1.65
Any GERS at both HUNT2 and HUNT3/Mini-q	1.91	1.68-2.17
Exposure to severe GERS[5]		
No severe GERS (reference)	1.00	-
Severe GERS in HUNT2 but not in HUNT3/Mini-Q	2.00	1.56-2.56
Severe GERS in HUNT3 /Mini-Q but not in HUNT2	1.94	1.60-2.36
Severe GERS at both HUNT2 and HUNT3/Mini-Q	1.92	1.37-2.69
Cohort 4 N= 18,025[6]	**Incident insomnia**[7]	
Exposure to any GERS4	OR	95% CI
No GERS (reference)	1.00	-
Any GERS in HUNT2 but not in HUNT3	1.51	1.05-2.16
Any GERS in HUNT3 but not in HUNT2	1.67	1.32-2.13
Any GERS at both HUNT2 and HUNT3	2.15	1.71-2.72
Exposure to severe GERS5		
No severe GERS (reference)	1.00	-
Severe GERS in HUNT2 but not in HUNT3	2.24	1.49-3.69
Severe GERS in HUNT3 but not in HUNT2	1.90	1.36-2.66
Severe GERS at both HUNT2 and HUNT3	1.75	0.94-3.25

[1] The crude ORs were very similar to the adjusted and are therefore not shown

[2]The cohort included participants in HUNT2 and HUNT3/Mini-Q without sleep problems in HUNT2

[3] Sleep problems were defined as having difficulty falling asleep several times a week

[4]Any GERS: minor or severe complaints with heartburn or acid regurgitation

[5]Severe GERS: severe complaints with heartburn or acid regurgitation

[6]The cohort included participants in HUNT2 and HUNT3 without insomnia in HUNT2

[7]Insomnia was defined as having daytime sleepiness and having difficulty falling asleep or waking up to early several times a week.

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

All studies included in this thesis are observational epidemiological studies of population-based design. For a study to be population-based it must have full coverage (at least in theory) over the specific population within the area that is being studied. Challenges in epidemiological studies include selecting the correct study design for the research question and to minimize errors, which can otherwise compromise the interpretation and generalizability of the results. There are two main types of errors in epidemiological studies, random errors and systematic errors. Random errors (chance) are variability in the data that we cannot explain and the impact of these will decrease with increased sample size. Systematic errors can be divided into three main types: selection bias, information bias and confounding. In contrast to random errors, systematic errors cannot be addressed by increasing the sample size, but are related to the design of the study and how the variables are measured.[105] The ideal epidemiological study, and what is regarded as giving highest quality evidence, is a randomized interventional trial. These trials, if performed correctly with a sufficiently large sample size, will take care of all confounding as a result of the randomization, and therefore findings will be due to the intervention under study. However, it is not always feasible or ethical to perform such trials, e.g. when it comes to research addressing associations between sleep problems and GERD, and large prospective cohort studies are regarded as the preferred observational study design in these cases.

In the section below, some of the methodological considerations of the studies will be discussed, using epidemiological concepts.

6.1.1 Study I and IV

Study I and IV are both prospective cohort studies with a longitudinal design, which use data from 2 time points, i.e. from HUNT2 1995-1997 and HUNT3/Mini-Q 2006-2009. Strengths of these datasets include the fact that they are large and represent the whole adult population in a well-defined area, i.e. residents of the county of Nord-Trøndelag. However, there was a drop in participation from 64% in HUNT2 (including those who reported GERS status) to 49% in HUNT3/Mini-Q. One of the reasons for the drop in participation in HUNT3 was that GERS was assessed in the main postal questionnaire in HUNT2 but in the second questionnaire administered at screening stations at HUNT3. This means that some people, e.g. those with a busy lifestyle, might be under represented, and analyses of non-participation also revealed that "had not time/inconvenient session" was the most common reason for not participating in HUNT3. Among the oldest (80+ years), "too ill to participate" was the most common reason for non-participation.[106] Both in HUNT2 and HUNT3 the participation rates were lower in younger age groups and among males compared to older age groups and females. A lower percentage of participants in Mini-Q reported any GERS (29.1%) compared to in HUNT3 (43.1%) and severe GERS (4.3%) compared to in HUNT3 (7.1%). The profile of participants in Mini-Q also differed in the sense that they were to a greater extent men

(51% compared to 44% in HUNT3), had a lower mean age, (45.9 years compared to 53.4 years in HUNT3) and lower mean BMI, (26.1% were obese compared to 27.2% in HUNT3).[107] There might be an overestimation of the occurrence of GERS in HUNT3 which might influence results in the parts of study IV where analyses were restricted to HUNT2 and HUNT3 only, but less so in study I as the results of Mini-Q and HUNT3 were combined. Non-participation of the elderly due to being too ill could theoretically be related to both GERS and sleep problems, and selection bias cannot be excluded, but these disorders would in most individuals not counteract participation. Moreover, these analyses were limited to participants under the age of 80. The relatively large sample size, particularly in study I, allowed robust sub-analyses and decreased the risk of chance findings.

There were on average 11 years between the assessments in HUNT2 and HUNT3/Mini-Q. Unfortunately, we could not follow participants between these assessments, leaving a risk that incident cases of GERS, insomnia and sleep problems might not be true incident cases but instead represent recurrent symptoms. Particularly in study IV the ability to measure person-years would have been an asset, thus giving us the ability to better measure the magnitude of effects.

In study IV, sleep problems were assessed with the question "Have you had difficulty falling asleep during the last month?" while in HUNT3/Mini-Q sleep problems were assessed with the question "How often during the last 3 months have you had difficulty falling asleep". This difference in time might introduce information bias due to misclassification. However, there is little reason to believe that they would be different among participants with GERD and those without GERD.

6.1.2 Study II

This study has a nested case-control design which uses a co-twin control method to assess the influence of heredity. The study is cross-sectional, which limits what can be inferred from the results. Therefore, we cannot say anything about the direction of associations, only that there are associations between sleep problems and GERD. In this study only same sex twins that were at least 65 years of age at the time of the interview were included. This restriction was due to the fact that only this group had answered the sleep questions. This age restriction in combination with the request for complete pairs (in the co-twin analyses with discordant DZ and MZ pairs) may have selected a group of elderly participants who are healthier (have the ability to participate in the interview) and do not have strong heritability for a deadly disease that occurs in younger ages. This was partly accounted for by letting an informant perform the interview if the twin was not able to participate himself/herself and thereby avoiding selection bias.[99] Both GERD and sleep problems are common and in older ages,[36,108,109] and symptoms might be more severe among older GERS patients,[110] and the results might not be generalizable to younger people. On the other hand, the risk of problems with generalizability due to the fact that they are twins *per se* is probably low, and twin studies reveal similar results to studies of singlrtons for a number of diseases.[111,112] In the analysis of discordant MZ

twins we were left with 210 twin pairs, and it cannot be excluded that smaller effects might not have been detected due to limited statistical power.

6.1.3 Study III

Study III has a case-control design and all cases came from the larger Brisbane area, Australia and were matched to population controls from the electoral role. Strengths of the study include a strict assessment of Barrett´s esophagus cases and reports of new cases of Barrett´s from all operating labs in the area. In the process of attaining information from patients' medical records, 44% either declined to be contacted by the researchers or could not be contacted before their diagnosis could be confirmed. Of the remaining cases, some were found ineligible due to previous diagnoses of Barrett´s, presence of adenocarcinoma of the esophagus or having moved out of the area. There was also a time gap between the databases SDH and BOMS, during which additional participants were diagnosed with adenocarcinoma of the esophagus, were too ill or moved out of the area or could not be contacted. Selection bias might have been present in this process and both cases and controls who remained in the study and chose to participate might e.g. have been more health conscious and had better diet, which might influence the frequency of symptoms of obstructive sleep apnea. There is also up to a 7 year time difference between the assessment of Barrett´s esophagus and the assessment of daytime sleepiness and sleep apnea symptoms. Changes in diet and exercise regime during the time interval, and a consequent decrease in BMI, which in turn has been shown to decrease OSA severity,[67] could influence the ability to correctly measure the association under study. However, a study investigating the association between abdominal obesity and Barrett´s esophagus using the same data compared BMI and smoking habits at the time of recruitment (close to the Barrett´s assessment) and BOMS assessment found a good correlation between measures.[59] There are also indications that OSA progresses rather than declines in mild to moderate cases over time.[67]

In study III we did not have the ability to measure clinical OSA, but used the Epworth sleepiness scale (ESS) to assess daytime sleepiness and a sleep apnea index to assess symptoms of obstructive sleep apnea instead. Both the ESS scale and the sleep apnea symptom index have been validated, and have been shown to correlate well with OSA,[104,113] but ESS has also been criticized to correlate with symptoms of psychiatric disorders.[114] The ESS does not measure daytime sleepiness in a defined time period just "in recent time" and a person with, e.g. depression might overestimate symptoms. We did not obtain a psychological assessment of our cases and controls, but even though there might be a risk of misclassification of symptoms of sleep apnea and the daytime sleepiness seen could have been due to other causes, it does not seem likely that it would differ between cases and controls, i.e. the misclassification should have been non-differential and dilute associations rather than increasing them. Such dilution might have contributed to the lack of statistically significant findings of this study

6.2 ETHICAL CONSIDERATIONS

All studies included in this thesis were approved by the relevant regional ethical review boards. For study I additional permission to link HUNT2 data with NorDP was obtained from the Norwegian Directorate of Health and the Data Inspectorate. This was needed due to the fact that at the time of HUNT2, linkage to NorDP was not possible and consent did not include this register. Written informed consent was gathered for all participants in HUNT2, HUNT3, Mini-Q, SDH and BOMS at the time of the data collections. For the twins participating in the SALT- study, interviews were held over the phone and not in person and only oral consent could be obtained. Information about the study was sent out prior to the interviews informing potential participants about the study, and all twins were sent a letter after the study confirming that they had consented and information on who to contact if they wished to withdraw consent. No interventions were performed on the participants and the risks involved in participating in the studies were perceived as low. To reduce integrity risks for participants, all data were kept on safe servers with limited access and without identifiers such as names and personal identity numbers.

6.3 FINDINGS AND IMPLEMENTATION OF RESULTS

6.3.1 Study I

In this study we found a substantial (30%) increase in the prevalence of any GERS between 1995-1997 (31.4%) and 2006-2009 (40.9%). The prevalence of severe GERS increased by 24%, from 5.4% to 6.7 % and an increase of at least weekly GERS of 47%, from 11.6 % to 17.1%. The absolute number of individuals with new GERS exceeded the number who lost GERS during the study period, even though the estimated annual loss of severe GERS was higher (1.22%) than the annual incidence (0.23%). Age had a larger influence on the incidence of GERS among women while among men the incidence was more stable with age. More young women lost their GERS compared to young men or older participants. This was not explained by pregnancy, as exclusion of pregnant women only marginally changed the results.

Previous research on population-based prevalence of GERS is heterogeneous which might be explained by the variability in definition of GERS between studies. Two American studies which used the same source population in 1980s to 1990s found that the prevalence of at least weekly heartburn increased from 13.2% (n=835, aged 30-64 years) to 17.8% (n=1,511, age 25-74 years).[115,116] The prevalence of at least weekly acid regurgitation remained however stable on 6.5% and 6.3% respectively. A Swedish study found an increase in the prevalence of any GERS from 20-21 % in 1986 (n=337, age 20-79 years) to 22-25% at follow-up 10 years later (n=197).[117,118] In contrast to our findings and the studies above, a recent Danish study found that the prevalence of at least mild GERS was stable over time, 22% at 1998-1999 (n= 6781, aged 40-65 years) and at the 5 year follow-up (n=5578).[119]

There are a few studies which have measured GERS at least two periods in time, providing a possibility to address incidence or loss of GERS. A Danish study with baseline data in 1982-1984 and follow-up assessment in 1987-1988 (n=2987; aged 30-60 years at baseline) reported an annual incidence of any GERS of 13-19% and an annual incidence of frequent GERS of 1-3%.[120] A Swedish study with baseline in 1988 and 1 year follow-up (n=1059; aged 20-79 years at baseline) reported an annual incidence of predominant GERS of 0.05% and an annual incidence of GERS with other concurrent gastrointestinal symptoms of 0.75%.[121] An American study from 1988-1991 with 12-20 months of follow-up (n=690; aged 30-64 years at baseline) reported a cumulative onset rate of heartburn several times a week or daily of 2.7%, corresponding to average annual onset rates of 1.6-2.7%.[122] In the most recent study from Denmark with baseline in 1998-1999 and follow-up 5 years later (n=5578; aged 40-65 years at baseline), an annual incidence of at least mild GERS of 2.2% was reported.[119] Our results are similar to the studies above, with exception of the first Danish study.

A few studies also measured the loss of GERS. The Danish study from 1982-1984 with follow-up in 1987-1988 reported cumulative loss of any GERS of 27-37%, corresponding to average annual loss of 6.2-9.0%.[120] The cumulative loss of frequent GERS from the same study was 59-77%, corresponding to average annual loss of 16.1-23.2%. The US study reported cumulative loss of heartburn several times a week or daily of 47.8%, corresponding to average annual loss of 36.9-61.3%.[122] The Swedish study with 1 year follow-up reported an annual loss of any GERS of 1.1-1.3%,[117] and the most recent Danish study reported annual loss of at least mild GERS of 8.6%.[119] These results, with exception of the Swedish study, deviates from our study, but the large sample size, the ability to adjust for anti-reflux medication strengthen the validity of our results. Also, apart from the most recent Danish study, our study ends in the 21st century and a recent review combining studies of at least weekly GERS from North America, East Asia, Europe and the Middle East, showed a statistically significant trend of higher prevalence numbers after 1995, compared to prior to 1995.[1] There might have been lifestyle changes over time that account for the higher prevalence seen in more recent years and people might to a higher degree maintain their GERS if loss due to antireflux medication is not accounted for.

The increasing prevalence of GERS found in this study may contribute to increasing incidence of Barrett´s esophagus and adenocarcinoma of the esophagus. GERD also has a negative impact on health related quality of life for patients[2] and increasing cost for medications and health care visits for society.[4] Effective treatment and more research concerning lifestyle prevention and medication use are needed.

6.3.2 Study II and study IV

These studies are discussed jointly as they are both investigating the association between sleep problems/insomnia symptoms and GERD/GERS.

In study II we investigated the association between sleep problems and GERD and adjusted for genetic and early environmental factors. Results from the external analyses (including all

twins) showed doubled occurrence of GERD for "often" having sleep problems (OR 2.0; 95% CI 1.8-2.4) compared to "seldom" and 50% increased occurrence for "sometimes" having sleep problem (OR 1.5, 95% CI 1.3-1.7) compared to seldom. When the results were compared with the results of the co-twin within-pair analyses for DZ and MZ twins, the effect of "often" having sleep problems compared to "seldom" having sleep problems ("never" as reference) remained for DZ twins, while the effects decreased and become non-significant in co-twin analysis with MZ twins. Such decrease among MZ twins indicates genetic influence. However, in the cross-trait correlations we found little evidence for genetic influence and the decrease in effect for MZ twins can also be due to limited sample size. An exception is the association seen for the item "disturbed sleep" which has an increased effect for "sometimes" having disturbed sleep among MZ twins but this could be a chance finding.

In study IV we found a strongly increased risk of developing GERS among individuals with sleep problems, and a moderately increased risk of developing sleep problems among persons with GERS. The association between insomnia symptoms and incident *severe* GERS was stronger (OR 5.39; 95% 2.83-10.26, non exposed as reference) than between sleep problems and incident *any* GERS (OR 1.84; 95% CI 1.48-2.30 exposed in both surveys, non-exposed as reference), and a longer exposure time (exposed in both surveys) entailed a higher risk than if the participant were exposed to sleep problems and insomnia in the first survey only. In the analyses with GERS as exposure and risk of incident sleep problems/insomnia the pattern with higher estimates among participants exposed in both surveys were also seen in the analyses with participants exposed to *any* GERS, but not when exposed to *severe* GERS. Furthermore we found a 2-fold association between exposure to *any* GERS at HUNT2 and HUNT3 (non-exposed as reference) and incident insomnia (OR 2.15; 1.71-2.72) while the effect for *severe* GERS (exposed at HUNT2 and HUNT3 compared to non-exposed) and incident insomnia symptoms was lower and become non-significant (OR 1.75; 95% CI 0.94-3.25).

As far as we know, there are no previous twin studies investigating the heritability association between sleep problem and GERD. We found little evidence for genetic confounding, but this should be investigated in a younger population as well. A clear association between sleep problems and GERD has however previously been seen in large epidemiological studies. In a population-based cross-sectional case-control study from our group, also using data from the Nord-Trøndelag, Norway (HUNT1 and HUNT2) (including 3,153 subjects with *severe* GERS and 40,210 controls), a positive dose-response association between problems falling asleep and *severe* GERS was found. The study also found a strong association between insomnia symptoms and *severe* GERS (OR 3.2; 95% CI 2.7-3.7), when adjusting for age, sex, smoking, BMI and education.[88] In another population-based study using the 2006 US National Health and Wellness Survey (including 11,685 with GERS (at least 2 times per month), and 29,643 population controls) found that participants with GERD had a 2-fold increased occurrence of sleep difficulties compared to those without GERD (OR 2.09 ; p< 0.001) and a 75% increased occurrence of sleep induction problems (OR 1.75 <.001).[89]

An effect of sleep problems on GERD has also previously been indicated. A recent longitudinal Chinese study from Hong Kong with a mean 5 year follow-up (185 cases with non-restorative sleep at baseline and 2106 participants without) found a clear association between non-restorative sleep at baseline and GERD at follow up (OR 2.44, 95% CI 1.33-4.46) after adjusting for age, gender, education, marital status, family income and regular medication use.[70] In a randomized clinical trial with crossover design, (including10 cases with erosive esophagitis and 10 healthy controls), participants were randomized to sleep deprivation (1 night with ≤3 hours of sleep) or sufficient sleep (3 days with ≥ 7 hours of sleep per night) and then after a week's washout time switched to the other arm.[93] The study found that following sleep deprivation compared to sufficient sleep, subjects with esophagitis had significantly shorter lag time to symptom generation and increase in acid perfusion sensitivity score, after stimulus to esophageal acid perfusions. In controls, no difference was seen and it was suggested that sleep deprivation can enhance esophageal sensitivity to acid in patients with GERD and increase GERD symptom severity in sleep deprived patients.[93] This mechanism might partly explain the findings of study IV, which showed a stronger effect of developing GERS in participants with sleep problems, than developing sleep problems in participants with GERS. It has previously been suggested that there is a bidirectional association between GERD and sleep problem and that sleep disturbances aggravate reflux which in turn worsen sleep problem and it then continues as a vicious circle.[6]

Because of this close link between GERS and sleep problems, combined treatment of these disorders might be called for. In an intervention study of primary care patients in Canada (n =1.388; 825 reported GERD-related sleep disturbance at baseline) where GERD patients were randomized to either PPI or their current treatment, showed that patients with sleep disorders experienced improvement of their sleep problems after the more aggressive PPI treatment.[123] Sleep medications such as benzodiazepines have on the other hand shown to be associated with heartburn during sleep,[94] so a choice of different sleep medications in patients with both GERD and sleep problem might be needed.

6.3.3 Study III

We hypothesized that OSA would increase the risk of Barrett's esophagus by increasing the intensity of GERD but no statistically significant associations between excessive daytime sleepiness, sleep apnea symptoms and Barrett's esophagus were found. In the last model in these analyses we included GERS and the small non-significant risk estimates completely disappeared, indicating that any association with Barrett´s esophagus is mediated through GERS. We found an association between sleep apnea symptoms and GERS among controls which remained after adjusting for BMI.

Only a few studies have previously investigated the potential association between OSA and Barrett´s esophagus. In a US study including 54 cases of Barrett's esophagus and 233 controls (62 upper endoscopy controls and 171 colonoscopy controls), found a 2-fold

increased risk of being at high risk for OSA among Barrett´s esophagus patients compared to colonoscopy controls (OR 2.08; 95% CI 1.12-3.88).[124] However, in the multivariable model adjusting for age and BMI, the association was attenuated and become non-significant (OR 1.51; 95% CI 0.72-3.15). No significant association was found between Barrett's esophagus and risk for OSA compared to upper endoscopy controls (OR 1.73; 95% CI 0.83-3.62). The Berliner Questionnaire was used to assess the risk of OSA and included questions regarding snoring, daytime somnolence and obesity/hypertension.[124] Another US study, including 7,590 patients from the Mayo Clinic Life Science System and Enterprise Data Trust databases who underwent polysomnography and upper endoscopy during a 12-year period, found a 37% increased risk of Barrett's esophagus among OSA patients (OR 1.4, 95% CI 1.1-1.7).[125] However, no adjustment for BMI was conducted. In another study from the Mayo Clinic, using a case-control design, found an 80 % increased occurrence of Barrett´s esophagus among patients with OSA (OR 1.8; 95% CI 1.1-3.2) after adjusting for age, sex, BMI, smoking history and GERD.[126] The sample strategy of the cases and controls of this study can however be questioned as they were sampled with a 2:1 ratio from three predefined groups of combinations of Barrett´s esophagus and OSA, and thereby sampled both with regards to outcome and exposure. The sample left for the analyses then consisted of the four groups of confirmed diagnoses: yes Barrett's and no OSA n=36, no Barrett's and no OSA n=74, no Barrett´s and yes OSA=78, and yes Barrett´s no OSAN=74,[126] leaving an already predefined ratio between OSA and Barrett´s. The study did however also find an association between increased severity of OSA and Barrett´s esophagus (OR 1.2 per 10-unit increase in the apnea-hypnea index, 95% CI 1.0-1.3) which suggests a true association.[126] To further invest this association, there is need for larger prospective population-based studies. In our study we did not find any statistically significant association between symptoms of OSA and Barrett´s esophagus, but an association between at least weekly GERS and symptoms of OSA and excessive daytime sleepiness among the controls. This latter association has been found also in previous studies,[97,127] and treatment with continuous airway pressure (CPAP) of OSA have shown to decrease GERS,[95] but conflicting results have also been found.[128]

7 CONCLUSIONS

- Between 1995-1997 and 2006-2009 the prevalence of GERS increased substancially. At lest weekly GERS increased with 47% , from 11.6% to 17.1%. The average annual incidence of severe GERS was 0.23% and the corresponding spontaneous loss was 1.22%.

- There is a dose-dependent association between sleep problems and GERS that does not seem to be confounded by hereditary factors.

- No statistical significant association between obstructive sleep apnea symtoms and Barrett´s esophagus were found. If there is an association it is probably mediated by GERS.

- The association between sleep problems and incident GERS seems to be bidirectional, and sleep problems seems to be a stronger risk factor for GERS than GERS for incident sleep problems.

8 FUTURE STUDIES

The association between sleep problems and GERD has been explored in a number of studies but there are still gaps to fill. This thesis explored the association by performing a cohort study with the ability to measure the cumulative incidence of sleep problems and GERD, but incidence measured by risk ratios are sparse. There is information on sleep problems and GERD in HUNT2, HUNT3/Mini-Q and in the planned HUNT4 that will be launched in 2017. NorPD includes all drugs dispensed by prescription in Norway since January 2004. In a future study it would be interesting to perform a classical cohort study, with a similar design as study IV. HUNT3 could be used as a baseline and time to sleep problem/GERD defined as the first prescription of sleep medication/GERD medication could be measured. By counting person-years and estimating risk ratios, the magnitude of the GERD sleep association could be measured.

In a study performed by our research group using HUNT2 and HUNT3, we found that weight loss in combination with GERD medication use gave a 4-fold chance to be free of GERS.[45] It would be interesting to perform a study addressing changes in weight between HUNT2, HUNT3, and HUNT4 and compare it with the usage pattern of GERD medication from NorPD. It could also be interesting to adjust the results for sleep problems, as studies have found an increased risk of weight gain in people with short sleep duration.[129,130]

In study III we studied the association of symptoms of OSA and Barrett´s esophagus but an important limitation of the study was the lack of clinical assessment of OSA. A recent study found an increased risk for Barrett´s esophagus in patients with OSA, but the study had a small sample size and methodological issues.[126] It would be interesting to perform a large register-based study in Sweden on OSA and the risk of Barrett´s esophagus, using data from the Patient Register which includes all in-patient care in Sweden since 1987 and also includes specialist open care visits since 2001, to study this association further.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Gastroesophageal refluxsjukdom innebär ett återflöde av magsäcksinnehåll upp i matstrupen och orsakar besvärande symtom i form av halsbränna eller sura uppstötningar. Halsbränna och sura uppstötningar är vanligt i befolkningen och i västvärden drabbas i genomsnitt över var fjärde person minst en gång i veckan. Refluxsjukdom kan också leda till allvarliga följdsjukdomar som matstrupscancer liksom försämrad livskvalitet för den som drabbas och höga behandlingskostnader för samhället. Sömnproblem är också ett vanligt hälsoproblem i västvärlden och drabbar ungefär en tredjedel av befolkningen. När man mäter sömnproblem brukar man fråga efter hur ofta under den senaste månaden/3 månaderna man har haft svårt att somna, har haft avbruten sömn med uppvaknanden eller om man vaknar för tidigt och har svårt att somna om igen. I flera tidigare studier har man sett ett samband mellan sömnproblem och refluxsjukdom och det har föreslagits att det är ett dubbelriktat samband, d.v.s. sömnproblem kan leda till refluxsjukdom och refluxsjukdom kan leda till sömnproblem. Syftet med den här avhandlingen var att vidare undersöka det här sambandet genom att se om det påverkas av ärftliga faktorer och undersöka sambandets riktning. Det närliggande sambandet mellan obstruktiv sömnapné och Barretts esofagus (en sjukdom som innebär cellförändringar i nedre delen av matstrupen för att bättre tåla magsyra och som senare kan utvecklas till matstrupscancer) studerades också.

I den första studien undersöktes förändringar i förekomst över tid, nyinsjuknande och förlust av reflux. Vi använde oss av datamaterialet Helseundersøkelsen i Nord-Trøndelag (HUNT) som innehåller flera stora enkätundersökningar som skickats ut till alla bofasta invånare över 19 år i fylket Nord-Trøndelag i Norge. Enkäterna har också kompletterats med hälsoundersökningar där bl.a. deltagarnas längd, vikt, och blodtryck mättes. Ungefär 60 000 personer svarade på HUNT2 (1995-1997) och ungefär 45 000 deltog i HUNT3 och Mini-Q (en enkät för dem som inte ville medverka i den omfattande enkätundersökningen utan i stället svarade på ett kortare frågeformulär) (2006-2009). Ungefär 30 000 personer svarade både på HUNT2 och HUNT3 och det är framför allt den kohorten vi använder i både studie I och studie IV. I studie I såg vi att förekomsten av reflux ökade mellan 1995-1997 och 2006-2009. Förekomsten av refluxsymtom minst en gång i veckan ökade med 47 %, från 11.6 % till 17.1 %. Ökning av förekomst av symptom sågs hos både kvinnor och män och i alla åldersgrupper. Under samma tidsperiod nyinsjuknade i genomsnitt 0.23 % av befolkningen årligen i nya allvarliga refluxsymtom medan 1.22% av dem med allvarliga refluxsymtom blev av med sina tidigare besvär. Bland dessa ingår inte dem som blev av med sin reflux med hjälp av medicinering för denna.

I den andra studien undersökte vi om sambandet mellan sömnproblem och refluxsjukdom som man sett i tidigare studier, kan bero på inverkan av genetiska och tidiga miljöfaktorer (som kommer till i moderlivet eller under uppväxten). Bakgrunden till att vi vill undersöka detta är att man i tidigare studier även sett att ärftlighet förklarar ca 31-40 % av variationen i förutsättningen att få refluxsjukdom och för sömnproblem förklarar ärftlighet för ca 33-44 % av variationen i sömnkvalitet och sömnlängd. Vi använde oss av Svenska Tvillingregistret

och inkluderade 8,014 tvillingar över 65 år som medverkat i en stor telefonintervju som utfördes 1998-2002. Genom att använda sig av tvillingar och jämföra resultatet från en extern analys som inkluderade alla tvillingar med resultat från analyser med komletta par tvääggstvillingar och enäggstvillingar, kan man se om ett samband delvis kan förklaras av genetiska och/eller miljömässiga faktorer. Vi hittade ett starkt samband mellan sömnproblem och refluxsjukdom i analysen som inkluderade alla tvillingarna, ungefär dubbelt så många av dem som angav att de ”ofta” hade sömnproblem hade reflux jämfört med dem som ”sällan” hade sömnproblem. I analyserna med endast tvääggstvillingar där en tvilling har reflux och den andra inte, kvarstod sambandet men i analysen med enäggstvillingar så försvagades det. Det var dock endast en liten minskning och i tilläggsanalyser såg vi att det var liten risk för att sambandet mellan sömnproblem och refluxsjukdom beror på genetiska faktorer.

I den tredje studien tittade vi på relationen mellan obstruktivt sömnapné symptom och Barretts esofagus. Obstruktiv sömnapné innebär att man har andningsstopp under sömnen, oftast på grund av att tungan ramlar bak i svalget och täpper till luftvägarna. Det leder till syrebrist och mikrouppvaknanden för att återfå syresättningen vilket leder till störd sömn. Det har tidigare föreslagits att obstruktiv sömnapné bidrar till ökad nattlig reflux genom att sänka trycket i den lägre esofageala sfinktern , vilket underlättar återflöde av magsyra i matstrupen. Vår hypotes var att sömnapné ger mer allvarlig reflux vilken i sin tur leder till fler fall av Barretts esofagus då exponering för magsyra är en av huvudorsakerna till Barretts esofagus. I studien inkluderades 237 fall av Barretts esofagus och 247 populationskontroller (personer utan Barretts) i en fall-kontrollstudie från Brisbane, Australien. Studien är en del av en tidigare större studie och där fallen av Barretts esofagus identifierades och personer utan Barretts från samma region, ålder och kön identifierades från vallängden. Data till studien inkluderade frågeformulär om symptom på obstruktiv sömnapné och refluxsymptom samt objektiva mått på bl.a. längd, vikt och nackomfång. Det var fler personer med Barretts som också upplevde att de ofta hade sömnapnésymptom (20%) jämfört med populationskontrollerna (13%), men vi fann inget betydande statistiskt samband mellan symptom på obstruktiv sömnapné och Barrets esofagus. Däremot fann vi ett samband mellan refluxsymptom och symptom på obstruktiv sömnapné som också setts i tidigare studier.

I den fjärde och sista studien försökte vi avgöra om sömnproblem i högre grad orsakar reflux än refluxs orsakar sömnproblem. Vi använde oss liksom i studie I av Helseundersøkelsen i Nord-Trøndelag (HUNT). Både vid HUNT2 (1995-1997) och vid HUNT3/Mini-Q (2006-2009) tillfrågades deltagarna om sömnproblem och refluxsymtom. Vi ville se om sömnproblem orsakar nya fall av reflux, och om det var någon skillnad i sambandets styrka om personen hade haft reflux både vid HUNT2 och HUNT3/Mini-Q eller bara vid ena tillfället. För att undersöka det inkluderades endast de som inte hade någon reflux vid första mättillfället. För att sedan undersöka hur förekomsten av reflux påverkar nya fall av sömnproblem analyserades på samma sätt de som inte haft några sömnproblem vid första mättillfället och om det var någon skillnad i sambandets styrka om personen haft reflux vid båda tidigare mättillfällena. Utav de 16,754 som inte hade någon reflux i HUNT 2 utvecklade 4,850 (29%) någon form av refluxsymptom till HUNT3/Mini-q och 396 (2%) allvarliga

refluxsymptom. Av de 21 500 utan sömnproblem vid HUNT2 utvecklade 1,725 deltagare (8%) sömnproblem and 497 (3%) insomniasymptom. I de statistiska analyserna fann vi ett starkare samband mellan sömnproblem och att utveckla reflux än mellan reflux och nya fall av sömnproblem. Vi såg också starkare samband mellan insomnia symptom och ”allvarliga refluxsymptom” än mellan sömnproblem och refluxsymtom samt starkare samband om personen haft den andra sjukdomen under längre tid (vid båda mättillfällena). Det tyder på att det är ett verkligt samband och inte ett slumpmässigt fynd. Sambandet mellan sömnproblem och reflux verkar vara dubbelsidigt, men i den här studien fann vi även ett starkare samband mellan sömnproblem och att utveckla reflux än det omvända.

10 ACKNOWLEDGEMENTS

I would like to express my gratitude towards a number of people, whom without your contributions in various ways, this thesis would not have been possible. Thank you:

Jesper Lagergren, my main supervisor. Thank you so much for giving me the opportunity to do research in your fantastic research group, for employing me as statistician in the beginning when money was tight and introducing me to interesting new methodologies. You are an attentive supervisor (never more than an email away), an inspiration with your never fading enthusiasm about research and amazing multi-tasking skills. Can I inherit your "timeturner"? We do not always agree on things, but no matter what, you always put the research first and I really appreciate that.

Helena Nordenstedt, co-super visor, globetrotter and "allkonstnär". You have an inspirational pathos for what is right and wrong and "you can do anything you want and it does not really matter that it is not done in a way that most people would"- attitude. Thank you very for adding much needed medical first-hand-knowledge in the treatment of reflux patients to my papers, for power point crash-courses and for letting me be a "medstudent" for a day at the gastroenterology clinic.

Catarina Jansson, co-supervisor, passionate epidemiologist and fantastic after-work company. I am grateful for your thorough reading and sharp methodological comments of my manuscripts, conference abstracts and thesis. You are an ambitious researcher, who do not take any shortcuts and I am grateful for your reminders of the need to be careful and meticulous in research. Also I really appreciate your extensive knowledge within the field of sleep problems and GERD

Christina Hultman for excellent mentorship, which started long before I ever got registered as a PhD student. And thank you for giving me my first "real" job as a statistician.

David Whiteman, co-author for paper III. Thanks for three fantastic months in your research group, for enthusiastic method discussions, wonderful thoughts on "blue sky- epidemiology" and fast replies to all my questions.

Kristian Hveem, Mr HUNT himself and co-author of paper I and V, for contributing with your wide knowledge in the HUNT database, Norwegian bureaucracy and research in general.

Eivind Ness-Jensen, fellow PhD-student (now days post-doc), and co-author of study I and IV, for a very fruitful collaboration, interesting discussions, common struggles in the HUNT mist and fun conference visits.

Nancy Pedersen, co-author of paper II, the queen of the Swedish Twin Registry, for inspiring co-authorship and guidance in the wonderful world of co-twin control-studies.

Australian co-authors of study III: **Bradley Kendall** and **Aaron Thrift**, fellow PhD students during my research months in Brisbane, for a nice time in Brissie, generously sharing your knowledge about BOMS and Barrett´s and for all the healthy, nutritious lunches. **Graeme Macdonald** for sharp comment and constructive remarks, **Suzanne O'Brian** for help with ethical applications and other matters concerning BOMS.

Yulan Lin and **Maartje van der Schaaf**, fellow musketeers and cohort PhD-students. Thanks you for inspiring and fruitful discussions about research and life in general and who laugh with (and at) me when times are good and stand firm when they are not. You are of the true grit.

Asif Johar, Yunxia Lu, Peter Konings and **Fredrik Mattsson**, fellow biostatisticians at UGIS/UGS, for interesting method discussions and first aid consultations when needed. And **Fredrik** for giving the most effective training/torture sessions.

Ulrika Eriksson, **Margrete Gellervik**, **Hanna Johans** and **Karin Vikström**, administrative staff at UGIS and SCS, thank you for all the help in practical matters, guidance in KI bureaucracy and all the pep-talks.

Rickard Ljung, colleague at UGIS and at the National board of health and welfare, for introducing me to UGIS (yes, coffee conversations can be life changing), putting in a good word and always adding something interesting to the discussions.

Poorna Arnard, Lovisa Backemar, John Blomberg, Nele Brusselaers, Maryam Derogar, Therese Djärv, Eva Doorakkers, Ana Hagström, Emma Forslund Helgesson, Ylva Hellstadius, Carl Kihlander, Katarina Lagergren, Pernilla Lagergren, Mats Lindblad, Hedvig Löfdahl, Lena Martin, John Maret Ouda, Magdalena Plecka Östlund, Dan Razavi, Omid Sadr-Azodi, Richard Shore, Tomas Sjöberg Bexelius, Emma Sverdén, Wenjing Tao, Andreas Wall and, Anna Wikman, former and current members of UGIS and SCS, thanks for a stimulating work environment, interesting seminars and many good laughs.

The EPI floor, **QIMR Berghofer Medical Research Institute**, for interesting methods seminars and for giving me such a wonderful time in Brisbane. In particular thanks to **Lynn Green** for helping me out with all the paperwork and **Annika Antonsson** for numerous life saving coffee conversations.

Paul Lichtenstein, thank you for letting me write my C and D level thesis in statistics in your research group. This was a really good introduction to KI and the research world and I learned that you can do a lot more interesting things with statistics than ARCH and GARCH models.

Anastasia Nyman, statistician and professor at MEB, for the best reference ever and for a nice introduction to medical epidemiology and biostatistics.

SINGS, Anita Ekberg, Ewa Willis, Olof Acre and fellow students for stimulating seminars, courses and discussions about register based research and science in general.

Lizzy Leigh, för invaluable language editing of this thesis and the last manuscript. **Poorna** and **Hanna** for last minute proof reading.

Martin Bäckdahl and **Annika Lindblom**, current and former head of **MMK** for creating a nice environment for research, **Ann-Britt Wikström** for your never ending helpfulness with all the paper work and practical PhD issues and **Janne Karre** and **Lennart Helleday** for invaluable it-support

Maria Lindam, my sister and her family **John**, **Mio** and **Clara** for numerous dinners, last minute sleepovers, and much needed distraction from work.

My parents **Hugo** and **Monika Lindam** who are always supportive and have always encouraged us to try new things, for all the love and care.

To all my friends outside research. Especially thanks to **Helena H, Helena B, Jenny, Ingeborg, Anna EM, Emma, Tina, Lina, Linda** for all the laughs and who in different ways kept me on the ground and in one piece during these last months.

And last but not least thank you Karolinska Institutet for an excellent PhD-education.

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