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# **GASTROESOPHAGEAL REFLUX DISEASE IN ADULTS**

**THE KALIXANDA STUDY  
A POPULATION-BASED  
ENDOSCOPIC STUDY**

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*“Golf is a game of feel”*

*To Birgit, Werner and Jemina*

## ABSTRACT

Gastroesophageal reflux disease (GERD) is a common burden on health care resources in the Western world and deteriorates the health-related quality of life of those affected, but its manifestations in the general population are as yet unclear. Also, the impact of gastroesophageal reflux symptoms (GERS) on health-related quality of life in the general population is poorly characterized. Barrett's esophagus (BE), a complication of GERD is associated with esophageal adenocarcinoma, the incidence of which has been increasing dramatically in the Western world during the last decades. Eosinophilic esophagitis (EE) is thought to be a very rare inflammatory condition in adults (estimated prevalence 0.2-3 in 10,000) but patient studies suggest its incidence may be increasing. Furthermore, its association with GERD is uncertain. However, the prevalence of these conditions in the general population remains unknown, as endoscopy, including biopsy, is required in a random population sample to acquire this knowledge.

The aims of this study were to estimate the prevalence of and to identify risk factors for GERS, erosive esophagitis, BE and EE, and to identify the frequency of troublesome reflux symptoms associated with impaired health-related quality of life (HRQoL) in the adult population of two Swedish municipalities.

A random sample (n=3,000) of the adult population (20-81 years of age) of two Swedish municipalities (n=21,610) was surveyed using a validated postal questionnaire assessing gastrointestinal symptoms. The response rate was 74%. A representative sub-sample (n=1,000, mean age 54 years, 49% men) of the responders was subsequently invited, in random order, for esophagogastroduodenoscopy with biopsy, evaluation of GERS, HRQoL, risk factors, and tests for *Helicobacter pylori* (*H. pylori*).

Troublesome GERS, at any time during the last three months, were reported by 40% and at least weekly by 20%, erosive esophagitis was found in 16%, BE in 1.6% and EE in 0.4% of the population. Of those with GERS, 25 % had erosive esophagitis while 37% of those with erosive esophagitis reported no GERS. Those with a current *H. pylori* infection had a statistically significantly increased risk for GERS without esophagitis (OR = 1.58, 95% CI 1.14-2.19). Hiatus hernia and obesity were significant risk factors for GERS and/or erosive esophagitis as were alcohol and smoking for BE and dysphagia for EE. Most aspects of health-related quality of life were impaired in individuals with daily or weekly GERS. However, the presence or absence of esophagitis did not predict the impairment of HRQoL.

In Conclusion: GERS and erosive esophagitis were highly prevalent in the Swedish adult population. Furthermore, asymptomatic erosive esophagitis was present in 6% of the adult population. BE was found in 1.6% and EE was more common than has been estimated earlier. Troublesome reflux symptoms at least weekly may identify gastroesophageal reflux disease.

Keywords: Barrett's esophagus, epidemiology, eosinophilic esophagitis, erosive esophagitis, gastroesophageal reflux disease, health-related quality of life, population-based

## LIST OF PUBLICATIONS

This thesis is based on the following papers, which are referred to by their Roman numerals:

- I. Ronkainen J, Aro P, Storskrubb T, Johansson S-E, Lind T, Bolling-Sternevald E, Graffner H, Vieth M, Stolte M, Engstrand L, Talley NJ, Agréus L. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand J Gastroenterol* 2005;40:275-285.
- II. Ronkainen J, Aro P, Storskrubb T, Lind T, Bolling-Sternevald E, Junghard O, Talley NJ, Agréus L. Gastroesophageal reflux symptoms and health-related quality of life in the adult general population – the Kalixanda study. *Alimentary Pharmacology and Therapeutics* 2006;23:1725-1733.
- III. Ronkainen J, Aro P, Storskrubb T, Johansson S-E, Lind T, Bolling-Sternevald E, Vieth M, Stolte M, Talley NJ, Agréus L. Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology* 2005;129:1825-1831.
- IV. Ronkainen J, Talley NJ, Aro P, Storskrubb T, Johansson S-E, Lind T, Bolling-Sternevald E, Vieth M, Stolte M, Walker MM, Agréus L. Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: The population-based Kalixanda study. (*Gut* in press).

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## LIST OF ABBREVIATIONS

ASQ	Abdominal symptom questionnaire
BE	Barrett's esophagus
BMI	Body mass index
CI	Confidence interval
CLE	Columnar lined esophagus
EE	Eosinophilic esophagitis
EGD	Esophagogastroduodenoscopy
GEJ	Gastroesophageal junction
GERD	Gastroesophageal reflux disease
GERS	Gastroesophageal reflux symptoms
GI	Gastrointestinal
HRQoL	Health-related quality of life
<i>H. pylori</i>	Helicobacter pylori
ID	Identification number
LES	Lower esophageal sphincter
NERD	Non-erosive reflux disease
TLESR	Transient lower esophageal sphincter relaxation



# 1 INTRODUCTION

Gastroesophageal reflux disease (GERD) manifests as a spectrum of disorders mainly caused by the retrograde flow of gastric contents from the stomach into the esophagus, causing symptoms and/or esophageal mucosal damage. GERD is found to be common in studies on patients and in different populations (up to 40%) and it is a chronic disease causing a public health problem (1-7). Heartburn and acid regurgitation are the most typical symptoms of GERD and have been shown to be related to regurgitation of gastric acid into the esophagus (8). They are often associated with impaired health-related quality of life (HRQoL), but due to the lack of international consensus, in the past, on the ground definition of the disease, epidemiological studies are challenging to compare (6, 9, 10).

GERD may expose to the risk of physical complications such as esophageal erosions, ulcers, strictures, Barrett's esophagus (BE) and esophageal adenocarcinoma, the incidence of which has been increasing dramatically in the Western world during the last decades, but its role in eosinophilic esophagitis (EE) is under debate (4, 11-16).

To our knowledge, the data acquired by validated symptom questionnaires together with invasive upper endoscopy with biopsy from representative unbiased cohorts of general population are sparse.

In the present thesis, which presents the GERD-related disorders of the Kalixanda Study, the manifestations of GERD were studied in a representative random sample of an adult population using validated questionnaires and standardized endoscopy and histology protocols by experienced endoscopists and experienced pathologists with a special interest in gastrointestinal (GI) pathology. Also the effect of gastroesophageal reflux symptoms (GERS) in HRQoL and a possible cut-off for symptom frequency when GERS become GERD was examined. Furthermore, BE a complication of GERD and an important risk factor for adenocarcinoma in the esophagus was studied in this representative cohort. In addition, the association of GERS and EE was examined.

Thus, the aims of this study were to estimate the prevalence of and to identify risk factors for GERS, erosive esophagitis, BE and EE, and to identify the frequency of troublesome reflux symptoms associated with impaired HRQoL in the adult population of two Swedish municipalities.

## **2 REVIEW OF THE LITERATURE**

### **2.1 HISTORICAL PERSPECTIVE**

Complaints of heartburn and dyspepsia date back to ancient history. Treatment recommendations since 4000 years ago to Paracelsus in the medieval times vary from baby urine, milk and coral powder to powder of pearls (17, 18). The substances in these recommendations have in common some acid buffering capacity. In 1955, Flood et al (19), showed that aspirated juice from the esophagus of patients with heartburn more often contained acid than that of controls. A few years later Bernstein and Baker (20) presented “A clinical test for esophagitis”, to determine whether patients’ symptoms were reproduced during esophageal acid perfusion.

Norman Ruppert Barrett, born in Australia but making his career as a distinguished British surgeon, published in 1950 a report in which he supported the theory of columnar lined esophagus being a tubular segment of stomach driven into the chest by a congenitally short esophagus (21, 22). In 1953, Allison and Johnstone presented that the columnar lined intrathoracic structure, labeled stomach by Barrett, was in reality the esophagus and that the ulcerations in it should be called Barrett’s ulcers (23). In 1957, Dr Barrett accepted the idea of the columnar lined organ being esophagus and he suggested that the condition should be called “lower esophagus lined by columnar epithelium” (22, 24). In 1960, columnar-lined esophagus was referred to as “Barrett epithelium” and the term “Barrett syndrome” was presented (25).

### **2.2 DEFINITIONS**

#### **2.2.1 Gastroesophageal reflux disease**

The diagnosis of GERD is clear if endoscopically visible mucosal breaks are present in the esophagus. However, the proportion of patients who lack visible signs of erosive esophagitis varies between 33 to 85% (26-29). Thus, a substantial proportion of GERD patients are macroscopically normal in their endoscopic appearance.

A few years ago, an international consensus group of experts defined GERD as “all individuals who are exposed to the risk of physical complications from gastro-oesophageal reflux, or who experience clinically significant impairment of health-related well being (quality of life) due to reflux-related symptoms, after adequate reassurance of the benign nature of their symptoms” – the Genval definition (9, 30).

Due to the lack of international consensus over the definition of GERD, Dent et al suggested that “GERD results from frequent or severe symptoms which are sufficient to impair the individual’s health-related quality of life” and they used at least weekly symptoms of GERD as a cut off for the diagnosis in the review article of the epidemiology of GERD (6).

In the Rome III criteria from 2006, GERD is the preferred diagnosis when reflux esophagitis or excessive esophageal acid exposure is present or when symptoms are closely related to acid reflux events or respond to antireflux therapy (31).

Finally, a very recent global, evidence-based consensus was presented at the 2005 World Congress of Gastroenterology in Montréal and was published in August 2006 defining GERD as a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications (10).

### **2.2.2 Gastroesophageal reflux symptoms**

Heartburn, defined as a burning sensation behind the breastbone (and radiating up to the jaws), and/or acid regurgitation, defined as upward flow of gastric contents to the mouth or hypopharynx, are the most typical symptoms of GERD (2, 8, 28, 32). The global Montréal definition and classification of GERD includes the requirement that the symptoms need to be troublesome. This has also been used by others (10, 33).

Dysphagia (difficulty on swallowing) and odynophagia (pain on swallowing) are usually associated with complications of GERD, such as esophageal stricture or esophageal adenocarcinoma, but asthma, non-cardiac chest pain, chronic cough, hoarseness and dental erosions are extraesophageal symptoms or signs of GERD (10, 34, 35).

### **2.2.3 Erosive esophagitis**

There have been a number of different classification systems of esophagitis over the years, of which the classical Savary-Miller (36) grading system and lately the Los Angeles classification have been most widely used and the latter has been thoroughly validated (37, 38). Visible mucosal breaks in the esophagus are the most reliable criteria for the diagnosis of erosive esophagitis (10, 37, 38). Mild, non-erosive “minimal changes”, like mucosal erythema, edema, increased vascularity etc are now known to be unreliable markers of esophagitis, but may possibly be of importance for the diagnosis with better image quality and special techniques in the future (38-40).

### **2.2.4 Barrett’s esophagus**

In BE, the normal squamous epithelium of the distal esophagus is replaced by columnar epithelium. The term BE has been under debate since the first publications in 1950 and 1957 by Norman R. Barrett and it has been applied only to mean the endoscopic appearance of the esophagus or with the requirement of histologically-proven specialized intestinal metaplasia of the endoscopically visible segment (21, 24, 41).

The updated definition of BE by the American College of Gastroenterology states that: “a change in the esophageal epithelium of any length that can be recognized at endoscopy and is confirmed to have intestinal metaplasia by biopsy in the tubular esophagus and excludes intestinal metaplasia of the cardia” are requirements for the BE diagnosis (42). Because of the discrepancies mentioned above, there has been a need for consensus on the definition and the 2004 AGA Chicago workshop presented a practical review on the diagnosis and management of BE, specifically of the endoscopically visible landmarks (43). The Global Montréal definition of GERD proposed a wider definition: “endoscopically suspected esophageal metaplasia (ESEM) describes endoscopic findings consistent with Barrett’s esophagus that await histological evaluation” (10). The same definition states that “multiple, closely spaced

biopsies are necessary to characterize ESEM” and that “when biopsies of ESEM show columnar epithelium it should be called Barrett’s esophagus and the presence or absence of intestinal-type metaplasia specified” (10).

## **2.2.5 Eosinophilic esophagitis**

EE has been defined by the presence of more than 20 eosinophils per high power field in the esophageal epithelium (44, 45). Even lower cut-offs have been used (46-48).

According to available reports, EE typically presents in younger males (male: female ratio 3:1) with dysphagia; food impaction may occur in two thirds and heartburn in a quarter of cases (49, 50). Endoscopic findings can include a normal esophagus (44, 51), although how often this occurs is uncertain, as the literature may be influenced by selection bias. Reports of abnormalities include esophageal rings or a corrugated appearance, edema or fragility, narrowing or structuring of the esophagus, especially more proximally, and whitish papules or exudates (46, 48, 50). Histological confirmation is needed for the diagnosis.

## **2.3 EPIDEMIOLOGY**

### **2.3.1 GERD**

Due to the lack of consensus in the past over the definition of GERD, or the fact that investigators have used arbitrary or own definitions of GERD, its prevalence (i.e. the number of cases with a disease in a given population at a specified point in time or during some period of time) is not well-defined. Heartburn and acid regurgitation are the symptoms that are best correlated to objectively measurable abnormalities in GERD. About two-thirds of those reporting these symptoms, have objectively detectable abnormalities present at endoscopy, 24 hours pH monitoring or lower esophageal sphincter pressure measurement (52) (53) (26) (8).

In a U.S. population, Nebel et al. (1) reported that heartburn was experienced daily by 7% and monthly by 36% of the population. There was no significant difference regarding age and gender, except for pregnant women, of whom 25% and 52% reported daily and monthly heartburn, respectively. In a Swedish study, Ruth et al. (54) reported symptoms suggestive of GERD in 25% of a randomly sampled adult population. Twenty-one per cent reported heartburn, 20% acid regurgitation and 12% non-cardiac chest pain. The overall figure of 25% was reproduced in another Swedish population based study by Agréus et al. (55). There was no difference regarding age or gender. In a population-based British study, Jones et al. (56), found that 31% had experienced heartburn in the preceding six months, but also that 56% of those with upper abdominal complaints reported concurrent heartburn. Talley et al. (57) found from the population of Olmsted County, Minnesota U.S., that 24% of the study population had had heartburn at least once a month during the preceding year, and that 11% reported acid regurgitation. They found no significant age or sex differences. Locke et al. (58), found a prevalence of 18% of at least weekly heartburn and/or acid regurgitation in a sample of Olmsted County residents between the ages of 25 and 74 years. Recently, Nocon et al. reported an overall prevalence of 43% and a prevalence of 18% of moderate and severe reflux symptoms in a representative cohort of German population (7)

GERS have been shown to be relatively stable over time unlike symptoms of irritable bowel syndrome or dyspepsia (4, 5, 59).

Erosive esophagitis has been shown to be the most common endoscopic diagnosis in patients with upper abdominal complaints and it is found in about one-third to two-thirds of patients with reflux symptoms who have been referred for investigation (26, 28, 60). However, the prevalence of erosive esophagitis in the general population has not been thoroughly studied. Erosive esophagitis in the general adult population has perhaps been best described in the Norwegian Sørreisa study (61), which was a case control study based on symptoms reported in a questionnaire given to a random population. Esophagitis was found in 9% of the controls, 11% in each of the groups with heartburn alone or in combination with epigastric pain, and in 16% of subjects with epigastric pain. In a recent Swedish, population-based esophagogastroduodenoscopy (EGD) study surveying people of 35 years of age and older, the prevalence of esophagitis was 8% (62). However, the response rate in that study (25%) does not guarantee that it is representative of the general population. In an as yet unpublished Italian study, the prevalence of reported esophagitis in an adult population was 9%, and 25% of those had no symptoms (63).

A recent systematic review by Dent et al. (6), which applied strict criteria for quality of the 15 accepted studies and used at least weekly heartburn and/or acid regurgitation as the definition of GERD, showed an approximate prevalence of 10-20% in the Western world while in Asia the prevalence was less than 5%. The annual incidence, (i.e. the number of new cases that develop in a given population during one year) was approximately 5 per 1000 person years in the Western world (6) consistent with the chronic nature of GERD.

### **2.3.2 Barrett's esophagus**

Due to patient selection and endoscopic and histological criteria used, the figures on BE prevalence vary considerably (64). In an autopsy study in Olmsted County, Cameron et al (65) found a prevalence of 0.4% in a forensic medicine population. In 1128 consecutive patients with reflux symptoms or dyspepsia referred for endoscopy in primary care in Finland, the prevalence of BE was 1% in the whole population and 4.4% in those with GERD (28). In a German study of 6215 patients with reflux symptoms, the overall prevalence of BE was reported to be 4.9 %, but in those with esophagitis, it was 8.4% (66). In the U.S., a remarkably high prevalence of BE (25%) was reported among mainly male veterans without reflux symptoms attending a sigmoidoscopy screening program, but who also had upper GI endoscopy (67). In a colonoscopy screening program, also in the U.S., Rex et al found a prevalence of BE of 8.3%, with long segment in 2.6% in those with reflux symptoms, compared with 5.6% and 0.4%, respectively, in those without reflux symptoms (68). A recent Canadian study showed a BE prevalence of 2.4% in primary care patients with dyspepsia in prompt endoscopy (69).

### **2.3.3 Eosinophilic esophagitis**

EE is thought to be a very rare inflammatory condition in adults (70) with an estimated prevalence 0.2-3 in 10,000 (16). However, no population-based studies are available. The epidemiology of EE may also be changing; Noel et al. reported a more than 4-fold increase in EE prevalence among children between the years 2000 and 2003 in the US and several case reports and case series on adults suggest that either the incidence is increasing or the disease is now being recognized more often (50, 71, 72). While many consider EE in adults to be distinct from GERD, data on its possible association with GERD are conflicting and no population-based information is available (15, 16).

## **2.4 PATHOPHYSIOLOGY OF GERD**

Retrograde flow of gastric contents from the stomach into the esophagus occurs at least a few times daily in all of us when the intragastric pressure overcomes the competence of the gastroesophageal junction (swallowing, belching). Usually it does not occur by compressing the abdomen, bending or straining. A mechanism at the gastroesophageal junction, which consists of functional and structural components, prevents reflux. The most important constituents of this mechanism are the lower esophageal sphincter (LES) and the external components such as the crural diaphragm and the intra-abdominal position of the LES (73-75). Normally, in the esophagus both reflux and distension trigger motor activity which results in peristaltic activity clearing the esophageal lumen (76).

In healthy individuals, and in endoscopy-negative and low-grade esophagitis, almost all reflux episodes are related to transient lower esophageal sphincter relaxation (TLESR) (30, 77, 78). In patients with GERD, the level of esophageal acid exposure is markedly increased due to frequent episodes of reflux (8). TLESRs are responsible for most of the reflux episodes also in those with hiatus hernia and permanently lower esophageal sphincter tonus, although these conditions are confined to more severe forms of GERD (30, 79). In patients with severe esophagitis, both daytime and nocturnal esophageal acid exposure are important and failure of the anti-reflux mechanism also contributes to the relatively high levels of acid exposure in this group of patients (80). However, nighttime heartburn has been shown to occur in a large majority of adults with GERD and to cause sleep disturbances with impaired next-day function (81). The anti-reflux mechanism of the crural diaphragm, together with the intra-abdominal pressure, is lost in patients with large hiatus hernias (30), although it doesn't always lead to severe reflux (82). In addition, esophageal acid clearance has been shown to be impaired in half of the patients with GERD (82).

Obesity is a well known risk factor for GERD (83, 84) and its complications (85), and it has been shown that obese subjects are more likely to have disruption of the esophagogastric junction which "provides a perfect scenario for reflux to occur" (86).

A minority of patients with reflux symptoms have normal levels of esophageal acid exposure (87). There is also an overlap in acid exposure between patients with different endoscopic findings and healthy control subjects (88). These observations suggest that barrier mechanisms within the epithelium of the esophageal mucosa, hypersensitivity of the esophageal mucosa (89, 90) or motor disorders (91) may be important for the

development of esophageal injury and symptoms. Differences in these factors between individuals may explain why the same level of acid exposure causes symptoms and esophageal damage in some individuals but not in others (92, 93).

### **3 AIMS OF THE STUDY**

The aims of the study were:

1. To estimate the prevalence of, and to identify risk factors for, gastroesophageal reflux symptoms and erosive esophagitis in a representative random sample of the adult population of two Swedish municipalities.
2. To determine the frequency of reflux symptoms associated with a clinically meaningful impairment of health-related quality of life in a representative random sample of the adult general population and to assess whether the presence of esophagitis correlated with the frequency of symptoms and/or impairment in health-related quality of life.
3. To determine the prevalence of Barrett's esophagus and associated risk factors in the adult general population, irrespective of reflux symptoms.
4. To determine the presence of eosinophils in the distal oesophagus and the prevalence of eosinophilic esophagitis in a random sample of an adult Swedish population, and to determine the association between oesophageal eosinophils and upper gastrointestinal symptoms and GERD.

## **4 MATERIALS AND METHODS**

### **4.1 DEFINITIONS OF TERMS**

#### **4.1.1 Gastroesophageal reflux symptoms**

GERS were defined as reporting troublesome heartburn and/or acid regurgitation at any time during the past three months (8, 33, 94) assessed by the Abdominal Symptom Questionnaire (ASQ) (see section 4.2.2). In addition, troublesome weekly or daily symptoms during the past three months were evaluated. The additive value of using the score for the specific reflux key-question in the Carlsson-Dent questionnaire (32) was also assessed.

#### **4.1.2 Dyspepsia**

Dyspepsia was defined as reporting troublesome pain or discomfort expressed as one or more of the 11 listed modalities (burning sensation, aching, pain, tenderness, gripe, twinge, stitch, cramp, colic, sinking feeling and butterflies) indicated in the epigastric part of the abdomen in a provided drawing (33), or reporting one or more of the symptoms uncomfortable feeling of fullness, early satiety or nausea in accordance with the Rome II definition of dyspepsia (95) (upper abdominal bloating not reported in the ASQ).

#### **4.1.3 Health-related quality of life**

A health status assessment, the Medical Outcome Study 36-item Short-Form (SF-36) Health Survey (96-98) was used in assessing the HRQoL in this study. The volunteers completed the acute version of the SF-36, which has a 1-week recall period.

#### **4.1.4 Erosive esophagitis**

Subjects with mucosal breaks in the esophagus at endoscopy were classified as those with erosive esophagitis and graded according to the Los Angeles classification (37, 38).

The Los Angeles classification of esophagitis grades the appearance of esophageal mucosal breaks (i.e. an area of slough or an area of erythema with a discrete lined demarcation from the adjacent or normal looking mucosa).

- |         |  |
|---------|--|
| Grade A | One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds   |
| Grade B | One (or more) mucosal break more than 5 mm long that does not extend between the tops of mucosal folds   |
| Grade C | One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involves less than 75% of the circumference |
| Grade D | One (or more) mucosal break which involves at least 75% of the esophageal circumference.   |

#### **4.1.5 Barrett's esophagus**

BE was searched for when a suspected columnar lined esophagus (suspected CLE) was identified at endoscopy, based on salmon pink mucosa in either a circumferential upward shift of the squamocolumnar junction or in adjacent mucosal tongues (42, 65) or islands (99).

The diagnosis of BE was based on the endoscopic finding of suspected CLE in the distal esophagus and histologically confirmed presence of specialized intestinal metaplasia (SIM) in the esophageal biopsy specimens (41, 43, 100, 101). BE was defined as long segment BE (LSBE) if the segment was 2 cm or more in length and short segment BE (SSBE) if it was shorter than 2 cm (102-104).

The gastroesophageal junction (GEJ) was defined as the junction of the proximal gastric folds and the tubular esophagus, which is in accordance with the only one definition for GEJ supported by all members of the Prague International Consensus Group for endoscopic grading system for BE: "the GEJ as being 'at the proximal margin of the gastric mucosal folds'" (Dr. Prateek Sharma, personal communication).

#### **4.1.6 Eosinophilic esophagitis**

Any eosinophilic infiltration of the oesophageal epithelium was defined as esophageal eosinophils present. Eosinophils were quantified by counting the number per high power field (x40 magnification). Any eosinophilic infiltration was classified as possible EE if 5-14 eosinophils/HPF, probable if  $\geq 15$ - $< 20$  eosinophils/HPF and definite EE if  $\geq 20$  eosinophils/HPF (44) were noted.

### **4.2 STUDY POPULATION**

#### **4.2.1 Setting, sampling, study design**

This study was performed in two adjacent municipalities in the northern part of Sweden, Kalix and Haparanda (= "the Kalixanda Study"), with 28, 988 inhabitants (as of December 1998) most of them living in urban areas (78% in year 2000), compared to the Swedish national average of 84%. The distribution of age and gender in this area was similar to the national average in Sweden (94), while some other socio-economic variables (unemployment status, income, proportion with higher education) were slightly lower in Kalix and this pattern was somewhat more marked in Haparanda as compared to this national average (105, 106). In Haparanda, a third of the inhabitants were born outside Sweden (mostly in Finland), while in Kalix this figure was slightly less than the average in Sweden (11%). Overall, 11.3% of responders answered the questionnaires in Finnish (2.1% in Kalix, 27.3% in Haparanda) (107).

All Swedish residents have a unique national registration number which includes date of birth and a gender code, stored in an official population register which by law must be kept up-to-date (108). By using this register, the adult population (18-80 years) living in the two municipalities was identified and defined as the target population (n = 21,610 in September 1998, Figure 1). A systematic sample (every seventh) of the target population (13.9% of the target population) was enrolled as the study population

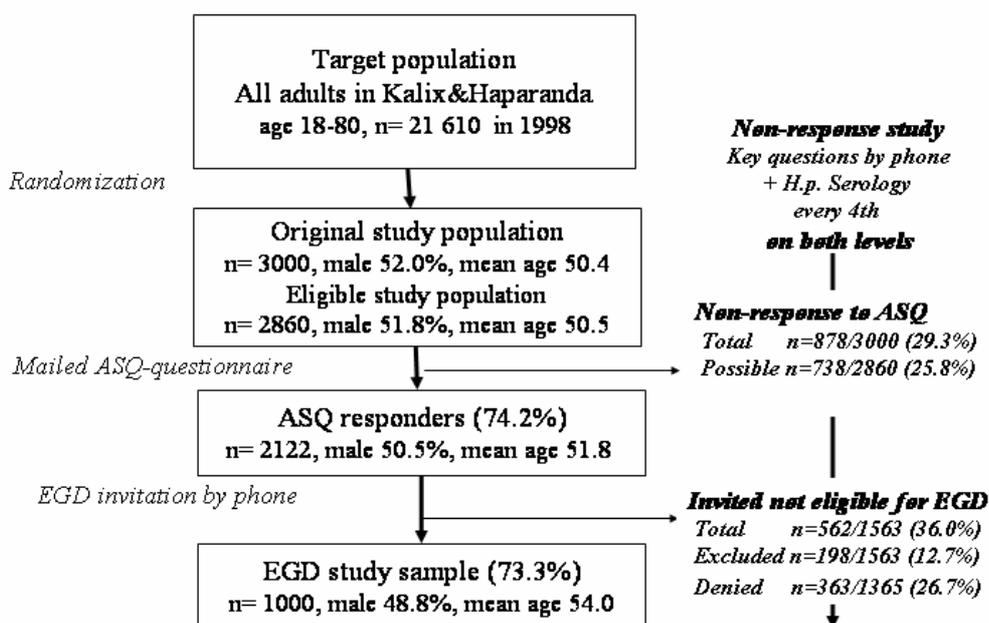
(n=3,000), a procedure equivalent to random sampling. The selected subjects were then given a computer-generated and randomized identification (ID) number (94).

It was planned to perform an EGD in one third of the study population, i.e. 1,000 individuals in a random order, who formed the EGD study sample (4.6% of the target population). The EGD study sample size was dimensioned to allow for appropriate precision of the prevalence estimates around the 95% confidence intervals ( $\sim \pm 2\%$ ).

A letter with an invitation and a validated postal questionnaire focusing on gastrointestinal symptoms, ASQ (33), was mailed to the study population, followed by up to two reminders. The responders to the initial ASQ were invited by telephone, in ascending ID order, to undergo an EGD and to complete a more comprehensive set of questionnaires. The eligible study population decreased over the two and a half year inclusion time from 3,000 to 2,860, mainly because of migration. The 140 non-eligible subjects had a mean age of 49.7 and 55% of them were men. These non-eligible subjects did not as a group differ from the original study population in terms of characteristics (94). Reasons for being non-eligible in the target population were: deceased=21, moved and questionnaire returned by relatives=38, mentally retarded/dementia=17, none of these three causes=15 (cause not defined in a sub sample of the first out mailing), incorrect address (may have moved since sampling) = 49.

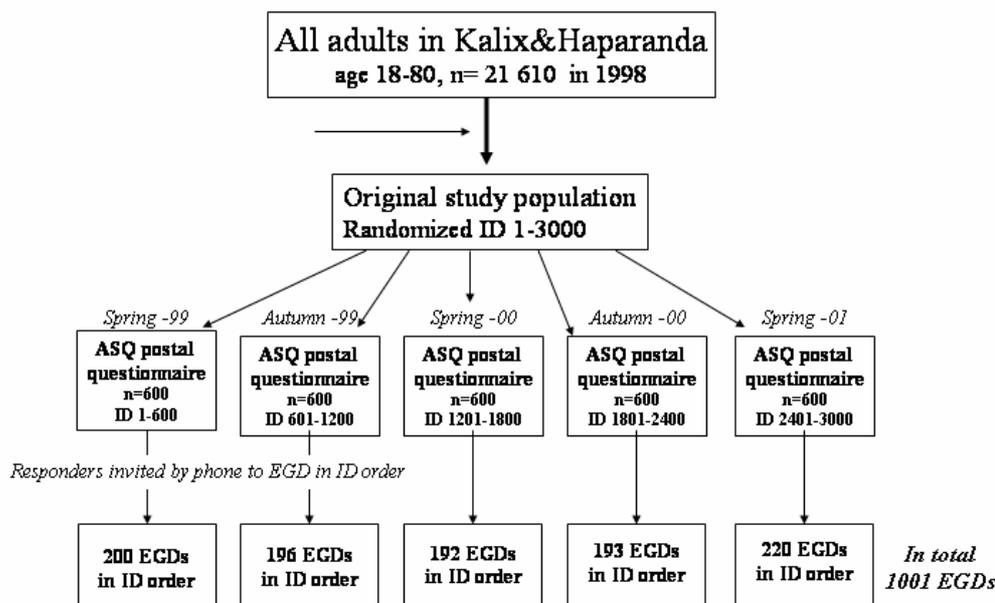
This study was approved by the Umeå University Ethics Committee on May 29, 1998 (Um dnr 98 -99) and conducted in accordance with the revised Declaration of Helsinki. All participants gave their informed consent to participate in the study. No economic reimbursement was given for participation in the study.

The study outline is shown in Figure 1.



For logistic reasons, the study population was divided into five groups in ascending order, ID 1-600, 601-1,200 etc., as shown in Figure 2. The first subset of study subjects was mailed the ASQ in November 1998 and the project took two and a half years to complete. The numbers of EGDs per subset are shown in Figure 2, and the total number of subjects that had EGDs was 1,001, from which biopsies for *H. pylori* culture and histology were available from 1,000 subjects.

Figure 2. Study logistics.



Every fourth non-responder to the initial ASQ was approached by telephone or mail for seven key questions including heartburn, acid regurgitation and level of education in order to collect non-response data. They were also asked to give a blood sample for *H. pylori* serology. Those who were not eligible for endoscopy and additional study questionnaires were analyzed regarding their mailed questionnaire responses.

#### 4.2.2 Questionnaires

The questionnaires used in this investigation have all been validated, found reliable and described in detail previously (32, 33, 94, 96, 98, 107, 109, 110).

The initial mailed ASQ asked the participants if they had been troubled (Yes/No) by any of a list of 27 general gastrointestinal symptoms over the prior three months. They were also asked if they had been troubled by any of 11 listed descriptors of abdominal pain or discomfort, and also about their location (upper, centre or lower abdominal, right and left flank, respectively). In order to better reflect the Rome II definitions of the functional gastrointestinal disorders (111), eight questions were added at applicable parts of the questionnaire, including the key question from the Carlsson-Dent questionnaire ("burning feeling rising from the stomach or lower chest up towards the neck") (32). The ASQ used in connection with the EGD, also recorded symptom

frequency (daily, weekly or monthly). Moreover, the participants were asked about the number of inhabitants in their household and their level of education (1: elementary, 2: comprehensive, 3: secondary, 4: upper secondary, 5: university).

In addition, the complete Carlsson-Dent questionnaire (32) and the HRQoL questionnaire, SF-36 (97) were completed by the study subjects immediately before the endoscopy.

The SF-36 questionnaire is a generic measure of HRQoL that was constructed to survey health status in the Medical Outcomes Study and has been widely used in patients with a range of diseases, including GERD (96, 112). The SF-36 consists of 36 items organized as eight dimensions: physical functioning, role-physical, bodily pain, general health, mental health, vitality, social functioning, and role-emotional. The raw scale scores from each of the SF-36 dimensions were transformed to a 0 to 100 scale (98). This transformation converts the lowest and highest possible scores to zero and 100, respectively, and a 5-point or greater difference in this scale has been shown to be clinically relevant (96-98). Scores between these values represent the percentage of the total possible score achieved. This allows the comparison with norms derived from Medical outcome Survey and the Swedish means (98). The definition of a clinically meaningful difference, i.e. a difference of 5 points or greater in SF-36, was also shown to be statistically significant ( $p < 0.05$ ) in our study.

The endoscopists did not have access to the results of the questionnaires, until the case record form for the EGD was completed and signed after the procedure.

A further questionnaire, completed during the clinic visit after the blinded part of the study, asked whether subjects had consulted a general practitioner or a specialist physician during the previous year and whether they had consulted a physician regarding their gastrointestinal (GI) or upper GI symptoms during this period. Subjects were also asked whether they had taken any GI or other medications over the last three months.

### **4.2.3 Upper gastrointestinal endoscopy**

The EGDs were performed by both primary and secondary care physicians in the two clinics, which provided sole medical cover to the area. The three endoscopists, one gastroenterologist in Kalix and two general practitioners in Haparanda involved in this study, were experienced each having previously performed between 2,500 and 6,000 EGDs. All three had been participating in regular quality assessment programs in Sweden and/or in Finland over several years. In order to achieve endoscopic assessment reliability, the endoscopists participated in training sessions before and during the study focusing on assessment of BE and esophagitis (94). A step-by-step process assessed internal validity of the endoscopies performed: a consensus meeting was held with an external consultant (a professor of GI surgery) who reviewed common macroscopic findings and standardized classification systems, such as the Los Angeles classification for erosive esophagitis, BE and gastric and duodenal ulcer disease, captured on video. Furthermore, a test session with a professor in gastroenterology, who first reviewed the video sessions as described above and then, focused on

esophageal findings, showed six cases and required each endoscopist to give a diagnosis. For the lower esophagus-cardia region, only one of the 18 diagnoses had a mismatch (Los Angeles grade A vs. normal). In Haparanda, an Olympus XQ-20 fiber endoscope (Olympus Co., Tokyo, Japan) was used and in Kalix an Olympus GIF-100 video endoscope (Olympus Co.) was used.

Inclusion criteria for the EGD were a response to the initial ASQ and accepting the investigation. Exclusion criteria were unwillingness to accept an EGD and also medical contraindications (n=124), including prior gastric or duodenal surgery (n=10), as listed below in the results.

#### **4.2.4 Histological evaluation**

In total, at least 20 biopsies were taken from each subject. At least two biopsies were taken from the following locations in the esophagus: 2 cm above the Z-line, at the Z-line and from any abnormal areas. In the stomach, biopsies were obtained according to the recommendations of the updated Sydney System (113). Biopsy specimens were examined independently by two experienced gastrointestinal pathologists who were unaware of the clinical data and endoscopic findings. Biopsies were stained with haematoxylin and eosin and those from the stomach were also stained with Warthin-Starry-silver stain. The kappa-value for agreement between observers in the evaluation of *H. pylori* was 0.76 (95% CI 0.56-0.96) for the corpus and 0.78 (95% CI 0.59-0.98) for the antrum (114).

The diagnosis of Barrett's epithelium was made only if specialized intestinal metaplasia (41), characterized by the presence of goblet cells, could be identified. Complete intestinal metaplasia (CIM) (115) of the cardia mucosa was not included in the definition.

In defining esophageal eosinophils and EE, biopsies in the primary analysis were scored in a semi-quantitative manner: none, mild, moderate and marked infiltration. Subsequently, for exact cell counts, biopsies with any eosinophils on the first evaluation were reviewed by a third pathologist, who was also blinded to the clinical data and endoscopic findings, paired with biopsies with no eosinophils on first assessment, such that an independent review of eosinophil counts could be undertaken. This confirmed the absence of eosinophils in paired biopsies without eosinophils on first assessment. In two cases 2 cm above the Z-line, biopsies were missing. At the Z-line, biopsy specimens were not available for evaluation in absolute number in six cases, five of these were classified as mild and one case had no eosinophils in the primary analysis.

#### **4.2.5 Laboratory analysis of *Helicobacter pylori***

For identification of *H. pylori*, both histology and culture were used. A Warthin-Starry-Silver-Stain was performed on gastric samples from the corpus and the antrum. Two biopsies for culture were obtained from the same locations and placed in freezing medium with 10% glycerol. The tubes were then frozen at - 20° C immediately after the endoscopy and moved to - 70° C within 2 weeks. These samples were analysed separately by standard procedures at the Institute for Infectious Disease Control (SMI),

Stockholm, Sweden (116). There was an overall agreement of 99.3% with a kappa value of 0.96 (95%CI: 0.94-0.98) between the tests (117).

Blood samples were taken for assessment of *H. pylori* serology. IgG antibodies to *H. pylori* were determined by EIA (Pyloriset EIA-G, Orion diagnostica, Espoo Finland) at the SMI, Stockholm, Sweden (118). Based on local validation for *H. pylori* positivity on either culture or histology as the gold standard, the sensitivity and specificity were 99% and 86%, respectively, and the positive predictive value (PPV) and negative predictive value (NPV) were 78% and 100%, respectively (117).

### 4.3 STATISTICAL ANALYSIS

P-values were all two tailed and the alpha level of significance was set at 0.05. The prevalence is shown as a percentage with a 95% confidence interval (CI). Likelihood ratio Chi-2 test and Fisher's exact test were used for testing comparison in univariate analyses. When comparing prevalence of symptoms for sub-populations, a t-test was applied and a p-value less than 0.05/2 equal with  $< 0.025$  (2 study samples were analyzed) was accepted as statistically significant. Correlations were calculated with Spearman's correlation test.

For study II, transformed (0-100) mean SF-36 scores (see section 4.2.2) and 95% confidence intervals were determined and graphed for the total study population in comparison with the Swedish mean (98), for the four subgroups with differing symptom frequencies (no troublesome GERS, less than weekly, weekly and daily troublesome GERS) and for subjects with or without esophagitis. Transformed mean SF-36 scores were compared to identify clinically relevant ( $\geq 5$ -point) differences (97). Statistical significance was assessed using Student's t-test, and Satterthwaite's approximation was used because the differences in transformed SF-36 scores between patients with no symptoms and patients with daily symptoms meant that equal variances could not be assumed (119).

A multiple logistic regression model (a main effect model after model improvement) was used to identify predictors of reflux-related manifestations by including a block of similar variables (120). The results are shown as odds ratios (OR) with 95% CI. The reference group was given an OR of 1. The goodness of fit of the models was judged from the Pearson Chi-2 test and degrees of freedom, which should be about equal. The fit of the model was considered to be acceptable with a p-value  $\geq 0.05$ . Age was tested for linearity and included as a continuous variable in the logistic regression models. If it was not linearly related a stratified analysis was performed. The Intercooled STATA 8 program (121) was used for the analyses.

Age, gender, education, hiatus hernia, esophagitis, obesity (BMI  $\geq 30$  (122)), reflux symptoms, dyspepsia, alarm symptoms (stated weight loss, dysphagia, anemia, hematochezia), asthma or allergy, tobacco use (smoking or snuff), alcohol, use of non steroidal anti-inflammatory drugs or aspirin, use of antacids/alginates, H<sub>2</sub>-receptor antagonists or proton pump inhibitors, use of asthma or allergy medication, current *H. pylori* infection, serology positive but no current infection of *H. pylori*, chemical gastritis, corpus-dominant *H. pylori* gastritis, atrophy of mucosa and dichotomized

histological presence of lymphocytes and granulocytes in the cardia of the stomach (“carditis”) were the dependent variables analyzed included in the logistic regression models as possible predictors for GERD.

## **5 RESULTS**

### **5.1 RESPONSE RATE**

The response rate to the mailed initial ASQ was 74.2% (50.5% men, mean age 51.8 years). In the non-response study every fourth subject (185 of the 738 non-responders) was approached and 143 (77.3%) replied. The prevalence of GERS was 31.7% (CI = 24.1-39.3) among the non-responders and 33.6% (CI = 31.6-35.6) among the responders (ns) (94).

In order to find 1,000 subjects who were willing to undergo EGD, 1,563 subjects had to be approached. Of the 563 subjects not available, 364 declined, 74 had moved, 124 had medical contraindications and one refused biopsy. Thus, the response rate for the eligible study subjects was 73.3% (1000/1365) (94). Contraindications to endoscopy in this study were the presence of serious physical or mental disorders, including unstable angina or recent myocardial infarction (n=2), heart failure (n=7), recent cerebral infarction or bleeding (n=6), psychosis and other severe mental disorders (n=13), mental retardation or dementia (n=9), anticoagulation (n=10), known bleeding tendency (n=0), artificial heart valve or known valve disorder (n=6), known esophageal varicose (n=0), alcoholism (n=2), previous upper GI surgery, excluding cholecystectomy (n=10), lung disease with low respiratory capacity (n=9), current malignant disease (n=21) and pregnancy (n=9) or other relevant severe disorders (n=20).

### **5.2 HEALTH CARE CONSUMPTION AND USE OF CONCOMITANT MEDICATION**

Of the 1,000 investigated subjects in the EGD study sample, 63.6% had visited a doctor during the past year. GI disorders were the reason for the visit in only 4.7% cases and in 2% the visit was because of upper GI symptoms. The proportion of subjects with GERS that had visited a doctor during the last year was 70.3%, compared with 59.2% of those without GERS (p=0.004). Among those with GERS, 6.5% had seen a doctor for any GI disorder compared with 3.5% of those without GERS (p=0.03) and the figures for upper GI disorders were 3.3% and 1.2% (p=0.03 respectively). Of those with erosive esophagitis, 61.9% had visited a doctor the past year and for 1.3% the visit was caused by upper GI disorders. The figures did not differ significantly between those with and without erosive esophagitis.

In the EGD study sample, 115 subjects had taken antacids/alginates, 31 H<sub>2</sub>-receptor antagonists and 49 proton pump inhibitors during the last three months. The week before the EGD, the corresponding figures were 55, 14 and 36, respectively.

### **5.3 PREVALENCE AND RISK FACTORS FOR GERD (STUDY I)**

The prevalence of GERS reported at all, at least weekly or daily during the last three months is shown in Table 1. Four hundred subjects (40%, 95% CI 37.0-43.0) reported, at the time of the EGD visit, that they had been troubled by GERS over the last three months (Table 1). Their mean age was 52.7 years and 45.3% were men. At least weekly symptoms were reported by 200 subjects (20%, 95% CI 17.5-22.5, mean age

52.4, 45% men) and daily symptoms by 59 subjects (5.9%, 95% CI 4.4-7.4, mean age 52.8, 44.1% men).

There were no statistically significant differences in the prevalence of esophagitis between the two study centers (13% vs.17%, p = 0.25).

Table 1: Prevalence (n, %), frequency (3 months, at least weekly or daily over the last 3 months) and risk (OR, 95% CI) of GERS, in relation to endoscopic findings (normal, erosive esophagitis or hiatus hernia) for all subjects and by gender.

	EGD Study sample	Endoscopic findings		
		Normal esophagus in endoscopy*	Erosive esophagitis	Hiatus hernia**
<u>All:</u>	n=1000	n=769	n=155	n=239
with GERS				
3 month, n(%)	400 (40)	<b>271 (35.2)</b>	<b>98 (63.2)</b>	<b>126 (52.7)</b>
OR, (95% CI)		<b>0.37 (0.28-0.53)</b>	<b>3.45 (2.39-4.99)</b>	<b>2.11 (1.57-2.85)</b>
Weekly, n (%)	200 (20)	<b>125 (16.2)</b>	<b>58 (37.4)</b>	<b>77 (32.2)</b>
OR, (95% CI)		<b>0.37 (0.26-0.52)</b>	<b>3.27 (2.22-4.81)</b>	<b>2.60 (1.86-3.65)</b>
Daily, n (%)	59 (6)	<b>31 (4.0)</b>	<b>21 (13.6)</b>	<b>34 (14.2)</b>
OR, (95% CI)		<b>0.28 (0.16-0.48)</b>	<b>3.73 (2.08-6.70)</b>	<b>5.14 (2.98-8.87)</b>
<u>Male:</u>	n=488	n=340	n=108	n=130
with GERS				
3 month, n (%)	181 (37.1)	<b>104 (30.6)</b>	<b>65 (60.2)</b>	<b>66 (50.8)</b>
OR, (95% CI)		<b>0.41 (0.27-0.61)</b>	<b>3.37 (2.15-5.27)</b>	<b>2.38 (1.57-3.63)</b>
Weekly, n (%)	90 (18.4)	<b>47 (13.8)</b>	<b>36 (33.3)</b>	<b>39 (30.0)</b>
OR, (95% CI)		<b>0.40 (0.25-0.63)</b>	<b>2.93 (1.79-4.82)</b>	<b>2.79 (1.72-4.56)</b>
Daily, n (%)	26 (5.3)	<b>12 (3.5)</b>	10 (9.3)	<b>17 (13.1)</b>
OR, (95% CI)		<b>0.35 (0.16-0.79)</b>	2.27 (1.00-5.18)	<b>6.20 (2.67-14.4)</b>
<u>Female:</u>	n=513	n=431	n=47	n=109
with GERS				
3 month, n, (%)	219 (42.7)	<b>167 (38.8)</b>	<b>33 (70.2)</b>	<b>60 (55.1)</b>
OR, (95% CI)		<b>0.37 (0.22-0.60)</b>	<b>3.55 (1.85-6.81)</b>	<b>1.88 (1.23-2.89)</b>
Weekly, n (%)	110 (21.4)	<b>78 (18.1)</b>	<b>22 (46.8)</b>	<b>38 (34.9)</b>
OR, (95% CI)		<b>0.35 (0.21-0.58)</b>	<b>3.77 (2.03-7.00)</b>	<b>2.46 (1.54-3.94)</b>
Daily, n (%)	33 (6.4)	<b>19 (4.4)</b>	<b>11 (23.4)</b>	<b>17 (15.6)</b>
OR, (95% CI)		<b>0.22 (0.11-0.47)</b>	<b>6.16 (2.77-13.7)</b>	<b>4.49 (2.18-9.23)</b>

The risk of GERS in each group was calculated as an odds ratio (OR) with 95% C.I., where the reference group, with or without GERS, had an OR of 1.

\* = No erosive esophagitis or other abnormal endoscopic findings. Includes 123 individuals with a hiatus hernia as only abnormal endoscopic finding.

\*\* = Hiatus hernia with or without other endoscopic abnormal findings.

All models had sufficient goodness of fit.

Statistically significant differences in **bold**.

Erosive esophagitis was found in 155 subjects (15.5%, 95% CI 13.2-17.7), with a mean age of 52.6 years (Table 1). The prevalence of erosive esophagitis in relation to gender, as well as L-A classification, is shown in Table 2. Erosive esophagitis was most prevalent in men (22%), especially so in the youngest age group (32%) and most often low-grade esophagitis (L-A grade A or B in 95.5% of cases) was diagnosed. Overall, men (n=108, 69.7%) had a higher risk of erosive esophagitis (OR = 2.83, 95% CI 1.96-4.09) than women (n=47) (Table 2).

Table 2: The prevalence (n, %) of erosive esophagitis and the three months prevalence (%) of GERS by esophagitis grade (according to the L-A classification).

	<b>Esophagitis</b>					
	<b>Normal*</b> <b>n (%)</b>	<b>Grade A</b> <b>n (%)</b>	<b>Grade B</b> <b>n (%)</b>	<b>Grade C</b> <b>n (%)</b>	<b>Grade D</b> <b>n (%)</b>	<b>Grade A-D</b> <b>n (%)</b>
All						
n=1000*	769 (76.9)	109 (10.9)	39 (3.9)	3 (0.3)	2 (0.2)	155 (15.5)
% with GERS	35.1	57.8	79.5	100	50.0	63.2
Male***						
n=488 (48.8)	340 (69.7)	77 (15.8)	26 (5.3)	1 (0.2)	2 (0.4)	108
% with GERS	30.6	54.6	80.8	100	50.0	60.2
Female						
n=512 (51.2)	429 (83.8)	32 (6.2)	13 (2.5)	2 (0.4)	0	47
% with GERS	38.8	65.6	76.9	100		70.2

\*No abnormal endoscopic findings in the esophagus

\*\*sCLE, polyps and diverticulae without erosive esophagitis not included in the table (n=76)

\*\*Missing classification data in 2 male subjects

Of the 400 subjects with any GERS during the last three months, 98 (24.5% of those with GERS and 9.8% of the EGD study sample) had erosive esophagitis (mean age 52.7 years, 38.4% men). Thus, 63.2% of the 155 individuals with erosive esophagitis reported GERS (Table 1). The 57 subjects with erosive esophagitis who did not report GERS (36.8% of those with erosive esophagitis, and 5.7% of the EGD study sample) had a mean age of 52.6 years and 75.4% of them were men. Moreover, of the 400 subjects reporting GERS the last three months, 271 (67.8% of those with GERS and 27.1% of the EGD study sample) had no macroscopic signs of erosive esophagitis.

Of the 200 subjects with troublesome GERS at least weekly, 58 (29%) had erosive esophagitis and of those 59 with daily symptoms, 21 (35.6%) had erosive esophagitis.

There was a significantly lower odds that men with GERS had no erosive esophagitis (OR = 0.70, 95% CI 0.52-0.95) than women, but there was a significantly higher odds of men having erosive esophagitis with (OR = 2.25, 95% CI 1.43-3.55) or without (OR = 3.55, 95% CI 1.89-6.68) GERS than women.

Subjects with GERS had a higher risk of erosive esophagitis (OR = 3.45) and hiatus hernia (OR = 2.11) than those without GERS in a gender- and age-adjusted model, as shown in Table 1.

When *H. pylori* infection was introduced into a logistic regression model, together with age and gender only, those with a current *H. pylori* infection had a statistically significantly increased risk for GERS without esophagitis (OR = 1.58, 95% CI 1.14-2.19), but decreased risk for esophagitis with (OR = 0.54, 95% CI 0.31-0.92) and without reflux symptoms (OR = 0.40, 95% CI 0.19-0.84), respectively (data not shown in tables). On the contrary, those with a “serological scar” of the infection (i.e. positive by serology but no *H. pylori* on histology or culture) had an increased risk for silent (i.e. without GERS) esophagitis (OR = 2.46, 95% CI 1.13-5.34).

However, when *H. pylori* infection was introduced into the main effect model in Table 3, a non-linear interaction between age and *H. pylori* infection was found in those with erosive esophagitis reporting GERS and therefore a stratified analysis (*H. pylori*-positive and *H. pylori*-negative separately) was performed. This showed that only the risk for GERS without concomitant erosive esophagitis at current *H. pylori* infection remained statistically significantly increased (Table 3).

Predictors for erosive esophagitis with and without symptoms are also presented in Table 3. For erosive esophagitis with GERS, male sex (OR = 2.21), hiatus hernia (OR = 10.05), overweight (OR = 2.18) and obesity (OR = 3.29) remained statistically significant risk factors in the stratified analysis for those who were *H. pylori*-negative. For those who were *H. pylori*-positive (current infection), hiatus hernia (OR = 8.88) and obesity (OR = 9.96) were significant risk factors for erosive esophagitis with GERS. For erosive esophagitis without GERS male sex (OR = 4.23), hiatus hernia (OR = 14.05) and obesity (OR = 2.90) were statistically significant predictors.

Table 3: The prevalence (%) and risk (OR, 95% CI) of GERS only and erosive esophagitis with and without GERS in different age groups and by gender in a main effect model including all statistically significant risk factors, as listed in the table

Outcome variable	Outcome variable			
	GERS without relevant EGD finding* n=271	Erosive esophagitis with GERS n=98		Erosive esophagitis without GERS n=57
		<i>H. pylori</i> ** positive n=21	<i>H. pylori</i> negative n=77	
Age groups				
20-34, %	36.5	0.0	12.2	6.7
Ref, OR = 1	1	NA <sup>(1)</sup>	1	1
35-49, %	<b>29.0</b>	10.8	9.3	<b>6.7</b>
OR (95% CI)	<b>0.57 (0.33-0.98)</b>	NA <sup>(1)</sup>	0.4 (0.15-1.06)	<b>0.31 (0.10-0.90)</b>
50-64, %	<b>26.2</b>	8.8	<b>11.4</b>	<b>5.0</b>
OR (95% CI)	<b>0.41 (0.24-0.69)</b>	NA <sup>(1)</sup>	<b>0.35 (0.14-0.91)</b>	<b>0.17 (0.06-0.51)</b>
>=65, %	<b>22.5</b>	1.6	15.6	<b>5.3</b>
OR (95% CI)	<b>0.30 (0.16-0.53)</b>	NA <sup>(1)</sup>	0.42 (0.15-1.20)	<b>0.13 (0.04-0.43)</b>
Gender				
Men, %	<b>21.3</b>	8.3	<b>15.9</b>	<b>8.8</b>
OR (95% CI)	<b>0.67 (0.49-0.91)</b>	2.00 (0.66-6.03)	<b>2.21 (1.20-4.08)</b>	<b>4.23 (2.09-8.58)</b>
Women, %	32.6	4.1	7.6	2.7
Ref, OR = 1	1	1	1	1
Risk factors				
HH <sup>^</sup> , %	<b>22.2</b>	<b>16.7</b>	<b>27.9</b>	<b>14.6</b>
OR (95% CI)	<b>1.71 (1.13-2.57)</b>	<b>8.88 (2.78-28.3)</b>	<b>10.05 (5.51-18.3)</b>	<b>14.05 (7.05-27.0)</b>
No HH, %	28.7	3.9	5.6	2.9
Ref, OR = 1	1	1	1	1
<i>H.p.</i> +, %	<b>32.5</b>	NA <sup>(2)</sup>	NA <sup>(2)</sup>	2.95
OR (95% CI)	<b>1.71 (1.23-2.38)</b>			0.58 (0.26-1.33)
No <i>H.p.</i> -, %	24.4			7.1
Ref, OR = 1	1	1	1	1
<i>H.p.</i> Scar***, %	20.4	NA <sup>(2)</sup>	NA <sup>(2)</sup>	10.8
OR (95% CI)	1.04 (0.58-1.89)			2.28 (0.94-5.54)
No <i>H.p.</i> Scar, %	27.8			5.18
Ref, OR = 1	1	1	1	1
BMI <sup>(3)</sup>				
Normal, %	26.0	1.7	6.3	4.56
Ref, OR = 1	1	1	1	1
Overweight, %	27.5	6.4	<b>13.4</b>	5.7
OR (95% CI)	1.32 (0.95-1.86)	3.55 (0.79-15.9)	<b>2.18 (1.08-4.41)</b>	1.26 (0.65-2.42)
Obesity, %	<b>27.8</b>	<b>14.4</b>	<b>20.0</b>	<b>8.6</b>
OR (95% CI)	<b>1.69 (1.06-2.70)</b>	<b>9.96 (1.83-54.2)</b>	<b>3.29 (1.45-7.51)</b>	<b>2.90 (1.33-6.36)</b>

Erosive esophagitis with GERS is stratified by current *H. pylori* infection. Reference group (Ref) is those without GERS and any relevant endoscopic abnormalities (N=498) and is given the value “OR = 1”. The models are also adjusted for gender.

\*= Reflux symptoms but no abnormal endoscopic findings in the esophagus.

Ref = Reference category.

^ = Hiatus hernia

\*\* = *H. pylori* outcome in histology and/or culture

(1)= Not applicable, age included as a continuous variable

\*\*\* = Serological scar of *H. pylori* (positive on serology only)

(2)= Not applicable

(3) = Missing data on 10 individuals

All models had sufficient goodness of fit.

Statistically significant differences in **bold**.

## 5.4 GERD AND HEALTH-RELATED QUALITY OF LIFE (STUDY II)

The data reported here are from the 999 subjects who underwent EGD and completed the SF-36 questionnaire. Transferred mean SF-36 scores ranged from 69 (general health) to 90 (social functioning) and differed little from mean scores previously reported for the Swedish general population (Figure 3) (98). Of the total study population of 999, 59 (6% of the study population) reported daily reflux symptoms, 141 (14%) experienced weekly symptoms (but less than daily), 199 (20%) experienced symptoms less than weekly, and 600 (60%) reported no reflux symptoms (Figure 4).

Figure 3. HRQoL (mean SF-36 scores with 95% CI) in the Swedish general population (98), the study population, and in subjects with and without esophagitis. PF: physical functioning; RP: role-physical; BP: bodily pain; GH: general health; V: vitality; SF: social functioning; RE: role-emotional; MH: mental health.

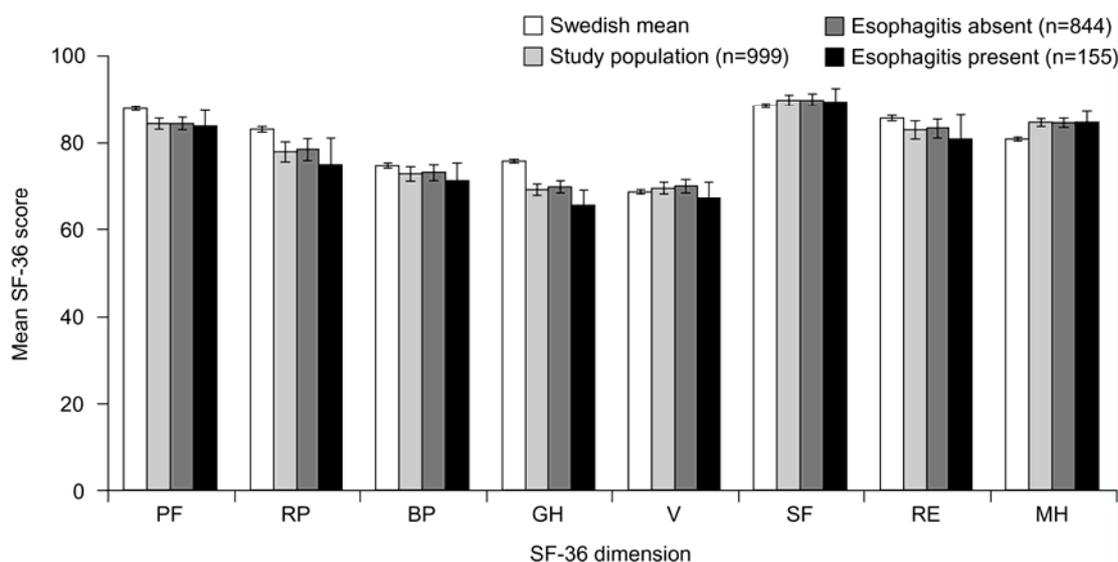
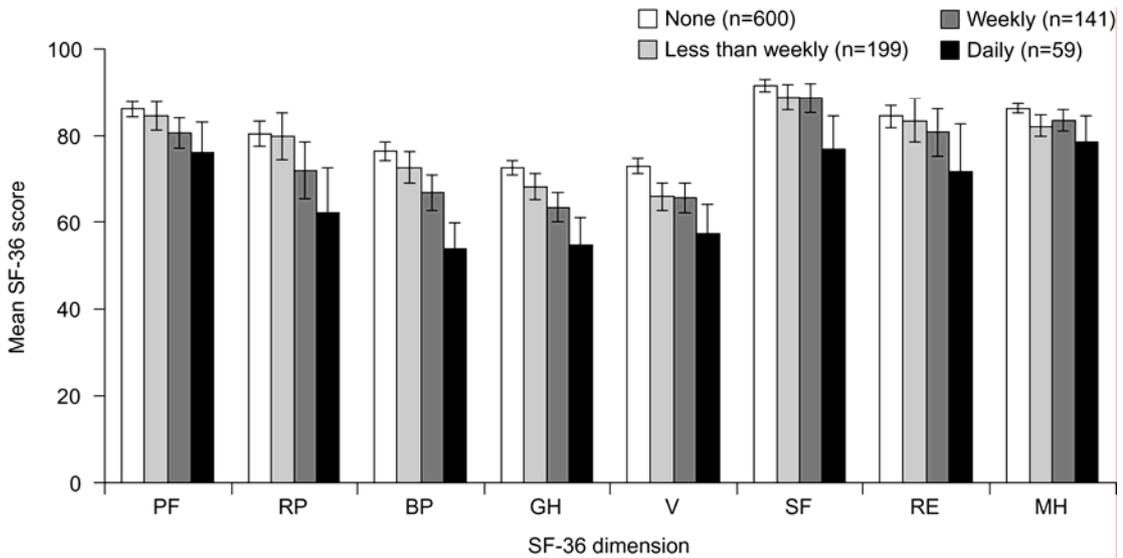


Figure 4. Effect of reflux symptom frequency on HRQoL (mean SF-36 scores with 95% CI).



In general, GERS had the greatest impact on the scores for bodily pain and related dimensions measuring physical and general health and least impact of GERS was seen on scores relating to psychosocial aspects of quality of life. Subjects with frequent symptoms experienced greater HRQoL impairment than those in whom symptoms were less frequent or absent (Figure 4). In comparison with subjects without reflux symptoms, subjects with daily reflux symptoms reported a clinically relevant (i.e. a  $\geq 5$ -point difference in SF-36 score and statistically significant difference,  $p < 0.05$ ) impairment of HRQoL in all eight dimensions of SF-36. Subjects with weekly reflux symptoms reported clinically meaningfully impaired HRQoL in five of eight dimensions (physical functioning, role-physical, bodily pain, general health and vitality) and subjects with less than weekly reflux symptoms reported such impairment in one dimension only (vitality).

There were no clinically relevant differences in SF-36 score between subjects with esophagitis and those without (Figure 3). Similarly, there were no meaningful differences in SF-36 scores between subjects with and without esophagitis in the subset without reflux symptoms.

## 5.5 PREVALENCE AND RISK FACTORS FOR BARRETT'S ESOPHAGUS (STUDY III)

Suspected CLE was found in 103 (10.3%) cases in the EGD study sample (mean age 55.7 years, 60.2% men). Twelve of them (1.2%) with a mean age of 59 years, (7 men) had a long segment (i.e.  $\geq 2$ cm in length). Among the 87 suspected CLE cases without SIM in the biopsies, there were 83 cases with columnar epithelium, three with squamous epithelium, and one case had missing biopsies. Hence, 96.1% of the suspected CLE at EGD had columnar epithelium in the biopsies.

Histologically confirmed BE was found in 16 individuals (1.6%), mean age 57 yr (9 men). LSBE occurred in 5 (0.5%) who had a mean age of 58 yr; 3 (60%) men. SSBE was found in 11 individuals (1.1%) with a mean age of 56 yr, and 6 (54.6%) were men (Table 4). The age distribution by gender is shown in Table 4. The mean age of the males with BE was 52.2 years (5/9 under 50 years of age) compared with 63 years for females with BE (6/7 over 50 years of age).

Table 4: Prevalence of BE by age and gender.

BE	Age group				Total
	20-34yr	35-49yr	50-64yr	>65yr	
Men	1	4	2	2	9
Women	0	1	1	5	7
Total	1	5	3	7	16

The prevalence of SIM in the esophageal biopsies was higher if the length of the suspected CLE was longer; 41.7% in segments  $\geq 2$  cm, 12.1% in segments  $<2$ cm and 4.5% without a visible suspected CLE segment (segment  $\geq 2$  cm vs. segment  $<2$ cm  $p=0.01$ , segment  $<2$ cm vs. no visible segment  $p<0.01$ , and in segment  $\geq 2$  cm vs. no visible segment  $p<0.01$  respectively).

There was no difference in the prevalence of endoscopically suspected CLE ( $p=0.93$ ), histologically diagnosed SIM ( $p=0.70$ ) or confirmed BE ( $p=0.99$ ) between the two endoscopy units.

The prevalence of BE in those with reflux symptoms was 2.3% and in those without 1.2% ( $p=0.18$ ). In those with esophagitis, the prevalence was 2.6% and in those without 1.4% ( $p=0.32$ ). The grading of esophagitis was not statistically significantly associated with BE. Of the 16 subjects with BE, 4 had low-grade (Los Angeles grade A or B) and none high-grade (grade C or D) esophagitis.

In univariate analyses by logistic regression adjusted for age and gender, alcohol (OR=3.0, 95% CI 1.03-8.54) and smoking (OR=2.87, 95% CI 1.01-8.13) were statistically significant risk factors for all BE. In the same analysis, esophagitis (OR=8.3, 95% CI 1.30-53.0) and hiatus hernia (OR=13.0, CI 1.43-118.0) were statistically significant risk factors for LSBE as were alcohol (OR=5.8, 95% CI 1.55-21.7) and smoking (OR=5.9, 95% CI 1.73-19.7) for SSBE.

## 5.6 PREVALENCE AND RISK FACTORS FOR EOSINOPHILIC ESOPHAGITIS (STUDY IV)

Eosinophilic infiltration in the oesophageal biopsies was present in 48 subjects (4.8%, 95% CI 3.5-6.1%, mean age 53.8 years, 62.5% men) (Table 5). Half of those ( $n=26$ ) had no reflux symptoms, four had asthma or allergy and three reported dysphagia. Proton pump inhibitors had been taken by two subjects, H<sub>2</sub> receptor antagonists by two and antacids by another six during the last three months before the endoscopy. They had significantly fewer doctor consultations (22/614 vs. 26/336,  $p=0.01$ ) than those

without eosinophils present; two had consulted for gastrointestinal complaints but none for upper gastrointestinal complaints in the previous year before the endoscopy.

Definite EE was present in 4 cases (0.4%, 95% CI 0.01-0.8%, mean age 50.7 years, 3 men) (Table 5). None of those had consulted a doctor for gastrointestinal symptoms in the previous year or received treatment for EE. Three of them reported reflux symptoms but none had erosive esophagitis. Probable EE was present in 7 (0.7%, 95% CI 0.2-1.2%, mean age 58.4 years, 42.9% men) and possible EE in 25 subjects (2.5%, 95% CI 1.5-3.5%, mean age 49.9 years, 72% men). Erosive esophagitis was present in two and reflux symptoms were reported by three of those with probable EE, and the corresponding figures for those with possible EE were 13 for esophagitis and 10 for reflux symptoms, respectively. There were 10 subjects (1.0%, 95% CI 0.4-1.6, mean age 59.5 years, 50.0% men) with low eosinophils/HPF counts (i.e.1-4).

The prevalence of eosinophils present two cm above the Z-line in subjects with reflux symptoms was 3.0% (95% CI 1.9-4.1) and 2.3% (95% CI 1.4-3.2) in those without such symptoms ( $p=0.52$ ). In subjects with erosive esophagitis, the prevalence was 6.6% (95% CI 5.1-8.1) and in those without 1.9% (95% CI 1.1-2.7) ( $p=0.003$ ).

At the Z-line, the prevalence of eosinophils was 5.3% (95% CI 3.9-6.7) in subjects with reflux symptoms and in those without 4.3% (95% CI 3.0-5.6) ( $p=0.51$ ). In those with erosive esophagitis, the prevalence was 11.6% (95% CI 9.6-13.6) and in those without 3.4% (95% CI 2.3-4.5) ( $p<0.001$ ).

Table 5. Prevalence (n, %) of eosinophils present, low grade eosinophil counts (i.e. eosinophils 1-4/HPF), possible (i.e. eosinophils 5-14/HPF), probable (i.e. eosinophils 15-19/HPF) and definite eosinophilic esophagitis (EE) (i.e. eosinophils  $\geq$ 20/HPF) at both oesophageal sites evaluated, at two cm above the Z-line, and at the Z-line in the oesophagus in the EGD study population, mean age and proportion of men.

<b>Kalixanda study population</b>			
	<b>N % (95% CI)</b>	<b>Mean age</b>	<b>Proportion of men,%</b>
	1000	53.5	48.8%
<b>Eosinophils present at both two cm above and at the Z-line*</b>			
Eosinophils present	48 4.8% (3.5-6.1)	53.8	62.5%
Eosinophils 1-4/HPF	10 1.0% (0.4-1.6)	59.5	50.0%
Possible EE	25 2.5% (1.5-3.5)	49.9	72.0%
Probable EE	7 0.7% (0.2-1.2)	58.4	42.9%
Definite EE	4 0.4% (0.0-0.8)	50.8	75.0%
<b>Eosinophils present two cm above the Z-line*</b>			
Eosinophils present	26 2.6% (1.6-3.6)	53.2	76.9%
Eosinophils 1-4/HPF	18 1.8% (1.0-2.6)	58.1	72.2%
Possible EE	5 0.5% (0.1-0.9)	42.4	100%
Probable EE	2 0.2% (0.0-0.5)	45.5	50%
Definite EE	1 0.1% (0.0-0.3)	35.0	100%
<b>Eosinophils present at the Z-line*</b>			
Eosinophils present	47 4.7% (3.4-6.0)	53.8	63.8%
Eosinophils 1-4/HPF	9 0.9% (0.3-1.5)	57.0	55.6%
Possible EE	24 2.4% (1.5-3.3)	50.9	70.8%
Probable EE	6 0.6% (0.1-1.1)	58.8	50.0%
Definite EE	3 3.0% (0.0-0.6)	56.0	66.7%

\* In 3 cases two cm above the Z-line biopsies were not available for evaluation in absolute number but did not contain eosinophils in the primary analysis. At the Z-line, biopsy specimens were not available for evaluation in absolute number in 6 cases, 5 of these cases were classified as mild and one case had no eosinophils in the primary analysis.

Compared with those without eosinophils present, subjects with eosinophils 2 cm above the Z-line, were more often men (20/468 vs. 6/506,  $p=0.003$ ) and were more likely to have esophagitis (10/145 vs. 16/829,  $p=0.004$ ) and they had significantly less dyspeptic symptoms (1/221 vs. 25/753,  $p=0.007$ ) and carditis (5/386 vs. 20/581,  $p=0.035$ ) in the univariate analysis. There was no significant association with reflux symptoms (Table 6). Male gender (OR=3.02, 95% CI 1.18-7.72) and esophagitis (OR=2.84, 95% CI 1.24-6.50) remained independent predictors for eosinophils 2 cm above the Z-line in the multivariate analysis by logistic regression.

Table 6. Prevalence of statistically significant predictors for eosinophils present in the distal oesophagus, eosinophils at two cm above the Z-line, eosinophils at the Z-line and eosinophils restricted to the Z-line in the EGD study population.

	<b>EGD study population n=1000</b>	<b>Eosinophils present n=48</b>	<b>Eosinophils two cm above the Z-line n=26</b>	<b>Eosinophils at the Z-line n=47</b>	<b>Eosinophils restricted to the Z-line n=22</b>
Male gender P	48.8%	62.5% ns. (0.051)	76.9% 0.003	63.8% 0.034	45.5% ns.
GERS P	40%	45.8% ns.	46.2% ns.	44.7% ns.	45.5% ns.
Dyspepsia P	22.2%	6.3% 0.002	3.9% 0.007	6.4% 0.003	9.1% ns.
Erosive esophagitis P	15.5%	37.5% <0.001	38.5% 0.009	38.3% <0.001	36.4% 0.013
Hiatus hernia P	23.9%	39.6% 0.013	38.5% ns.	40.4% 0.010	40.9% ns.
Esophageal ulcer P	2.2%	12.5% <0.001	7.7% ns.	12.8% <0.001	18.2% 0.001
Narrowing in the esophageal lumen P	1.7%	6.3% 0.044	3.9% ns.	6.4% 0.042	9.1% ns. (0.051)
<i>H. pylori</i> * P	33.9%	16.7% 0.006	19.2% ns.	17.0% 0.008	13.6% 0.029
Carditis P	39.4%	23.4% 0.017	20.0% 0.035	23.9% 0.023	27.3% ns.

\* *Helicobacter pylori* positive by histology and/or culture.

In the univariate analysis, eosinophils present at the Z-line was associated with male gender (30/458 vs. 17/495,  $p=0.034$ ), esophagitis (18/137 vs. 29/816,  $p<0.001$ ), hiatus hernia (19/220 vs. 28/733,  $p=0.010$ ), esophageal ulcer (6/16 vs. 41/937,  $p<0.001$ ) and narrowing in the esophageal lumen (3/14 vs. 44/939,  $p=0.042$ ). There was a negative association with between eosinophils at the Z-line and *H. pylori* infection (8/331 vs. 39/622,  $p=0.008$ ), carditis (11/380 vs. 35/566,  $p=0.023$ ) and dyspeptic symptoms (3/219 vs. 44/734,  $p=0.003$ ) compared with those without eosinophils present (Table 6). In the multivariate analysis by logistic regression, erosive esophagitis (OR=2.54, 95% CI 1.23-5.21), esophageal ulcer (OR=4.39, 95% CI 1.39-13.88) and having less dyspepsia (OR=0.22, 95% CI 0.07-0.73) remained independent predictors for eosinophils present at the Z-line.

In the univariate analysis, evaluating both esophageal sites biopsied, definite EE was associated with dysphagia (2/66 vs. 2/926,  $p=0.025$ ) and probable EE with narrowing in the esophageal lumen (2/15 vs. 5/978,  $p=0.005$ ) compared with those without esophageal eosinophils. Multivariate analysis was not appropriate due to low number of these cases.

## 6 DISCUSSION

Within the framework of a population-based study using endoscopy, we have examined the prevalence of GERD and associated risk factors in a representative randomly selected adult population in the Northern part of Sweden. The impact of the frequency of GERS in HRQoL was also studied. Furthermore, the prevalence and the associated risk factors for complications of GERD, like erosive esophagitis and Barrett's esophagus, were evaluated. In addition, the prevalence of eosinophilic esophagitis and esophageal eosinophils and their association to GERD were also assessed.

To our knowledge, the data acquired by validated symptom questionnaires together with invasive upper endoscopy with biopsy from representative unbiased cohorts of general population are sparse. By all comparisons to date, the Kalixanda study subjects hold up as a representative population sample, aged 20 to 80 years of age, from a reliable national population register in Sweden covering all inhabitants in the area and thus may differ from all the potentially biased (f. ex. by seeking or consulting behaviour) cohorts of patients from primary care or specialist care settings reported earlier. Recruiting selected patient populations is cheaper and easier than obtaining unbiased samples from the general population. However, we would argue that population-based research here is the only way to obtain precise prevalence estimates, and that surrogate, potentially unrepresentative, clinical samples remain inadequate for quantifying the magnitude of GERD-related disorders in the general population.

In this population, GERS were common (40%), as was erosive esophagitis (15.5%), the latter often (36.8%, 6% of the study population) being silent. *H. pylori* infection was correlated with GERS without erosive esophagitis. We also showed that GERS adversely affect HRQoL in the general population, and that this effect correlates with symptom frequency. We found that the prevalence of BE was 1.6% (LSBE 0.5% and SSBE 1.1%). The prevalence of any esophageal eosinophils present was close to five in 100 in adults. A histological diagnosis of definite EE was made in one case (0.1%) 2 cm above the Z-line and in three cases (0.3%) at the Z-line.

The study population was sampled from the official population registers of the two municipalities of Kalix and Haparanda (108). The register covers the whole population with no exceptions. Stratified sampling (every seventh) was used because it was available from the population register and in this case, due to the large sample size, the procedure is considered equivalent to random sampling. The two communities were also chosen because of the possibility to perform endoscopies both in primary and in secondary care and thus optimizing the prerequisites for logistics and study compliance.

The EGD study sample had a mean age which was about four years higher than that of the original study population and also than that of the general Swedish population, mainly due to a lower response rate among the symptom free youngest quarter of the study sample. The prevalence of reported GERS in the initial ASQ was significantly lower for all 2122 responders (33.6%, CI = 31.6-35.6) compared with those in the EGD study sample in the initial ASQ (38.7%, CI = 35.7-41.7) ( $p=0.005$ ) (94). This was, however, mainly contributed by the of the youngest age cohort of the EGD study

sample. For the EGD subjects between 20-34 years of age (n=105), the prevalence of GERS was 47.1%, i.e. 13.1% higher (p=0.015) than that for all initial ASQ responders (34.0%) in this age group and for those between 35-49 years of age (n=269), the corresponding figure was 8.1% (ns) (94). For subjects aged 50 years or more (n=627), who are of most interest from a health risk perspective, there was no such bias (=3.2%, ns) (94). When the youngest age group was excluded, no significant difference in overall GERS prevalence remained. Moreover, the prevalence of GERS in the EGD study sample from the initial ASQ showed no statistically significant difference (38.7% vs. 40.0%) from the prevalence they reported at the EGD. The differences are also controlled for in the analyzes by logistic regression. In conclusion, among the EGD study sample, the prevalence of GERS was representative of the general population, with the exception of the youngest subjects.

Although the socio-economic status in the study catchment area was somewhat lower than the Swedish average (105, 106), the difference was still negligible from an international perspective. Furthermore, the prevalence of positive *H. pylori* serology of 42% (94), is well in line with that of other similar countries in northern Europe (123). *H. pylori* infection rate is known to correlate with socio-economic welfare (124). Also, the prevalence of 42% in *H. pylori* serology among the non-responders, despite the small sample size, contradicts fears of potential bias caused by socio-economic status. In our study *H. pylori* status was the same in this group as in the responders, although the education level was slightly lower. Moreover, there is no apparent difference in morbidity from GI disorders, as measured by hospitalization and death, between the Northern part of Sweden in 1998-2001 and the rest of Sweden or the Western world (125). Our overall conclusion is, therefore, that it is unlikely that socio-economic factors have markedly influenced the results at the present study.

Thus, the main strengths of the Kalixanda study are that it assessed a representative sample of the general population using endoscopy, with extensive number of biopsies, validated symptom questionnaires and a predefined endoscopy and histology protocol. Also the response rates, both in answering to the postal questionnaire and accepting the EGD, were excellent, being 74% and 73%, respectively.

The use of three different observers for endoscopy could be considered as a potential weakness in the study. Therefore, the experienced (2500 to 6000 endoscopies each) endoscopists took part in training sessions for landmarks at EGD (37, 38, 126) and endoscopic diagnosis (99) and were tested for concordance to minimize the inter-observer variation (94, 127). Furthermore, the landmark for GEJ used in this study was the same as the one supported by all members from the Prague International Consensus Group for endoscopic grading of BE (Dr. Prateek Sharma, personal communication). There was neither a difference in the prevalence of erosive esophagitis (13% vs. 17%, p=0.25) or BE (1.6% vs. 1.6%, p=0.99), nor in the endoscopic diagnosis of suspected CLE (p=0.93) or histological diagnosis of SIM (p=0.70) between the two endoscopy units (127, 128), and the validation process before the study showed a good agreement between the endoscopists (see section 4.2.3). Thus, we believe that the endoscopy results are reliable.

The histological evaluation was done by experienced pathologists with a special interest in GI pathology, who were unaware of the clinical data and endoscopic findings. The kappa-value for agreement between observers was good, for example in the evaluation of *H. pylori* it was 0.76 (95% CI 0.56-0.96) for the corpus and 0.78 (95% CI 0.59-0.98) for the antrum of the stomach (114). Biopsies with any eosinophils on the first evaluation were reviewed by a third pathologist, who was also blinded to the clinical data and endoscopic findings, paired with biopsies with no eosinophils on the first assessment, such that an independent review of eosinophil counts could be undertaken. This confirmed the absence of eosinophils in paired biopsies without eosinophils on first assessment and further strengthened the reliability of the histological evaluation.

In this study, the number of contraindications to EGD was higher than is normal among patients who are usually referred for endoscopy. This is because the study population consisted of adults with no known indication for endoscopy, and as such, they could not be put at risk in any way from the study. Thus, subjects with unstable angina or pregnant subjects, for example, were not endoscoped. Any influence of subject exclusion on the outcome in terms of observed disorders and reliable symptom reporting would most probably have arisen only from the exclusion of the 10 subjects (1% of the EGD study sample) with previous upper GI surgery (94).

The main limitation of the study is, that it collected data at a single point in time, which does not allow the assignment of cause and effect and can't measure incidence. Another limitation of the present study is that 24-hour oesophageal pH monitoring was not available (129). However, the Montréal definition supports the diagnosis of GERD based on symptoms only (10). A potential source of bias in the study may lie in the questionnaires used. The ASQ used for symptom registration has been validated previously and has been shown to be reproducible and robust (33, 94, 110). The intensity of reflux symptoms reported by the ASQ correlated well with the reflux score from the Carlsson-Dent questionnaire (32). The cut off for reporting symptoms, i.e. troublesome symptoms, has been shown to reliably differ from "any symptoms" (33, 109). This cut off is now also included in the global Montréal definition of GERD (10). Other limitations of the study include the fact that the different questionnaires completed by the study subjects used different recall periods. For the SF-36 questionnaire this was one week, for the ASQ and questions about medication use it was three months, and for questions regarding healthcare consultations it was one year. This is to some extent an unavoidable limitation associated with the use of validated questionnaires that have been applied widely and for different purposes in other studies.

Another potential limitation in the study is the fact that dietary habits were not assessed. Some lifestyle measures may provide limited benefit in gastroesophageal reflux disease (130, 131). Avoidance of specific foods and drinks that exacerbate symptoms may help, although it does not usually result in healing of the esophagitis (9) and is not associated with less GERS, perhaps due to avoiding mechanisms among reflux sufferers (132). Although stopping smoking and losing weight are of benefit to the patient's general health, they have little or no effect on gastroesophageal reflux disease (130). However, studies on this can be difficult because of reversed causality: subjects who get

symptoms from wine or coffee will avoid them and epidemiological studies might conclude that these substances might protect from GERD (133).

GERD, with or without esophagitis, are known to affect quality of life at least among GERD patients (9, 134), who suffer from a chronic (4, 5), costly (134, 135) and potentially dangerous (12, 136) disease. The clinically relevant difference for SF-36 dimensions (which are measured on a scale of 0–100) is a difference of 5 points (97) which we could confirm to be also statistically significant in our study. Subjects with daily symptoms had clinically relevant impairment of HRQoL in all eight SF-36 dimensions (both physical and psychosocial), and weekly reflux symptoms were associated with clinically relevantly impaired HRQoL in the physical dimensions of SF-36 (physical functioning, role-physical, bodily pain and general health) and vitality. The clinically relevant impairment of only one dimension (vitality) in subjects with less than weekly reflux symptoms suggests that these individuals do not have GERD. We therefore propose that the presence of troublesome heartburn and/or acid regurgitation occurring at least weekly is likely to indicate GERD (6, 137).

Nebel et al. (1) reported that heartburn was experienced daily by 7% and monthly by 36% in a U.S. population. There was no significant difference between age-groups or gender except for pregnant women, of whom 25% and 52% reported daily and monthly heartburn, respectively. In one Swedish study, Ruth et al. (54) reported symptoms suggestive of GERD in 25% of a randomly sampled adult population and in another study, Agréus et al. (55) found the same prevalence of symptom reporters among unselected adults. There was no difference between ages or gender. In a population-based British study, Jones et al. (56), found that 31% had experienced heartburn in the preceding six months. Locke et al. (58) found a prevalence of at least weekly heartburn and/or acid regurgitation of 18% in a sample of Olmsted County residents between the ages of 25 and 74 years. Consistently with our study, Dent et al (6), concluded that the prevalence of GERD (weekly reflux symptoms) in Western countries is in the range of 10-20 % and typically below 5% in Asian countries based on thorough review of current literature in 2005.

Esophagitis in the general adult population has, so far, been best described in the Norwegian Sørreisa study (61). However, this was a case-control study in subjects reporting dyspepsia (defined as epigastric pain or heartburn) based on a questionnaire given to a random population and they used the Savary-Miller classification system for esophagitis. Among cases with dyspepsia, the prevalence of esophagitis was 12%, and among those who were symptom-free it was 8.1%. Of those with esophagitis, 11% reported heartburn and the corresponding figure among the controls was 9.0%. In a recent Swedish population-based EGD study surveying people of 35 years of age and older, the prevalence of esophagitis was 8.0% (62). However, the response rate in that study (25%) does not guarantee that the results are representative of the general population. Similar to our results, in an as yet unpublished Italian report, the prevalence of reported esophagitis in an adult population was 8.9%, and 25% of those had no symptoms (63). Recently, in a preliminary report involving 915 US employees, where 226 subjects accepted an EGD, the prevalence of esophagitis was 22% (138) but the cohort and response rate were not representative of the general population.

In our study, erosive esophagitis per se did not seem to induce health care seeking. On the other hand, subjects with GERS did see doctors annually on significantly more occasions than those without GERS, although the difference was small (70.3% vs. 59.2%) and probably not clinically significant. Only very few, 3.3% had consulted a doctor for upper GI problems and only 6.5% for any GI problem. So, even those with GERS seemed to be mainly a non-patient population, thus justifying our study.

The prevalence of BE in our study is in accordance with recently reported prevalence figures in large selected cohorts (28, 66, 69). The prevalence of LSBE (0.5%) is also only modestly higher compared with the Cameron autopsy study of 1990, where it was 0.34% (336/100,000) (65). Although Gerson et al. and Rex et al. have reported significantly higher prevalence rates of BE in selected cohorts, 25% and 6.8% respectively (67, 68), we found a notably lower prevalence of BE in the adult general population, probably due to no selection bias and robust diagnostic criteria. This is in accordance with the recent Canadian study where the prevalence was 2.4% in patients with dyspepsia getting prompt endoscopy (69). A once in a lifetime endoscopy has been debated for subjects with chronic reflux symptoms in order to identify BE and in order to try to reduce the risk of adenocarcinoma, but it is still controversial whether and when this should be performed (42, 43, 139). Since 43.7% of those with BE in this study had no reflux symptoms and the prevalence overall was low, this suggests that screening based on reflux symptoms only may be inadequate to detect BE. Thus, the results of this study present an evidence-based number of adults with BE in the community to be identified (140).

The aetiology of EE is not known and there is sparse information of its prevalence (47, 70) but recent case reports have implied that the prevalence of EE may be increasing (47, 72). This study could not address the incidence of EE but provides, for the first time to our knowledge, reasonably robust current community prevalence estimates. Our finding of the prevalence of esophageal eosinophils and histological EE is higher than previously estimated. This could be explained by the fact that we took biopsies from every subject and even from the esophagus with a normal appearance. In 1985, Lee reported 11 patients with marked esophageal eosinophils, 10 of whom had reflux esophagitis (141). Since this time, the connection between GERD and EE has been under debate (16, 44, 47, 142). In a recent systematic review, only 10% of EE cases were found to have pathological acid reflux (50). Similarly, we did not find a statistically significant association between GERS and eosinophils in the esophagus, possibly due to a lack of statistical power. However, eosinophils present was associated with erosive esophagitis, hiatus hernia, esophageal ulcer and narrowing of the esophageal lumen, consistent with other clinical reports of eosinophils being present in the distal esophagus in GERD (142). Thus, our results support the concept that esophageal eosinophils may be a manifestation of reflux esophagitis, although this might also reflect a non-specific association between mucosal injury of the esophagus and esophageal eosinophils. Those, with eosinophils 2 cm above the Z-line were more often men and those of them with  $\geq 5$  eosinophils/HPF were younger suggesting either a different severity of the disease or a different pathogenesis (perhaps true EE vs. reactive eosinophils at the Z-line due to GERD?).

Taking all the strengths and potential limitations of our study in consideration, we believe that the findings of the population-based Kalixanda study are generalizable to Western Caucasian populations. This opinion is also shared by others: “The Kalixanda study therefore represents a unique, population based, non-biased cohort of adults who have been well characterized concerning symptoms, *H. pylori* status, endoscopic status and various risk factors” (133), and “The definition of the population-based prevalence of BE in a random sample of an adult population undergoing endoscopy represents a major step forward” (140).

## **7 CONCLUSIONS**

The following conclusions can be drawn from this first, endoscopic population-based study with a high response rate from a representative random sample of the adult population - the Kalixanda Study.

### **7.1 STUDY I**

Symptoms of gastroesophageal reflux and erosive esophagitis are highly prevalent in a general unselected population (40% and 15% respectively) and constitute a general health problem among adults. Moreover, esophagitis is silent in around one third of cases. Gastroesophageal reflux symptoms without esophagitis were more prevalent among those with current *H. pylori* infection. Hiatus hernia and obesity were significant risk factors for GERS and/or erosive esophagitis.

### **7.2 STUDY II**

Individuals experiencing daily and weekly troublesome reflux symptoms are likely to have a clinically significant reduction in most aspects of HRQoL. In contrast, the presence or absence of esophagitis does not appear to predict impairment of HRQoL. Occurrence of troublesome reflux symptoms at least once a week thus appears to be a useful indication of underlying GERD. As defined in study II, using this cut-off, the prevalence of GERD was 20%.

### **7.3 STUDY III**

Barrett's esophagus was found in 1.6% in the general adult population in Sweden. Alcohol and smoking were found to be statistically significant risk factors for Barrett's esophagus.

### **7.4 STUDY IV**

Esophageal eosinophils were found in nearly 5% of the general Swedish adult population; 0.4% had marked infiltration consistent with definite eosinophilic esophagitis while 0.7% had probable eosinophilic esophagitis. Asymptomatic low-grade counts of epithelial eosinophils (< 15/HPF) may be more common than has been estimated but are of uncertain clinical significance. Presence of esophageal epithelial eosinophils may be a manifestation of reflux disease, and appears to be independently associated with erosive esophagitis in adults.

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