

From
DEPARTMENT OF NEUROBIOLOGY, CARE SCIENCES
AND SOCIETY,
CENTRE FOR FAMILY AND COMMUNITY MEDICINE,
Karolinska Institutet, Stockholm, Sweden

**PEPTIC ULCER DISEASE IN
AN ADULT POPULATION.
THE KALIXANDA STUDY: A
POPULATION-BASED
ENDOSCOPIC STUDY**

Pertti Aro



**Karolinska
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To Tuula, Sakari and Sanna

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ABSTRACT

Introduction: The pattern of symptoms and perception of disease among patients seeking care does, due to health care seeking behavior, most probably not reflect the true health status in the general population. Upper esophagogastroduodenoscopy (EGD) is considered to be gold standard for upper gastrointestinal (GI) disease assessment, but is seldom used in epidemiological studies. We aimed to explore whether the EGD affects symptom reporting and sampling among volunteers and to clarify the prevalence of peptic ulcer disease (PUD) and its risk factors in a general adult population.

Methods: A random sample of 3,000 adults aged 20-80 years (mean age 50.4), from two Swedish municipalities (n=21,610) was surveyed using a validated postal abdominal symptom questionnaire. A random sub-sample of the responders (n=1,001) was invited, in random order, to undergo an upper endoscopy with biopsies and repeated symptom reporting with the same questionnaire, as well as for blood samples for *Helicobacter pylori* (*H. pylori*) serology and other biomarkers, medical history taking, measuring and weighing the subjects.

Results: The response rate to the initial questionnaire was 74.2% and the participation rate for those eligible for the upper endoscopy was 73.3% (n=1,001, mean age 54.0 years, 48.8% male). No major social or symptom sampling error was encountered from the selection process, except for an excess of symptom reporters among the youngest subjects (< 35 years). The prevalence of gastroesophageal reflux symptoms (GERS), dyspepsia and the Irritable Bowel Syndrome (IBS) was 40%, 37.6% and 29.6%, respectively. The prevalence of peptic ulcer was 4.1% (gastric ulcers (GU) n=20; duodenal ulcers (DU) n=21). Nausea and GERS, but not epigastric pain/discomfort, were significant predictors of PUD. Six individuals with GU and two with DU were asymptomatic (in all 20%). Eight DU subjects (38%) lacked evidence of current *H. pylori* infection. Five (25%) of the GU and four (19%) of the DU were idiopathic (no aspirin/NSAID use, no *H. pylori* infection and normal Gastrin-17). Smoking, aspirin and obesity were risk factors for GU; smoking, low dose aspirin (≤ 160 mg) and *H. pylori* infection were risk factors for DU. There were more endoscopic findings in obese subjects than in normal weight subjects, but the differences were not significant except for esophagitis and GU; the prevalence of reflux esophagitis in obesity was 26.5% versus 9.3% in normal weight subjects and the corresponding figures for GU were 5.6% and 1.4% respectively. Different types of tobacco use do not seem to have uniform health risks. While smoking increases the risk for PUD, smokeless tobacco use does not, or might even contribute to a lower risk. Use of smokeless tobacco is a significant risk for higher prevalence of reflux esophagitis and for intestinal metaplasia in the antrum (a pre-neoplastic marker).

Conclusions: Valid epidemiology through upper endoscopy is possible. Smoking, aspirin and obesity are risk factors for GU; smoking, low dose aspirin (≤ 160 mg) and *H. pylori* infection for DU. Smokeless tobacco is not a risk factor for PUD but most probably not harmless anyhow. Idiopathic ulcer may be more common than anticipated. PUD is often asymptomatic or coexists with atypical symptoms.

Key words: Epidemiology, esophagogastroduodenoscopy (EGD), peptic ulcer disease (PUD), population-based.

LIST OF PUBLICATIONS

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

- I. **Aro P**, Ronkainen J, Storskrubb T, Bolling-Sternevald E, Carlsson R, Johansson S-E, Vieth M, Stolte M, Engstrand L, Talley N, Agréus L. Valid symptom reporting at upper endoscopy in a random sample of the Swedish adult general population, The Kalixanda study. *Scand J Gastroenterol* 2004;39:1280-1288.
- II. **Aro P**, Storskrubb T, Ronkainen J, Bolling-Sternevald E, Engstrand L, Vieth M, Stolte M, Talley NJ, Agréus L. Peptic ulcer disease in a general population. The Kalixanda study: A random population-based study. *Am J Epidemiol* 2006;163:1025-1034.
- III. **Aro P**, Ronkainen J, Talley NJ, Storskrubb T, Bolling-Sternevald E, Agréus L. Body mass index and chronic gastrointestinal symptoms: an adult endoscopic population-based study. *Gut* 2005; 54:1377-1383.
- IV. **Aro P**, Ronkainen J, Storskrubb T, Bolinder G, Bolling-Sternevald E, Vieth M, Stolte M, Engstrand L, Alving K, Johansson S-E, Talley NJ, Agréus L. Smokeless tobacco use and gastrointestinal morbidity: an endoscopic population- based study. The Kalixanda-study. (Submitted).

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LIST OF ABBREVIATIONS

ASQ	Abdominal symptom questionnaire
BMI	Body mass index
CI	Confidence interval
DU	Duodenal ulcer
EGD	Esophagogastroduodenoscopy
GERD	Gastroesophageal reflux disease
GERS	Gastroesophageal reflux symptoms
GI	Gastro intestinal
GU	Gastric ulcer
<i>H. pylori</i>	<i>Helicobacter pylori</i>
H ₂ RA	Histamine-2 receptor antagonist
IBS	The Irritable Bowel Syndrome
ID	Identification number
NSAID	Non-steroidal anti-inflammatory drug
NUD	Non-ulcer dyspepsia
OR	Odds ratio
PPI	Proton pump inhibitor
PUD	Peptic ulcer disease

1 INTRODUCTION

1.1 EPIDEMIOLOGY

Human symptoms and diseases do not occur at random, and that there are causal and preventive factors that can be identified by systematic investigation of the population. These are the two main assumptions in epidemiology. The frequency of a disease or a symptom is possible to describe, as is their distribution in the population. The temporal geographic and demographic patterns of disease occurrence may generate hypotheses concerning possible causal or preventive factors in the individuals or in the environment and also have impact on health economy assumptions.

The father of medicine Hippocrates laid one of the corner-stones of epidemiology in the fifth century B.C. It is obvious that he considered the development of human disease to be related to external environment as well as to personal factors of an individual (1). Not until 1662 were those ideas systematically used to increase medical knowledge. In that year, a haberdasher named John Graunt (2) published an article where he analyzed the weekly reports of births and deaths in London and for the first time quantified patterns of disease in a population by routinely collection of data.

The British physician John Snow's work (3) in 1853-4 was another milestone in epidemiology showing that data collected from a human population could be used to learn about disease. He tabulated the number of deaths from cholera on a map and compared the figures with the water supply system of London. He was thereby able to formulate a hypothesis on the etiology of the disease despite of the fact that microbiology was an unknown science at that time.

Until the latter part of the nineteenth century, infections caused most of the fatal diseases, thereby giving epidemiology its name as the study of epidemics of infectious disease, to which now also peptic ulcer disease (PUD) belongs.

Time changes and developments in society and medicine became feasible to study with the population-based epidemiological technique. For example the main causes of deaths in the US, reflecting the development of the society, were studied at two different occasions in *total population surveys*: in 1900, when pneumonia/influenza caused 12%, tuberculosis 11%, heart disease 9% and cancer 5% of the deaths in the country, and in 1982, when heart disease caused 34%, cancer 24% and pneumonia/influenza 2% of the deaths. Tuberculosis was no longer on the top ten list of death causes. The same results can be found in a sample of the total population, if the sample is randomly chosen from the total population, big enough to allow generalization to the total population and with non-responders being as few as possible and as equal as possible to the responders, i.e. with a minimum of bias. The method is called for *cross-sectional population-based study*.

The nature of the disease/disorder is an important factor for choosing the most suitable epidemiological method and the study base is thus of course essential to define. Serious diseases or events, such as neurosurgery after car accidents can of course be studied in

hospital case record registers, while a study of those with hyperglycemia in the population, often unknown even to primary health care and to the subjects, needs other sources for data collection. The study of randomly selected population samples with is more manageable and suitable for the latter purpose.

Case-control study is another approach. The study by Doll and Hill in 1950 (4) of 700 patients ("cases") with lung cancer and 700 matched patients hospitalized for nonmalignant conditions ("controls") that showed the relationship between lung cancer and smoking is a classical example of such a study design, and the for example U.S. Surgeon General then stated in 1964 that there was proof beyond reasonable doubt that cigarette smoking caused lung cancer (5). Epidemiological research has thus often provided information that has formed the basis for public welfare decisions long before the basic mechanism of a particular disease was understood.

Follow-up study of a cohort is used for follow-up of changes in disease incidences in a population over a certain time and a good example of this kind of observational study is the Framingham study (6). This method can be used for follow-up of a selected population cohort exposed to medication, environmental or other factors compared to an unexposed matched control group, then called *Interventional cohort follow-up*, and thereby to define the relative differences between the groups and thus to define the effect of the exposure in a population cohort.

This thesis is based on a randomly selected sample of an entire adult general population in two adjacent Northern Swedish municipalities, Kalix and Haparanda. The method applied in our study is called *descriptive and also analytical epidemiology* applying cross-sectional methodology. It describes the general characteristics of the distribution of gastrointestinal (GI) symptoms and endoscopic findings in relation to demographic factors such as age, gender, education level, use of medication, use of tobacco products and other important exposure variables.

1.2 CONSULTATION BEHAVIOUR

Abdominal symptoms are mostly non-fatal and show differences in their tendency to provoke consultation behavior (7-11). This is obviously not determined only by the severity or frequency of the symptoms or associated symptoms, but also by fear of serious disease like cancer and also by disruptive and stressing earlier life events (7, 12), or by wishes from relatives (13). It is well known, that many people with gastrointestinal (GI) symptoms never consult a physician or complain to a physician at consultation (11, 14-17), for example in a Swedish study half of those with dyspepsia and 15% of those with the irritable bowel syndrome (IBS) never consulted a physician during their lifetime for these symptoms (18). It has been estimated by Jones et al. that only 5% of dyspeptic adults consult annually and the proportion of consultants rises with higher age and is connected to some extent to social status (9, 19), and according to Johnston et al., psychological and social factors have influence on the decision to seek medical help for gastroesophageal reflux disease (GERD) (20). There is a tendency for gastroenterologists, as specialists, to see only the patients at the more severe end of the disease spectrum (21). Thus, the proportion of investigated patients with an outcome defined as "functional" (i.e. without organic findings) goes down from

about 50% in primary care, (22, 23) to about 20% in patients referred to specialists (24, 25). Thus, the pattern of symptoms and perception of disease among patients seeking care might very well be biased not reflecting the true health status in the general population. As most textbooks are written by specialists, it is important to be aware of that there might be selection bias in the populations they describe and that their findings cannot reasonably and realistically be extrapolated to the general population. Also, knowledge about the true natural history of a disease, and accordingly the correct prognosis, is dependent on unbiased medical history.

Case record registers in hospitals as well as in primary health care centers, are therefore not suitable for epidemiological research in this field and true and valid population based studies therefore are required in this type of epidemiological research. The official Swedish population register is very suitable to recruit subjects for such studies as it covers all inhabitants without exception (26).

1.3 GASTROINTESTINAL SYMPTOM PREVALENCES, OVERLAP AND TURNOVER

The literature on prevalences of gastroesophageal reflux disease (GERD)/gastroesophageal reflux symptoms (GERS), dyspepsia and IBS is large. It has to be considered though, that reported prevalence rates vary considerably between different surveys, at least partly reflecting use of different symptom definitions of the disorders, and also various retrospective time periods under surveillance.

For example, Thompson et al. reported that heartburn was experienced weekly by 10%, monthly by 21% and some time during the last year by 34% of a study population among British volunteers (27), and Dent et al. reported prevalences of 10-20% of GERD in Western world and less than 5% in Asia during the preceding week (28). Talley et al. found that 24% of a US population reported heartburn at least once a month during the preceding year and that 11% reported acid regurgitation (11) and Jones et al. (9) found that 31% had experienced heartburn the preceding six months in a UK population. In a Swedish example Agréus et al. found that 25% of an adult population reported GERS during the latest 3 months (29). Recently a population-based German study reported a prevalence of reflux symptoms of 43% (30). An overall prevalence of 25%, during the preceding three months, is estimated to be a reasonable average for GERS in the international literature (31).

The definitions of dyspepsia have varied a lot over the years and the main definitions are shown in Table 1, which illustrates the difficulty of comparing the different studies and their symptom risk profile. The term dyspepsia is used to denote one or more upper GI symptoms, but does not link the symptoms with any specific cause. Functional dyspepsia, also called non-ulcer dyspepsia (NUD), is a term covering dyspeptic symptoms when there is no evidence of PUD, cancer or other organic cause after investigation, primarily esophagogastroduodenoscopy (EGD).

Table 1. Definitions of dyspepsia and functional dyspepsia over time

Rhind and Watson 1968 (32)	Epigastric discomfort after meal, a feeling of fullness so “that clothing is loosened, eructation with temporary relief and regurgitation of sour fluid into the mouth, with heartburn (flatulent dyspepsia).
Crean et al. 1982 (33)	Any form of episodic or persistent abdominal discomfort or other symptom referable to the alimentary tract, except jaundice and bleeding.
Talley and Piper 1988 (34)	Pain, discomfort or nausea referable to the upper alimentary tract which is intermittent or continuous, has been present for a month or more, is not precipitated by exertion nor relieved by rest, and is not associated with jaundice, bleeding or dysphagia.
Nyrén et al. 1987 (35)	Epigastric pain or discomfort a key symptom, in absence of irritable bowel symptoms and organic disease (“epigastric distress syndrome”).
Colin-Jones et al. 1988 (36)	Upper abdominal or retrosternal pain discomfort, heartburn, nausea, vomiting or symptom considered to be referable to the proximal alimentary tract.
Barbara et al. 1989 (37)	Episodic or persistent abdominal symptoms, often related to feeding, which patients or physicians believe to be due to disorders of the proximal portion of the digestive tract.
Heading 1991 (38)	Episodic or persistent abdominal symptoms which include abdominal pain or discomfort. The term dyspepsia is not applied to patients whose symptoms are thought to be arising from outside the proximal GI tract.
Rome I (39, 40)	(1) Chronic or recurrent abdominal pain or discomfort centered in the upper abdomen (2) No clinical, biochemical, endoscopic or ultrasonographic evidence of any known organic disease that is likely to explain the symptoms and no history of major gastric or intestinal surgery. Patients with history of past chronic PUD should not be classified as having functional dyspepsia at least until the relationship between these entities is clarified.
Rome II (41)	The diagnosis of a functional gastroduodenal disorder always presumes the absence of a structural or biochemical explanation the symptom. BI. Functional dyspepsia At least 12 weeks, which need to be consecutive, in the preceding 12 months of: 1. Persistent or recurrent symptoms (pain or discomfort centered in the upper abdomen); 2. No evidence of organic disease(including at the endoscopy) that is likely to explain the symptoms, and 3. No evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel)
Rome III (42)	*One or more of: 1. Bothersome postprandial fullness, early satiation, epigastric pain or epigastric burning. And 2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms. * Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

The present study was planned during the Rome I era and was performed when the Rome II definition was published, and therefore we have applied both definitions with modifications. The dyspepsia definition in both Rome I and II splits dyspepsia into supposed etiological sub-groups (dysmotility-like and ulcer-like dyspepsia), but it has subsequently been shown by several research groups, that these sub-groups do not have clinical relevance (11, 24, 43-45).

The reported prevalence span over the years is striking: Dyspepsia has been reported to affect from 7% ("non-colonic abdominal pain") of healthy British men during one year

(46) to 63% during six months in central Birmingham (9), and from Lima a prevalence of dyspepsia among adults of 86% has been reported (47). In the mainstream, Johnsen et al., in a Norwegian population-based survey found the life-time prevalence of non-ulcer dyspepsia (NUD) to be 23% among men and of 18% among women (48), and Talley et al. (11), in an US study, reported a one-year overall prevalence of 26%. In a Swedish study, the three month prevalence of dyspepsia, in an unselected adult population, was 25% (29). In a recent Taiwanese study the prevalences of functional dyspepsia were 24% and 12% according to the Rome I and Rome II criteria, respectively (49), and Minocha et al., in a Mississippi metropolitan area study, reported a dyspepsia prevalence of 25% (un-investigated dyspepsia) according to the Rome II criteria (50). Also for dyspepsia a 25% prevalence in the adult population seems to be a reasonable average in the literature (31).

IBS prevalences also vary between studies, partly due to inconsistent disease definitions applied. Manning's criteria (51) was widely used during the eighties and during the nineties the Rome I criteria (40) have gained increasing acceptance and in the new century the Rome II criteria for IBS came into use (41). Thompson et al. reported a prevalence of "spastic IBS" of 14% in apparently healthy UK people (46) and Talley et al. reported an IBS prevalence of 18% in an US study (52). From Sweden Agréus et al. reported an IBS prevalences of 9-14% in a population cohort follow-up study (53), in Nigeria a 30% (54) and in New Zealand a 17% one year prevalence of IBS is reported (55). A fifteen percent population prevalence seems to be a reasonable reported average for IBS prevalence in the literature (31).

Depending on definition used, symptom overlap, which means that the same individual can report more than one of the GI symptoms concomitantly, is common. For example, Jones et al. in Scotland and England found a symptom overlap of 56% between GERS and dyspeptic symptoms (9) and Talley et al. in a US general population study found that 29% of those with IBS also had frequent dyspepsia (11). Jones and Lydeard (17) reported that over 90% of those with IBS in the general population also reported dyspepsia and showed that 79% of them also had reflux symptoms. In a Swedish study, 87% of those with IBS also fulfilled the dyspepsia criteria applied (56). This illustrates the complexity of GI symptomatology in relation to diagnosis and it also illustrates the large symptom burden of patients.

Longitudinal natural history studies of the GI disorders/diseases are considerably less numerous. GERS, dyspepsia and IBS are all more or less chronic disorders with abundant fluctuation in intensity and duration of symptomatic periods and also with symptom overlap and flux in between them (31, 53, 57). In a follow-up study over 1 and 7 years, there was a substantial symptom fluctuation and symptom profile flux between those reporting dyspepsia or IBS (53). Only less than 10% with GERD changed to dyspepsia and/or IBS, or vice versa over the assessment period. GERS in outpatients are known to persist for at least 10 years in up to three quarters of patients (58). In a Swedish follow-up study over 10 years period, GERS were very stable and 83% reported the same symptom at the end of the follow-up as at the study start (59) and similar results are reported by others (11, 60-63). The symptom-free subjects, alike those with GERS, seem relatively stable and remain symptom free or report only minor GI symptoms in about 90% of cases (53).

Prior data on more short time fluctuation is even more scarce than longitudinal follow-up data, but Johannessen et al. reported that only 10% showed stable GI symptoms over a 2 week period (57).

1.4 LINGUISTIC ASPECTS (VALIDATION)

The way people describe and interpret symptoms may differ depending on whether they use their own language in their own country or use the language of their adopted country (immigrants). People also tend to judge and verbalize their health and symptoms according to their cultural origin but also their assimilation into the host culture interacts (64). The degree of cross-cultural adaptation depends to a large extent on differences between the structures of the languages, but also to cultural background and socio-economic circumstances of the individuals. As Haparanda is situated at the Finnish border, a substantial part of the population are of Finnish origin (35%), and 27% of the sampled population preferred to reply in Finnish, compared with the corresponding figure in Kalix of only 2% (65). In this study, we used some questionnaires primarily validated in Swedish and then translated into Finnish. Hence, it was necessary to validate, according to accepted principles, for the first time the Finnish translation of the Abdominal Symptom Questionnaire (ASQ) which was used in the study (65).

1.5 HISTORY OF PEPTIC ULCER DISEASE

The first classification of stomach diseases, including only gastric ulcer (GU), came in 1793 by M. Baillie and in 1828 by J. Abercrombie's descriptions of symptoms and anatomic changes due to both GU and duodenal ulcer (DU). The different entities of GU and DU were also described by these investigators (66). After these works 1860 there were already more than 100 publications on this topic in the medical literature. The first prevalences of ulcer disease were published 1857 from an autopsy material by William Brinton. He noted that GU was found in 2-13% of persons dying from all causes,(67) followed by numerous published autopsy materials, x-ray materials and other materials on prevalences of PUD(66, 67). The etiology of the disease was still unknown. The recommended treatment consisted mainly of opiates, bismuth, alkaline carbonate and avoidance of large meals, meat, hot food or drinks and a bland diet of soft food and milk (67).

The first clinical population-based studies of GI symptoms were published by Hill (1937; "Case-population study on employees of London Passenger Transport Board") and Schellog (1937; "Abdominal symptoms of construction workers in Königsberg"). Alsted's "Studies on the changing incidence of peptic ulcer of the stomach and duodenum" study in Denmark may be the first real epidemiologic study on PUD (66). According to Alsted, the incidence of PUD was 2.4 in men and 1.0 in women/1000 individuals/year in 1940. Another well known study on the epidemiology of PUD in a rural community was done by Weir et al. According to this study, the prevalence of PUD, mainly DUs, was 10% in men over 15 years of age (68). The prevalence of PUD during 1940-1965 varied in different studies between 1-15% and most of these studies were patient-based and some were based on autopsy materials (66).

GU, especially in women, was the most common type of PUD in the 19th century, whereas DU was rather rare (69). Similarly perforations due to GU were most common in young women and this trend reached its peak in the second half of the century. This trend was, for unknown reasons, changed at the beginning of the 20th century and then these perforating ulcers were juxta-pyloric ulcers in young and middle aged men (70). This pattern change continued until the mid-20th century, when DU became more common than GU in most parts of the world (69). The total prevalence of PUD has since then probably declined, and this decrease began already before the breakthrough in the treatment of PUD with strong acid production inhibitory agents (71-76). The most probable main reason for the declining prevalence of PUD is likely the declining *H. pylori* prevalence, but this was not understood until the late 1990's (77). The era of antacid therapy for PUD began with Shippy in 1915 by neutralizing the stomach acid using cream and sodium bicarbonate (78). This treatment dominated PUD therapy in the second and third decades of 20th century, and its influence is still felt. Treatment with Histamine-2 receptor antagonist (H₂ RA) was introduced in 1977 and the first proton pump inhibitor (PPI) was introduced in 1988. Although Lykoudis in the 1950's concluded, that PUD was an infectious disease and treated it accordingly (79, 80) combination therapy with PPI and antibiotics, was not being documented until the late 1990's, when the *H. pylori* etiology for PUD was understood (81). This totally changed the treatment paradigms with ensuing transfer of PUD patient treatment to primary care and the role of surgery of PUD diminished mainly to emergency situations (76).

There are also investigation landmarks in making epidemiological surveys possible in PUD. The first was development of x-ray equipment by W. Röntgen in 1895 and investigation with barium contrast, which came into use for the first time already 1896 by Roux and Balthaser (82) and the method was further developed by Cannon (67, 82). After that, it was possible to confirm the clinical PUD diagnosis with x-ray. Furthermore the development of endoscopy methods, which started in 1935, improved these possibilities considerably and endoscopy has become the major investigational method also in epidemiological research first after development of flexible fiber optic instruments in the 1960's.

The 1982 finding of *H. pylori* as a possible cause of PUD changed the earlier paradigms of risk factors of PUD and caused a revolution also in epidemiological research of PUD and in treatment of the disease (83). This discovery dedicated the Nobel Prize in Medicine and Physiology to B. Marshall and R. Warren in 2005.

1.6 PEPTIC ULCER DISEASE PREVALENCE IN A POPULATION

There are very few population-based studies on PUD prevalence using modern diagnostic endoscopy. The Sørreisa Gastrointestinal Disorder Study from the 1990's (84) was population-based but with a case-control design for the endoscopies Dyspeptic individuals and matched asymptomatic controls were endoscoped, and a point prevalence of PUD of 4% among controls and 8% among persons with dyspepsia was found. In a Swedish population-based study (85), with a response rate of 25%, 3% of participants had current PUD and a further 3% had evidence of past ulceration.

Few other data are available and all those are from more selected population samples: Ihamäki et al. (86) found less than 2% PUD and 4% duodenal scars among healthy controls matched to cancer patients in Finland. Khuroo et al. (87) found a point prevalence of 4.7% for PUD and a lifetime prevalence of 11.2% in a population-based case-control study in India; most had DU. Katelaris et al. (88) found a 6% prevalence of DU, 2% GUs and 7% prepyloric or duodenal deformity among monks in India. Lond et al., in Estonia (89), found a prevalence of 9% for DU and 4% for GU in a random population sample reporting dyspepsia. In a recent preliminary report from Italy (90), the prevalence of PUD among adults was 4.5%, and a third of these (six of the 18 with DU, four of the 12 with GU) were asymptomatic.

1.7 RISK FACTORS FOR PEPTIC ULCER DISEASE

1.7.1 *Helicobacter pylori* and peptic ulcer disease

The revolutionary discovery by Barry Marshall and Robin Warren in the late 1980's and early 1990's of the *H. pylori* infection as an etiology for PUD can be summarized from their key publication as follows: "Biopsy specimens were taken from intact areas of antral mucosa in 100 consecutive consenting patients presenting for gastroscopy. Spiral or curved bacilli were demonstrated in specimens from 58 patients. Bacilli cultured from 11 of these biopsies were gram-negative, flagellate, and microaerophilic and appeared to be a new species related to the genus *Campylobacter*. The bacteria were present in almost all patients with active chronic gastritis, DU, or GU and thus may be an important factor in the aetiology of these diseases." (83). This article is the base for subsequent intensive research on *H. pylori* and PUD and led to total change in treatment paradigms. However, according to Marshall: "The *Campylobacter pylori* story began before the turn of the century, with early works describing 'spirochetes' in the gastric mucosa of animals. Culture of the organism in 1982 enabled investigators (i.e. Marshall & Warren) to make sense of the many previous works concerning the microbiology, biochemistry, and histology of the gastric mucosa. Whereas some physicians remain sceptical of *Campylobacter pylori's* pathogenic role, those who have studied the new organism believe it is a major GI pathogen and see the possibility of curative therapy for what is now called "acid peptic disease." (91).

The causal role of *H. pylori* in the development of PUD has been confirmed in an overwhelming number of studies (92-95). The declining prevalence of PUD in the Western world is also related to effective final eradication of *H. pylori*, making the disease no longer chronic, but also by the fact that the prevalence of infected individuals decreases with higher prosperity (96), but despite this the disease is still far from harmless (97).

1.7.2 Other main risk factors

Smoking, use of NSAIDs and regular use of aspirin are well known risk factors for PUD. A high consumption of analgesics and NSAIDs seems to predispose to GU that requires hospital care (98-101).

Kurata et al. based their analyses of overall risk ratios for each risk factor for PUD-related GI events by meta-analyses of English-language studies of risk ratios. According to them the general population's attributable risk percent were 24% for NSAIDs, 48% for *H. pylori* and 23% for cigarette smoking and between 89% and 95% of serious PUD-related upper GI events were estimated to be attributed to NSAID use, *H. pylori* infection or cigarette smoking (102). A Polish study reported similar findings and also showed that age plays a role in the pathogenesis of PUD, but also that about 20% of peptic ulcers in the Polish population were so called idiopathic ulcers, that is ulcers unrelated to *H. pylori* and NSAID use, (95). Rosenstock et al. from Denmark showed that tobacco smoking and *H. pylori* infection are the main risk factors for PUD in Danish adults and physical activity may protect against PUD in those infected with *H. pylori* (94). In a Norwegian cross-sectional survey, PUD was strongly associated with age, a family history of peptic ulcer, body mass index (BMI), and smoking (48). NUD, on the other hand, showed closest association with psychological factors and social conditions (48, 103). The role of long-term use of corticosteroids as a cause of PUD is controversial but in a Finnish study corticosteroid use was an independent risk factor for GU development (104).

There is some evidence that coffee might be a risk factor for peptic ulcer (105, 106) perhaps due to stimulation of gastric acid secretion (107), but most studies do not implicate coffee, alcohol, any food or beverage as causes of PUD (94, 108, 109)

1.7.3 Genetic factors

Johnsen et al. reported that inheritance is a risk factor for PUD (110). In a study performed also before the "*H. pylori* era", the first-degree relatives of patients with DU had a two- to threefold increase in risk of getting DU and first-degree relatives of GU patients had a similarly increased risk of getting a GU (105). However, in a more recent twin cohort study by R ih a et al. controlling also for *H. pylori* infection, it was found that familial aggregation of PUD is modest, and attributable almost solely to genetic factors (111).

1.7.4 Psychological factors

There is some evidence for an association between PUD and psychological factors (112). In one study depression was the variable that best discriminated PUD patients from non-ulcer controls; a negative perception of life events also had discriminating value for PUD risk. Emotional stress might also predispose for PUD development (113, 114). In a study by Levenstein et al., they found that depression, maladjustment and hostility are prospectively associated with PUD. These associations are partially accounted for by confounding or mediation by standard risk factors and are to some extent related to socioeconomic status (115). Goodwin et al. in an US population-based survey reported a clear dose-response relationship between generalized anxiety disorder and self-reported PUD among adults (116). Some studies have shown that psychological factors may contribute to delayed ulcer healing and on the other hand psychotherapy may have a positive role in healing of PUD (117, 118).

1.7.5 Socioeconomic factors

According to some earlier reports, DU is a more common condition in persons with a low level of education and heavy work (119, 120), often explained by the fact that the latter are more often smokers (120), but also by difficulties of being able to respond to demands, inability to exert any influence on or ability to find satisfaction in work (121, 122). Shift work and a trying private life also seemed to predispose to PUD (113, 122, 123) A lower frequency of PUD, in people with a higher education, has been described from the US (124). These weak associations mainly apply to DU disease and all these studies have been done before the “*H. pylori* era”, and subsequently not controlled for this prosperity dependent infection.

More relevant is therefore for example the study by Jones et al. that showed that the lowest rate for ulcer diagnosis (4.7%) was found in the highest social class and the highest (17.1%) in the lowest social class (9), and the study by Levenstein et al. showed that psychological stress, health risk behaviors, analgesic use and hard physical labor may contribute to the increased risk of ulcer in low socioeconomic populations (125) and also that low socioeconomic status and concrete life difficulties are associated with peptic ulcer in the general population (126). In a recent Danish study, they found that poor socioeconomic status is an important risk factor for PUD exerting its effect independently of *H. pylori* infection and that strenuous work may increase the risk of PUD in people with *H. pylori* infection. (127). Researchers in China concluded recently that the incidence of PUD in the Wuhan area of China is highly associated with age, gender, occupation and geographic environmental factors (128).

1.7.6 Geographic and ethnic factors

The prevalence of *H. pylori* varies by geographical location, ethnic background, socioeconomic conditions and age and it is decreasing in developed countries or those with rapidly improving socioeconomic conditions (129). These differences in *H. pylori* prevalence might also explain the differences in PUD prevalences between different ethnical groups and geographic areas: the Chinese population in Singapore had a higher frequency of peptic ulcer than people of Malayan or Indian origin, whereas recognized risk factors were equally common in these groups (130).

Researches in China also found associations to geographical environmental factors (128) and in New Zealand ethnicity appears to be a risk factor for *H. pylori* independent of socioeconomic status (131) providing an explanation for possible differences in PUD prevalences.

GU was at least three times more common than DU in some regions of the world. This applies particularly to Japan, but GU was more common also in Turkey, Sri Lanka, Chile, in some parts of Peru and in northern Norway (132). The incidence of duodenal stenosis, bleedings and perforations in PUD patients were different in India compared with Western world, which may suggest that different pathogenetic mechanisms are involved in the development of the DU (133).

1.7.7 Seasonal variations

There is no good evidence to support the popular belief that PUD is most common in the spring and autumn, however some data are available. Kurata and Haile found that the most consistent seasonal variation appears to be lower PUD rates in the summer. (105) The mortality from PUD in the study of Ivy (134) was also highest during the winter months. In an investigation from the William Beaumont Society (135) a summer decline in frequency of hemorrhages was seen. Gibinski et al. studied 50 patients with a PUD with medical history taking and endoscopy over a period of 5 years. Ulcer pain was at its lowest in the spring and in August, highest in the early autumn and in December, whereas the number of demonstrable ulcers was lowest in August and December (136).

1.8 IDIOPATHIC PEPTIC ULCER

Peptic ulcers, which are not associated to *H. pylori* infection or use of NSAIDs/aspirin, are labeled "idiopathic ulcers". Hypersecretory syndrome (Zollinger-Ellison syndrome) should also be excluded before making the diagnosis of idiopathic ulcer (137). The etiology might be multifactorial and may include genetic predisposition, altered acid secretion, rapid gastric emptying, defective mucosal defense mechanisms, psychological stress, and smoking.(137) Xia et al. reported a 17% prevalence of idiopathic DU in a study in Hong Kong (138). About 20% of ulcers in a Polish study were 'idiopathic ulcers', i.e. without NSAID use and *H. pylori* absent and the ratio of these ulcers to all ulcers was significantly increased during the 5 years of the study (95). In a Danish study Sondergaard et al. found that 9.6% (12/125) of peptic ulcers were idiopathic (139). The prevalence of *H. pylori* infection is decreasing and *H. pylori*-associated PUD is also decreasing as illustrated. in a Danish study where only 49% of PUD patients were *H. pylori* infected (139). It is, however, still unclear if the absolute prevalence of idiopathic ulcer has increased.

1.9 ASYMPTOMATIC PEPTIC ULCER DISEASE

The reason why some ulcers are asymptomatic is not known. Both asymptomatic DU and GU have been found in a substantial proportion of cases in well designed and controlled trials. Gibinski et al. in their study found, that 4% of ulcer patients did not feel abdominal pain (136). Jorde et al. found that of 22 peptic ulcer patients, 14 had no dyspeptic complaints, 4 had minimal symptoms and did not need antacids and 4 were taking antacids for the relief of dyspepsia (140). The Sørreisa study found that approximately 10% of ulcers were asymptomatic (141). A recent Italian study found, that one third of peptic ulcers were asymptomatic (90). A conclusion from these studies might be, that the proportion of asymptomatic PUD is substantial and since these asymptomatic individuals do not consult, the prevalence is likely underestimated. The natural history of asymptomatic PUD requires longitudinal studies.

2 THE AIMS OF THE STUDY

The aims were:

- to explore the possibility of performing a well designed population based EGD study among adults and to evaluate whether the inconvenience of an endoscopy actually biased symptom reporting. (Study I)
- to investigate the prevalence of peptic ulcer disease, including idiopathic ulcers, and concomitant symptoms and risk factors in a randomly selected adult population. (Study II)
- to reveal the relationship between Body Mass Index and gastrointestinal symptoms and findings. (Study III)
- to explore the impact of use of smokeless tobacco and/or smoking cigarettes on the macroscopic and histological gastrointestinal health in the upper gastrointestinal tract and its influences on the prevalence of *H. pylori* and the possible changes of inflammatory activity caused by *H. pylori* . (Study IV)

3 MATERIALS AND METHODS

3.1 SETTING, SAMPLING AND STUDY DESIGN

The setting consisted of two adjoining municipalities in northern Sweden, Kalix and Haparanda (“the Kalixanda study”), with 18,408 and 10,580 inhabitants, respectively (total 28,988 in December 1998). Among these subjects, 78% lived in urban areas (in year 2000), compared to the Swedish national average of 84%. The distribution of age and gender in both municipalities was similar to the national average for Sweden, while some other socioeconomic variables (unemployment status, income, proportion with higher education) were slightly lower in Kalix than the Swedish average, and this pattern was somewhat more marked in Haparanda (142, 143). In Haparanda, a third of the inhabitants were born outside Sweden (mostly in Finland), while from Kalix this figure was slightly less than the average in Sweden (11%). Overall, 11.3% of responders answered the questionnaires in Finnish (27.3% in Haparanda, 2.1% in Kalix).

In September 1998, a representative sample of 3,000 (every seventh person) was drawn from the target population of 21,610 adults aged between 20 and 80 years in the municipalities, using the national population register covering all citizens in the area. This was considered to be equivalent to a random sampling procedure. The sampled subjects were then given an identification (ID) number from 1 to 3,000 by computer, in random order.

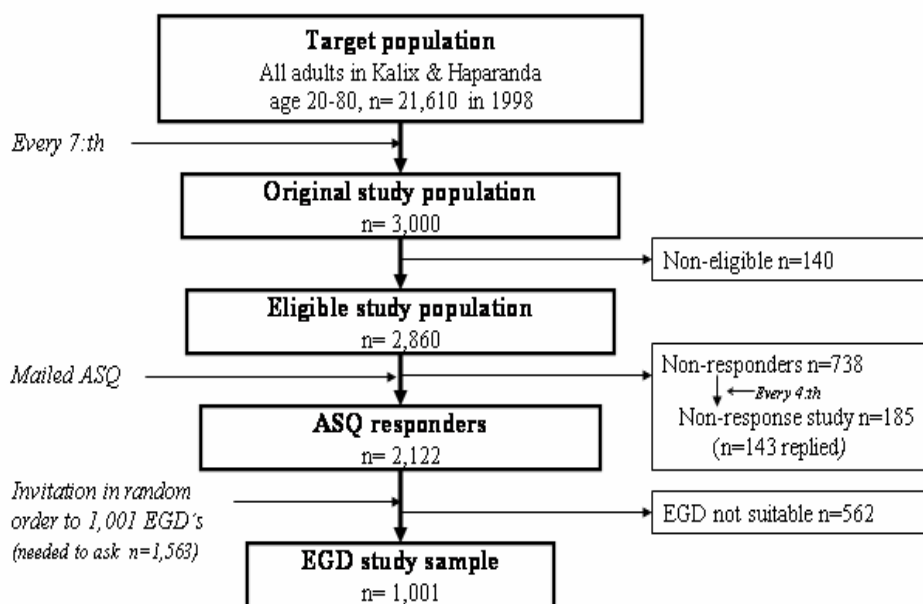
Of the original study population ($n = 3,000$), 140 (4.7%) persons turned out to be non-eligible for screening (21 were deceased, 17 had mental retardation or dementia, 87 had moved or had an incorrect address, and 15 were ineligible either of these reasons as the cause was not defined in a sub-sample of the first outmailing) (Table 2). The main reason for being non-eligible was that subsets of the participants were not approached until up to two and a half years after the sample was drawn, as described in section 3.2. Study Logistics below. Thus, at screening, the eligible study population consisted of 2,860 persons. They were first approached by mail with an invitation letter, including information of an eventual EGD further on, and a postal questionnaire (the ASQ, see below) (144). Up to two reminders were sent when necessary. There were 2,122 responders providing us with a response rate of 74.2%.

The ASQ responders were then invited by telephone for an EGD in ID order, starting with the lowest available ID number. The telephone caller was unaware of the symptoms of the responder. The aim was to perform a complete EGD with biopsies in a third of the study population, i.e. in 1,000 adult subjects (4.6% of the target population). Of the 1,563 subjects invited for inclusion, 1,365 were eligible for further participation, and of those 1001 (73.3%) accepted, of whom one refused biopsies. The reason for non-participation is reported in the results of Study I.

The principles of the sampling process are shown in Figure 1 and, Table 2 in the results shows sociodemographic and other details in each sampling step. The study logistic details are described below.

Figure 1. Study sampling process.

Fig. 1.

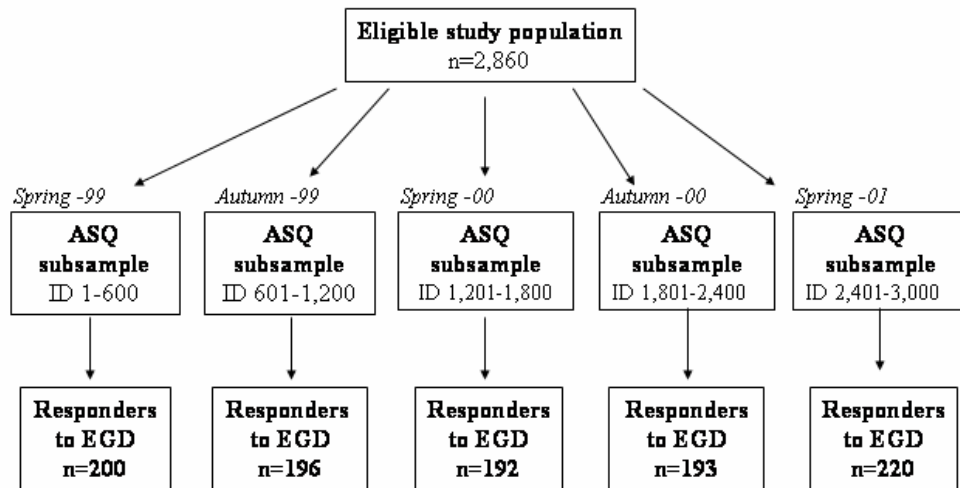


3.2 STUDY LOGISTICS

The three endoscopists had the capacity to perform 200 EGDs every five months, excluding holidays. The study population was therefore 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 approached with the mailed ASQ in November 1998 and the project took two and a half years to complete. The number of EGDs per subset is shown in Figure 2 and the total number of EGDs performed was 1,001, with biopsies for *H. pylori* culture and histology available from 1,000 subjects. Reasons for non-participation is given in the Results, Study I, “Non-eligible subjects for EGD”.

Figure 2. Study logistics

Fig. 2.



3.3 STUDY SIZE ESTIMATE

The number of EGDs was calculated to obtain appropriate prevalence estimates (95% confidence intervals $\sim \pm 2\%$). From this estimate the aim was to perform 1,000 complete EGDs.

3.4 ETHICAL APPROVAL

Approval for the study was obtained from the Ethics Committee of Umeå University on May 29, 1998 (Um dnr 98-99). The study was conducted in accordance with the revised Helsinki Declaration and all participants gave their oral informed consent.

3.5 ESOPHAGOGASTRODUODENOSCOPY

The upper endoscopies were provided by both primary and secondary care physicians in the two clinics, which gave sole medical cover to the area. The three endoscopists, one gastroenterologist in Kalix and two general practitioners in Haparanda were highly 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 Finland over several years.

The endoscopists were unaware of the symptoms of the subjects before and during the EGD. Thus, the EGD findings were recorded when the endoscopist still was unaware of the symptomatology. The EGDs were performed with topical (spray) anesthesia only and standardized biopsies for histology were taken in all subjects from the cardia, the corpus, the angulus (except for the first 246 subjects), and from the antrum for histological analysis. In addition, biopsies were taken from the antrum and the corpus for *H. pylori* culture. Any visible lesions were also biopsied. Just before the EGD, a more comprehensive version of the ASQ was filled out (with symptom frequency ratings) and a complete medical history was taken and recorded after the blinded research part of the session. Blood samples for *H. pylori*, Gastrin-17 and Pepsinogen-1 serology were also taken at the visit.

3.5.1 Endoscopy validation

The following step-by-step process assessed internal validity of the endoscopies performed:

1. A consensus meeting with an external consultant (Professor of GI surgery) who reviewed common macroscopic findings and standardized classification systems, such as the Los Angeles classification (145) for erosive esophagitis, Barrett's esophagus as well as GU and DU disease, as captured on video.
2. A test session with a Professor in gastroenterology who first showed video sessions as described in 1. (above), and then, focusing on esophageal findings, showed six cases and required each endoscopist to give a diagnosis. For the lower esophagus-cardia region, only one of 18 diagnoses had a mismatch (Los Angeles grade A vs. normal).

3.6 THE ABDOMINAL SYMPTOM QUESTIONNAIRE

The ASQ has been validated previously and been found to be reliable and reproducible (56, 65, 144, 146). The original questionnaire asked the participants if they had been *troubled* (Yes/No) by any of a list of 27 general GI 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 (burning sensation, aching, pain, tenderness, gripe, twinge, stitch, cramp, colic, sinking feeling, "butterflies"), and also about its location (upper, centre or lower abdominal, right and left flank, respectively). In order to better reflect the Rome II definitions of the functional GI disorders (147), eight questions were added at applicable parts of the questionnaire. The key question from the Carlsson-Dent questionnaire ("burning feeling rising from the stomach or lower chest up towards the neck") (148) was also added. 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). Persons who agreed to participate to the EGD part of the study filled out a more comprehensive ASQ including frequency of the symptoms (daily, weekly or past three months) at the EGD visit.

3.7 NON-RESPONSE MONITORING

Non-responder documentation was filled in for every fourth (n=185 out of 738) of the non-responders to the mailed ASQ by the investigators after a telephone interview (n=115) or a postal questionnaire (n=28) with seven key symptom questions from the ASQ: Heartburn, acid regurgitation, epigastric and general abdominal pain or discomfort, diarrhea and constipation, and the level of education as described above. They were also asked to give a blood sample for *H. pylori* serology.

3.8 DEFINITIONS OF SYMPTOM GROUPS

3.8.1 Gastroesophageal reflux symptoms

Those who reported troublesome heartburn and/or acid regurgitation over the past three months were considered to have GERS (144, 149), which definition also other investigators have accepted (150).

3.8.2 Dyspepsia

Dyspepsia was defined as troublesome pain or discomfort expressed as one or more of the 11 listed pain or discomfort modalities indicated in the upper (epigastric) part of the abdomen, or reporting one or more of the symptoms uncomfortable feeling of fullness, early satiety or nausea (upper abdominal bloating was not reported in the ASQ). The listed symptoms are as similar to those used in the Rome II definition of dyspepsia (151) as possible, given linguistic limitations.

3.8.3 “Epigastric pain or discomfort”

In order to compare the responders with the non-responders (mostly by telephone interview), a simplistic definition of dyspepsia, labelled “Epigastric pain or discomfort” was also used. “Epigastric pain or discomfort” in the ASQ was defined as troublesome pain or discomfort expressed as one or more of the 11 listed pain or discomfort modalities indicated in the upper (epigastric) part of the abdomen only. This definition is based on the Rome I definition of dyspepsia (39, 40).

3.8.4 Abdominal pain

Abdominal pain was defined as troublesome pain or discomfort expressed as one or more of the 11 listed pain or discomfort modalities located anywhere in the abdomen.

3.8.5 The Irritable Bowel Syndrome

Symptoms of IBS were defined as reporting of one or more of the 11 listed abdominal pain or discomfort modalities located at any site, combined with reported bowel habit disturbances (troublesome constipation, diarrhea or alternating constipation and diarrhea), a definition justified to have accurate diagnostic agreement with both the Manning and the Rome I criteria (152).

3.8.6 No, minor or atypical symptoms

No or minor symptoms did not fulfill any of the above symptom classifications, or absence of symptoms in the ASQ.

“Atypical PUD symptoms” were defined as GI symptoms other than dyspepsia or “epigastric pain or discomfort” in subjects with PUD.

The above definitions allowed concomitant reporting of GERS, dyspepsia, and IBS.

3.9 *HELICOBACTER PYLORI* INFECTION BY HISTOLOGY AND SEROLOGY

Biopsy samples were stained with hematoxylin and eosin. *H. pylori* infection was histologically detected by means of Warthin-Starry silver staining (153). The histological parameters of the gastric mucosa were assessed using the updated Sydney System score definitions (154). Gastritis, including features of former *H. pylori* (minimal chronic inactive or ex-*H. pylori*) gastritis, was diagnosed according to the method of Oberhuber et al. (155).

Chemical-reactive gastritis proposed to be caused by aspirin, NSAIDs, or bile reflux was defined according to the updated Sydney System definitions (154, 156, 157).

Two experienced pathologists (Prof. M. Vieth. and Prof. M. Stolte, Institute of Pathology, Bayreuth, Germany) evaluated the biopsies and gave a common report and then a third experienced pathologist (Dr. M. Walker, Imperial College London, UK, re-evaluated the biopsies from 100 randomly chosen subjects. The kappa value for agreement between observers in the evaluation of *H. pylori* infection was 0.76 (95% CI; 0.56-0.96) for the corpus and 0.78 (95% CI; 0.59-0.98) for the antrum. The corresponding figures for granulocyte infiltration were 0.57 (95% CI; 0.37-0.76) and 0.73 (95% CI; 0.53-0.93), respectively.

Samples taken from the antrum and corpus were cultured and analyzed as described previously (153, 158).

Current *H. pylori* infection was defined as a positive culture or histological finding. There was overall agreement of 99.3%, with a kappa value of 0.96 (95% CI; 0.94-0.98) for agreement between the tests (153).

The presence of immunoglobulin G antibodies against *H. pylori* was determined by enzyme immunoassay (Pyloriset EIA-G; Orion Diagnostica, Espoo, Finland) (159). A positive test in the absence of *H. pylori* (culture or histology) was considered indicative of a past infection.

3.10 DEFINITION OF GASTRIC ULCER AND DUODENAL ULCER

Ulcer was defined as a mucosal break at least 3 mm in diameter, with or without a necrotic base in the middle of the lesion, in either the stomach (GU) or the duodenum (DU). In the case of several ulcers/erosions, at least one had to fulfill this definition.

3.11 CLASSIFICATION OF REFLUX ESOPHAGITIS

Reflux esophagitis was classified according to Los Angeles classification system (145).

3.12 COVARIATES

3.12.1 Demographics and history

Demographic data were collected at the clinic visit (gender, age, length, weight, use of tobacco products, use of alcohol and use of medication) after the EGD part of the study. The subjects' level of education and number of inhabitants in their household was confirmed by questions in the mailed ASQ.

3.12.2 Use of aspirin, NSAIDs and other medication

All participants were thoroughly interviewed face to face regarding their medication use. Reported use of aspirin or NSAIDs for all subjects with idiopathic ulcers was rechecked by means of a telephone interview and a review of the subjects' medical records.

Data on medication use was recorded after the endoscopy. In addition to any acid suppressing drug, medications concurrently being taken that may reduce lower oesophageal sphincter pressure (nitrates, theophylline, calcium channel blockers, opiates, beta agonists, phenothiazines, tricyclic antidepressive drugs, nicotine substitutes, anticholinergics and benzodiazepines) were recorded (160-165).

3.12.3 Body mass index (BMI) categories

Height and weight were measured at the endoscopy visit. The data on weight and height were used to calculate BMI; weight in kilograms divided by the square of height in meters (Kg/m^2). Participants were categorized based on BMI as underweight (BMI <18.5), normal (BMI ≥ 18.5 and <25), overweight (BMI ≥ 25 and <30), obese class I (BMI ≥ 30 and <35), class II (≥ 35 and <40) and class III (≥ 40) (166). Because there were relatively few subjects in the extreme obesity categories, these were all combined and there were also too few individuals in the underweight group (n=8) to be analyzed separately.

3.12.4 Smoking and use of smokeless tobacco

A complete medical history was taken and recorded after the EGD. The doctor asked about previous medical history and utilization of medical services. The participants were also asked about their present and past use of smokeless tobacco and the current amounts/week in a standardized fashion. The investigator also actively explored the present and former smoking habits and the number of cigarettes per day.

3.12.4.1 Definitions of tobacco user groups

Current smokeless tobacco users were those using moist snuff or chewing tobacco (one individual) without any present or former use of smoked tobacco.

Current smokers were individuals smoking cigarettes and having no other present or former tobacco use.

Users of both were individuals both smoking cigarettes and using smokeless tobacco.

Former users were former cigarette smokers and/or former users of smokeless tobacco.

Non-users were individuals without any present or former use of tobacco products.

3.12.5 Other serology

Gastrin-17 (cut off ≥ 10 pmol/liter) and pepsinogen-1 (cut off <25 $\mu\text{g/l}$ for low and >100 $\mu\text{g/l}$ for high levels) were analysed using specific EIA tests (Biohit Plc, Helsinki, Finland).

3.13 STATISTICAL ANALYSIS

Student's t-test, Pearson Chi-2 test and Fisher's exact test were used for testing comparison in univariate analyses. A two-sided p -value less than 0.05 was regarded as statistically significant. The prevalence is shown as percentage with a 95% confidence interval (CI). The odds ratios (OR) for a given specific symptom, combined symptom or other binary dependent variable, and 95% CI were calculated by exponentiation from the coefficients and standard errors obtained in the logistic regression models (167).

When symptoms were compared for sub-populations by testing the prevalences with a Student's t-test, p -values were adjusted for multiple comparisons (e.g. for three study samples a significance level of $p < 0.025$ was accepted as statistically significant).

The influence of age and gender on the combined symptoms GERS, "epigastric pain and discomfort", dyspepsia, abdominal pain and IBS was tested by applying a logistic regression model.

The association of individual symptoms, combined symptoms, *H. pylori*, use of acid-reducing drugs (antacids, H_2 RA, and PPI), obesity, use of NSAIDs, use of aspirin, smokeless tobacco and smoking with the risk to have PUD, was analyzed by applying a multivariate logistic regression model adjusting for age and gender.

We applied a logistic regression model to assess the association between the presence of each specific symptom (the binary dependent variable) and BMI (entered as a categorized independent variable), adjusting for age, gender and education level. Individual symptoms combined symptoms and other possible exposure variables were analyzed separately in different analyses by endoscopy findings. A multivariate logistic regression model was applied to assess the association between BMI and GERS or separately esophagitis, adjusting for medication use as well as age, gender and education level. Linear regression analysis was applied to analyze the independent associations between BMI and possible binary exposure variables smoking, education level and alcohol.

The association of use of different tobacco products with GERS, dyspepsia, "epigastric pain or discomfort", overall abdominal pain and IBS was analyzed applying logistic regression model adjusting for age and gender and using non-users as reference group (OR=1). The association of use of different tobacco products with esophagitis, GU, DU, overall PUD and dichotomized histological variables from 2 centimeters above the esophagogastric junction, at the esophagogastric junction, at the cardia, in the corpus and the antrum of the stomach and in the duodenum was analyzed applying a multivariate logistic regression model including possible exposure variables (*H. pylori* infection, use of aspirin and/or NSAIDs, use of alcohol and obesity), adjusting for age and gender and using non-users as reference group (OR=1). The results were controlled for possible interactions.

The goodness of fit of the models was judged from the Pearson χ^2 test. The fit of the model was considered acceptable if the p value was ≥ 0.05 . The Intercooled Stata 8 program was used for the analyses (168).

4 RESULTS

4.1 VALID SYMPTOM REPORTING AT UPPER ENDOSCOPY (STUDY I)

The original study population

Sociodemographic variables for the entire Swedish population and for all study sub-populations are presented in Table 2. In the original study population of 3,000 subjects, 1,560 (52.0%) were men and the overall mean age was 50.4 years.

Eligible and non-eligible subjects in the original study population

As more than two and a half years passed from the sample identification until the last person was screened, the eligible study population decreased from 3,000 to 2,860 subjects (4.7% not eligible). The reasons for being non-eligible are shown under Table 2. The 140 non-eligible subjects had a mean age of 49.7 and 55% of them were men. The small group of non-eligible subjects did not differ significantly from the original study population. Of the 2,860 eligible subjects, 2,122 responded to the mailed ASQ (74.2%), and 738 did not.

Table 2. Socio-demographic variables in the Swedish population and in the different samples of the population under surveillance. Data from current study and from official national data bases (169, 170)

	Swedish population age 20-80	Target population age 20-80	Original study population	Non-eligible in original study population*	Eligible study population	Responders to ASQ	Non-responders to ASQ	Analysed non-responders to ASQ***	Invited to EGD	Non-responders to EGD	EGD sample
n=	6,323,016	21,610	3,000	140	2,860	2,122	738	143***	1,563	562#	1,001
Response rate %						74.2		77.3***			73.3#
Mean age	50.0	-	50.4	49.7	50.4	51.8	46.4	46.6	52.3	49.1	54.1
% males	49.7	50.7	52.0	55.0	51.8	50.5	55.8	49.7	50.3	51.2	48.8
% speaking Finnish						11.3			11.8	10.8	12.3
% studied at college/university	23	15/21**				18		10	18	18	18
Persons per household (m)	1.5 ^{##}	-	-	-	-	2.6	-	-	2.5	2.5	2.5
% <i>H.p.</i> + serology								42.0****			43.0

*Non eligible in original study population (see logistics) n=140: Deceased=21, moved and questionnaire returned by relatives=38, mentally retarded/dementia=17, either of these three causes=15 (cause not defined in a sub sample of the first outmailing), incorrect address (may have moved after sampling) =49

** 15% Haparanda, 21% Kalix, age 20-64

***Every fourth eligible non-responders (n=738/4=185) was approached. 143/185=77.3%

**** 19 (n=8 or 42% male, mean age 51.0, 6% with college/university studies) of the 143 responders in the non-response study gave blood sample for *H.pylori*

of the 562 subjects not eligible for EGD at invitation, 364 declined, 74 had moved and 124 had medical contraindications. Thus, possible response rate was (1,001/1,001+364) = 73.3%

All ages

Non-responders to the mailed ASQ

The gender distribution among the 738 (25.8%) non-responders did not differ significantly from the original study population (male non-responders 55.8% versus original study population males 52.0%, $p=0.6$), although the non-responders were significantly younger (46.4 versus 50.4 years of age, $p=0.007$). Every fourth non-responder to the initial mailing (185 out of 738) was approached by telephone or mail for a short interview with seven key symptom questions and one question about their level of education. The 143 subjects (77.3%) who were reached and willing to answer did not differ significantly from the rest of the non-responders (mean age 46.6 years, 49.7% male). Nineteen of them also agreed to give blood samples for *H. pylori* serology.

The symptom profiles reported by the 143 subjects in the telephone interview are shown in Table 3. The proportion (10%) of those interviewed who had studied at college or university was significantly lower than among the 2,122 responders to the mailed ASQ (18%, $p=0.01$), but their prevalence of *H. pylori* positive serology was the same as for those endoscoped (42% vs. 43%, ns).

Responders to the mailed ASQ

Totally, 2,122 subjects responded to the mailed ASQ, after two postal reminders, which corresponds to a response rate of 74.2%. The mean age was 51.8 years, and 50.5% were men. The distribution of age and gender did not differ significantly from the original study population. Their symptom profile is shown in Table 3. No symptoms were reported by 24.0% (95% CI; 22.2-25.8) and minor symptoms by 17.7% (95% CI; 16.1-19.3).

Non-eligible subjects for EGD

In order to complete the 1,001 EGDs, 1,563 of the responders to the mailed ASQ had to be approached. Of the additional 562 invited responders, 364 declined, 74 had moved or could not be reached and 124 had medical contraindications.

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 ($n=20$).

Thus the participation rate for those eligible for investigation was $1,001/(1,001+364)$, i.e. 73.3%. The proportion of men in non-eligible subjects ($n=562$) was 51.2%, mean age was 49.1 years and level of education did not differ significantly from the original study population.

Subjects eligible for EGD

Altogether, 1,001 subjects had an EGD performed, of whom one refused biopsies. Of the participants, 488 (48.8%) were men, with no statistically significant difference in gender distribution compared with the original (n=3,000) study population and 52.0% were men (p=0.08). They were, however, significantly older than the original study population (54.0 vs. 50.4 years of age, p<0.0001), mostly due to a lower response rate in the younger age group. The symptom prevalences for those endoscoped, by age group and for all subjects, are shown in Table 3 and they were significantly higher (n.b. cut of p< 0.025) for all symptom groups than for the 2,122 ASQ responders: 5.1% for GERS (p=0.006), 3.9% for dyspepsia (p=0.04), 4.6% for “epigastric pain or discomfort” (p=0.005), 5.9% for abdominal pain (p<0.0001) and 4.2% for IBS (p<0.0001). The differences depended mostly on the younger group illustrated in Table 3. No symptoms were reported by 16.6% (95% CI; 14.1-18.7) and minor symptoms by 17.8% (95% CI; 15.4-20.2) subjects.

In order to assess whether the symptom prevalence recorded in connection with the EGD differed from the previously reported prevalences in the mailed screening ASQ as shown in Table 3, those 1,001 subjects who went through the EGD completed the ASQ again at endoscopy. This latter symptom report is shown in Table 4. The only significant difference in symptom prevalence as reported at those two occasions was a higher prevalence of epigastric pain or discomfort at the EGD investigation (p=0.007).

Table 3. Prevalence of symptoms per age group (%) and overall (n, %, 95%CI) among non-responders to mailed ASQ (n=143), among all responders to mailed ASQ (n=2,122) and among those of the latter participating in the EGD study (n=1,001) respectively. Differences in symptom prevalence are calculated between the first two (143 vs. 2,122) and between the last two samples (2,122 vs. 1,001)

	Age 20-34*	Age 35-49*	Age 50-64*	Age 65+*	All ages n	Prevalence %*	95% CI
GERS							
Non-responders	23.5	29.7	37.5	38.7	46	31.7	24.1-39.3
ASQ responders	34.0 ^{AE}	37.4	32.3	30.4	712	33.6^{AE}	31.6-35.6
EGD study sample	47.1 ^{AE}	45.5	35.5	32.5	387	38.7^{AE}	35.7-41.7
Epigastric pain/discomfort							
Non-responders	17.7	29.7	20.8	16.1	31	21.5	14.8-28.2
ASQ responders	23.4 ^{AE}	24.2	24.1	12.8	454	21.4^{AE}	19.7-23.1
EGD study sample	37.5 ^{AE}	30.2	27.2	14.6	260	26.0^{AE}	23.3-28.7
Dyspepsia							
Non-responders**	-	-	-	-	-	-	-
ASQ responders	43.7	38.8	35.8	26.5	760	35.8^{AE}	33.8-37.8
EGD study sample	55.8	45.2	39.2	27.6	397	39.7^{AE}	36.7-42.7
Abdominal pain							
Non-responders	43.1	18.9 ^{NA}	29.2	12.9 ^{NA}	40	28.0^{NA}	20.6-35.4
ASQ responders	49.9 ^{AE}	50.7 ^{NA, AE}	43.4	32.6 ^{NA}	974	45.9^{NA, AE}	43.8-48.0
EGD study sample	65.4 ^{AE}	61.9 ^{AE}	50.1	37.8	519	51.8^{AE}	48.7-54.9
IBS							
Non-responders	23.5	2.7 ^{NA}	16.7	6.5	19	13.1^{NA}	7.6-18.6
ASQ responders	27.6	29.8 ^{NA}	24.7	16.9	544	25.6^{NA, AE}	23.7-27.5
EGD study sample	37.5	36.6	29.0	20.3	298	29.8^{AE}	27.0-32.6

*Statistically significant differences ($p < 0.025$) within each age group and for all, column wise, are indicated with ^{NA} for difference between “Non-responders” and “ASQ responders”, and with ^{AE} for “ASQ responders” and “EGD study sample”.

**Not asked according to definition

Table 4. The three months prevalence of troublesome symptoms at the EGD visit (% per age-group) and associations to age and sex

	Men (n=488)					Women (n=513)					Men & Woman*	Test of sex and age	
	20-34	35-49	50-64	65+	Total	20-34	35-49	50-64	65+	Total		All ages	Age
n=	51	130	183	124	488	53	137	199	124	513	1,001 (95% CI)	p	p
GERS	54.9	40.8	36.1	27.4	37.1	39.6	45.3	41.7	42.7	42.7	40.0 (37.0-43.0)	0.046	ns
Epigastric pain/discomfort	21.6	17.7	12	9.7	13.9	37.7	33.6	29.2	13.7	27.5	20.9 (18.4-23.4)	<0.0001	<0.0001
Dyspepsia	51	36.2	26.8	17.7	29.5	50.9	51	47.7	32.3	45.2	37.6 (34.6-40.6)	<0.0001	<0.0001
Abdominal pain	66.7	49.2	36.1	29	40.1	62.3	62	53.8	39.5	53.4	51.4 (48.5-54.5)	<0.0001	<0.0001
IBS	33.3	28.5	20.8	16.1	23	41.5	38.7	29.2	25	32	29.6 (26.8-32.4)	0.001	0.004

*Logistic regression model for age and sex for symptoms. Goodness of fit was good for all models (p>0.05)

Potential selection bias

The youngest age group had the lowest response rate. Of the original study population 21.4% were 20-34 years old, compared with 16.9% of the responders to the mailed ASQ and 10.4% of EGD participants. The younger responders had a more pronounced increase in prevalence of symptoms as the selection process proceeded. Table 3 gives the prevalence per symptom group by age at different stages of the selection process. To summarize, there was an obvious selection bias in the youngest age group with significantly more symptoms among those accepting the EGD compared with all responders to the mailed ASQ.

In an attempt to remove any bias caused by the youngest age group (20-34 yr), an additional analysis was performed excluding them. The only statistically significant difference that remained was a significantly higher prevalence reported for abdominal pain ($p=0.01$) mainly confined to the 35-49 years age group.

4.2 PEPTIC ULCER DISEASE IN THE POPULATION (STUDY II)

Gastric ulcer

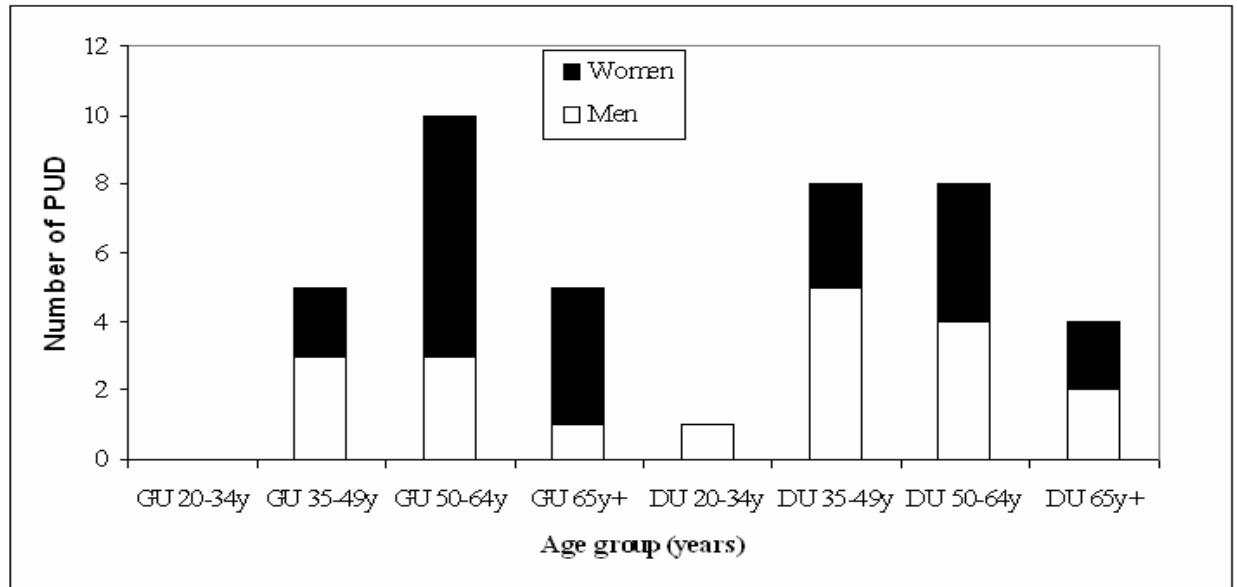
Twenty subjects (2.0%, 95% CI; 1.1-2.9) had GU. A single ulcer was found in 12 subjects (60%); two ulcers were found in two subjects (10%); and one subject (5.0%) had three ulcers, one subject (5.0%) had four ulcers, and one subject (5.0%) had five ulcers. Three subjects (15%) had more than five ulcers. Fifteen of the subjects (75%) had their ulcers located in the prepyloric/antral area, while four (20%) had ulcers in the middle of the stomach at either the angulus ($n = 1$) or the curvatura major ($n = 3$). One subject (5.0%) had ulcers in both the fundus and the antrum. The mean age of the subjects with GU was 58.1 years.

Duodenal ulcer

Twenty-one subjects (2.1%, 95% CI; 1.2-3.0) were found to have DU. Fourteen (66.7%) had a single ulcer, five (23.8%) had two ulcers, and two (9.5%) had three ulcers. The mean age of the subjects with DU was 53.3 years.

No one had both GU and DU. Thus, there were 41 subjects (4.1%, 95% CI; 2.9-5.3) with PUD. The age and gender distributions of subjects with GU and DU are shown in Figure 3.

Figure 3. Age and gender proportions of GU and DU



Gastric cancer

One 78-year-old woman who did not report any alarm symptom (e.g. difficulties in swallowing, stated weight loss or blood in the stool) was found to have an adenocarcinoma upon the histological analysis in a benign-appearing GU.

Symptoms at endoscopy and their relation to PUD

The 3-month prevalences of the 27 individual symptoms reported in ASQ are shown in table 5, and the 3-month prevalences of grouped symptoms (GERS, dyspepsia, “epigastric pain or discomfort”, overall abdominal pain, and IBS) are shown in table 6. Thirty-three persons with PUD (80.5%) reported symptoms. Nausea was significantly associated with DU and PUD, as were GERS and dyspepsia.

Dyspepsia was the only weekly symptom associated with PUD (OR=2.16, 95% CI; 1.11-4.19). Daily abdominal pain was associated with DU (OR=3.96, 95% CI; 1.39-11.29) and with PUD (OR=3.26, 95% CI; 1.49-7.13).

Eleven subjects (1.1%, 95% CI; 0.5-1.7) with PUD, i.e. 26.8 % of those with PUD of which 4 had GU and 7 had DU, reported “atypical PUD symptoms” but not dyspepsia or “epigastric pain or discomfort”. Eight (72.7%) of these persons were aged 50 years or more, and nine (81.8%) were women.

The prevalence of asymptomatic PUD was 0.8% (95% CI; 0.2-1.4) (six GU and two DU), i.e. 19.5% of all PUD.

TABLE 5. Three-month period prevalence (%) of individual GI symptoms and their associations with age, gender, and PUD

Symptom	Men (48.8%)			Women (51.2%)			All subjects (n = 1,001)									
	Ages 20–49 years (n = 178)	Ages 50–81 years (n = 310)	Total (n = 488)	Ages 20–49 years (n = 188)	Ages 50–81 years (n = 325)	Total (n = 513)	Prevalence (%)	95% CI*	p value†		Gastric ulcer		Duodenal ulcer		All peptic ulcer disease	
									Age	Sex	OR*	95% CI	OR	95% CI	OR	95% CI
Loss of weight	0	1.3	0.8	4.8	2.8	3.5	2.2	1.3, 3.1	NS*	0.008‡	5.10	1.18, 24.01	NS		3.99	1.11, 14.38
Poor appetite	5.7	1.3	2.9	7.5	2.5	4.3	3.6	2.4, 4.8	<0.001	NS	NS		NS		NS	
Uncomfortable feeling of fullness	21.5	8.1	13.0	24.3	20.7	22.0	17.6	15.2, 20.0	<0.001	<0.001‡	NS		NS		NS	
Difficulties in swallowing	2.8	7.8	6.0	7.5	7.7	7.6	6.8	5.2, 8.4	NS	NS	3.35	1.09, 10.37	NS		NS	
Retching	26.6	19.1	21.8	20.9	28.5	25.7	23.8	21.2, 26.4	NS	NS	2.58	1.05, 6.32	NS		NS	
Acid regurgitation	32.2	18.8	23.6	27.7	29.4	28.8	26.3	23.6, 29.0	0.02	NS	NS		NS		2.33	1.23, 4.41
Early satiety	11.4	9.4	10.1	17.6	14.2	15.4	12.9	10.8, 15.0	NS	0.01‡	NS		NS		NS	
Nausea	18.1	6.8	10.9	20.9	13.6	16.2	13.6	11.5, 15.7	<0.001	0.02‡	4.49	1.76, 11.45	NS		2.61	1.25, 5.45
Vomiting	4.5	1.9	2.9	4.3	3.4	3.7	3.3	2.2, 4.4	0.03	NS	NS		NS		NS	
Heartburn	36.4	27.0	30.4	39.0	34.3	36.0	33.3	30.4, 36.6	NS	NS	NS		NS		2.34	1.24, 4.41

								36.2						4.44
Pain behind breastbone	25.1	16.1	19.4	17.0	27.6	23.7	21.6	19.1, 24.1	NS	NS	NS	NS	NS	
Burning feeling rising§	20.1	14.9	16.8	21.7	19.6	20.4	18.6	16.2, 21.0	0.02	NS	NS	NS	NS	
Constipation	11.4	17.7	15.4	34.8	30.3	32.0	23.9	21.3, 26.5	NS	<0.001‡	NS	NS	NS	
Diarrhea	34.4	22.8	27.9	25.7	19.3	21.8	24.8	22.1, 27.5	<0.001	0.03	NS	NS	NS	
Alternating constipation and diarrhea	10.3	9.5	9.8	21.4	13.0	16.1	13.0	10.9, 15.1	NS	0.004‡	NS	NS	NS	
Feeling incomplete evacuation	24.3	21.1	22.3	37.0	35.4	36.0	29.3	26.5, 32.1	NS	<0.001‡	NS	NS	NS	
Pain/discomfort upon defecation	11.9	5.5	7.9	18.7	9.4	12.8	10.4	8.5, 12.3	<0.001	0.01‡	NS	NS	NS	
Pain/discomfort relieved by defecation	25.0	12.0	16.7	32.5	19.5	24.3	20.6	18.1, 23.1	<0.001	0.004‡	NS	NS	NS	
Straining	14.1	18.9	17.2	34.0	30.1	31.6	24.6	21.9, 27.3	NS	<0.001‡	NS	NS	NS	
Urgency	23.7	18.8	20.6	23.7	21.9	22.5	21.6	19.1, 24.1	NS	NS	NS	NS	NS	
Flatus	31.6	21.1	25.0	26.1	28.4	27.5	26.3	23.6, 29.0	NS	NS	NS	NS	NS	
Borborygmi	35.2	21.8	26.7	38.8	28.1	32.1	29.4	26.6,	<0.001	NS	NS	NS	NS	

(gurgling sounds)								32.2							
Abdominal distension	32.2	19.7	24.2	51.1	40.2	44.2	34.5	31.6, 37.4	<0.001	<0.001‡	NS	NS		NS	
Urge to defecate during night	9.6	5.5	7.0	5.4	6.5	6.1	6.5	5.0, 8.0	NS	NS	NS	3.53	1.15, 10.88	2.67	1.07, 6.61
Black stools	1.7	1.0	1.2	4.8	1.0	2.4	1.8	1.0, 2.6	0.003	NS	NS	NS		NS	
Blood stains in stool	10.9	5.8	7.6	8.0	6.5	7.1	7.3	5.7, 8.9	0.02	NS	NS	NS		NS	
Mucus	5.7	5.2	5.4	9.6	12.4	11.4	8.5	6.8, 10.2	NS	0.001‡	NS	NS		NS	

* CI, confidence interval; OR, odds ratio; NS, not significant.

† *p* value from logistic regression analysis (significance level: $p < 0.05$).

‡ More common in women.

§ A burning feeling rising from the stomach or lower chest towards the neck.

TABLE 6. Three-month period prevalence (%) of grouped GI symptoms and their associations with age, gender, and PUD

Symptom group	Men (48.8%)			Women (53.2%)			All subjects (n = 1,001)									
	Ages 20–49 years (n = 178)	Ages 50–81 years (n = 310)	Total (n = 488)	Ages 20–49 years (n = 188)	Ages 50–81 years (n = 325)	Total (n = 513)	Prevalence (%)	95% CI*	p value†		Gastric ulcer		Duodenal ulcer		All peptic ulcer disease	
									Age	Sex	OR*	95% CI	OR	95% CI	OR	95% CI
GERS	44.9	32.6	37.1	43.6	42.2	42.7	40.0	37.0, 43.0	0.04	NS*	NS		2.58	1.06, 6.30	2.46	1.3, 4.68
Dyspepsia	40.5	23.2	29.5	51.1	41.9	45.2	37.6	34.6, 40.6	<0.001	<0.001‡	NS		2.48	1.01, 6.08	2.08	1.10, 3.95
Epigastric pain/discomfort	18.5	11.3	13.9	34.6	23.4	27.5	20.9	18.4, 23.4	<0.001	<0.001‡	NS		NS		NS	
Abdominal pain	55.6	38.4	44.7	64.4	53.9	57.7	51.4	48.5, 54.5	<0.001	<0.001‡	NS		NS		NS	
Irritable bowel syndrome	31.5	21.6	25.2	39.9	30.2	33.7	29.6	26.8, 32.4	<0.001	0.003‡	NS		NS		NS	

* CI, confidence interval; OR, odds ratio; NS, not significant. † p value from logistic regression analysis (significance level: $p < 0.05$).

‡ More common in women.

Risk and protective factors for PUD

Of the 1,001 subjects in the EGD cohort of the study, 62 had taken NSAIDs during the past 3 months, two had used a cyclooxygenase-2 inhibitor, 107 had taken aspirin, and 108 had taken acetaminophen. Of the persons consuming aspirin, 59 had used low-dose aspirin (≤ 160 mg/day) and 48 had used standard-dose aspirin (>160 mg/day) either daily ($n = 11$) or on demand ($n = 37$). Two subjects had used bisphosphonates but did not have PUD.

Antacids had been taken by 115 subjects during the previous 3 months, H₂ RA had been taken by 31 subjects, PPIs had been taken by 49 subjects, and any of the above had been taken by 190 subjects. The corresponding numbers of subjects who had used these drugs during the week before EGD were 55, 14, 36, and 102, respectively.

A total of 187 subjects smoked cigarettes, and 118 used moist snuff; 22 persons of these used both. In total, 339 subjects of the EGD cohort (33.9%) were *H. pylori* positive upon culture and/or histological analysis. Of the 20 persons with GU, 10 (50.0%) were *H. pylori*-positive, as were 13 (61.9%) of the 21 persons with DU.

Use of acid-reducing drugs during the past 3 months predicted PUD in the EGD (OR=2.37, 95% CI; 1.16-4.86). Smoking, obesity, and overall aspirin intake were independent risk factors for GU (OR=3.12, 95% CI; 1.13-8.64, OR=4.15, 95% CI; 1.31-13.13, and OR=7.44, 95% CI; 2.78-19.93, respectively). Smoking, overall aspirin intake and *H. pylori* infection were independent risk factors for DU (OR=2.84, 95% CI; 1.11-7.27, OR=4.28, 95% CI; 1.52-12.10 and OR=3.56, 95% CI; 1.40-9.09, respectively).

The presence of esophagitis was an independent risk factor for DU (OR=3.39, 95% CI; 1.17-9.86) and PUD (OR=3.47, 95% CI; 1.57- 7.69). Low-dose aspirin use was an independent risk factor for both GU (OR=8.88, 95% CI; 2.64-29.88) and DU (OR=9.38, 95% CI; 2.71-32.46), while standard-dose aspirin use was a risk factor for GU only (OR=4.85, 95% CI; 1.25-18.83). Use of NSAIDs or acetaminophen did not change the outcome.

One person with GU (5.0%), a 57-year-old woman, had taken NSAIDs, and eight persons with GU (40.0%) had taken aspirin. None of the subjects with DU had used NSAIDs; six (28.6%) had used aspirin. Fifty-nine persons who underwent EGD (5.9%) reported former, previously treated PUD (28 GUs, 21 DUs, and 10 with no given localization) before the study started, and 15 of them had received *H. pylori* eradication therapy. Seven of these 59 subjects had PUD (four GU, three DU) in this study and none had received eradication therapy before.

Idiopathic ulcers

Altogether, five (25.0%) of the persons with GU and four (19.0%) of the persons with DU were found to have no known risk factors (NSAID/aspirin use or *H. pylori* infection) for PUD, and hence their cases were considered idiopathic. The prevalence

of idiopathic PUD was 0.9% (95% CI; 0.3-1.5), and six of the nine subjects (0.6%, 95% CI; 0.1-1.1) did not have histological signs or serologic evidence of former *H. pylori* infection. Five of them had chemical-reactive gastritis in the antrum, and one had normal histology. None of the nine subjects had any antral granulocyte activity, but one of them had the lowest degree of granulocyte activity in the corpus. Only four of the nine subjects with idiopathic ulcer smoked, and one had an elevated gastrin-17 level (76 pmol/liter) but a low pepsinogen-1 level (7.2 µg/liter), suggesting a low gastric acid output. There was no significant association between idiopathic PUD and GERS, dyspepsia, “epigastric pain or discomfort”, IBS, obesity, or smoking. The only individual symptoms significantly associated with idiopathic PUD were stated weight loss ($p=0.015$) and loss of appetite ($p=0.041$).

4.3 BMI AND UNEXPLAINED GASTROINTESTINAL SYMPTOMS (STUDY III)

Of 1001 subjects endoscoped, 10 did not have BMI data collected.

Prevalence of obesity

The prevalence of those underweight was only 0.8% (n=8); therefore these subjects were excluded from the analysis leaving 983 subjects in the subsequent analyses. The prevalence of being overweight was 46% (n=456, 95% CI 42.9-49.1) while the prevalence of obesity was 16% (n= 162, 95% CI 14.0-18.7). Table 7 shows the proportion of patients in each BMI category, as a whole and by gender, age groups, education levels, smoking and alcohol status. Smoking was independently associated with decreased BMI by linear regression analysis (beta coefficient -0.7) and low education was associated with increased BMI (beta coefficient 0.6). Alcohol use was not significantly associated with BMI changes.

Table 7. Distribution of demographic variables by BMI categories

	N % (95% CI)	Age		Gender		Education		Smoking#		Alcohol/week	
		=54* n %	>54* n %	female* n %	male* n %	low* n %	high* n %	no* n %	yes* n %	≤100g* n %	>100g* n %
Underweight (<18.5)	8 0.8% (0.3-1.4)	4 0.8% (0.0-1.6)	4 0.8% (0.0-1.6)	6 1.2% (0.3-2.1)	2 0.4% (0.0-1.0)	5 0.9% (0.1-1.7)	3 0.7% (0.0-1.5)	6 0.7% (0.1-1.3)	2 1.1% (0.0-2.6)	8 0.9% (0.3-1.5)	0
Normal weight (≥18.5 - <25)	365 36.8% (33.8-39.8)	200 41.1% (36.7-45.5)	165 32.7% (28.6-36.8)	213 41.9% (37.6-46.2)	152 31.5% (27.4-35.6)	177 31.2% (27.4-35.0)	183 45.0% (40.2-49.8)	280 34.8% (31.5-38.1)	85 45.7% (38.5-52.9)	331 37.5% (34.3-40.7)	34 31.2% (22.5-39.9)
Overweight (≥25-<30)	456 46.0% (42.9-49.1)	211 43.3% (38.9-47.7)	245 48.6% (44.2-53.0)	197 38.8% (34.6-43.0)	259 53.6% (49.2-58.0)	281 49.5% (45.4-53.6)	166 40.9% (36.1-45.7)	384 47.7% (44.2-51.2)	72 38.7% (31.7-45.7)	399 45.2% (41.9-48.5)	57 52.3% (42.9-61.7)
Obese (≥30)	162 16.3% (14.0-18.7)	72 14.9% (11.7-18.1)	90 17.9% (14.6-21.2)	92 18.1% (14.8-21.4)	70 14.6% (11.5-17.7)	105 18.5% (14.9-21.3)	55 13.5% (10.2-16.8)	135 16.8% (14.2-19.4)	27 14.5% (9.4-19.6)	144 16.3% (13.9-18.7)	18 16.5% (9.5-23.5)
Total	991	487	504	508	483	568	407	805	186	882	109

*prevalence and 95% CI /column

current smokers at the time of endoscopy

Prevalence of troublesome GI complaints and upper endoscopy findings

At the time of endoscopy, 65.6% of the 1001 subjects reported one or more troublesome GI complaints on the questionnaire completed prior to endoscopy. The prevalence of major endoscopic findings by BMI category is summarized in Table 2. Of those with esophagitis (n=155), most were grade A (n=109); 39 had grade B, 3 grade C, 2 grade D and 2 were unable to be classified. There were more endoscopic findings in obese subjects than in normal weight subjects, but the differences were not significant except for esophagitis and GU; the prevalence of esophagitis in obese subjects was 26.5% (95% CI; 19.7-33.3) versus 9.3% (95% CI; 6.3-12.3) (p<0.0001) in normal weight subjects while the prevalence of GU in obese subjects was 5.6% (95% CI; 2.0-9.1) versus 1.4% (95% CI; 0.2-2.6) (p=0.006) in normal weight subjects.

Table 8. Prevalance (%) of PUD, reflux esophagitis and gastric cancer in different BMI categories

Endoscopic finding	BMI category n (%) (95% CI)			
	Underweight BMI<18.5 (n=8)	Normal BMI≥18.5 <25 (n=365)	Overweight BMI≥25 <30 (n=456)	Obese BMI ≥30 (n=162)
Gastric ulcer	0 (0)	5 (1.4) (0.2-2.6)	6 (1.3) (0.3-2.4)	9 (5.6) (2.0-9.1)
Duodenal ulcer	0 (0)	7 (1.9) (0.5-3.3)	9 (2.0) (0.7-3.2)	4 (2.5) (0.1-4.9)
Esophagitis	1 (12.5) (10.4-35.4)	34 (9.3) (6.3-12.3)	76 (16.7) (13.2-20.1)	43 (26.5) (19.7-33.3)
Cancer	0 (0)	0 (0)	1 (0.2) (0.0-0.7)	0 (0)

Relationship between BMI, GI Symptoms and other exposure factors

The distribution of individual GI symptoms in the total cohort by BMI categories is summarized in Table 9.

Table 9. Distribution of GI symptoms by BMI categories

GI symptom	Normal weight BMI <25	Overweight BMI ≥25 - <30	Obese BMI ≥30
	n % of category (95% CI)	n % of category (95% CI)	n % of category (95% CI)
Stated weight loss	16 4.3 (2.3 – 6.4)	5 1.1 (0.1 -2.1)	1 0.6 (0.0– 1.8)
Loss of appetite (anorexia)	15 4.0 (2.0 – 6.0)	18 4.0 (2.2 – 5.8)	3 1.9 (0.0 – 3.9)
Uncomfortable feeling of fullness	61 16.4 (12.7 – 20.2)	82 18.2 (14.7 - 21.8)	29 18.4 (12.3 – 24.4)
Difficulty swallowing	23 6.2 (3.7 – 8.6)	28 6.2 (4.0 – 8.4)	16 9.9 (5.3 – 14.6)
Retching	78 21.0 (16.9 – 25.2)	103 22.7 (18.9 – 26.6)	53 32.7 (25.5 – 39.9)
Acid regurgitation	80 21.6 (17.4 – 25.7)	115 25.5 (21.5 – 29.5)	62 38.3 (30.8 – 45.8)
Early satiation	45 12.1 (8.8 – 15.4)	63 13.9 (10.7 – 17.1)	19 11.7 (6.8 – 16.7)
Nausea	49 13.2 (9.7 – 16.6)	59 13.0 (9.9 – 16.1)	25 15.4 (9.9 – 21.0)
Vomiting	9 2.4 (0.9 – 4.0)	14 3.1 (1.5 – 4.7)	10 6.2 (2.5 – 9.9)
Heartburn	100 26.9 (22.4 – 31.4)	159 35.1 (30.7 – 39.5)	68 42.5 (34.8 – 50.2)
Central chest pain	71 19.2 (15.2 – 23.2)	98 22.0 (18.1 – 25.8)	42 26.1 (19.3 – 32.9)
Burning feeling rising in chest	53 14.4 (10.8 – 18.0)	89 19.9 (16.2 – 23.6)	39 24.7 (18.0 – 31.4)
Constipation	96 25.9 (21.4 – 30.3)	96 21.2 (17.5 – 25.0)	38 23.8 (17.2 – 30.3)
Diarrhea	64 19.9 (15.6 – 24.3)	106 26.1 (21.8 – 30.4)	46 33.1 (25.3 – 40.9)
Alternating constipation/diarrhea	45 12.3 (8.9 – 15.7)	58 13.0 (9.8 – 16.1)	23 14.5 (9.0-19.9)
Feeling incomplete rectal evacuation	100 27.3 (22.8 – 31.9)	125 27.8 (23.7 – 32.0)	60 37.7 (30.2 – 45.3)
Pain at defecation	43 11.7 (8.4 – 15.0)	43 9.5 (6.8 – 12.2)	16 10.0 (5.4 – 14.6)
Pain relieved by defecation	75 20.4 (16.3 – 24.6)	96 21.2 (17.4 – 25.0)	33 20.5 (14.3 – 26.7)

Straining	96 25.9 (21.4 – 30.3)	103 22.8 (19.0 – 26.7)	40 24.7 (18.0 – 31.3)
Urgency	73 19.8 (15.7 – 23.8)	94 20.8 (17.1 – 24.5)	46 28.6 (21.6 – 35.5)
Flatus	82 22.2 (18.0 – 26.5)	130 28.6 (24.4 – 32.7)	46 28.8 (21.7 – 35.8)
Borborygmi	106 28.7 (24.0 – 33.3)	140 30.9 (26.7 – 35.2)	43 27.0 (22.3 – 36.5)
Abdominal distension	133 36.2 (31.3 – 41.2)	152 33.5 (29.1 – 37.8)	55 34.2 (26.8 – 41.5)
Nightly urge to defecate	20 5.4 (3.1 – 7.7)	25 5.5 (3.4 – 7.6)	20 12.4 (7.3 – 17.4)
Black stools	8 2.2 (0.7 – 3.6)	9 2.0 (0.7 – 3.3)	1 0.6 (0.0 – 1.8)
Blood in stool	24 6.5 (4.0 – 9.0)	37 8.2 (5.7 – 10.7)	10 6.2 (2.5 – 9.9)
Mucus	37 10.0 (6.9 – 13.1)	27 6.0 (3.8 – 8.2)	20 12.4 (7.3 – 17.4)

There were significant associations between obesity and GERS (OR=2.05, 95% CI; 1.39-3.01), “epigastric pain or discomfort” (OR=1.63, 95% CI; 1.05-2.55), IBS (OR=1.58, 95% CI; 1.05-2.38), any abdominal pain (OR=1.59, 95% CI; 1.08-2.35), vomiting (OR=3.11, 95% CI; 1.18-8.20), retching (OR=1.74, 95% CI; 1.13-2.67), diarrhea (OR=2.21, 95% CI; 1.38-3.46), any stool urgency (OR=1.60, 95% CI; 1.04-2.47), nocturnal urgency (OR=2.57, 95% CI; 1.33-4.98) and feelings of incomplete rectal evacuation (OR=1.64, 95% CI; 1.09-2.47), adjusted for age, gender and education (Table 10).

Table 10. Association of individual GI symptoms with being overweight and obese based on BMI versus those of normal weight, among the study subjects (n=973)

	BMI 25 - <30 OR (95% CI)	BMI ≥30 OR (95% CI)
Stated weight loss	0.31 (0.11 – 0.89)	No cases
Anorexia	1.23 (0.57 – 2.65)	0.56 (0.15 – 2.04)
Uncomfortable feeling of fullness	1.36 (0.93 - 2.01)	1.19 (0.72-1.99)
Difficulty swallowing	0.95 (0.53 – 1.69)	1.49 (0.76 – 2.93)
Retching	1.11 (0.78 – 1.57)	1.74 (1.13 – 2.67)
Acid regurgitation	1.33 (0.95 – 1.86)	2.30 (1.52 – 3.48)
Early satiation	1.32 (0.86 – 2.03)	1.0 (0.55 – 1.79)
Nausea	1.20 (0.78 – 1.85)	1.43 (0.83 – 2.47)
Vomiting	1.47 (0.59 – 3.63)	3.11 (1.18 – 8.20)
Heartburn	1.64 (1.20 – 2.24)	2.11 (1.41 – 3.15)
Central chest pain	1.17 (0.83 – 1.67)	1.38 (0.88 – 2.16)
Burning feeling rising in chest	1.51 (1.03 – 2.23)	1.99 (1.24 – 3.21)
Constipation	0.86 (0.61 – 1.22)	0.83 (0.53 – 1.31)
Diarrhea	1.43 (0.99 – 2.07)	2.2 (1.38 – 3.46)
Alternating constipation/diarrhea	1.14 (0.73 – 1.76)	1.25 (0.72 – 2.18)
Feeling incomplete rectal evacuation	1.16 (0.84 – 1.60)	1.64 (1.09 – 2.47)
Pain at defecation	0.96 (0.60 – 1.52)	0.88 (0.47 – 1.67)
Pain relieved by defecation	1.23 (0.86 – 1.76)	1.08 (0.67 – 1.75)
Straining	0.90 (0.64 – 1.26)	0.86 (0.55 – 1.34)
Urgency	1.05 (0.74 – 1.49)	1.60 (1.04 – 2.47)
Flatus	1.47 (1.06 – 2.05)	1.44 (0.94 – 2.21)
Borborygmi	1.23 (0.90 – 1.69)	0.97 (0.63 – 1.50)
Abdominal distension	1.08 (0.79 – 1.47)	0.98 (0.64 – 1.48)
Nightly urge to defecate	0.97 (0.52 – 1.80)	2.57 (1.33 – 4.98)
Black stools	1.21 (0.43 – 3.42)	0.37 (0.05 – 3.07)
Blood in stool	1.37 (0.78 – 2.39)	1.06 (0.49 – 2.30)
Mucus	0.61 (0.36 – 1.04)	1.16 (0.64 – 2.12)
GERS	1.53 (1.14 – 2.06)	2.05 (1.39 – 3.01)
Dyspepsia	1.00 (0.74-1.36)	1.42 (0.96 - 2.11)
“Epigastric pain or discomfort”	0.96 (0.67-1.39)	1.63 (1.05 - 2.55)
Abdominal pain	1.19 (0.89-1.58)	1.59 (1.08 - 2.35)
IBS	1.21 (0.88-1.66)	1.58 (1.05 - 2.38)

Significant differences are shown in bold.

When subjects with esophagitis, PUD and gastric cancer at endoscopy were excluded, diarrhea (OR=1.94, 95% CI; 1.13-3.32), feelings of incomplete rectal evacuation (OR=1.68, 95% CI; 1.04-2.71) and vomiting (OR=3.98, 95% CI; 1.26-12.52) remained significantly associated with obesity. However, GERS was no longer significantly associated with obesity.

Medication use, BMI and GERS

Use of acid reducing drugs was a significant predictor for overall GERS (OR=9.8, 95% CI; 6.5-14.7) and for the following individual symptoms: heartburn (OR=6.4, 95% CI; 4.5-9.2), acid regurgitation (OR=6.2, 95% CI; 4.3-8.8) and retching (OR=3.0, 95% CI; 2.1-4.2). Drugs that potentially lower oesophageal sphincter pressure (nitrates (n=24), theophylline (n=10), calcium channel blockers (n=44), opiates (n=20), beta agonists

(n=22), phenothiazines (n=2), tricyclic antidepressants (n=2), nicotine substitutes (n=0), anticholinergics (n=0) and benzodiazepines (n=2)) as a group were univariately associated with the symptom of a burning feeling rising in the chest (“the Carlsson-Dent question”) (OR=1.8, 95% CI; 1.1-3.1) and with central chest pain (OR=1.6, 95% CI; 1.0-2.6), but were not significantly associated with overall GERS. Only calcium channel blockers (OR=3.0, 95% CI; 1.5-5.9) were univariately associated with the Carlsson-Dent symptom; none of the other individual drug classes were significant. Lower esophageal sphincter relaxing drugs were not individually or as a group significantly associated with esophagitis. Adjusting for medication use, age and gender, the association between GERS and being overweight remained significant (OR=1.4, 95% CI; 1.04-2.0) and similarly, the association between GERS and obesity remained significant (OR=1.9, 95% CI; 1.3-3.0). The association between esophagitis and BMI did neither alter substantially adjusting for medication use (OR for overweight =1.7, 95% CI; 1.1-2.6 and OR for obesity =3.4, 95% CI; 2.0-5.8).

4.4 SMOKELESS TOBACCO USE AND GASTROINTESTINAL MORBIDITY (STUDY IV)

Of the 1,001 subjects endoscoped, 12 did not have data on the use of smokeless tobacco or cigarette smoking, leaving 989 subjects for analysis. Of these, 96 (9.7%) were current smokeless tobacco users, 165 (16.7%) were current cigarette smokers, 22 (2.2%) were combined users and 274 (27.7%) were former smokeless tobacco users and/or smokers. Overall 432 (43.7%) individuals had never smoked or used smokeless tobacco. The smokeless tobacco users consumed on average 3.2 cans/week, smokers consumed on average 11.5 cigarettes/day and combined smokeless tobacco users/smokers consumed 2.2 cans/week and 6.2 cigarettes/day.

The gender distribution, mean age, mean BMI and education level in different user and non-user groups are shown in Table 11.

Table 11. Demographic data of tobacco user/non-user groups

Demographic variable	Non-user n=432	Current smokeless tobacco user n=96	Current smoker n=165	Using both n=22	Former user n=274
Proportion of men	38.2 (33.6 - 42,8)	84.4* (77,1 - 91,7)	34.5 (27,2 - 41,8)	54.5 (33,7 - 75,3)	60.2* (54,4 - 66,0)
Prevalence (95% CI) [†]					
Mean age (SD) [‡]	55.6 (15.5)	48.5* (13.4)	50.4* (12.5)	47.5* (12.9)	56.5 (13.1)
Mean BMI [§] (SD) [‡]	26.6 (3.8)	26.2 (3.5)	25.8* (4.5)	26.5 (3.9)	26.8 (4.2)
Low education	57.1 (52,4 - 61,8)	54.7 (44,7 - 64,7)	58.0 (50,5 - 65,5)	56.8 (36,1 - 77,5)	62.5 (56,8 - 68,2)
Prevalence (95% CI) [†]					

*Significant difference compared with non-users ($p < 0.05$)

[†]95 percent confidence interval

[‡]Standard deviation

[§]Body mass index

Use of acid reducing drugs (PPI, H₂ RA and antacids) during the last week or during the last 3 months before the EGD was not significantly associated with smoking or use of smokeless tobacco.

Symptoms

Symptom prevalences in different tobacco user groups are shown in Table 12. Risk factors for GERS, IBS, dyspepsia, epigastric pain, overall abdominal pain and no or minor symptoms are shown in Table 13. No symptom complexes were associated with smokeless tobacco use.

Endoscopy and histology

The prevalences of esophagitis, GU, DU and overall PUD, split by tobacco use category, are presented in Table 14.

Table 12. Symptom prevalence in tobacco user/non-user groups (last 3 months before upper endoscopy)

Symptom	Non-user n=432 Prevalence (95% CI) [†]	Current smokeless tobacco user n=96 Prevalence (95% CI) [†]	Current smoker n=165 Prevalence (95% CI) [†]	Using both n=22 Prevalence (95% CI) [†]	Former user n=274 Prevalence (95% CI) [†]
GERS [‡]	39.1 (34.5-43.7)	38.5 (28.8-48.2)	37.6 (30.2-45.0)	50.0 (29.1-70.9)	41.6 (35.8-47.4)
Dyspepsia	34.5 (30.0-39.0)	32.3 (22.9-41.7)	42.3 (34.8-49.8)	59.1 (38.6-79.9)	35.8 (30.1-41.5)
IBS [§]	27.6 (23.4-31.8)	20.8 (12.7-28.9)	30.3 (23.3-37.3)	54.6* (33.8-75.4)	32.9 (27.3-38.5)
Epigastric pain	18.5 (14.8-22.2)	16.7 (9.2-24.2)	26.7 (19.9-33.5)	50.0* (29.1-70.9)	19.7 (15.0-24.4)
Abdominal pain	49.5 (44.8-54.2)	42.7 (32.8-52.6)	52.1 (44.5-59.7)	68.2 (48.7-87.7)	54.4 (48.5-60.3)
No GI symptoms	38.2 (36.6-42.8)	39.6 (29.8-49.4)	37.0 (29.6-44.4)	27.3 (8.7-45.9)	31.0 (25.5-36.5)

*Significant difference compared with non-users ($p<0.05$)

[†]95 percent confidence interval

[‡]Gastroesophageal reflux symptoms

[§]The Irritable Bowel Syndrome

^{||}Gastrointestinal

Table 13. Tobacco use as a predictor of gastrointestinal symptoms

Symptom	Current smokeless tobacco user OR* (95% CI) [†]	Current smoker OR* (95% CI) [†]	Using both OR* (95% CI) [†]	Former user OR* (95% CI) [†]
GERS [‡]	ns	ns	ns	ns
Dyspepsia	ns	1.50 (1.03-2.18)	2.68 (1.09-6.61)	ns
IBS [§]	ns	ns	3.04 (1.26-7.33)	1.44 (1.03-2.03)
Epigastric pain	ns	ns	4.75 (1.91-11.84)	ns
Abdominal pain	ns	ns	ns	1.42 (1.03-1.95)
No or minor GI symptoms	ns	ns	ns	0.64 (0.46-0.90)

*Odds ratio

[†]95 percent confidence interval

[‡]Gastroesophageal reflux symptoms

[§]The Irritable Bowel Syndrome

^{||}Gastrointestinal

Table 14. Prevalences of findings in tobacco user/non-user groups

Endoscopic finding	Non-user n=432 Prevalence (95% CI) [†]	Current smokeless tobacco user n=96 Prevalence (95% CI) [†]	Current smoker n=165 Prevalence (95% CI) [†]	Using both n=22 Prevalence (95% CI) [†]	Former user n=274 Prevalence (95% CI) [†]
Esophagitis	13.7 (10.5-16.9)	21.9 (13.6-30.2)	12.7 (7.6-17.8)	18.2 (2.1-34.3)	17.2 (12.7-21.7)
Gastric ulcer	1.6 (0.4-2.8)	1.0 [‡] (0.0-1.8)	3.6 (0.8-6.4)	4.5 (0.0-13.2)	1.8 (0.2-3.4)
Duodenal ulcer	1.9 (0.6-3.2)	0	4.2 (1.1-7.3)	4.5 (0.0-13.2)	1.5 (0.1-2.9)
Overall PUD*	3.5 (1.8-5.2)	1.0 [‡] (0.0-1.8)	7.9 (3.8-12.0)	9.1 (0.0-21.1)	3.3 (1.2-5.4)

*Peptic ulcer disease

[†]95 percent confidence interval

[‡]A user of chewing tobacco and using only < 5g/week

Esophagus

Smokeless tobacco users had a significantly higher prevalence of esophagitis compared with non-users (p=0.04).

Use of smokeless tobacco was a significant risk factor for thickening of the basal cell layer and for elongation of papillae (OR=1.84; 95% CI; 1.09-3.10) and OR=1.75; 95% CI; 1.03-3.00, respectively) at the esophagogastric junction, both histological markers of cell turnover due to chronic chemical irritation alike in GERS.

Former users had a significantly higher risk for thickening of the basal cell layer 2 cm above the esophagogastric junction (OR=1.54; 95% CI; 1.01-2.37).

Stomach

There was a significantly lower risk for PUD in smokeless tobacco users compared with smokers (OR=0.12; 95% CI; 0.003-0.85), but it was not significantly lower compared with non-users (OR=0.34; 95% CI; 0.04-2.80). Smoking cigarettes was an independent risk factor for PUD (OR=2.44; 95% CI; 1.09-5.49).

Use of smokeless tobacco was significantly associated with intestinal metaplasia in the antrum (OR=2.43; 95% CI; 1.10 – 5.38). Smoking was an independent risk factor for corpus-dominant gastritis (OR=2.48; 95% CI; 1.03-5.96) and also for chemical-reactive gastritis in the antrum (OR=1.65; 95% CI; 1.04-2.60). Smoking habits were not significantly associated with high granulocyte or lymphocyte counts in the antrum or the corpus and neither with atrophy in these locations.

Duodenum

Smoking cigarettes was independently associated with gastric metaplasia in the duodenal bulb (OR=2.06; 95% CI; 1.02-4.15) but smokeless tobacco was not.

H. pylori and serology

There were no significant associations between current *H. pylori* infection or seropositivity and different tobacco user groups. The proportion of cag-A positive *H. pylori* genotypes did not differ significantly between different tobacco user groups and non-users. *H. pylori* infection prevalence and seropositivity are presented in Table 15. The differences between non-users and different user groups were not significant.

Table 15. *H. pylori* prevalences in tobacco user/non-user groups (culture/histology and serology)

<i>Hp</i> * infection and serology in age groups	Non-user n Prevalence (95% CI) [†]	Current smokeless tobacco user n Prevalence (95% CI)	Current smoker n Prevalence (95% CI)	Using both n Prevalence (95% CI)	Former user n Prevalence (95% CI)
Age 20-49	n=148	n=45	n=75	n=10	n=82
Current <i>Hp</i> infection	16.2 (10.3 – 22.1)	17.8 (6.6 – 29.0)	21.6 (12.3 – 30.9)	10.0 (0.0 – 28.6)	30.5 (20.5 – 40.5)
Positive <i>Hp</i> serology	21.6 (15.0 – 28.2)	26.7 (13.8 – 39.6)	25.3 (15.5 – 35.1)	20.0 (0.0 – 44.8)	35.4 (25.0 – 45.8)
Age 50 +	n=284	n=51	n=90	n=12	n=192
Current <i>Hp</i> infection	44.0 (38.2 – 49.8)	33.3 (20.4 – 46.2)	47.8 (37.5 – 58.19)	33.3 (6.6 – 60.0)	38.0 (31.1 – 44.9)
Positive <i>Hp</i> serology	53.2 (47.4 – 59.0)	47.1 (33.4 – 60.8)	60.0 (49.9 – 70.1)	41.7 (13.8 – 69.6)	50.5 (43.4 – 57.6)
All ages	n=432	n=96	n=165	n=22	n=274
Current <i>Hp</i> infection	34.5 (30.0 – 39.0)	26.0 (17.2 – 34.8)	36.0 (28.7 – 43.3)	22.7 (5.2 – 40.2)	35.8 (30.1 – 41.5)
Positive <i>Hp</i> serology	42.4 (37.7 – 47.1)	37.5 (27.8 – 47.2)	44.2 (36.6 – 51.8)	31.8 (12.3 – 51.3)	46.0 (40.1 – 51.9)

**Helicobacter pylori*

[†]95 percent confidence interval

Gastrin-17 and pepsinogen-1

Use of smokeless tobacco or smoking were not associated with an abnormal gastrin-17 level but both were associated with high Pepsinogen-1 level (OR=2.30, 95% CI; 1.40–3.78 and OR=2.96, 95% CI; 1.99–4.40, respectively) without changing the Pepsinogen-1/Pepsinogen-2 ratio significantly. When all *H. pylori* infected and all with histological mucosal atrophy for other reasons were excluded, both smoking and use of smokeless tobacco were associated with high Pepsinogen-1 levels (OR= 4.52, 95% CI; 2.67–7.67 and OR=2.28, 95% CI; 1.21–4.31, respectively) but not with abnormal Gastrin-17 levels.

5 DISCUSSION

As there is very scarce data from endoscopic, population-based studies and the symptom prevalences reported in patient-based studies is biased compared with population-based studies, it was important to conduct the Kalixanda study to get reliable, as unbiased symptom data as possible and also data on endoscopic findings in a random adult population. We have shown that it is possible to perform an EGD investigation, in combination with a symptom survey, by means of accepted epidemiological methodology (171) in a random sample of the adult population. We consider our method as viable and the symptom outcome to be generalizable despite the EGD intervention. In this randomly selected population of adults aged 18-80 years or more, we found a point prevalence of 4% for PUD, but the symptomatology did not conform to a classical pattern; “epigastric pain or discomfort” did not predict PUD, while nausea and gastroesophageal reflux symptoms did, as did stated loss of weight. An unexpectedly high proportion of persons with DU were *H. pylori*-negative (38%) and 25% of the GUs and 19% of the DUs were idiopathic. Continuous use of low-dose aspirin was a risk factor for PUD. In addition, obesity was a risk factor for GU. We also found that reflux symptoms as well as diarrhea, incomplete evacuation and vomiting were linked to obesity. The use of smokeless tobacco was associated with a significantly higher prevalence of distal esophagitis, and the risk for esophagitis was also confirmed by histological findings. On the other hand, smokeless tobacco users had a significantly lower risk for PUD compared with smokers, but not compared with non-users, while they had an increased risk for intestinal metaplasia, a pre-neoplastic mucosal change, in the antrum.

The mean age of endoscoped subjects in the two municipalities in Northern Sweden, Kalix and Haparanda, was only about four years higher than that of the original study population and of the Swedish population in the selected age band, as shown in Table 2 of Study 1. The difference was almost entirely due to a lower response rate among the youngest age group. Consequently, the non-responders to the initial questionnaire were on average 4 years younger, as were those included in the non-response interview. These age differences *per se* are most probably irrelevant for the interpretation of our results. Similarly, the exclusion of the 140 (4.7%) subjects, who were not eligible for study at the time of approach, did not alter the mean age and gender distribution of the remaining eligible group.

The higher prevalence of symptoms among those 1,001 endoscoped compared with the total 2,122 ASQ responders was largely contributed by the youngest age group, where those who declined endoscopy had fewer symptoms, as shown in Study I, Table 3. The overall differences of prevalence were fairly stable between the combined symptom groups (GERD, dyspepsia etc.) (3.9%-5.9%). This difference is of minor clinical importance and the difference between age groups is easy to control for. Moreover, 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). The tendency towards more symptom reporting in younger age groups has been reported previously (9, 29).

As those endoscoped were shown to be representative of the background population, except perhaps for the youngest, it was not considered of interest to show detailed data for the 562 subjects who did not attend to the EGD. In conclusion there appears to be no sampling error among those endoscoped, with the exception of the youngest age group. It is also important, that data can very reliably be interpreted in the age groups where serious diseases are more common.

The significantly lower prevalence of abdominal pain among the non-responders, might very well be due to the fact that they were asked only one question about abdominal “pain or discomfort”, while those who responded to the ASQ had a list of 11 choices of pain modalities. IBS prevalence, also significantly lower, is dependent on the reply to the abdominal pain question, since by definition, abdominal pain is a mandatory part of the IBS definition. Bearing this in mind, the responders to the mailed ASQ most probably reflect the original study population.

A potential source of bias is that the two municipalities in this study have a lower socio-economic status than the Swedish average (142, 143), particularly Haparanda. This is also reflected in the different samples under surveillance. The study was performed in the Northern part of Sweden, but the population studied appears to be representative of the Swedish population in terms of most sociodemographic factors and the response rates were excellent suggesting that the results are likely to be reliable and representative. The proportion with higher education was slightly lower in these communities and a low education was associated with a higher BMI, but education was controlled for in the analyses. Education level, as used here, was shown to be strongly associated with socioeconomic status in Sweden (172). However, differences in socioeconomic status between municipalities in Sweden are small by international standards.

Could these socioeconomic differences affect GI symptomatology in anyhow? Faresjö (172) stated that this was the case in Sweden, while Johansson (173), in another Swedish study, found no such association. In a study in mid-Sweden, Agréus (18) found a very weak, but also J-shaped association, making any trend interpretation hazardous. Kay et al. (174) in Denmark, Jones et al. (9) in the UK and Talley et al. in Australia (175) and in the US (176), also found that dyspeptic symptoms were unrelated to socio-economic status. Lower socioeconomic status has, however, been shown to be associated with more GI symptoms in Norway (48), Canada (177) and Australia (178). Thus, the evidence remains conflicting.

H. pylori prevalence, which is declining since decades, is another well-known indirect indicator of socioeconomic status, decreasing with higher prosperity. The prevalence of positive *H. pylori* serology (showing also those with a “serologic scar” (179)) in this study is 43%, as shown in Table 1. This is in line with other Northern European countries (180-182). We do not know of any population-based data from Northern Europe on the prevalence of current *H. pylori* infection, which was 34% in this study, although available data from Southern Europe show a prevalence that is markedly higher (183). The prevalence of 42% of positive *H. pylori* serology among the non-responders, despite the small sample size, contradicts fears of potential bias caused by socioeconomic status, as defined in our study, i.e. *H. pylori* serology status was the

same, irrespective of the education level. Furthermore, 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 (169). Our overall conclusion is, therefore, that it is unlikely that socioeconomic factors have markedly influenced present study findings.

In our study, the number of contraindications to EGD was higher than is found among patients who are referred for EGD. 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 in our study. Thus, patients with unstable angina, 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 with previous upper GI surgery.

Another confounder might be the symptom questionnaire used. The ASQ has, however, been the subject of extensive validation processes and has been found to be reliable and valid, also in a test/retest situation, in both Swedish and Finnish (56, 65, 144, 146). Some questions found to be relevant for the disorders in focus were added to the originally validated questionnaire (147). All except one (the key question from (148)) was added at the end of the questionnaire.

The minimum requirement for symptom reporting in this study was that symptoms needed to be troublesome (144, 146). This symptom cut off definition has also very recently been agreed for in the Global, Montreal definition of GERD (150).

The prevalence of most symptoms was higher than has been reported before in Sweden (31, 56), and it was also higher than in some investigations conducted elsewhere (16, 141, 184). Despite this prevalence rates were in no way extreme and prevalences of a similar magnitude have been reported by other investigators (185). Atypical symptoms in PUD patients, especially among the elderly, have also been reported before (186). In other Swedish studies with subjective symptom reporting, it has also been shown that symptoms likely to be non-organic in their cause most of the time, like muscle and joint pain, are reported to a somewhat greater extent in Northern Sweden than in the Southern part, while mental symptoms like anxiety are not (187). Thus, the somewhat higher symptom prevalence reported in our study is not only a GI phenomenon and consequently not necessarily caused by fear of having an EGD.

The upper age limit of 80 years in this study was decided by the Ethical Committee because of the risk of complications during EGD and concerns about obtaining informed consent and the lower age limit of 18 years was set due to the Helsinki declaration's requirements of informed consent.

Another weakness is that we cannot provide any physiological data, aside from Gastrin-17 and Pepsinogen-1 levels, and due to our descriptive epidemiologic study design it is not possible to draw definite conclusions about any causal connections between exposure and different GI disorders. In our study, the reported consumption of alcohol is low compared with average consumption in Northern Sweden and Northern Finland.

Underreporting use of alcohol in this region is possible due to cultural and religious reasons of our study population.

The statistics used in this study includes many comparisons and the statistical method mainly used was multivariate logistic regression model including possible exposure variables and adjusting for age and gender. All the models were controlled applying Goodness of fit test to be sure that we used an appropriate method in each step of the analysis. The analyses including fewer than 15 individuals as cases were controlled applying Fisher's exact test.

The main strength of the study is the population-based design in a region where a population register covers all inhabitants without exception, and the high participation rate! There is also an endoscopy unit both in primary care and in secondary care, providing the sole cover of the whole Kalix – Haparanda area. The three experienced endoscopists have been working in the area for a long time and they are well known by the local inhabitants. The population seems to have a positive attitude to this kind of medical surveys and the participation rates to all parts of the study were high; moreover nobody in this area wants to be called “knapsu” (knapsu = “feminine” like behaviour) and thus be ashamed, if somebody else in the neighbourhood participated in the EGD part of the study.

The histological evaluation was done by experienced pathologists with a special interest in GI pathology and who also were unaware of the clinical data and EGD findings. The kappa value for agreement between observers was good, e.g. in the evaluation of *H. pylori* it was 0.76 (95% CI; 0.59-0.96) for the corpus and 0.78 (95% CI; 0.59-0.98) for the antrum.

There is debate as to whether the concept of dividing dyspepsia symptoms into “ulcer-like” and “dysmotility-like” symptoms is valid (151). The proportion of patients with PUD has been found to be approximately the same in both symptom groups (24, 43), suggesting that those symptom profiles are not clinically useful predictors of PUD. Our study shows that “epigastric pain or discomfort” does not predict PUD, while the so-called dysmotility-like symptom nausea was a weak positive predictor. We also found, as have other investigators (24), that PUD was common also in patients with GERS. This suggests that treating all patients with GERS empirically by acid suppression may not represent optimal management. The empirical treatment with acid suppression might lead to non-optimal treatment of possible concomitant *H. pylori* infection. We also found that 34% of subjects with unknown PUD were taking acid-reducing drugs.

We found that GU was associated with obesity. The association to BMI has, to our knowledge, been shown only once before in a Danish study (48), and recently also confirmed in a preliminary US report (188). *H. pylori* infection, use of NSAIDs or aspirin, serum Gastrin-17 level, and smoking habits did not appear to explain this observation. It remains unknown whether elevated acid secretion, increased stress, or mechanical factors could explain excess GU disease in obese persons, but in the era of “epidemic obesity” this is an urgent field for further research.

The reason why some ulcers are asymptomatic is unknown. In controlled trials, both asymptomatic DUs and GUs have been found in a substantial proportion of cases (136, 140). We found that eight subjects (19.5% of all ulcer patients and 0.8% of the study population) had asymptomatic PUD. Similarly, in the Sørreisa Gastrointestinal Disorder Study, one percent of persons who underwent upper endoscopy had asymptomatic PUD (141). The clinical implications of asymptomatic peptic ulcers in our study are uncertain; evaluation of this issue would require a longitudinal natural history study.

To our knowledge, there have been no large-scale studies of PUD in a randomly selected adult population that have had a satisfactory participation rate (189). The Sørreisa Gastrointestinal Disorder Study, from the 1980s, was population-based (84), but a case-control design was applied for the endoscopies. Those investigators found prevalences of PUD of 4% among controls and 8% among persons with dyspepsia (84). The only other comparable study was performed in Sweden (85), but had a low participation rate of 25%; 3% of those subjects had current PUD and a further 3% had evidence of past ulcers. Few other data are available and the data are mostly from more selected cohorts as discussed above in Introduction 1.6.

The proportion of *H. pylori*-negative DU (38%) was surprising and worrying, since such results could alter current dyspepsia management algorithms. A rising proportion of idiopathic ulcers among patients has been shown in recent studies (95, 137, 138, 190). Lanas et al. (191) have shown that the number of idiopathic ulcers may be overestimated if the participants with PUD underreport aspirin or NSAID use. In our study, aspirin or NSAID use for subjects with idiopathic ulcers was double-checked through an extra telephone interview and a review of those subjects' medical records. In total, use of either aspirin or NSAIDs during the past 3 months was confirmed for 169 subjects (16.9%), which is consistent with estimated use for the region (192).

H. pylori infection and use of NSAIDs are well-recognized causes of PUD and some studies have suggested a synergistic effect of these risk factors (193). We could not identify any such synergy in the development of PUD. A higher risk of both GU and DU with low-dose aspirin (≤ 160 mg) use as compared with use of standard-dose aspirin can probably be explained by the continuous use of low-dose aspirin.

Another indicator of aspirin or NSAID use can be antral chemical-reactive gastritis (156), although this can also be caused by bile reflux or excessive alcohol consumption (194). Earlier reports suggested that the sensitivity of this histological finding for NSAID use is 73% (156), but in this study only 32% of our 169 subjects with reported use of aspirin or NSAIDs during the previous 3 months had chemical-reactive gastritis. The three cases in which *H. pylori* was detected by serologic analysis but not by histological analysis or culture are another potential source of bias. None of those subjects had any granulocyte activity to indicate an ongoing but hidden infection.

We also, like others (195-199), found that GERS were linked to obesity, but this did not remain significant if subjects with reflux esophagitis and PUD were excluded. Intake of lower esophageal sphincter relaxing medication did not substantially alter the association between GERS and BMI or esophagitis and BMI. Symptoms independently

associated with obesity were diarrhea, incomplete evacuation and vomiting. The association with diarrhea has been highlighted by others (197, 198, 200), but the reason seems obscure. We hypothesize that excess intake of poorly absorbed products causing osmotic diarrhea could explain the increased lower GI symptoms in obesity. For example, there has been a very substantial increase in the use of corn syrup containing fructose in the USA and excess ingestion of this could induce fructose malabsorption (201, 202). Other mechanisms that might explain the increased bowel frequency associated with increased BMI may also include abnormal bile salt turnover because of rapid small intestinal transit or rapid gastric emptying, which has been reported in some groups of obese patients (203, 204).

In our study there were 19% men and 5% women using smokeless tobacco, which is consistent with the Swedish average, 22% men and 4% women, respectively, and the amounts consumed are also comparable to use in Sweden (3 cans/week) (205).

Smokeless tobacco users had less PUD but the reasons for this are uncertain. Smokeless tobacco contains high amounts of nitrate (206), which is associated with an increased nitrite formation in the oral cavity and further to formation of nitric oxide in the stomach (207-209). In contrast, cigarette smoking seems to be related to reduced levels of nitrite in saliva (206). Salivary nitrite has marked gastroprotective effects through nitric oxide formation (210). These effects include elevated gastric mucosal blood flow and increased mucus thickness. Acidified nitrite has bactericidal effects (211), possibly including *H. pylori*. Smokeless tobacco did not alter *H. pylori* status significantly in this population. We also observed that both smokeless tobacco use and cigarette smoking caused significantly higher levels of Pepsinogen-1 without significantly affecting Gastrin-17 level. Thus, the difference in PUD prevalences seems not to be due to the acid- Gastrin-17 axis.

Intravenously infused nicotine has been shown to decrease pancreatic bicarbonate secretion in animals (212). Similarly, reduced bicarbonate has been causally related to a higher risk of PUD in cigarette smokers (213). There are no studies examining this effect in smokeless tobacco users, whose serum nicotine levels are similar to or higher than those of smokers. The role of swallowed alkaline tobacco-contaminated saliva against the development of PUD is unclear in smokeless tobacco users.

The calculation of the not significantly lower risk for PUD among smokeless tobacco users compared to non- users (OR, 0.34; 95% CI, 0.04-2.80) needs an explanation. According to Table 14, the latter group had an overall PUD prevalence of 3.5%, which corresponds to an expected number of PUD of 3.3 among the 95 subjects using the moist snuff variant of smokeless tobacco, but they had no ulcers at all. The gastric ulcer among the 96 subjects in the entire smokeless tobacco group was in the only individual using a very low dose of chewing tobacco (<5g/week) and not moist snuff. We assume that these two variants of smokeless tobacco might be equal in effects, and most probably the chewing tobacco user swallowed small amounts of nicotine, nitrosamines and nitrites like moist snuff users. The reason that we did not exclude her to avoid any doubt is simply that the risk calculation needs at least one case to work, but the interesting trend towards fewer ulcers compared to non-users was not significant anyhow.

We hypothesize that smokeless tobacco use theoretically might increase the risk of esophageal and cardia adenocarcinoma. When saliva including dietary nitrate, converted to nitrite, meets acidic gastric juice, the nitrite is converted to nitrous acid, nitrosative species, and nitric oxide (208, 209, 214). In healthy volunteers this potentially mutagenic chemistry appears to be focused to the gastric cardia (214). Hence, in patients who already have Barrett's esophagus, the interaction between acidic gastric refluxate and nitrite rich saliva activates potentially mutagenic luminal nitrosative chemistry (214).

Other studies show a possible risk elevation for death of cancer and also of cancer in the gastro-intestinal tract when using chewing tobacco/smokeless tobacco (215). In a Swedish study however esophageal squamous cell cancer was strongly associated with cigarette smoking but not with the use of smokeless tobacco and smoking was also a strong risk factor for adenocarcinoma of the cardia (216). A Swedish review on the possible harmful effects of smokeless tobacco use found that the carcinogenic effect is probably due to the content of tobacco specific nitrosamines (217). There are also other negative effects of smokeless tobacco use, such as increased risk of diabetes and also reproductive disorders (218, 219). There is little knowledge regarding the relationship between GI symptoms and smokeless tobacco. The nicotine intake is usually higher than in smokers and a great deal of tobacco juice contaminated saliva is swallowed during use. In a Swedish cross-sectional study of symptoms in 130,000 construction workers, smokers reported "ulcer-like" dyspepsia three times as often as the non tobacco users, while smokeless tobacco users reported significantly fewer symptoms than both smokers and non-tobacco users (220).

Taking all the strengths and potential limitations of our study into consideration, we believe that the findings of the population-based Kalixanda study are generalizable in 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" (189).

6 CONCLUSIONS

The Kalixanda study is the first large-scale study of PUD in a randomly selected adult population that has had a satisfactory, high participation rate. Our study represents a population-based, non-biased cohort of adults, who have been well characterized concerning symptoms, endoscopy findings and *H. pylori* status.

Study I: It is possible to conduct upper endoscopy studies in adults that are representative of the general population in terms of unbiased symptom reporting with a possible exception of the youngest age group. Prevalence of GERS during the latest 3 months was 40.0%, dyspepsia 37.6%, “epigastric pain or discomfort” 20.9%, abdominal pain 51.4% and IBS 29.6%.

Study II: Both GU and DU are common in the general population and persons with ulcer frequently show atypical symptoms. In this general adult population from Sweden, 22% of all cases of PUD were idiopathic, and almost 40% of DU was *H. pylori*-negative. Obesity was a risk factor for GU, as was use of low-dose aspirin for PUD.

Study III: GERS were independently associated with BMI. Importantly, the association was explained by increased upper endoscopy findings in obesity. In addition, the obese individuals had significantly higher PUD prevalence compared with normal weight individuals.

Study IV: The use of smokeless tobacco significantly increases the prevalence of esophagitis and the risk for antral intestinal metaplasia, but the users of smokeless tobacco have a significantly lower risk for PUD compared with smokers. Smokeless tobacco does not significantly affect perceived upper GI symptoms. The possible role of nitrogen compounds and other chemical contents in smokeless tobacco need to be further examined.

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