Clinical epidemiological studies in patients with unexplained chest and/or epigastric pain

PhD thesis

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Faculty of Health Sciences
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Preface

The studies in this PhD thesis were performed during my employment at the Department of Clinical Epidemiology, Aarhus University Hospital, in cooperation with the Center of Visceral Biomechanics and Pain, Aalborg Hospital, the Department of Gastroenterology, Aalborg Hospital, the Department of Surgical Gastroenterology L, Aarhus University Hospital, and the Department of Medicine V, Aarhus University Hospital.

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Estrid Muff Munk
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- Estrid Muff Munk, Bente Nørgård, Claus Dethlefsen, Hans Gregersen, Asbjørn Mohr Drewes, Peter Funch-Jensen, Henrik Toft Sørensen. **Mortality and Ischemic Heart Disease in Patients with Unexplained Chest/Epigastric Pain and Normal Upper Endoscopy: A Danish 10-Year Cohort Study.** Submitted.

- Estrid Muff Munk, Asbjørn Mohr Drewes, Anders Gorst-Rasmussen, Peter Funch-Jensen, Hans Gregersen, Bente Nørgård. **Risk of Gastrointestinal Cancer in Patients with Unexplained Chest/Epigastric Pain and Normal Upper Endoscopy: A Danish 10-Year Follow-up Study**. *Dig Dis Sci* 2007;52:1730-7.

- Estrid Muff Munk, Asbjørn Mohr Drewes, Anders Gorst-Rasmussen, Hans Gregersen, Peter Funch-Jensen, Bente Nørgård. **Risk of Peptic ulcer, Oesophagitis, Pancreatitis, or Gallstone in Patients with Unexplained Chest/Epigastric Pain and Normal Upper Endoscopy: A 10-Year Danish Cohort Study**. *Aliment Pharmacol Ther* 2007;25:1203-10.

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Abbreviations

CAG	Coronary angiography
CI	Confidence interval
CNS	Central nervous system
ECG	Electrocardiogram
ENS	Enteric nervous system
FGIDs	Functional gastrointestinal disorders
GERD	Gastro-esophageal reflux
HDR	Hospital Discharge Registry
ICD	International Classification of Diseases
IR	Incidence rate
IHD	Ischemic heart disease
MRR	Mortality rate ratio
NCCP	Non-cardiac chest pain
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PAS	Patient Administrative System
SMR	Standardized mortality ratio
UCEP	Unexplained chest/epigastric pain

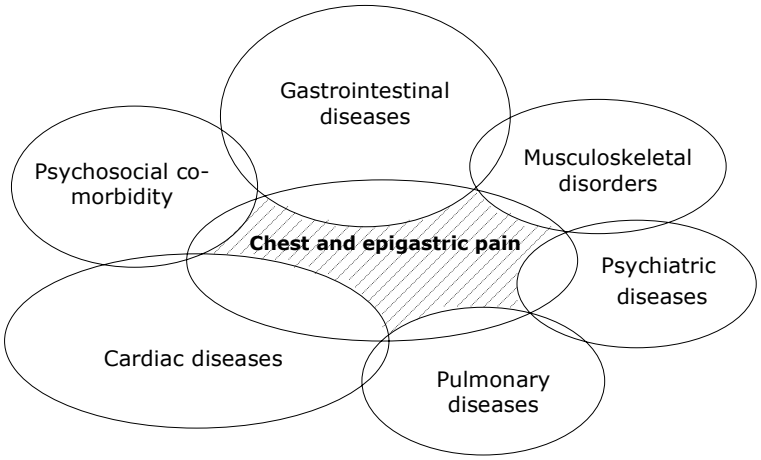
1.0 Introduction

The origin of pain in the chest and the epigastrium is often complex, presenting a challenge in clinical practice. Such pain is primarily explained by ischemic heart disease (IHD) or upper gastrointestinal diseases. However, commonly there is no obvious organic cause, and the pain may, consequently, be diagnosed as "unexplained chest/epigastric pain" (UCEP). Reportedly as many as 33% of patients may have UCEP-related symptoms, though there is considerable variation in the populations studied [1-3]. Continuous pain causes reduced quality of life in these patients [4-11], and their prognosis is unclear. Evidence regarding mortality is sparse and conflicting [12-15], while the risk of gastrointestinal cancers or upper gastrointestinal diseases is essentially unknown. Better understanding of the prognosis in UCEP patients can be obtained from properly designed epidemiological studies based on a well-defined study population of UCEP patients. This thesis includes prognostic studies among UCEP patients, specifically addressing mortality, IHD, gastrointestinal cancers, and selected non-malignant upper gastrointestinal diseases.

1.1 UCEP as a part of a heterogenic symptom complex

Pain in the chest and the epigastrium is difficult to localize and it reflects often overlapping symptoms from a wide spectrum of organ systems in the chest and upper abdomen [16-18]. Thus, investigation of the origin of pain is complicated by existence and often co-existence of many differential diagnoses, as illustrated in Figure 1 [19]. IHD may be the underlying cause in 25-40% of the patients with chest/epigastric pain [20;21], whereas gastrointestinal diseases may be the cause in up to 40% of cases [22]. If no obvious organic explanation is found despite several examinations and diagnostic tests, the patients may be diagnosed as having UCEP. Since it is impossible to examine all potential differential diagnoses in common clinical practice, typically the most likely or potentially lethal ones are pursued. Consequently, published studies of patients with UCEP-related diagnoses have considerably heterogeneous populations, defined by ruling out specific organic causes of the chest and epigastric pain.

Figure 1. Potential causes of chest and epigastric pain. The hatched area represents UCEP



Gastrointestinal diseases may include
- Gastro-esophageal reflux (GERD)
- Peptic ulcer disease
- Gallstone diseases
- Cholecystitis
- Pancreatitis

Musculoskeletal diseases may include
- Costochondritis
- Cervical-thoracic spine disease
- Muscle syndromes

Pulmonary diseases may include
- Pneumonia
- Pleurisy
- Pulmonary embolism
- Pneumothorax

Cardiac diseases may include
- IHD
- Pericarditis
- Micro-angina

Psychiatric diseases may include
- Depression
- Anxiety-panic disorders
- Hypochondria

Psychosocial factors
- Influences of work and family life
- Stress
- Impaired social life
- Low socioeconomic status

1.2 UCEP in a historical view

Several terms have been used to describe patients with UCEP-related symptoms, with some of the terms overlapping depending on whether patients have been defined from a cardiovascular or a gastroenterological point of view. Non-cardiac chest pain (NCCP) and upper functional gastrointestinal disorders (FGIDs) are both important terms used for disorders that are most likely to include UCEP patients. For this thesis on UCEP, we mainly focused on patients defined with either NCCP or upper FGIDs.

NCCP

The main approach to uncovering the causes of pain originating in the chest and upper epigastrium has been to exclude cardiovascular diseases; therefore, most information on UCEP derives from patients with NCCP. In 1892, Osler noted that differentiating patients with "pseudo-angina" from those with IHD was difficult, and despite improved diagnostic skills and technological tools, such distinction is still not easy [23]. From the late 1960's, the most important test used in examining patients for possible IHD has been coronary angiography (CAG) [24]. At first, patients with chest pain and a normal CAG were classified as having no IHD and diagnosed as NCCP patients, however, it has been later shown that a normal CAG is not guaranteed to rule out IHD [25].

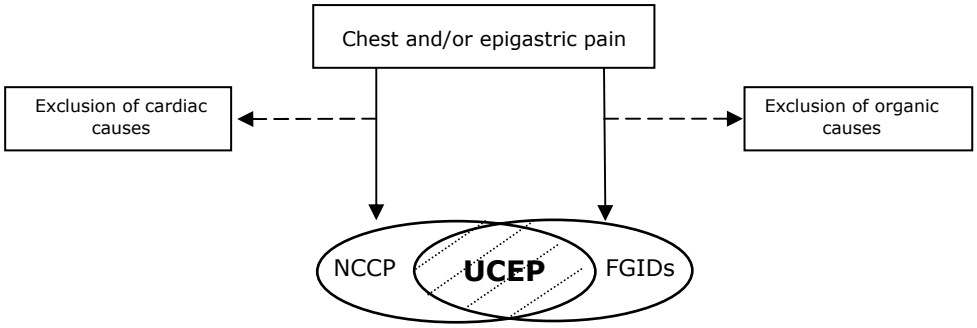
In the literature, NCCP has been used broadly, comprising patients with chest pain and normal CAGs as well as patients with chest pain and no other clinical signs of IHD (termed *e.g.,* unspecific chest pain, non-specified chest pain, angina-like chest pain, chest pain of undetermined origin) [4;6;11;12;14;15;26-36]. Because of differences in cardiovascular approach to the pain in studies of NCCP, the ability to completely exclude underlying IHD varies substantially. Moreover, ruling out of other organic, non-cardiac causes of the chest pain is not included in the classical definition of NCCP. Therefore, majority of the published studies do not exclude patients with upper gastrointestinal diseases *e.g.,* peptic ulcer, esophagitis, and, in particular, GERD, though such organic diseases may be the underlying causes of the pain in 20-50% of the NCCP patients [33;37-40].

It could thus be argued that due to inconsistent exclusion of underlying IHD and the general failure to exclude organic non-cardiac causes of the pain (specifically, upper gastrointestinal diseases, including GERD), previous studies of NCCP only rarely were restricted to patients with truly 'unexplained' pain.

FGIDs

FGIDs constitute gastroenterological organ-related diagnostic entities defined in detail since 1988 (Rome I), revised in 1999 (Rome II) [41], and recently re-classified according to the Rome III criteria [1]. Overall, FGIDs consist of symptom-defined diagnoses that are not explained by any organic (structural or biochemical) abnormality. The term "functional" is rather misleading, since increased histological knowledge has blurred the distinction between "organic" and "functional", and, therefore, the FGIDs are better characterized by their motor and sensory physiology, and central nervous system (CNS) relationships (described in section 1.3) [42].
The FGIDs are classified into organ-related subgroups, which tend to overlap and co-exist [1;1;7]. Three specific subgroups of FGIDs are likely to include UCEP patients: i) functional chest pain of presumed esophageal origin [43], ii) functional dyspepsia (with epigastric pain only), or iii) epigastric pain syndrome [44]. Refinement of the FGIDs' definitions is ongoing, with the aim of creating more clearly defined pathophysiological subgroups [44]. For example, the epigastric pain syndrome is now defined as an independent disorder. In addition, epigastric discomfort and heartburn are excluded from functional dyspepsia definition. Heartburn is excluded to reduce potential overlap with defined organic causes, mainly GERD. Epigastric discomfort is excluded primarily to avoid confusion in the understanding of the symptom, which has been interpreted with substantial lack of consistency in previous studies [44;45].
Overall, FGIDs are diagnostic entities that during the past three decades have been under development marked by refinement of definitions. The interpretation of the results of earlier studies on FGIDs is therefore complicated by less clear definitions. The relation between pain location, NCCP, upper FGIDs, and UCEP is shown in Figure 2.

Figure 2. Illustration of the relation between UCEP, NCCP, and upper FGIDs. Solid arrows represent included patients whereas dotted arrows represent excluded patients



IHD=ischemic heart disease, UCEP=unexplained chest/epigastric pain

1.3 Pathophysiology of UCEP

Investigations of the possible pathophysiological mechanism of UCEP are ongoing, and research in the area has focused on three main explanatory abnormalities: i) sensory abnormalities (visceral hypersensitivity and distorted central signal processing), ii) abnormal motility, and iii) psychosocial abnormalities (susceptibility) [43;44;46]. These abnormalities are believed to interact in a bio-psychological model as illustrated in Figure 3 [1].

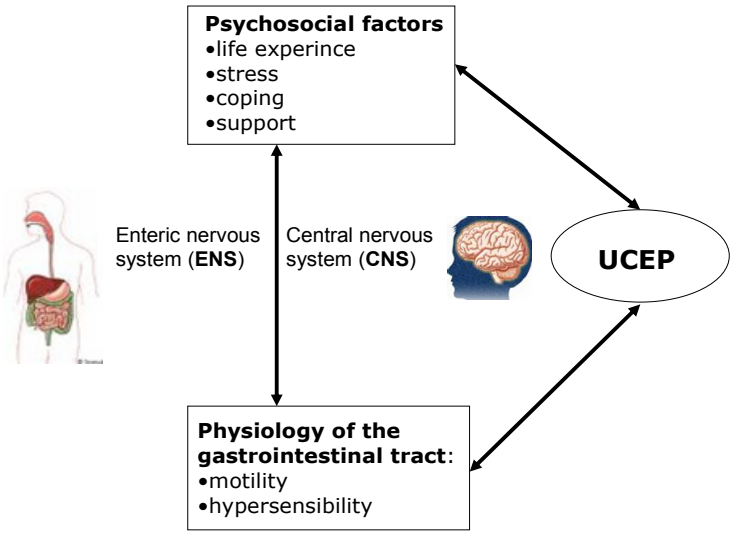
The visceral hypersensitivity is suggested to be a primary abnormality that, in the esophagus, might be caused by physiological acid reflux or by increased sensitivity to spontaneous distension events, marked by swallowing or belching [43]. In the stomach, the hypersensitivity is believed to be caused by distension of the organ (with abnormal accommodation) or by abnormal responses to acid or lipids from the duodenum [44]. In many patients there are no obvious organ-related pathological findings, implying that the hypersensitivity is likely to be related to abnormalities in the central processing of pain. This may occur due to amplification of the response to afferent (sensory) signals from either the esophagus or the stomach [43;46;47], which is thought to be caused by hyper excitability and plastic alteration of spinal and supraspinal neurons, along with opening of latent connections between neurons [48].

The motility abnormalities in the esophagus are believed to be caused by sustained contraction of the longitudinal muscle fibers [43], whereas the mechanism suggested for the stomach is related mainly to theories of *e.g.* impaired gastric emptying, disturbed gastric rhythm, and excess of localized contractions [44].

The psychosocial susceptibility is influenced by *e.g.* life experiences (abuse, family history), stress, coping, and social support [1;42].

The overall result of these interacting abnormalities is lower threshold against pain due to distension, increased sensitivity to even normal function (allodynia), and increased area of somatic referral of visceral pain among patients with UCEP symptoms [43].

Figure 3. The bio-psychological model of UCEP



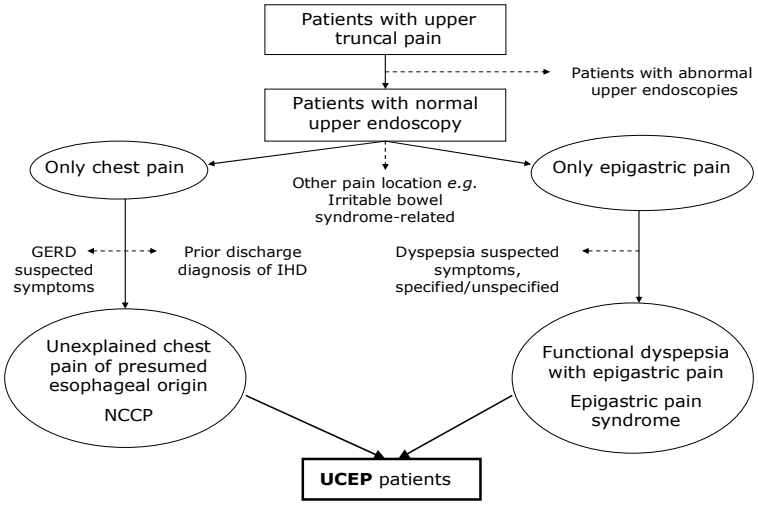
Modified figure from Drossman '*The functional gastrointestinal disorders and the Rome III process*' [1].
UCEP=unexplained chest/epigastric pain

1.4 Definition of UCEP in this thesis

UCEP in this thesis is defined as *pain localized only to the chest and/or the epigastrium in patients without a prior discharge diagnosis of IHD and with a normal first-time upper endoscopy*. Pain in the chest and pain in the epigastrium were combined into one category, because these pain locations could not be differentiated in the available historical data on the study patients. At the same time, as shown in experimental studies, pain from viscera is often difficult to localize since there is a major overlap in manifestations of pain emanating from the esophagus and that from related organs [17;47;49;50]. Hence, the combination of pain from the chest and epigastrium appears to be a suitable description of a common clinical situation.
We aimed to select the UCEP patients in a way that would exclude those with known upper gastrointestinal diseases, determined by upper endoscopy and through detailed description of symptoms. Likewise, patients with prior discharge diagnoses of myocardial infarction, angina, and/or heart failure (as the main elements of IHD [51]) were excluded as were patients with pain in other locations and patients with symptoms suggestive of GERD or dyspepsia. Figure 4 shows the flow chart of the patients included in (or excluded from) the UCEP cohort.

By applying this definition we intended to identify a clearly defined cohort of UCEP patients without organic gastrointestinal diseases and without previously diagnosed IHD.

Figure 4. Flow chart of patients defined as having unexplained chest/epigastric pain (UCEP). Solid arrows represent included patients whereas dotted arrows represent excluded patients



IHD=ischemic heart disease, GERD=gastro-esophageal reflux disease, NCCP=non-cardiac chest pain, UCEP=unexplained chest/epigastric pain

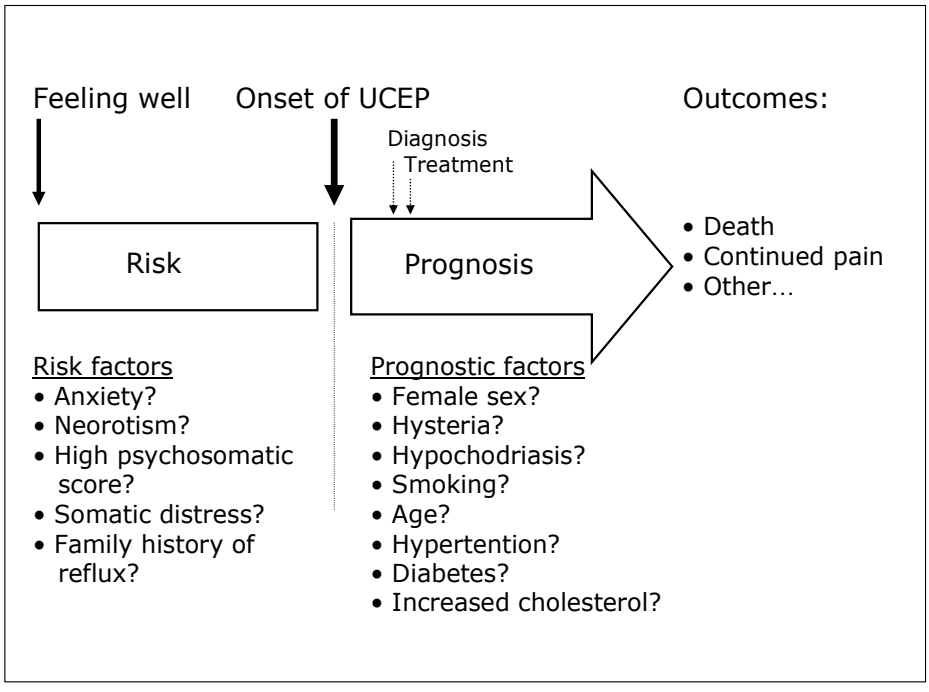
1.5 Risk factors for UCEP

Characteristics associated with an increased risk of a disease are called risk factors [52]. Studies on risk and risk factors are traditionally related to the classical epidemiology, which focuses on distribution of diseases and their determinants within populations [53]. The main evidence regarding risk factors for UCEP stems from studies of patients with NCCP and upper FGIDs, and a number of potential risk factors or causes have been examined. GERD has been suggested as the most important risk factor for NCCP in a few cross-sectional studies [3;39;40;54]. In these studies, up to 50% of the NCCP patients also had GERD symptoms. However, as chest pain is a well-known symptom of GERD, [39] such NCCP patients with GERD are better described just as GERD patients. Findings from studies of NCCP patients would be more informative if NCCP patients with GERD were separated from those without GERD (or excluded).

This point of view is supported by another study on risk factors for NCCP, in which NCCP patients were grouped according their GERD status (present/absent) [40]. The two groups differed in risk factors: the NCCP-no-GERD patients tended to be younger than NCCP-GERD patients, were more likely to be obese, and tended to have higher somatic symptoms score [40]. Other suspected risk factors for NCCP include anxiety, neurosis, smoking, family history of reflux, and alcohol intake [3;40]. In contrast, obesity, smoking, or alcohol intake have been reported not to be associated with functional dyspepsia [55;56], while family history of GERD and anxiety, neurosis, and somatic distress are possible risk factors for more upper FGIDs [2;55].

Risk factors for UCEP are unknown, but some of the suspected characteristics may include family history of reflux, anxiety, high psychosomatic symptom score/somatic distress, and neurosis, all of which are also risk factors reported for both NCCP and FGIDs (Figure 5).

Figure 5: Model of the clinical course in UCEP, modified from Fletcher ' Clinical Epidemiology: *The Essentials*' [52]



UCEP=unexplained chest/epigastric pain

1.6 The burden of UCEP – prevalence, incidence, and prognosis

The burden of patients with UCEP in the health care system is heavy and is probably increasing, as shown in a recent study, which found a 50% increase in admissions due to chest pain and a three- to four-fold increase in the number of CAGs performed over the last decade [57]. It has been shown that 65-75% of patients with FGIDs have consulted their physician in the past year due to their symptoms [2], and about 41% of all diagnoses in gastroenterological practices are due to FGIDs [58]. The main health care professionals consulted by NCCP patients are reportedly general practitioners (consulted in 80-85% of the cases [59;60]) and gastroenterologists (consulted in 30-76% of the cases [59;60]). It has been estimated that this health care seeking behavior, along with secondary expenses (including work absenteeism), amounts to an extremely high yearly social expense: 8 billion dollars is the estimate reported for the initial care of NCCP patients in the U.S. in 2000, and about 114,000 dollars per 1,000 citizens reported in Sweden in 1991 [61-63].

Prevalence and incidence of UCEP

Prevalence is a fraction (proportion) of a group of people, which possesses a clinical condition (or outcome) at a given point of time [52]. Since no study examined the prevalence of UCEP, its estimate has to be based on studies of NCCP and upper FGIDs. According to population-based studies, the annual prevalence of NCCP varies from 10-33% [3;12;39;54], whereas the prevalence of upper FGIDs (mainly functional chest pain and functional dyspepsia) varies from 5-16% [45;55;64-66].

The large variability of the reported prevalence of NCCP and FGIDs is probably due to substantial differences in the definitions of these conditions and to true geographic variation (estimates are available in studies from the U.S.[39;55;64], England [12], Australia [3;65], China [54], and Sweden [66]). The prevalence of NCCP appears to be nearly the same in males and females, whereas prevalence of upper FGIDs is higher among females [2;3;55]. Furthermore, while prevalence of NCCP tends to decrease with increasing age, the opposite trend is reported for upper FGIDs [2;3;55].

The incidence, which is the rate of new events over time [52], of NCCP and FGIDs remains unknown.

The prevalence as well as the incidence of UCEP in the Danish population has never been studied, however, it is likely to be lower than prevalence of NCCP or FGIDs because of the UCEP's narrower definition.

UCEP and prognosis

Prognosis is a prediction, quantitative or qualitative, of the future course of a disease following its onset, and it may be separated into i) the natural history and ii) the clinical course [52;67]. The natural history is the biological progression of a disease in the absence of medical intervention, whereas the term *clinical course* is used to describe the evolution of a disease after diagnosis and medical treatment [52]. Prognosis in clinical epidemiology often means studying frequency of disease outcomes [67], which range from death to emotional perceptions, and have been referred to as 'the five Ds', as in Box 1 [52].

Box 1 Outcomes of diseases from Fletcher ' Clinical Epidemiology: *The Essentials*' [52]

• Death	An unwanted outcome if untimely
• Disease*	A set of symptoms, physical signs, and laboratory abnormalities
• Discomfort	Unpleasant symptoms such as *e.g.* pain, nausea, dyspnea
• Disability	Impaired ability to usual activities at home, work etc.
• Dissatisfaction	Emotional reactions to the disease

* Illness or other diseases developed as a consequence of the primary disease

Evidence regarding prognosis of UCEP patients obtained from studies of patients with NCCP or FGIDs is sparse, but outcomes of worse quality of life and continued pain [4-11] have been reported among these patients. Other reported outcomes include increased health care seeking behavior [6;11] and continued drug use (*e.g.* antianginal drugs) [26;27]. Mortality and risks of selected diseases in patients with NCCP or FGIDs will be described in section 1.7.

Prognostic factors related to outcomes of UCEP are unknown; however, some studies have examined prognostic factors related to outcomes of NCCP [15;28;36]. In NCCP patients, possible prognostic factors for continued pain are female sex, hysteria, and hypochondria; whereas factors prognostic of all-cause death may include smoking, high age, increased serum cholesterol, hypertension, and diabetes (Figure 5) [15;28;36]. The latter factors are also risk factors to IHD, which may indicate that NCCP could reflect undiagnosed underlying IHD [68]. Evidence of prognostic factors with respect to outcomes of upper FGIDs is not clear [45].

1.7 Review of the literature

We used the MEDLINE database to systematically review the literature on the association of UCEP-related symptoms with overall and cause-specific mortality (relevant to study I), risk of IHD (relevant to study I), risk of gastrointestinal cancers (stomach, colorectal, liver, and pancreatic cancer) (relevant to study II), and risk of upper gastrointestinal diseases (peptic ulcer, esophagitis, pancreatitis, or gallstone) (relevant to study III).

The search was performed using the following MeSH (Medical Subject Heading) terms related to UCEP: "unexplained chest pain", "non-cardiac chest pain", "angina-like chest pain", "chest pain", "normal coronary angiography (arteries) and chest pain", "functional gastrointestinal disorders (FGIDs)", "functional chest pain", "functional dyspepsia", "functional abdominal pain", "non-ulcer dyspepsia" both isolated searched and combined with "prognosis", "ischemic heart disease", "mortality", "death", "gastrointestinal cancer", "stomach cancer", "colorectal (colon, rectum) cancer", "pancreas cancer", "liver cancer", "gastrointestinal diseases", "(O)esophagitis", "peptic ulcer", "gallstone", and "pancreatitis". The search was limited to studies of human adults aged 19+ and published in English with abstracts available. In addition, publications by key authors as well as reference lists of selected publication were searched for other articles of interest.

We classified studies as *case series* if patients with UCEP-related symptoms were studied for an outcome relevant for this thesis and not compared with a control group. In contrast, if patients with UCEP-related symptoms were studied for a relevant outcome in comparison with a control group, they were classified as *cohort studies*.
We excluded case reports, comments, and reviews.

Sixteen studies were deemed important in relation to this thesis and are reviewed carefully.

Studies on mortality and IHD as outcomes
Mortality and risk of IHD among patients with UCEP-related symptoms have been assessed in four cohort studies that used population controls [12-15] (Table 1), five case series [4;27;29;30;36] (Table 2), and eight cohort studies with patients with IHD as the control group [6;14;26;28;31;32;34;35] (Table 3). One cohort study, which used both population controls and IHD controls, is listed in Tables 1 and 3 [14].

One of the population-based cohort studies reported that compared with asymptomatic controls, NCCP patients had a 1.99 increase [95% confidence interval (CI), 1.71-2.31] of all-cause mortality for NCCP patients, while the relative risk of cardiac death was 2.77 (95% CI, 2.20-3.50) [15]. Another population-based cohort study reported a relative risk of 1.19 (95% CI, 1.01-1.40) of a major cardiovascular event (non-fatal or fatal myocardial infarction or sudden cardiac death) for NCCP patients compared with asymptomatic controls [12]. These findings of increased all-cause and cause-specific mortality in patients with UCEP-related symptoms were, however, in contrast to results of the hospital-based cohort study of patients with non-ulcer dyspepsia (functional dyspepsia), in which cumulative survival among non-ulcer dyspepsia patients [82% (95% CI, 77%-87%)] was similar to that in the background population [85% (95% CI, 77%-87%)] [13]. Likewise, another hospital-based cohort study reported standardized mortality ratios (SMR) for all-cause and cardiac mortality of 0.85 (95% CI, 0.68-1.02) and 0.92 (95% CI, 0.57-1.28), respectively, in male NCCP patients; and 0.80 (95% CI, 0.61-0.98) and 0.85 (95% CI, 0.37-1.32), respectively, in female NCCP patients [14].

The findings from the case series and the remaining cohort studies involving NCCP patients (patients with chest pain and normal CAGs [4;26-31;35;36] or patients with non-IHD chest pain [6;14;32;34]) are conflicting and often fail to provide an estimate of relative effect. However, one study reported a hazard ratio for cardiac deaths and/or non-fatal myocardial infarction of 3.98 (95% CI, 3.09-5.14) as well as an increased all-cause mortality hazard ratio of 1.42 (95% CI, 1.03-1.96) among NCCP patients compared with IHD controls [14].

To summarize, few studies examined mortality and risk of IHD among patients with NCCP, and the results are conflicting. Only one study examined mortality in patients with upper FGIDs, with a reassuring result. The risk of IHD among patients with FGIDs is unknown.

Studies on gastrointestinal cancers and upper gastrointestinal diseases as outcomes

Only one cohort study reported findings regarding peptic ulcer in patients with FGIDs (non-ulcer dyspepsia): four peptic ulcers observed vs. four expected during the follow-up [13]. No study has examined the association between UCEP and risk of esophagitis, pancreatitis, or gallstones. The risks of gastrointestinal cancers (stomach, colorectal, liver, and pancreatic cancer) in UCEP patients, as compared with those in general population, are unknown.

Table 1. Studies on risk of IHD and/or mortality among patients with UCEP-related symptoms and population controls					
Author, Country, Year	Design	Study population	Outcome measures	Adjustment	Results
Wilhelmsen et al Sweden, 1998 [15]	Population-based cohort study, 16 years of follow-up	*Exposed*: men, aged 51-59 years with non-specified chest pain (NCCP), N=441 *Controls*: men, aged 51-59 years, without chest pain, N=4,905	i) All-cause mortality ii) Cardiac mortality	Not described	i) All-cause mortality in NCCP patients=44.2% vs. 25.5% in controls All-cause relative risk of death=1.99 (95% CI, 1.71-2.31) ii) Cardiac mortality in NCCP patients=19.5% vs. 8.0% in controls Relative cardiac risk of death=2.77 (95% CI, 2.20-3.50)
Lampe et al England, 1998 [12]	Population-based cohort study, 14.7 years of follow-up	*Exposed*: men, aged 40-59 years with non-IHD chest pain (NCCP), N=1,849 *Controls*: men, aged 40-59 years, without chest pain, N=4,787	Major IHD event (non-fatal/fatal myocardial infarction or sudden cardiac death)	Yes, for age	i) IR for major IHD event: 8.6/1,000/year among UCEP patients vs. 7.5/1,000/year among controls ii) Adjusted relative risk for the combined outcome=1.19 (95% CI, 1.01-1.40)
Lindell et al Sweden, 1995[13]	Hospital-based cohort study, 10 years of follow-up	*Exposed:* patients with non-ulcer dyspepsia (functional dyspepsia), 30% had irritable bowel syndrome, N=165 *Controls*: a standardized population	i) Survival ii) Cause-specific mortality iii) Peptic ulcer	No, but controls matched by age, gender, and calendar time	i) Survival observed: 82% (95% CI, 77%-87%) vs. 85% (95% CI, 77%-87%) expected ii) In exposed: cardiac mortality=8%, gastrointestinal cancer deaths=1.5%, peptic ulcer death 0.4%, other cancer=3% iii) Peptic ulcer observed=4 vs. 4 expected
Sekhri et al U.K., 2006 [14]	Hospital-based cohort study, up to 4.2 years of follow-up	*Exposed:* patients with NCCP, N=6,396 *Controls*: a standardized population	i) All-cause mortality ii) Cardiac mortality	No, but stratification by age and gender	i) SMR (all-cause mortality) in exposed males=0.85 (95% CI, 0.68-1.02) and SMR in exposed females=0.80 (95% CI, 0.61-0.98). ii) SMR (cardiac deaths) in exposed males=0.92 (95% CI, 0.57-1.28) and SMR in exposed females=0.85 (95% CI, 0.37-1.32)

CI=confidence interval, IHD= ischemic heart disease, IR=incidence rate, NCCP=non-cardiac chest pain, SMR=standardized mortality ratio, UCEP=unexplained chest/epigastric pain

Table 2. Case series on risk of IHD, peptic ulcer and/or mortality among patients with UCEP-related symptoms

Author, Country, Year	Design	Study population	Outcome measures	Results
Lavey et al U.K., 1979 [29]	Hospital-based, mean 3.5 years of follow-up	*Exposed*: patients with chest pain and normal CAG, N=45	i) All-cause mortality ii) Myocardial infarction	i) All-cause mortality=0% ii) Myocardial infarction=0%
Isner et al U.S., 1981 [27]	Hospital-based, up to 11 years of follow-up	*Exposed*: patients with chest pain and normal/ near normal CAG, N=121	i) All-cause mortality ii) Non-fatal myocardial infarction iii) development of IHD judged by endpoint CAG	i) All-cause mortality=2.5% ii) Non-fatal myocardial infarction=3.4% iii) 3 of 7 who underwent an endpoint CAG showed progression=2%
Wielgosz et al U.S., 1984 [36]	Hospital-based, 1 year of follow-up	*Exposed*: patients with chest pain and normal/near normal CAG, N=821	i) Cardiac mortality ii) Non-fatal myocardial infarction	i) Cardiac mortality=0.3% ii) Non-fatal myocardial infarction=0.2%
Lichtlen et al Germany, 1995 [30]	Hospital-based, up to 15 years of follow-up	*Exposed*: patients with chest pain and normal CAG, N=176	i) All-cause mortality ii) Cause specific mortality iii) Non-fatal myocardial infarction	i) All-cause mortality=6.8% ii) Cardiac mortality rate=1.1%, Cancer deaths: 8/176=4.5% iii) Non-fatal myocardial infarction: 4/176=0.7%
Potts et al U.K., 1995 [4]	Hospital-based, mean 11.4 years of follow-up	*Exposed*: patients with chest pain and normal/near normal CAG, N=46	i) All-cause mortality ii) Cardiac mortality	i) All-cause mortality:4/46=9% ii) Cardiac mortality:1/46=2%

CAG=coronary angiography, IHD= ischemic heart disease, UCEP=unexplained chest/epigastric pain

Table 3. Studies on risk of IHD and/or mortality among patients with UCEP-related symptoms and IHD controls

Author, Country, Year	Design	Study population	Outcome measures	Adjustment	Results
Marchandise et al Canada, 1978 [31]	Hospital-based cohort study, 3.5 years of follow-up	*Exposed*: patients with chest pain and normal CAG, N=22 *Controls*: patients with no significant CAGs, N=26	Progression in CAG from study entry	No	Progression in CAG=0% in exposed vs. 27% in controls
Kemp et al U.S., 1986 [28]	Hospital-based cohort study, 7 years of follow-up	*Exposed*: patients with chest pain and normal CAG, N=3,136 *Controls*: patients with mild abnormal CAG, N=915	i) Survival ii) Cardiac mortality	Yes, for age	i) Survival in exposed=96% vs. 92% in controls, ($p<0.001$) ii) Cardiac mortality: 14/3,136=0.4% of exposed vs. 18/915=2% in controls

Smyllie U.K., 1986 [34]	Hospital-based cohort study, 10 years of follow-up	*Exposed*: patients with acute NCCP, N=63 *Controls*: patients with IHD: myocardial infarction (N=175) and coronary ischemia (N=123)	i) Survival ii) Cardiac mortality (=sudden deaths, myocardial infarction, heart failure, arrhythmia, pulmonary embolism)	No	i) Survival in exposed=75% vs. 50% in controls ii) Cumulative cardiac mortality in exposed 15/63=24% vs.106/298=26% in controls
Metcalfe et al U.K., 1990 [32]	Hospital-based cohort study, 6 years of follow-up	*Exposed*: patients with acute NCCP, N=66 *Controls*: a) patients with myocardial infarction, N=290 b) patients with IHD, N=164 c) patients with pericarditis, N=16	All-cause mortality	No	All-cause mortality in exposed 16% (95% CI, 6%-25%) vs. 36% (95% CI, 29%-42%) in patients with myocardial infarction vs. 24% (95% CI, 17%-31%) in patients with IHD vs. 0% in patients with pericarditis
Sullivan et al U.K., 1994 [35]	Hospital-based cohort study, 2.4 years of follow-up	*Exposed*: a) women with chest pain and normal CAG, N=83 b) men with chest pain and normal CAG, N=55 *Controls*: a) women with abnormal CAG, N=119 b) men with abnormal CAG, N=119	i) All-cause mortality ii) Cardiac mortality iii) Myocardial infarction	No, but controls matched for age and year of CAG	i) All-cause mortality: 2/83=2% in exposed women and 1/55=2% in UCEP men ii) Cardiac mortality: 1% in exposed women and 0% in exposed men vs. 3% in female controls and 7% in male controls iii) 1% exposed women and 0% exposed men vs. 4% female controls and 8% male controls developed myocardial infarction
Tew et al U.K., 1995 [6]	Hospital-based, cohort study, 5 years of follow-up	*Exposed*: patients with acute NCCP, N=19 *Controls*: patients with IHD, N=71	i) All-cause mortality	No	i) All-cause mortality in exposed=0% vs. 14/71=19.7% in controls (p=0.08)
Gurevitz et al Israel, 2000 [26]	Hospital-based cohort study, up to 7 years of follow-up	*Exposed*: women <=50 years with chest pain and insignificant CAG, N=56 *Controls*: women with abnormal CAGs, N=79	i) All-cause mortality ii) Congestive heart failure iii) Myocardial infarction	No	i) All-cause mortality in exposed=0% vs. 6% in controls, (p=0.05) ii) Congestive heart failure in exposed=2% vs. 12% in controls, (p=0.05) iii) Myocardial infarction in exposed=0 % vs. 4% in controls, (p=0.14)

Sekhri et al U.K., 2006 [14]	Hospital-based cohort study, up to 4.2 years of follow-up	*Exposed:* patients with NCCP, N=6,396 *Controls*: patients with angina, N=2,366	i) Combined outcome: cardiac deaths and/or acute coronary syndrome (unstable angina/non-fatal myocardial infarction) ii) Overall mortality	Yes, for age, gender, ethnicity, diabetes, smoking, heart rate, character of chest pain, and resting ECG	i) Cumulative probability of the combined outcome in exposed=2.73% vs. 16.52% in controls. Adjusted hazard ratio=3.98 (95% CI, 3.09-5.14) ii) Adjusted all-cause mortality hazard ratio=1.42 (95% CI, 1.03-1.96) in NCCP patients compared with controls

CAG=coronary angiography, CI=confidence interval, ECG= electrocardiogram, IHD= ischemic heart disease, NCCP=non-cardiac chest pain, UCEP=unexplained chest/epigastric pain

1.8 Methodological considerations of the reviewed studies

Several methodological problems have hampered the reviewed studies of patients with UCEP-related symptoms; the most important of the weaknesses are discussed below.

Study design

Study design bears significantly on the interpretation of its findings. A case series may delineate the clinical picture of the disease in question [52]. Five cases series were reviewed in this thesis (Table 2), but in the absence of a comparison group any inference regarding potential causality is impossible. In contrast, analytic studies, such as cohort studies, may provide strong basis for a causal interpretation. Only six of the eleven reviewed cohort studies reported between-group comparisons despite the inclusion of control groups in the study design [6;12;14;15;26;28]. Length of follow-up is important, especially if the outcome under study is rare or if the time to event is presumed to be long, as is the case for cancers or IHD. The problem of insufficient follow-up can be compensated by a very large study population, but it is worsened if the study population is small. Six studies on mortality [6;14;29;35;36] and development of IHD [14;29;31;35;36] had short follow-up periods ranging from 1 to 5 years. Moreover, four studies had very small study populations (<50 exposed) [4;6;29;31]. Consequently, the validity of the findings in these studies can be questioned.

Study population

The study population must be selected carefully according to the aim of the study. Most patients in the reviewed studies were selected from a cardiovascular perspective and often based on the result of a CAG [4;26-31;35;36]. One study included patients if they had a normal CAG despite other clinical signs of IHD (*e.g.* abnormal stress-test, abnormal electrocardiogram (ECG) [30]); in other studies patients reporting typical angina symptoms were excluded from the study population [12;14;15]. Three studies were restricted to patients with *acute* chest pain [6;32;34], two studies were restricted to men aged 40-59 years [12;15], and one study was restricted to women younger than 50 years [26]. Some studies excluded patients with a history of IHD [12;14;15;28;29;36], whereas only two studies excluded patients with 'organic' causes of the pain (details not given) [6;13]. Thus, patient characteristics in existing studies differ substantially, making comparison of the findings very difficult or even impossible. The only study with a gastrointestinal approach had a broadly and heterogeneously defined study population that included, for instance, patients with

epigastric discomfort, patients with reflux-like symptoms, as well as patients with overlapping FGIDs symptoms (from the irritable bowel syndrome) [13].
Four of the cohort studies used population controls [12-15], including two studies in which controls had to be asymptomatic [12;15]. Eight cohort studies used IHD controls [6;14;26;28;31;32;34;35], which is why their results cannot be generalized to the general population.

Outcome and statistics
With the exception of one study [31], all reviewed studies reported results on death. Eight studies reported also results on the development of IHD [12;14;26;27;30;31;35;36], and one study examined also the development of peptic ulcer [13].
The occurrence of the events (death or disease) were - except for one study - reported as cumulative proportions (the number of events observed during follow-up divided by the number of subjects initially being followed) [4;6;13-15;26-32;34-36]. This represents the probability, or prevalence, of the events in the cohorts [52;67]. Only one study reported its findings in terms of incidence rates of the outcome among UCEP patients or controls (the number of events observed during the follow-up divided by the total time at risk) [12]. Three studies estimated the relative risk of death or disease in NCCP patients compared with controls [12;14;15]. One study reported SMR, calculated as the observed mortality rate divided by the expected mortality rate, with the expected rate based on national statistics [14].
Few studies reported estimates accompanied by 95% CI [12-15;32]. Otherwise, the statistic reported, if any, was P-value [6;26;28], whose interpretation is difficult and clinical relevance, questionable [67].

Confounding factors
One of the four studies comparing NCCP patients with the general population, used analysis adjusted for age [12]. In one study, the analysis was stratified by age and gender [14] and in one study, comparison groups were matched on age, gender, and calendar time [13]. One of the studies comparing NCCP patients with IHD controls used analysis adjusted for age, gender, ethnicity, diabetes, smoking, heart rate, character of chest pain, and resting ECG [14], one study used analysis adjusted for age [28], and in one study, the comparison group was matched on age and year of CAG [35].

Conclusion
No study specifically examined patients with UCEP. However, some studies have examined patients with UCEP-related symptoms (mainly NCCP and upper FGIDs).

The evidence about mortality and risk of IHD among UCEP patients is sparse and conflicting, and, except for one gastroenterological study, is based on studies with a cardiovascular approach to the pain. The association between UCEP-related symptoms and risk of subsequent gastrointestinal cancer or upper gastrointestinal diseases (except peptic ulcer) has not been studied.

The main conclusions of the reviewed studies are:

- It is unclear whether mortality and risk of IHD among NCCP patients is different from that in the general population; the reported findings are inconsistent and are hampered by study restrictions.
- Compared with the general population, reassuring findings are reported on survival and subsequent risk of peptic ulcer in one study of patients with non-ulcer dyspepsia (FGIDs).
- Compared with IHD controls, NCCP patients have a lower risk of death and IHD.
- More importantly, none of the reviewed studies excluded patients with gastrointestinal diseases diagnosed by upper endoscopy or patients with GERD-suspected symptoms. Consequently, a large proportion of the patients studied may suffer from well-defined upper gastrointestinal diseases and not from UCEP.

1.9 Considerations for choice of study design

To examine the association between UCEP and mortality, IHD, gastrointestinal cancers, and upper gastrointestinal diseases, one needs accurate information on symptoms from medical records as well as routinely recorded information from large and valid data sources with prospective data collection. A well-designed observational study using standardized methods and a representative study population would be appropriate to study these associations while controlling for potential confounding by co-morbidity, alcohol- and smoking-related diseases.

The main advantage of a cohort study is the ability to study causality because data collection follows the temporal sequence of events. The basic measurement of disease occurrence used in a cohort study is the number of new events, *e.g.* diseases, among cohort members over time (the incidence) [52], which is a direct measure of the absolute risk. From these values of rates of risks it is possible to estimate relative risks (risk ratios) of various outcomes by comparing UCEP patients

with population controls. This is in contrast to case-control studies, where only the odds ratio (as an estimate of the relative risk) can be calculated [67].

With the exception of IHD, the outcomes under study in this thesis have low to moderately low incidences in the general population (Table 4). Based on the estimated incidences of the outcomes of interest, ten years was chosen as an appropriate length of follow-up.

Table 4: Incidence rates of the outcomes studied in the studies I-III

Outcome studied	Incidence*
Myocardial infarction † [69] (as proxy for IHD)	500-1000
Stomach cancer [70]	4-8
Liver cancer [70]	2-4
Colorectal cancer [71]	16-34
Pancreas cancer [70]	7-8
Esophagitis [72]	240
Peptic ulcer [73]	40
Pancreatitis [74]	30
Cholecystectomy [75] (as proxy for gallstone)	143

IHD=ischemic heart disease, * per 100,000 person-years, † aged 65-74 years

Though the cohort design is not well suited for studying rare outcomes, this shortcoming may be compensated by selecting a large number of UCEP patients and/or by choosing a long follow-up period. In a case-control study, on the other hand, the investigator starts off with collecting data on the outcome, often a disease, that has already occurred and then retrospectively ascertains the exposure status (UCEP) among the diseased (cases) and the non-diseased (controls) [52]. However, it would be impossible to find information on the exposure status (UCEP) in a case-control design, since the UCEP patients in our study were selected by searching medical endoscopy records for symptoms of UCEP and normal endoscopy. Moreover, we aimed to study several outcomes associated with UCEP – a goal attainable in a cohort study, but not in a case-control study [67].

The sufficient sample size is essential to achieving high statistical precision of estimates [76]. The power calculation for this thesis was based on the outcome of mortality. Assuming that the 1-year mortality in the general population was 2%, and seeking the ability to detect a 1-year risk of death of 3% among UCEP patients (a rate ratio of 1.5), we would need to include 294 UCEP patients (on condition of a

power of 90% and an alpha-level of 5%) [52]. Initially, we reviewed medical endoscopy records from one year, but subsequently expanded the period to two years, as the frequency of UCEP in the records was lower than expected.

For this thesis, we conducted three historical cohort studies based on data from population-based registries and from medical endoscopy records. We aimed to examine the short- and long-term risk of all-cause mortality and cause-specific mortality (study I), risk of IHD (study I), risk of stomach, colorectal, liver, and/or pancreatic cancers (study II), and risk of peptic ulcer, esophagitis, pancreatitis, or gallstone (study III) in UCEP patients as compared with controls from the background population.

2.0 Hypothesis and aims of the thesis

2.1 Hypothesis of the thesis

- UCEP patients have a higher risk of death than population controls.
- UCEP patients have a higher risk of IHD than population controls.
- UCEP patients have a higher risk of development of esophageal, stomach, small bowel, colorectal, liver, biliary tract, and/or pancreatic cancers than population controls.
- UCEP patients have a higher risk of peptic ulcers, esophagitis, pancreatitis, or gallstone than population controls.

2.2 Aims of the thesis

Study I

- To calculate the 10-year cumulative all-cause mortality rate; to estimate the short- and long-term all-cause mortality rate ratio (MRR) and cause-specific MRR among UCEP patients compared with population controls.
- To estimate the 10-year cumulative risk and the short- and long-term relative risk of hospitalization for IHD among UCEP patients compared with population controls.

Study II

- To estimate the 10-year cumulative risk as well as the short- and long-term relative risks of site-specific gastrointestinal cancers (esophageal, stomach, small bowel, colorectal, liver, biliary tract, and/or pancreatic tumors) in UCEP patients compared with population controls.

Study III

- To estimate the 10-year cumulative risk as well as the short- and long-term relative risk of hospitalization for peptic ulcers, esophagitis, pancreatitis, or gallstone in UCEP patients compared with population controls.

3.0 Subjects and methods

3.1 Data sources

This thesis is based on historical cohort studies among patients referred for upper endoscopy to Aarhus University Hospital, Aarhus County, Denmark. The county has a population of 650,000 (approximately 12% of the entire Danish population). It is a predominantly Caucasian, mixed rural and urban population with access to free, tax-supported health care.

Aarhus University Hospital has the county's largest Internal Medical and Surgical Departments of Gastroenterology, and the majority of all upper endoscopies in the county are performed here.

Aarhus University Hospital Endoscopy Registry (identification of patients with chest and epigastric pain)

This registry contains both hard-copy (paper) medical records and electronic information on all patients referred for upper endoscopy at Aarhus University Hospital since 1976. The hard-copy medical records consist of endoscopy records (written by physicians performing the procedure) and of referral notes (about 90% of the patients were referred by general practitioner as out-patients). The endoscopy reports include patient's identification (the civil registration number), description of patient's symptoms, indication for endoscopy, description of the endoscopy procedure, diagnoses made during endoscopy, biopsies taken, and subsequent pathological findings. This information is entered both in the standardized form (checklists) and as free text. The referral notes are not standardized and include mainly information on the patient's medical and surgical history and symptoms. We extracted information on the patients' symptoms both from the endoscopy records and the referral notes. For the majority of patients the description of the presenting symptom in the endoscopy record and that in the referral note were in agreement. The electronic information was obtained from the county's Patient Administrative System (PAS). Since 1977, PAS includes information on the patients' civil registration numbers, dates of hospital admission and discharge, dates and types of performed procedures, and diagnoses coded by physicians according to the International Classification of Diseases (ICD). ICD-8 was used in 1977-1993 and was replaced with ICD-10 thereafter (ICD-9 was never implemented in Denmark) [77].

To obtain 10 years of follow-up, data on patients were used if they underwent an upper endoscopy between January 1, 1992 and December 31, 1993. In total, 7,272 records of upper endoscopies (in 4,742 different patients) were identified during this period. In order to establish a research database, information from the 7,272 hard-copy medical records was manually coded and categorized by a single physician (the author of the thesis) according to the following categories:

Diagnoses:

1. Normal upper endoscopy, possibly incident.
2. Normal upper endoscopy, possibly not incident.
3. Normal upper endoscopy, unknown whether incident or not.
4. Esophagitis or esophagus ulcers.
5. Barrett's Esophagus.
6. Peptic ulcers (including pylorus and cardia).
7. Duodenal ulcers.
8. Duodenitis.
9. Erosions in the stomach, esophagus, duodenum and Mallory-Weiss lesions.
10. Esophageal varices, portal hypertensive gastropathy, watermelon stomach, cherry-red spots, and gastric fundal varices.
11. Diagnostic procedures for *e.g.* celiac disease, allergy or Giardia lamblia.
12. Tumors or polyps located in the esophagus, stomach or duodenum. First-time diagnosis or control procedure.
13. Preoperative evaluation or treatment of a tumor located in the esophagus, stomach or duodenum.
14. Benign stricture/Schatzki's ring.
15. Other, *e.g*. percutaneous endoscopic gastrostomy, unsuccessful procedure, removal of foreign bodies, vascular abnormalities, Crohn's disease, fistulas, diverticula.
16. Complications after surgery.
17. Hernia.

Pathological diagnoses:

1. Normal tissue.
2. Inflammation of the esophagus or reserve cell hyperplasia.
3. Erosive inflammation of the esophagus.
4. Esophagus ulcers or ulcerative inflammation.
5. Intestinal metaplasia, gastropathy or dysplasia of the esophagus.
6. Intestinal metaplasia, gastropathy or dysplasia of the stomach.
7. Inflammation of the stomach.
8. Erosive inflammation of the stomach.
9. Peptic ulcers.

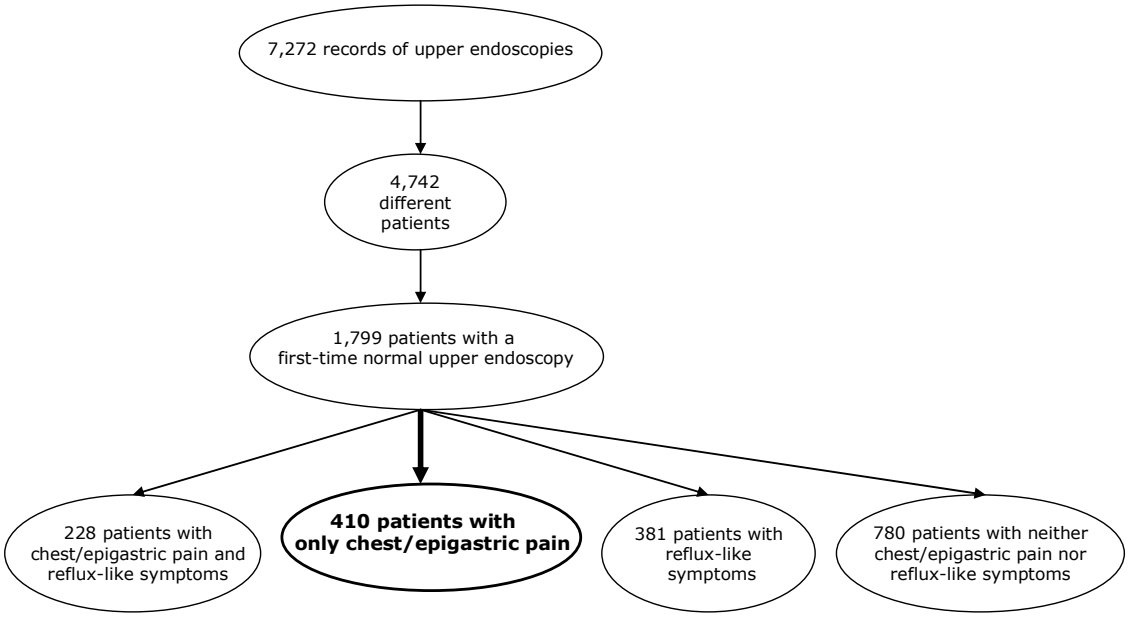
10. Helicobacter positive.
11. Duodenal inflammation.
12. Malignant abnormalities of the esophagus.

The patients with normal upper endoscopy were further categorized according to symptoms:

1. Only chest and/or epigastric pain.
2. Reflux-like symptoms (specified/unspecified dyspepsia, heartburn and/or acid regurgitation).
3. Both chest/epigastric pain and reflux-like symptoms.
4. Neither chest/epigastric pain nor reflux-like symptoms.

With the help of civil registration numbers, data on patients with normal upper endoscopies were linked to the electronic PAS information, and only patients with *incident* normal upper endoscopies in the inclusion period were selected (1,799 patients, aged ≥15 years). These 1,799 patients had following symptoms: 1) only chest/epigastric pain (N=410), 2) reflux-like symptoms (specified/unspecified dyspepsia, heartburn and/or acid regurgitation) (N=381), 3) both chest/epigastric pain and reflux-like symptoms (N=228), and 4) neither chest/epigastric pain nor reflux-like symptoms (N=780) (Figure 6).
Considering the description of pain localization in the medical record, in most cases it was impossible to separate chest and epigastrium pain, and therefore the two pain locations were combined when defining the exposure. If there was a sign of doubt of the location or character of the symptom or if symptom description in the endoscopy record differed from that in the referral note, category 4) was chosen.
The study cohort of interest for this thesis was group 1), with a total of 410 (23%) patients having only chest/epigastric pain.

Figure 6. Flowchart of patients with upper endoscopy included from January 1, 1992 to December 31, 1993, and distribution of patients according to symptoms.



The Hospital Discharge Registry

The nationwide Hospital Discharge Registry (HDR), established in 1977, includes administrative hospital information, which is used to monitor hospital admissions, waiting lists, and treatment (including operations). Since 1995, data on outpatients has been included as well. HDR includes the civil registration number, dates of hospital admission and discharge, procedures performed, and up to 20 discharge diagnoses coded by physicians at discharge according to the ICD [77]. The registry contains data on 99.4% of all discharges from Danish non-psychiatric hospitals [78].

The Danish Cancer Registry

The Cancer Registry is a nationwide registry with data on incident cases of cancer in Denmark since 1943 [79]. Since 1987 reporting to this registry became mandatory. Registration is based on notification forms, which include information on the civil registration number, diagnoses of cancers with dates, method of verification of the cancer, clinical stage at the time of diagnosis, and residence on the date of diagnosis. All available data are classified according to the modified Danish version of the ICD-7 [79]. The notification forms are completed by hospital departments (including departments of pathology and forensic medicine), general practitioners, and practicing specialists. Annually the data are linked to the national HDR and to the Danish Causes of Death Registry in order to capture unreported cases [79].

The Danish Causes of Death Registry

This nationwide registry contains information on all deceased Danish citizens since 1973. The registry is 100% complete [80]. In addition to data on name, age, address, civil registration number, and municipality of residence, the registry also holds information on the date of death, four ranking causes of deaths, manner of death (natural, accident, suicide or unknown), and place of death. Paper death certificates, completed exclusively by physicians, are used to report data to this registry. In Denmark the overall autopsy rate is about 12% [80;81]. The findings of any autopsy are recorded in the death certificate, but the diagnoses provided as causes of death are mainly obtained from the patient's medical record.

The Civil Registration system

The nationwide Civil Registration System, established in 1968, contains information on date of birth, gender, all changes of address, date of emigration, vital status (dead or alive), and date of death on every Danish citizen [82]. The system assigns a unique 10-digit civil registration number to all Danish citizens shortly after birth, and this number enables unambiguous linkage of data from all registries.

3.2 Exposed cohorts and comparison cohorts

Table 5 gives an overview of the studies I-III: exposed cohorts, comparison cohorts, and outcomes.

Exposed cohorts of patients with UCEP

With the aim of excluding patients with previously diagnosed IHD among the 410 patients with chest/epigastric pain only and an incident normal upper endoscopy, we linked the patients' civil registration numbers to the HDR. As a result, we excluded 24 patients with discharge diagnoses of myocardial infarction, angina, and/or heart failure (categorized as IHD [51]) recorded prior to the date of the upper endoscopy (ICD-codes for IHD according to Appendix 1). The remaining 386 patients were defined as UCEP patients and constitute the basis of the thesis.

In study I, data on the 386 UCEP patients were used for the analysis.

In study II, we aimed to study incident upper gastrointestinal cancers (esophageal, stomach, small bowel, colorectal, rectum, liver/biliary tract, or pancreatic cancers) occurring after the date of the upper endoscopy. Therefore, we linked the civil registration numbers of the 386 UCEP patients to the Danish Cancer Registry and excluded two patients with a pre-existing diagnosis of colon cancer; no other prior gastrointestinal cancers of interest were present. Data on the remaining 384 UCEP patients were used for the analyses.

In study III, we aimed to examine occurrence of upper gastrointestinal diseases after the date of upper endoscopy in four sub-studies according to the outcome: i) peptic ulcer study, ii) esophagitis study, iii) pancreatitis study, and iv) gallstone study. Therefore, we linked the civil registration numbers of the 386 UCEP patients to the HDR and excluded 15 patients with a prior discharge diagnosis of peptic ulcer, 3 patients with a prior diagnosis of esophagitis, 10 patients with a prior diagnosis of pancreatitis, and 28 patients with a prior diagnosis of gallstone. We thus obtained four sub-cohorts of UCEP patients for each outcome under study: 371 patients in the peptic ulcer study, 383 patients in the esophagitis study, 376 patients in the pancreatitis study, and 358 patients in the gallstone study.

Comparison cohorts (population controls)

For each of the initial 386 UCEP patients, 10 population controls were selected from the Civil Registration System, matched on age, gender, and county of residence (Aarhus county) (N=3,860). Ten controls were selected to foster statistical precision [76]. These unexposed persons (population controls) were

selected on the date on which their matched UCEP patient underwent his or her first-time normal upper endoscopy (index date).

In study I, linkage to the HDR was conducted in order to exclude controls with discharge diagnoses of IHD prior to the index date. A total of 67 controls were thus excluded, and the remaining 3,793 controls were used for the analyses.

In study II, we linked data to the Danish Cancer Registry and excluded controls with a prior diagnosis of esophageal, stomach, small bowel, colorectal, rectum, liver/biliary tract, or pancreatic cancers. A total of 44 controls were excluded, and the remaining 3,816 were used for the analyses.

In study III, through linkage to the HDR, we excluded controls in the four sub-studies with the relevant discharge diagnosis prior to the index date: peptic ulcer - 204 controls excluded, esophagitis - 38 controls excluded, pancreatitis - 114 controls excluded, and gallstone - 7 controls excluded. Thereby four sub-cohorts of controls remained: 3,656 controls in the peptic ulcer study, 3,822 in the esophagitis study, 3,746 in the pancreatitis study, and 3,543 in the gallstone study.

Table 5. According to study I-III, characteristics of the exposed cohorts of UCEP patients included from January 1, 1992 to December 31, 1993, population controls, and outcomes of interest.

Cohort study	Exposed cohort	Population controls[#]	Outcome(s)
I Mortality and risk of IHD in UCEP patients	UCEP patients*, N=386	No prior discharge diagnosis of IHD, N=3,793	- Overall mortality - Cause specific mortality - IHD
II Risk of stomach, colorectal, liver, and pancreatic cancer‡ in UCEP patients	UCEP patients* with no prior diagnoses of gastrointestinal cancers†, N=384	No prior diagnosis of gastrointestinal cancers†, N=3,816	- Stomach cancer - Colorectal cancer - Liver cancer - Pancreatic cancer
III Risk of peptic ulcer, esophagitis, pancreatitis, or gallstone in UCEP patients (four sub-studies)	UCEP patients* with no prior discharge diagnoses of peptic ulcer, esophagitis, pancreatitis, or gallstone. i) Peptic ulcer study, N=371 ii) Esophagitis study, N=383 iii) Pancreatitis study, N=376 iiii) Gallstone study, N=358	No prior discharge diagnoses of peptic ulcer, esophagitis, pancreatitis, or gallstone N=3,656 N=3,822 N=3,746 N=3,543	- Peptic ulcer - Esophagitis - Pancreatitis - Gallstone

IHD=ischemic heart disease, UCEP=unexplained chest/epigastric pain, * patients with incident normal upper endoscopy, chest pain/epigastric pain, and no prior discharge diagnosis of IHD, # matched on age, gender, and county of residence, † stomach, colorectal, liver, and/or pancreatic cancer, ‡ no esophageal, small bowel or biliary tract cancers were found in UCEP patients during follow-up

3.3 Data on outcomes

Mortality as the outcome (study I)

Mortality was ascertained from the Civil Registration System and the Danish Causes of Deaths Registry. Electronic data from the Danish Causes of Deaths Registry were available until December 31, 2000. From January 1, 2001 to December 31, 2003, data on 583 deceased UCEP patients and population controls were available only as hard-copy death certificates. These were manually recorded and categorized according to the relevant ICD-7 codes (by the author of the thesis) and in this study added to the electronic data from the Causes of Deaths Registry. Only a very few patients and controls died of unnatural causes, and therefore we disregarded the manner of death.

Diseases as outcomes (study I-III)

Data on hospitalization for IHD (study I), and upper gastrointestinal diseases (peptic ulcer, esophagitis, pancreatitis, or gallstone) (study III) were collected from the HDR. Data on gastrointestinal cancer (esophageal, stomach, small bowel, colorectal, rectum, liver/biliary tract, or pancreatic cancers) (study II) were collected from the Danish Cancer Registry. However, only cancers of stomach, colon, rectum, liver, and/or pancreas occurred among UCEP patients during the follow-up and were, therefore, the focus for the analyses. Data from the HDR and the Danish Cancer Registry were available from the date of the study entry until December 31, 2003.

3.4 Data on potential confounders

A confounder is defined as a factor that masks or distorts the effect of the exposure on the outcome under study [83]. To be a confounding factor in the studies I-III, the factor itself must i) be a risk factor for the outcome under study, ii) be associated with UCEP iii) be unevenly distributed between UCEP patients and population controls, and iv) not be a part of the causal pathway between UCEP and the outcome under study.

Potential confounding factors in the studies of mortality, risk of IHD, risk of gastrointestinal cancer, and risk of upper gastrointestinal diseases among UCEP patients may include co-morbidity, even if the evidence of an association between UCEP and co-morbid disease is sparse [3;54]. However, evidence of co-morbid diseases as risk factors for mortality and IHD is strong [84;85], whereas it is less obvious whether co-morbid diseases are risk factors for gastrointestinal cancer

and upper gastrointestinal diseases. Factors such as alcohol abuse and smoking may be associated with UCEP [40] and may also be risk factors for mortality [28;86], IHD [85;86], gastrointestinal cancer [87], and upper gastrointestinal diseases [88-92].

Co-morbidity

In order to control potential confounding by co-morbidity, we computed a co-morbidity index score on each UCEP patient and its controls as described by Charlson *et al.* [84;93], based on data from the HDR. The Charlson Comorbidity Index covers 19 major disease categories weighted according to their prognostic impact on survival, and it has been adapted for use with hospital discharge registry data (Appendix 2). We computed the Charlson index based on ICD-codes for all hospitalizations registered since 1977 and before the index date. Whenever necessary for a specific analysis, we excluded the outcomes of interest; alcohol- and smoking-related diseases were also excluded from the index calculation. Three levels of the index were defined and used for adjustment in the analyses: no co-morbidity [Charlson index 0 as the reference (no recorded underlying diseases relevant to the Charlson index)], co-morbidity 1 (Charlson index 1-2), and co-morbidity 2 (Charlson index >2).

Alcohol and smoking

With the aim of adjusting separately for alcohol use and smoking, we obtained data from the HDR on discharge diagnoses on alcohol- and smoking-related diseases among UCEP patients and controls. These diagnoses were used as proxies for alcohol abuse and smoking and adjusted for in the analyses.

3.5 Statistical analyses

For all studies, we constructed contingency tables for the main study variables.

Follow-up began on the date of normal incident upper endoscopy, or the index date for controls, and ended on the date of a first-time diagnosis of IHD (study I), gastrointestinal cancer (stomach, colorectal, liver, and/or pancreatic) (study II), upper gastrointestinal disease (peptic ulcer, esophagitis, pancreatitis, or gallstone) (study III), on the date of death, on the date of emigration, or at the end of the study period, whichever came first.

In all studies, we used the life-table technique to estimate the incidence rates and cumulative incidence of hospitalizations for the disease of interest [IHD (study I),

gastrointestinal cancer (study II), and upper gastrointestinal disease (study III)]. Cox's regression analysis was used to estimate the incidence rate ratios and 95% confidence intervals as estimates of the corresponding relative risks comparing UCEP patients with population controls while adjusting for confounders.

In study I, we constructed Kaplan-Meier survival curves and used the life-table technique to estimate the risk. We then summarized risk over time of all-cause and cause-specific mortality. Cox's regression was used to calculate the all-cause and cause-specific MRR and associated 95% CI for UCEP patients, relative to controls, adjusted for confounders. MRRs were, moreover, estimated within time periods of <1 year, 1-2 years, 3-4 years, and ≥ 5 years after the index date. For pneumonia we also estimated its cause-specific MRR within <7 days, 7-31 days, and ≥31 days after the endoscopy/index date.

In study I, we performed analyses of the risk of first hospitalization for IHD within time periods of <1 year, 1-2 years, 3-4 years, and ≥ 5 years after the date of upper endoscopy among UCEP patients, relative to that of controls. Separate analyses were, performed for each type of IHD: myocardial infarction, angina, and heart failure during follow-up and within time periods of <1 year, 1-2 years, 3-4 years, and ≥ 5 years for the first appearance of each diagnosis.

In study II, we constructed Kaplan-Meier curves of the probability of remaining free of event [gastrointestinal cancer (stomach, colorectal, liver, and/or pancreatic)] after normal upper endoscopy. We then performed analyses of the risk of gastrointestinal cancer within time periods of < 1 year and ≥ 1 year from the endoscopy/index date.

Additionally, in study III we plotted, for UCEP patients, frequency of each outcome under study (peptic ulcer, esophagitis, pancreatitis, or gallstone) against the time after the upper endoscopy. Furthermore, we estimated the relative risk of hospitalization for peptic ulcer, esophagitis, pancreatitis, or gallstone within time periods of < 1 year and ≥ 1 year from the index date.

The proportional hazards assumptions for the models within time-windows were assessed graphically and were fulfilled.
Analyses were performed using STATA version 9.1SE.

4.0 Results

Below is a summary of the main results obtained in the three studies of the thesis.

4.1 Study I. Mortality and risk of IHD in UCEP patients

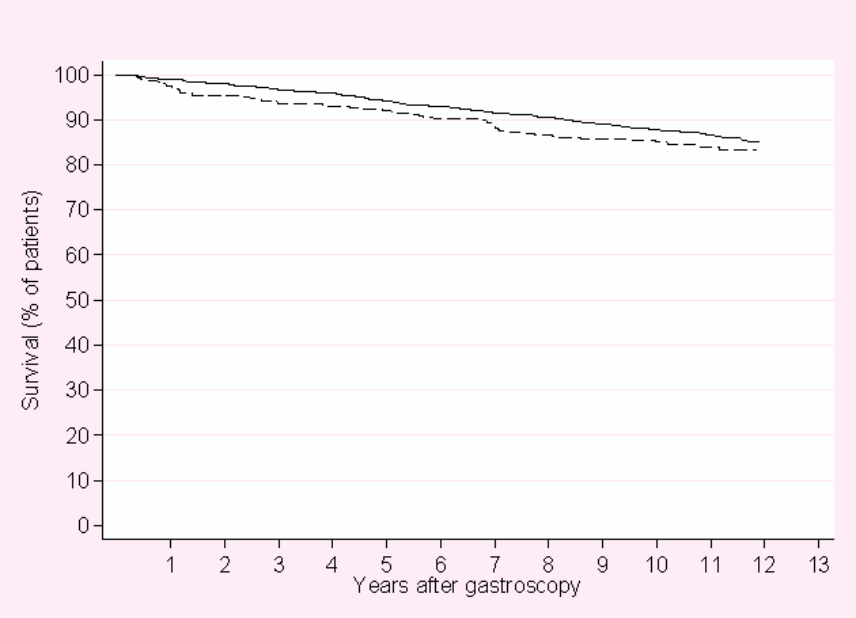
During the inclusion period, we identified 386 UCEP patients and 3,793 population controls, all of whom were free of an IHD discharge diagnosis before the index date.

UCEP patients were more likely than controls to have a co-morbidity score of 1-2 (12% vs. 7%), but there were no substantial differences in alcohol- and smoking-related diseases between UCEP patients and population controls.

Mortality

Sixty-two UCEP patients and 508 population controls died during the 10 years of follow-up. Kaplan-Meier survival curves for UCEP patients and population controls are shown in Figure 7. The 10-year cumulative all-cause mortality was 16% in UCEP patients vs. 13% in population controls. The all-cause mortality rate was 16 per 1000 person-years in UCEP patients and 13 per 1000 person-years in controls, yielding a crude MRR of 1.2 (95% CI, 1.0-1.6), Table 6. Adjusting for co-morbidity, alcohol- and smoking-related diseases did not change the estimate. The mortality rate ratio was the highest within the first two years after upper endoscopy, whereupon the MRR declined to unity [adjusted all-cause MRRs within <1 year, 1-2 years, 3-4 years, and ≥ 5 years after upper endoscopy were 2.4 (95% CI, 1.3-4.5), 1.7 (95% CI, 0.8-3.9), 0.9 (95% CI, 0.6-1.6), and 0.9 (95% CI, 0.6-1.4), respectively]. We did not find a substantially increased risk of cardiac death among UCEP patients compared with population controls [adjusted MRR 1.1 (95% CI, 0.5-2.2), Table 6]. However, we found an increased risk of death from alcohol dependence, pneumonia, and lung cancer among UCEP patients compared with population controls [adjusted MRRs 1.5 (95% CI, 0.3-8.2), 2.7 (95% CI, 1.4-5.2), and 1.7 (95% CI, 0.6-4.4), respectively, Table 6]. All deaths from pneumonia occurred after 31 days following the upper endoscopy.

Figure 7. Kaplan-Meier survival curves for UCEP patients (dotted line) and population controls (solid line).



UCEP=unexplained chest/epigastric pain

Table 6. Crude and adjusted mortality rate ratios (MRR) and 95% confidence intervals (CI) in UCEP patients compared with population controls

	UCEP patients (N=386), n (%)	**Population controls** (N=3,793), n (%)	**Crude MRR** (95% CI)	**Adjusted MRR** (95% CI)
All-cause deaths	62 (16)	508 (13)	1.2 (1.0-1.6)	1.1 (0.9-1.5)
Death from				
IHD	8 (2)	76 (2)	1.1 (0.5-2.2)	1.1 (0.5-2.2)
alcohol dependence	3 (1)	5 (0.1)	3.4 (0.7-16.8)	1.5 (0.3-8.2)
pneumonia	12 (3)	41 (1)	2.8 (1.5-5.4)	2.7 (1.4-5.2)
lung cancer	5 (1)	27 (1)	1.9 (0.7-4.9)	1.7 (0.6-4.4)

IHD=ischemic heart disease (myocardial infarction, angina and/or heart failure),
UCEP=unexplained chest/epigastric pain

Risk of hospitalization for IHD

Thirty-nine UCEP patients and 241 population controls had a discharge diagnosis of IHD during the follow-up. The 10-year cumulative incidence proportion (risk) of

IHD was 11% in UCEP patients vs. 6% in population controls. The incidence rate of IHD in UCEP patients was 11 per 1000 person-years and 6 per 1000 person-years in controls, yielding a crude relative risk of 1.7 (95% CI, 1.2-2.4). Adjustment for co-morbidity, alcohol- and smoking-related diseases had no effect on the relative risk estimate. The relative risk was the highest within the first two years after upper endoscopy, but increased risk persisted even beyond five years after the procedure [adjusted relative risks within <1 year, 1-2 years, 3-4 years, and ≥ 5 years following upper endoscopy were 1.9 (95% CI, 0.7-5.0), 2.5 (95% CI, 0.9-6.7), 1.4 (95% CI, 0.6-2.8), and 1.5 (95% CI, 0.9-2.3), respectively, Table 7]. With respect to the type of IHD, the adjusted relative risk was 1.4 (95% CI, 0.8-2.4) for myocardial infarction, 1.9 (95% CI, 1.2-3.0) for angina, and 1.7 (95% CI, 1.0-2.9) for heart failure. The adjusted relative risk for angina and heart failure was the highest in the first and the second year after the upper endoscopy [4.6 (95% CI, 1.1-18.4) and 5.6 (95% CI, 1.3-23.4), respectively]. For myocardial infarction, the relative risk was the highest ≥5 years following the upper endoscopy [2.0 (95% CI, 0.9-4.3)].

Table 7. Crude and adjusted relative risks and 95% confidence intervals (CI) of hospitalization for IHD in UCEP patients compared with population controls - overall and by the time of the first-time IHD diagnosis

	UCEP patients (N=386), n (%)	**Population controls** (N=3,793), n (%)	**Crude relative risk** (95% CI)	**Adjusted relative risk** (95% CI)
IHD	39 (11)	241 (6)	1.7 (1.2-2.4)	1.6 (1.1-2.2)
Time to diagnosis after upper endoscopy				
<1 year	5 (1.3)	24 (0.6)	2.1 (0.8-5.4)	1.9 (0.7-5.0)
1-2 years	5 (1.3)	19 (0.5)	2.7 (1.0-7.2)	2.5 (0.9-6.7)
3-4 years	8 (2.1)	57 (1.5)	1.5 (0.7-3.1)	1.4 (0.6-2.8)
≥5 years	21 (5.4)	141 (3.7)	1.6 (1.0-2.5)	1.5 (0.9-2.3)

IHD=ischemic heart disease (myocardial infarction, angina, and/or heart failure), UCEP=unexplained chest/epigastric pain

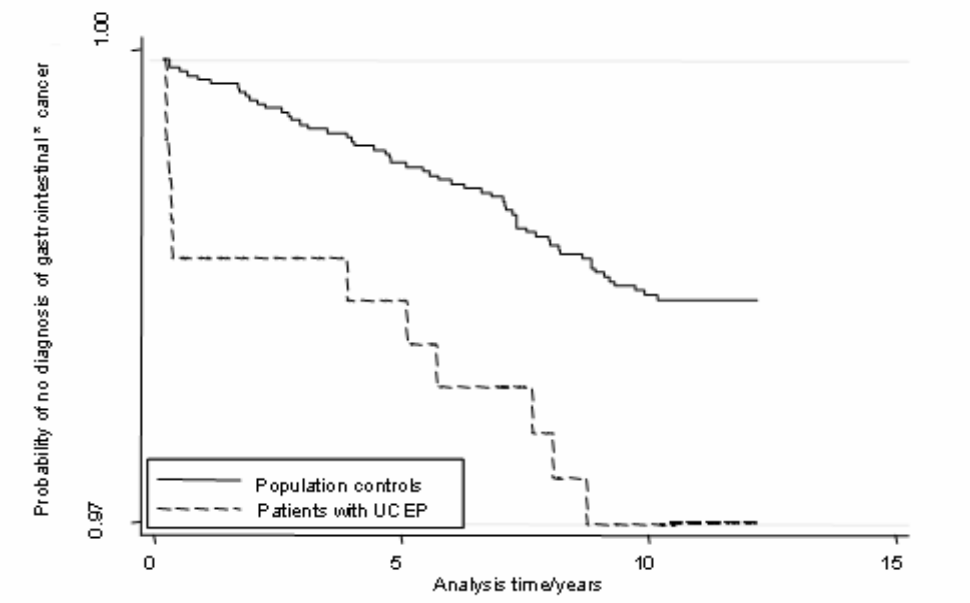
4.2 Study II. Risk of gastrointestinal cancers in UCEP patients

We identified 384 UCEP patients and 3,816 population controls for this study. At the time of inclusion all were free of a gastrointestinal cancer under study. UCEP patients were more likely than population controls to have an alcohol-use-related

discharge diagnosis (8.1% vs. 2.4%), but there was no substantial difference in smoking-related discharge diagnoses or in the distribution of the co-morbidity score.

Eleven UCEP patients and 56 population controls were diagnosed with a first-time gastrointestinal cancer during follow-up (none of the UCEP patients developed cancers of the esophagus, biliary tract, or small bowel). The most frequent gastrointestinal cancer among UCEP patients was colorectal cancer (six out of 11=54.5%). Two (18.2%) UCEP patients were diagnosed with liver cancer, two (18.2%) with pancreatic cancer and one (9.1%) with stomach cancer.
The Kaplan-Meier curve for UCEP patients and their population controls shows that the majority of cancers among UCEP patients were diagnosed within the first year after upper endoscopy, Figure 8.

Figure 8. Kaplan-Meier curves for probability of remaining free of gastrointestinal cancer (stomach, liver, colorectal and/or pancreatic) after the index date among UCEP patients (dotted line) and population controls (solid line).



UCEP=unexplained chest/epigastric pain, * stomach, liver, colorectal and/or pancreatic cancer

The 10-year cumulative incidence proportion (risk) of gastrointestinal cancer was 2.9% for UCEP patients vs. 1.5% for population controls. The crude relative risk was 2.0 (95% CI, 1.1-3.8), Table 8. The estimate remained unchanged after adjustment for alcohol- and smoking-related diseases and for co-morbidity.

Compared with population controls, the risk increase among UCEP patients was substantial within the first year after upper endoscopy and declined thereafter [the adjusted relative risks of gastrointestinal cancer for UCEP patients within < 1 year and ≥ 1 year after upper endoscopy were 8.4 (95% CI, 2.6-27.5) and 1.2 (95% CI, 0.5-2.9), Table 8].

Table 8. Crude and adjusted relative risks and 95% confidence intervals (CI) of a gastrointestinal cancer after upper endoscopy in UCEP patients compared with population controls - overall and by time to diagnosis

	UCEP patients (N=384), n (%)	**Controls** (N=3,816), n (%)	**Crude relative risk** (95% CI)	**Adjusted relative risk** (95% CI)
Overall gastrointestinal cancer	11 (2.9)	56 (1.5)	2.0 (1.1-3.8)	2.0 (1.0-3.8)
Time to diagnosis after upper endoscopy				
<1 year	5	6	8.3 (2.5-27.4)	8.4 (2.6-27.5)
≥1 year	6	50	1.2 (0.5-2.9)	1.2 (0.5-2.9)

UCEP=unexplained chest/epigastric pain

4.3 Study III. Risk of upper gastrointestinal diseases in UCEP patients

This study included four sub-studies and we identified:

i) 371 UCEP patients and 3,656 population controls in the peptic ulcer study,
ii) 383 UCEP patients and 3,822 population controls in the esophagitis study,
iii) 376 UCEP patients and 3,746 population controls in the pancreatitis study,
iv) 358 UCEP patients and 3,543 population controls in the gallstone study.

UCEP patients and population controls were all without a prior discharge diagnosis of the upper gastrointestinal disease in question (*e.g.* no subject in the peptic ulcer study had a prior discharge diagnosis of peptic ulcer).

Within each of the four sub-studies, UCEP patients were more likely, than controls, to be diagnosed with the disease of interest, Table 9. The most frequently diagnosed disease was gallstone (7.3% of the UCEP patients vs. 1.6% of the controls).

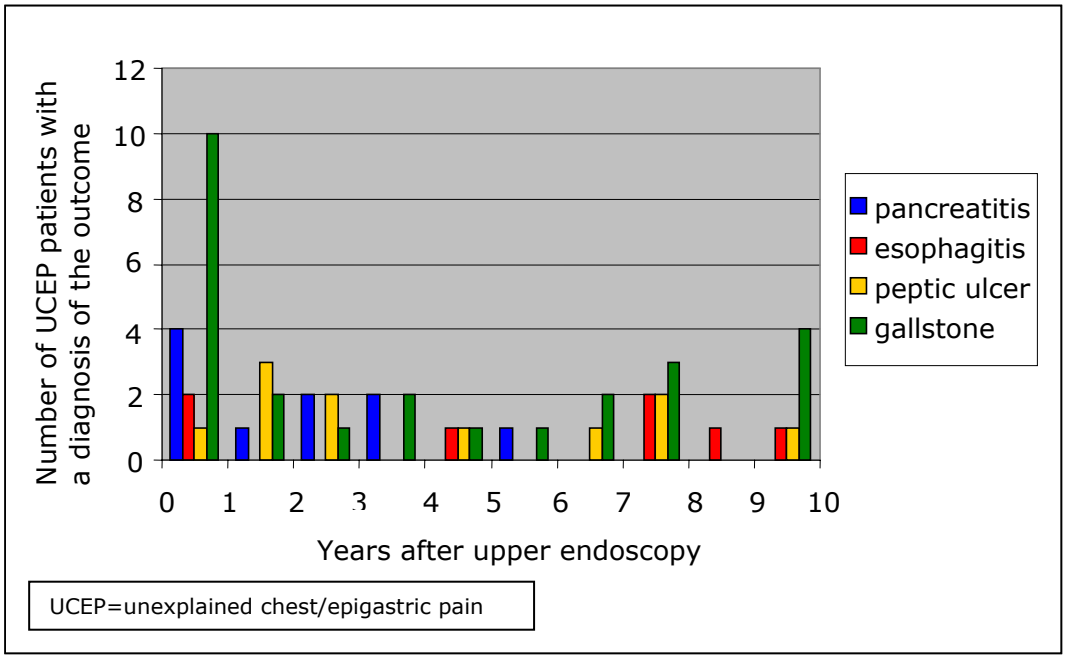
Table 9. Distribution of the UCEP patients and population controls according to a first-time discharge diagnosis of peptic ulcer, esophagitis, pancreatitis, or gallstone during 10 years after upper endoscopy

	UCEP patients Outcome/total (%)	**Population controls** Outcome/total (%)
Discharge diagnosis after index date		
Peptic ulcer	11/371 (3.0%)	55/3,656 (1.5%)
Esophagitis	7/383 (1.8%)	24/3,822 (0.6%)
Pancreatitis	10/376 (2.7%)	15/3,746 (0.4%)
Gallstone	26/358 (7.3%)	58/3,543 (1.6%)

UCEP=unexplained chest/epigastric pain

About 50% of the hospitalizations for peptic ulcer, pancreatitis, or gallstone occurred within 1-2 years after the upper endoscopy, whereas about 50% of the hospitalizations for esophagitis occurred within 5 years after upper endoscopy, Figure 9.

Figure 9. Numbers of first-time discharge diagnoses of peptic ulcer, esophagitis, pancreatitis, or gallstone among UCEP patients against time after upper endoscopy



The 10-year cumulative risks of hospitalization for peptic ulcer, esophagitis, pancreatitis, or gallstone among UCEP patients were, respectively, 3.0%, 1.8%, 2.7%, and 7.3%, vs. 1.5%, 0.6%, 0.4%, and 1.6%, among population controls. The adjusted relative risks of hospitalization for peptic ulcer, esophagitis, pancreatitis, or gallstone were 1.7 (95% CI, 0.9-3.4), 2.4 (95% CI, 1.0-5.6), 5.0 (95% CI, 2.2-11.4), and 4.6 (95% CI, 2.9-7.4), respectively, Table 10. Relative risks of all outcomes among the UCEP patients compared with population controls were the highest within the first year following the upper endoscopy [adjusted relative risks of hospitalization for peptic ulcer, esophagitis, pancreatitis, or gallstone were 2.0 (95% CI, 0.2-18.4), 8.2 (95% CI, 1.2-59.2), 9.2 (95% CI, 2.0-41.8), and 14.1 (95% CI, 5.4-37.2), respectively]. Beyond the first year after the upper endoscopy, the adjusted relative risks of hospitalization for pancreatitis and gallstone remained high [3.9 (95% CI, 1.4-10.5) and 3.3 (95% CI, 1.9-5.8), Table 10].

Table 10. Crude and adjusted relative risks of hospitalization for peptic ulcer, esophagitis, pancreatitis, or gallstone in UCEP patients compared with population controls - overall and by the time of the first diagnosis of the outcome under study after upper endoscopy

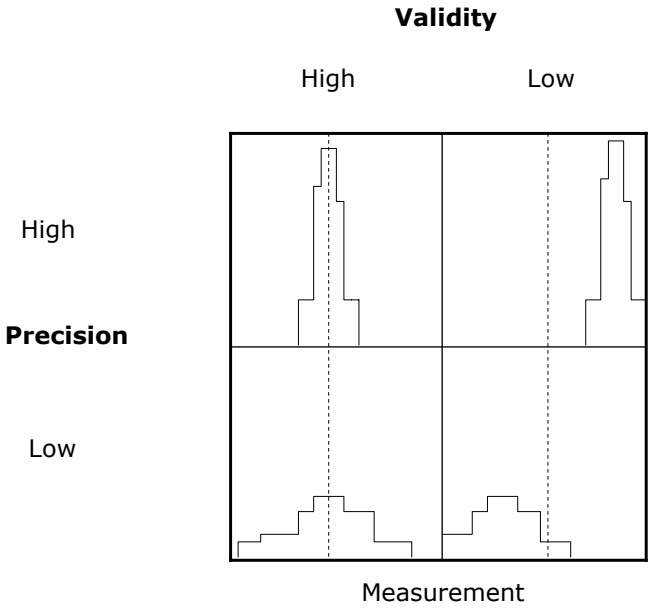
	Crude relative risk, (95% CI)	**Adjusted relative risk**, (95% CI)	**Adjusted relative risk**, By time after upper endoscopy, (95% CI)	
			<1 year	≥1 year
Study outcome				
Peptic ulcer	2.1 (1.1-4.0)	1.7 (0.9-3.4)	2.0 (0.2-18.4)	1.7 (0.9-3.4)
Esophagitis	3.0 (1.3-7.0)	2.4 (1.0- 5.6)	8.2 (1.2-59.2)	1.9 (0.7-5.0)
Pancreatitis	6.9 (3.1-15.4)	5.0 (2.2-11.4)	9.2 (2.0-41.8)	3.9 (1.4-10.5)
Gallstone	4.7 (3.0-7.5)	4.6 (2.9-7.4)	14.1 (5.4-37.2)	3.3 (1.9-5.8)

UCEP=unexplained chest/epigastric pain

5.0 Methodological considerations of the studies in the thesis

When interpreting our study findings, we have to consider factors affecting the validity and precision of our results. The validity is threatened by systematic errors, which arise from bias: selection bias, information bias (misclassification), and confounding. The precision is decreased by random errors, stemming from the unexplained variation in data. Figure 11 shows the correlation between validity (lack of systematic error) and precision (lack of random error). In every study the aim is to obtain high validity and high precision.

Figure 11. Validity and precision (dotted line is the true value) from Fletcher 'Clinical Epidemiology: *The Essentials*' [52]



In the following, we discuss the data quality in the studies I-III in this thesis in relation to such possible errors.

5.1 Selection bias

Selection bias arises if the association between exposure and outcome in study participants and non-participants differs. Selection bias results from selection procedures or factors influencing study participation [52;67]. In cohort studies, selection bias may be caused either by lack of inclusion into the cohort or by loss to follow-up. Thus, in our studies, we have to consider these two possibilities of selection bias.

Bias introduced by loss to follow-up is absent from our studies due to the high degree of completeness of the data in the Civil Registration System, which allows complete follow-up on all members of the study population.

Considering the UCEP patients in our studies, selection into the cohort depended on having a normal upper endoscopy and, thereby, on the indication for the procedure. Patients referred for upper endoscopy may have had more severe symptoms and therefore potentially a higher risk of the studied outcomes than UCEP patients not referred for endoscopy. If so, we might have overestimated the true relative risk. On the other hand, it may be argued that because of an increased general interest UCEP patients, on the part of general practitioners and other treating physicians, most UCEP patients, and not only those with the most severe symptoms, are referred for endoscopy. If the group of patients referred for endoscopy in our study is a selected group of UCEP patients for whom special early preventive initiatives are undertaken, then the risks of the outcomes among them may underestimate the risks among UCEP patients who are not referred to endoscopy. Several outcomes in this thesis were defined by hospital discharge diagnoses. Thus, if the included UCEP patients were less frequently hospitalized than UCEP patients who were not included – for example, due to heightened diagnostic effort and early treatment made solely by the general practitioner – then the discharge-diagnoses-based risk estimates would underestimate the true risks.

5.2 Misclassification

Misclassification arises from errors in data collection. Misclassification can occur in measurement of the exposure (UCEP), the outcome, or the confounders [52;67]. If rates of misclassification error differ between the comparison cohorts, bias may result.

Misclassification of the exposure (UCEP)

The UCEP patients in our study were defined as patients with first-time, normal upper endoscopy, chest/epigastric pain as a sole symptom, and no prior diagnosis of IHD. Misclassification of the UCEP status could arise due to incorrect registration of the incident upper endoscopy or through errors in the paper medical records. The information on incident upper endoscopies was obtained from the PAS and therefore depended on the quality of data in that data source.

The validity of the data in the PAS is high, implying that such misclassification was unlikely [94]. Though data from the paper records were transferred into a research database by a single physician, misclassification of UCEP cannot be ruled out, either due to errors in the symptoms' description, erroneous interpretation of the symptoms by the recording physician, or by incorrect diagnosis of the upper endoscopy. Furthermore, we intended to exclude patients with GERD or IHD from the UCEP cohort, but a normal upper endoscopy without description of reflux-like symptoms may not completely rule out GERD. Likewise, absence of a prior discharge diagnosis of IHD may not completely exclude underlying IHD. If a proportion of the selected patients actually had IHD or GERD, and not UCEP, and if IHD or GERD were more likely to be associated with the outcomes under study than UCEP, such misclassification would lead to overestimation of risks in our studies. Patients with IHD or GERD may have a higher risk of death and hospitalization for IHD, esophagitis and peptic ulcer than UCEP patients [95;96] – though only in theory, because the risks of these outcomes in patients with IHD or GERD as compared with UCEP patients, is unknown. Nevertheless, we believe that few of the patients in our UCEP cohort were potentially misclassified with IHD or GERD and therefore any associated overestimation of the relative risks is probably minor.

Misclassification within the control cohort could also occur if some population controls had undetected UCEP. This is a possibility, if the prevalence of UCEP in the Danish background population is truly as high as is suggested in other populations [2;3;64]. If there is a positive association between UCEP and the outcomes studied, such misclassification of controls would result in underestimation of relative risks in our studies.

Misclassification of the outcome

The outcomes in our studies are defined through discharge diagnoses, cancer-registry-derived diagnoses and information obtained from death certificates. The quality of most outcome variables from these data sources is high, and any misclassification is most likely non-differential, which would be expected to reduce in the strength of the estimated UCEP–outcome(s) association (bias towards the null value).

Differential misclassification could occur if the likelihood of being diagnosed correctly with an outcome of interest differed between UCEP patients and controls. Thus, relative risks of the UCEP patients could be overestimated if, for instance, they were more likely than controls to be diagnosed with the diseases

under study because of their increased health-care seeking behavior [2;59;64]. Such increased health-care seeking behavior, however, is only known among patients with NCCP or FGIDs – and has not been reported in patients with UCEP.
On the other hand, relative risks among UCEP patients could be underestimated if they were hospitalized less often than the population controls due to heightened diagnostic effort and early outpatient treatment undertaken by the general practitioners. Such scenario is, however, purely theoretical.

In study I, we examined risks of death and IHD among UCEP patients as compared with population controls. Data on mortality were obtained from the Civil Registration System and the Danish Causes of Deaths Registry, both of which are 100% complete with respect to the information regarding the fact of death [80]. However, the quality of data on causes of deaths recorded on death certificates is low, with positive predictive value in the 57-81% range [97]. IHD was ascertained from the HDR, and the reported positive predictive value of heart-related diagnoses in this registry is about 75% overall [94] and 80% for myocardial infarction [98], while the validity of angina and heart failure discharge diagnoses has not been examined.
IHD is a serious disease often leading to hospitalization (by admission to a hospital either directly or through out-patient clinics), and probably only a minority of patients are diagnosed and treated exclusively by a general practitioner or a cardiologist in private practice. Therefore, it is likely that nearly all UCEP patients and controls with subsequent IHD are included in our study.

In study II, we examined the outcome of gastrointestinal cancer. Cancer diagnoses were ascertained from the Cancer Registry, and its overall reported completeness is 95-98% [79]. Specific positive predictive values for cancers of stomach, colon, rectum, liver, or pancreas have not been reported. Given the mandatory registration of cancers, diagnosed both in- and outpatient, essentially all cancers among UCEP patients and controls are likely to be captured in our study.

In study III, we studied the outcome of gastrointestinal diseases. Reported positive predictive values of gastrointestinal site-specific discharge diagnoses in the HDR are generally high [94], *e.g.,* 82% for acute pancreatitis [74] and 94% for gallstone treatment [99]. Positive predictive values for peptic ulcer and esophagitis have not been examined. Unlike patients with IHD, some patients with peptic

ulcer, esophagitis, pancreatitis, or gallstone might not reach hospitalization. Some patients may be diagnosed with these less severe diseases by their general practitioner – or not diagnosed at all. However, there is no reason to believe that hospitalization rates for these conditions differ between UCEP patients and controls, implying that any such misclassification is likely to be non-differential.

Misclassification of confounding factors is discussed below.

5.3 Confounding

Despite our ability to adjust the analyses for co-morbidity, including alcohol- and smoking-related diseases, the relative risk estimates could remain contaminated by residual (stemming from misclassification or inaccurate categorization of a confounder variable) of unmeasured confounding [52;67].

To adjust for co-morbidity, we used the Charlson Comorbidity Index [84]. The Charlson index was originally developed to predict the risk of death from co-morbid diseases. The index has been adapted and widely used with hospital discharge registry data based on ICD-codes. The index has high specificity, but sometimes a worse sensitivity than diagnoses abstracted from medical records [100]. The Charlson index is based on discharge diagnoses and, theoretically, it is possible that the co-morbid diseases were coded differently in UCEP patients and in population controls. Such misclassification of co-morbidity, which may lead to residual confounding, could arise if UCEP patients were more thoroughly examined for diseases - including co-morbid diagnoses, or if patients with a co-morbid diagnosis were more likely to be diagnosed with UCEP (Berkson's bias [101]).

In order to control for alcohol abuse and smoking we used discharge diagnoses of alcohol- and smoking-related diseases as proxy measurements. Using administrative data as a proxy for smoking were considered appropriate due to the high positive predictive value of 90%, which is reported for smoking-related discharge diagnoses in a recent Danish study (not yet published). The validity of discharge diagnosis of alcohol abuse is more uncertain, though, no positive predictive value has been calculated [102]. Misclassification of alcohol abuse and smoking by the proxy measures could lead to residual confounding by these variables.

In none of the three studies did we find evidence of strong confounding by co-morbidity or alcohol- and smoking-related diseases, suggesting that any residual confounding is probably minor.

Unmeasured confounding may have influenced our relative risk estimates. Some of the potential confounding variables are discussed below.

Socioeconomic status

Low socioeconomic status has been reported as a risk factor of death [103], IHD [104;105], gastrointestinal cancer (positive association for pancreas, liver, and stomach cancer, but inverse association for colon cancer [106]), and other gastrointestinal diseases (positive association for peptic ulcer [107] and gallstone [89], but inverse association for esophagitis [108]). There are reports of low socioeconomic status being associated with functional dyspepsia; therefore, theoretically, it could also be associated with UCEP [64;109]. If UCEP patients in studies I-III were more likely to have lower socioeconomic status than controls, and if low socioeconomic status is positively associated with an outcome, then inability to adjust for socioeconomic status may have lead to overestimation of the effect of UCEP on death, IHD, gastrointestinal cancer, peptic ulcer, esophagitis and gallstone. At the same time, the association between UCEP and low socioeconomic status is hypothetical, and therefore, we do not expect important confounding by socioeconomic status.

Helicobacter pylori

H. pylori infection may be a risk factor for stomach cancer [87] and peptic ulcer [110], but may be also associated with functional dyspepsia and therefore, theoretically, with UCEP [111-113]. If UCEP patients in studies II and III were more likely to be *H. pylori*-positive than controls, then the magnitude of the observed association of UCEP with gastrointestinal cancer (study II) and peptic ulcer (study III) may partially reflect confounding by *H. pylori* infection. In study II we were unable to conduct separate analyses on each type of gastrointestinal cancer because of the low number of events during the follow-up. Thus, even if we had data on *H. pylori* infection, adjustment for it would be irrelevant in that study. If UCEP patients in study III were more likely to have an *H. pylori* infection than controls and if such infection is positively associated with the outcome, then not adjusting for *H. pylori* infection could result in overestimation of the effect of UCEP on peptic ulcer. Still, an association between UCEP and *H. pylori* is hypothetical, and

therefore, we expect any confounding by this infection to have only minor influence (study II and III).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Use of NSAIDs is a risk factor for IHD [114], peptic ulcer [115], esophagitis [115;116] and pancreatitis [117], but may protect against colon cancer [87]. Evidence of an association between UCEP-related symptoms and NSAIDs use is sparse and conflicting [55;56;118]. Differences in the use of NSAIDs in UCEP patients and controls could confound the estimates of the relative risks of IHD (study I), colon cancer (study II), peptic ulcer, esophagitis, and pancreatitis (study III), with the direction of the bias due to confounding depending on the outcome of interest. However, as an association between NSAIDs and UCEP is mainly speculative, we do not expect an important confounding by NSAIDs.

5.4 Precision
The width of the 95% CI is a measure of statistical precision of the relative risk estimates. The statistical precision of an estimate depends mainly on the study size [76]. Despite our studies being among the largest reported in the literature on this topic, the CIs for some of our relative risk estimates were rather wide – indicating merely modest statistical precision. This applies, in particular, to the estimates derived from analyses based on few outcome events (study I-III), cause-specific deaths (study I), and for risk of pancreatitis and gallstone (study III). Suboptimal precision of these estimates complicates their interpretation.

6.0 Discussion in the context of the existing literature

In the following the results of the three studies in this thesis will be discussed in the context of the existing literature.

6.1 UCEP and all-cause and cause-specific mortality

We were able to identify four cohort studies that examined mortality in patients with UCEP-related symptoms in comparison with the general population [12-15]. In addition, a number of case series [4;27;29;30;36] and cohort studies using IHD controls [6;14;26;28;32;34;35] have examined mortality in patients with UCEP-related symptoms.

All-cause mortality

Sekhri *et al.,* in a hospital-based cohort study, in 2006, in England showed no increased all-cause mortality in 6,396 patients with chest pain and no suspicion of IHD (NCCP) during four years of follow-up, compared with the background population [SMR in males=0.85 (95% CI, 0.68-1.02) and in females=0.80 (95% CI, 0.61-0.98)] [14]. In contrast to our study, the NCCP patients were not examined by upper endoscopy, suggesting that a proportion of them may not have had truly 'unexplained' chest pain, but instead had pain caused by diseases in the gastroenterological tract (mainly peptic ulcer and esophagitis [37]). Furthermore, the observation period of four years is relatively short for measuring mortality. Our study likewise showed no increased all-cause mortality in UCEP patients compared with population controls. However, we excluded patients with underlying upper gastrointestinal disease and estimated the risk of death during 10 years of follow-up. Thus, to some extent the findings reported by Sekhri and colleagues support our findings.

Our findings are also only partially in agreement with those by Lindell *et al.* from a Swedish hospital-based cohort study, in 1995. The authors reported similar 10-year survival in 165 patients with non-ulcer dyspepsia (FGID) and in the background population [survival 82% (95% CI, 77%-87%) and 85% (95% CI, 77%-87%), respectively] [13]. In this study, patients with abnormal upper endoscopies were excluded from the study population, but in contrast to our study, patients with epigastric discomfort, reflux-like symptoms, or other FGIDs (*e.g.* irritable bowel symptom) were not excluded. The study by Lindell and colleagues was hampered by a relatively small and very heterogeneously defined study population, whose subjects could have pain due to GERD and not 'unexplained' pain.

In another Swedish population-based cohort study, from 1998, Wilhelmsen *et al*. [15] reported an all-cause 16-year mortality of 44% among 441 patients with non-specified chest pain (NCCP) vs. 26% in asymptomatic population controls, yielding a two-fold increased risk in NCCP patients [relative risk 1.99 (95% CI, 1.71-2.31)]. These findings are not in line with ours, and there are several possible explanations of this discrepancy. First, Wilhelmsen and colleagues restricted their study to 51-59–year-old men. Such high age at study entry significantly increases the risk of death during the 16 following years – especially deaths from cancer and IHD, which was also shown in the study. Second, all NCCP patients had chest pain while exercising, which is a symptom of suspected angina [119]. Thus, a question arises whether underlying IHD was the true cause of chest pain in these patients, even though they were categorized as having NCCP. Such undiagnosed IHD among some of the NCCP patients was likely to increase the apparent risk of IHD deaths in the NCCP cohort. These limitations, along with the failure to exclude patients with underlying gastrointestinal diseases, complicate a direct comparison between our findings and those by Wilhelmsen *et al*.

In contrast to our study, Sekhri *et al.* [14], Lindell *et al.* [13], and Wilhelmsen *et al*. [15] were unable to control for confounding by co-morbidity, alcohol- or smoking-related diseases in the analyses. Thus, it is unclear to what extent such potential confounding factors might have influenced the relative risk estimates reported in these studies.

Cause-specific mortality

Apart from cardiac mortality, to the best of our knowledge, our study is the first to examine cause-specific mortality in UCEP patients in comparison with the general population.

Sekhri *et al.* found no increased cardiac mortality in NCCP patients compared with the background population during the four years of follow-up [SMRs of 0.92 (95% CI, 0.57-1.28) and 0.85 (95% CI, 0.37-1.32) in male and female NCCP patients, respectively] [14]. By contrast, Wilhelmsen *et al*. reported a nearly three-fold increase in cardiac mortality in NCCP patients compared with asymptomatic population controls during 16 years of follow-up (restricted to men aged 51-59) [15]. However, limitations of these two studies hinder a comparison of their findings

with ours. First, neither study excluded patients with underlying gastrointestinal diseases. Furthermore, the study by Sekhri *et al.* was limited by a short follow-up period [14], and as mentioned above, the study by Wilhelmsen *et al*. was limited by the subjects' advanced age at study entry and by incomplete exclusion of patients with underlying IHD from the cohort of NCCP patients [15].

Lampe *et al.,* in a population-based cohort study in England (restricted to men aged 40-59), from 1998, examined the 15-year risk of a major cardiovascular event (a combined outcome of fatal and non-fatal myocardial infarction or sudden cardiac death) among 1,849 patients with NCCP, compared with asymptomatic population controls [12]. A marginally increased risk in NCCP patients was found [relative risk 1.19 (95% CI, 1.01-1.40)]. This finding is in line with the cardiac MRR of 1.1 (95% CI, 0.5-2.2) found in our study. However, a direct comparison is not possible, primarily because non-fatal myocardial infarction was included in the outcome examined by Lampe *et al.* [12], but also because patients with upper gastrointestinal diseases were not excluded from the NCCP cohort.

An increased risk of death from alcohol dependence, pneumonia, and lung cancer among UCEP patients compared with population controls, found in our studies, have not been previously reported. With the exception of one UCEP patient, all pneumonia-related deaths occurred beyond 31 days following the index upper endoscopy. Pneumonia due to aspiration could be related to upper endoscopy only if it occurred shortly (often within the first week) after the procedure [120]. Therefore, the upper endoscopy itself is not a likely explanation of the increased risk of death from pneumonia among the UCEP patients. Underlying potential pathophysiological causes of these increased cause-specific deaths shown in our study are overall not obvious.

A number of case series [4;27;29;30;36] as well as cohort studies of NCCP patients (in comparison to IHD-affected controls) [6;14;26;28;32;34;35] have examined all-cause and cardiac mortality, but with substantial variation in reported findings (Table 2 and 3). However, as none of these studies excluded patients with upper gastrointestinal diseases from the NCCP cohort or used general population as control group, comparison of their results to ours is not meaningful.

6.2 UCEP and risk of IHD

We were able to identify one cohort study examining the risk of IHD in patients with UCEP-related symptoms as compared with asymptomatic population controls [12]. This study, by Lampe *et al.,* whose subjects were men aged 40-59 years, reported an incidence rate of a major cardiovascular event (fatal and non-fatal myocardial infarction and sudden cardiac death) of 8.6 cases per 1000 person-years among NCCP patients [12], which was only slightly greater than the corresponding incidence among asymptomatic population controls. Sekhri and colleagues reported a four-fold increased hazard of a similar combined outcome (cardiac death and/or acute coronary syndrome) in NCCP patients compared with IHD controls [14]. However, the outcome in the studies by Lampe *et al.* [12] and Sekhri *et al.* [14] was, in contrast to our study, a combination of disparate events, thus complicating comparison of the results of these studies to ours. In addition, neither of these studies ruled out underlying gastrointestinal diseases among the NCCP patients. Sekhri *et al*., moreover, had a short follow-up period and compared the risk among NCCP patients with that among IHD controls only [14].

A number of case series and cohort studies with IHD controls have reported findings on subsequent IHD (myocardial infarction [14;26;27;29;30;35;36], progression in CAG [31], or heart failure [26]) in NCCP patients. The reported cumulative incidence proportions varied from 0% [26;29;31] to 3.4% [27] during one [36] to 15 years [30] of follow-up (Table 2 and 3). However, these studies had limitations, the most important being failure to exclude patients with upper gastrointestinal diseases from the NCCP cohorts. In addition, none of the studies examined development of angina (which is the most common symptom of IHD [85]), or compared NCCP patients with population controls.

6.3 UCEP and risk of gastrointestinal cancer

To the best of our knowledge, our study was the first one to examine the risks of stomach, colorectal, liver, and/or pancreatic cancers in UCEP patients as compared with the corresponding risks in population controls.

Three cross-sectional population-based studies have suggested that GERD could be associated with NCCP [3;39;40]. GERD has also been reported as a risk factor for esophageal adenocarcinoma [121]. These findings suggest an increased risk of esophageal cancer in UCEP patients, although the association between endoscopy-negative GERD and the risk of adenocarcinoma of the esophagus is

not strong [122]. We did not observe any esophageal cancers among UCEP patients despite the 10 years of follow-up. This may be explained, above all, by the intentional exclusion of patients with possible GERD from the UCEP cohort. GERD is a well-defined gastrointestinal disease and it should be separated from UCEP, which is why we studied only patients with normal upper endoscopies and solely chest/epigastric pain.

Underlying potential pathophysiological causes of the apparently increased short-term risk of gastrointestinal cancer among UCEP patients in our study are not clear. The pain location in UCEP may relate to cancers of the stomach, liver, and pancreas but, intuitively, not to colorectal cancer. Anaemia is a common symptom of colorectal cancer, and upper endoscopy is often a part of the evaluation for unspecified iron deficiency anaemia or gastrointestinal bleeding [123]. However, anaemia or gastrointestinal bleeding were not among the indications for referral to upper endoscopy in the included UCEP patients, and is thus an unlikely cause of the colorectal cancers observed in our study.

6.4 UCEP and risk of upper gastrointestinal disease

We were able to identify one other study examining the risk of peptic ulcers among ulcer-free patients [13]. Otherwise, to the best of our knowledge, our study was the first one to examine the risks of esophagitis, pancreatitis, and gallstone in UCEP patients in comparison with population controls.

Regarding the risk of peptic ulcer in UCEP patients, our findings are in line with those by Lindell and colleagues, who observed four peptic ulcers (2%) during 10 years of follow-up in patients with non-ulcer dyspepsia – the same number as was expected in a matched population [13]. However, this study was, in contrast to ours, based on a smaller and less homogeneous study population, in which underlying GERD was not ruled out.

Esophagitis is described as a complication of GERD [124] and GERD has been linked with NCCP [3;39;40]. Therefore, esophagitis and NCCP might also be associated. However, the positive association between GERD and NCCP has only been shown in cross-sectional studies [3;39;40], while a positive association between UCEP and GERD has never been described. In contrast to the mentioned cross-sectional studies of NCCP patients, we deliberately excluded patients with GERD-suspected symptoms or abnormalities diagnosed by upper endoscopy from the UCEP cohort

at the study entry. Thereby we aimed to exclude known diseases of the upper gastrointestinal tract as causes of the chest/epigastric pain among our UCEP patients. We also examined the association between UCEP and the risk of upper gastrointestinal diseases (*e.g.* esophagitis) in a follow-up study, which, unlike a cross-sectional study, follows the chronological order of events.

7.0 Main conclusions

Study I. UCEP and all-cause mortality, cause-specific mortality, and risk of IHD

Mortality

Overall we offer reassuring results regarding the all-cause mortality among UCEP patients. During the 10 years of follow-up, we found that all-cause mortality among UCEP patients was not substantially higher than that among the population controls. We also found that the relative risk of death was the highest within the first years after upper endoscopy, a result that could be explained by the presence of underlying severe diseases undiagnosed at the time of upper endoscopy but acting to increase the risk of death shortly after the procedure. Furthermore, our findings may reflect an increased relative risk of death from alcohol dependence, pneumonia, and lung cancer, but we detected no increased IHD-related mortality among UCEP patients compared with population controls. However, because we have little data on cause-specific mortality, it is uncertain whether factors underlying the apparent associations are causal, or are due to unmeasured confounding or chance. Our findings need to be reproduced by additional studies, as well as by studies investigating the pathophysiological mechanisms behind these putative associations, especially concerning the cause-specific deaths.

Risk of IHD

We found that UCEP patients have an increased short-term risk of IHD compared with population controls, indicating that UCEP could be a symptom of IHD undiagnosed at the time of upper endoscopy. The long-term risk of IHD in UCEP patients was likewise increased, suggesting that UCEP could be an early marker of IHD. Our findings may not be unexpected given the location of the pain but their importance lies in emphasizing the importance of continued surveillance of UCEP patients for development of IHD, especially angina and heart failure.

Study II. UCEP and risk of gastrointestinal cancer

We found that, compared with the population controls, the UCEP patients have an increased risk of stomach, colorectal, liver, and/or pancreatic cancer in the first year following upper endoscopy. The most frequently observed cancers were tumors in the colon and in the rectum. The increase in their short-term risk may

indicate that early UCEP symptoms could reflect gastrointestinal cancer. Such information may have important clinical implications for UCEP patients, in whom thorough early investigations for stomach, colorectal, liver, and pancreas cancers should be considered. The main limitation of study II was low statistical precision of its estimates, resulting from observing few events during the follow-up; time-stratified estimates were particularly imprecise. Small number of cancer events likewise did not allow for a meaningful tumor-specific analysis. Thus, larger studies are desirable to confirm our findings and to allow for stratified analyses according to the type of cancer. Investigation of the pathophysiological mechanism behind chest and epigastric pain as potential symptoms of stomach, liver, pancreas, and, especially, colorectal cancer also need to be addressed in future studies.

Study III. UCEP and risk of upper gastrointestinal disease

We found that, compared with the population controls, the UCEP patients have an increased short-term risk of peptic ulcer, esophagitis, pancreatitis, or gallstone. This may indicate that the pain could be a symptom of these diseases, undiagnosed at the time of upper endoscopy. More importantly, the risk of pancreatitis and gallstone remained increased more than one year after upper endoscopy. Thus, UCEP might either itself predict pancreatitis or gallstone, or be a prolonged marker of these diseases. Such knowledge is important when dealing with UCEP patients in clinical practice, and our results suggest that UCEP patients ought to be monitored carefully early in the diagnostic process for peptic ulcer, esophagitis, pancreatitis and gallstone. Moreover, continued surveillance for the development of pancreatitis and gallstone among these patients may be required, even on a long-term basis. The main limitation in study III was low statistical precision of the estimates, especially of those stratified by time. Hence, larger studies are necessary to verify our findings.

8.0 Perspectives

In this thesis we focused on a symptom that commonly occurs in the general population. Studies of UCEP patients are absent from the literature, even though UCEP is a frequent clinical problem deserving attention. With our studies we showed that population-based and hospital-based registries are valuable data sources for studying UCEP, owing to their near-universal coverage and the possibility of longitudinal design through data linkage. Still, not all hypotheses involving UCEP patients may be suitable for testing in such routinely recorded data; in particular, experimental and laboratory studies are also needed – especially to improve the understanding of the pathophysiology of UCEP.

Despite the availability of large administrative databases allowing longitudinal design and complete follow-up, our studies were hampered by a relatively low number of UCEP patients. A larger study sample of UCEP patients, with more outcome events, would produce more precise estimates and allow further stratified analyses. In the future, we will extend our research database to include more UCEP patients. This will require careful review and abstracting information from a very large number of endoscopy records. Such upper endoscopy records could be identified either in the Aarhus University Hospital Endoscopy Registry (by expanding the inclusion period) or by manual search in hospital medical files after linkage to the HDR, which holds information on all procedures performed. Electronic medical records are increasingly implemented in the Danish hospital system, with the ultimate goal of phasing out all paper medical records. Thus, in time it will be possible to access endoscopy records electronically. Furthermore, it would likely be possible to establish international collaborations by linkage of electronic information between countries.

In this thesis we studied the prognosis of UCEP by examining the risk of selected serious outcomes in comparison with the corresponding risks in the background population. As UCEP patients are a newly defined population, several other important prognostic outcomes in these patients are unknown and need attention in the future. For example, information of medication use is important and can be obtained by linkage of the data from this study population to the nationwide Pharmacoepidemiological Prescription Database. We were unable to examine medication use in the present studies because data on drug use are available for our study population only starting from 1995 (our study subjects were identified

in 1992 and 1993). In the future such studies of drug use either as outcomes (*e.g.* anxiolytics, sedatives, hypnotics, and neuroleptics) or as risk factors (*e.g.* NSAIDs or paracetamol) in UCEP patients, in comparison with the background population, would be of major interest.

Another very interesting hypothesis worth examining is whether UCEP is associated with psychiatric outcomes, mainly depression. Information on psychiatric outcomes is available through linkage to the population-based Danish Psychiatric Central Register.

Based on our findings, we conclude that UCEP patients may have a long-term increased risk of IHD, pancreatitis, or gallstone. Therefore, in the future studies it will also be important to identify potential prognostic factors (*e.g.* drug use, age, gender) associated with these outcomes.

Prognosis of UCEP patients in comparison with population controls is important, but comparing their prognosis with that of patients with defined gastrointestinal diseases is also of major interest. The routinely recorded data from the Aarhus University Hospital Endoscopy Registry contains detailed information on *all* patients who underwent an upper endoscopy at this hospital. Thus, it is possible to study the prognostic outcomes in UCEP patients as compared, for example, with patients who have esophagitis, peptic ulcer, or GERD. Such studies would improve the understanding of the natural history of UCEP and help clarify the severity of the symptom in relation to well-known gastrointestinal diseases.

9.0 Summary

Unexplained chest and epigastric pain (UCEP) is a common symptom, reported to affect up to one-third of the general population. Knowledge regarding prognosis of patients with UCEP-related symptoms is sparse, although it has been suggested that these patients may suffer from chronic pain, reduced quality of life and may engage in increased health-care seeking behavior, especially in the primary sector. Mortality, risk of ischemic heart disease (IHD, including myocardial infarction, angina, and heart failure), risk of gastrointestinal cancer and upper gastrointestinal diseases among these patients are essentially unknown.

This thesis is based on three historical cohort studies of UCEP patients thoroughly selected by searching 7272 upper endoscopy records from the Aarhus University Hospital Endoscopy Registry. Data from these records were recorded into a research database and linked to the Hospital Discharge Registry (HDR), the Cancer Registry, the Danish Causes of Death Registry, and the Civil Registration System. Patients with chest and/or epigastric pain as a sole symptom, first-time, normal upper endoscopy, and without a prior discharge diagnosis of IHD were defined as having UCEP. For each UCEP patient, ten controls, matched on age, gender, and county of residence, were selected from the Civil Registration System. Information on outcomes (death and diseases) and potential confounders (co-morbidity, alcohol- and smoking-related diseases) were obtained from the HDR and the Cancer Registry, based on discharge diagnoses coded according to the International Classification of Diseases (ICD), versions 7, 8 and 10.

We aimed to compare UCEP patients with population controls with respect to their short- and long-term risk of all-cause and cause-specific mortality (study I), risk of IHD (study I), risk of gastrointestinal cancer (stomach, liver, colorectal, and/or pancreatic cancer) (study II), and risk of upper gastrointestinal diseases (peptic ulcer, esophagitis, pancreatitis, or gallstone) (study III).

In study I, we found an all-cause MRR of 1.1 [95% CI, 0.9-1.5] in UCEP patients compared with population controls. The MRR was the highest within the first year after upper endoscopy [MRR=2.4 (95% CI, 1.3-4.5)]. The cause-specific MRRs were 1.1 (95% CI, 0.5-2.2) for IHD, 1.5 (95% CI, 0.3-8.2), for alcohol dependence, 2.7 (95% CI, 1.4-5.2) for pneumonia, and 1.7 (95% CI, 0.6-4.4) for

lung cancer. Furthermore, in study I the overall 10-year relative risk of IHD among UCEP patients was 1.6 (95% CI, 1.1-2.2); the highest increase in risk was within the first year after upper endoscopy, but the risk remained increased more than five years after the procedure [relative risk=1.5 (95% CI, 0.9-2.3)].
In study II, the overall relative risk of a gastrointestinal cancer (stomach, liver, colorectal, and/or pancreatic cancer) within the first year after upper endoscopy was 8.4 (95% CI, 2.6-27.5) among UCEP patients compared with the population controls. The relative risk declined to 1.2 (95%CI, 0.5-2.9) more than one year after the procedure.
In study III, within the first year after the upper endoscopy, the relative risks were 2.0 (95% CI, 0.2-18.4) for peptic ulcer, 8.2 (95% CI, 1.2-59.2) for esophagitis, 9.2 (95% CI, 2.0-41.8) for pancreatitis, and 14.1 (95% CI, 5.4-37.2) for gallstone, among UCEP patients compared with population controls. Thereafter the relative risks tended to decline, although the relative risks for pancreatitis and gallstone remained high [3.9 (95% CI, 1.4-10.5) and 3.3 (95% CI, 1.9-5.8), respectively].

We conclude that UCEP patients do not have substantially increased ten-year all-cause mortality; the IHD-related mortality is likewise not increased. However, increased risk of death from alcohol dependence, pneumonia, or lung cancer cannot be ruled out. Within the first year after upper endoscopy, the increased risk of death, and the increased risks of IHD, gastrointestinal cancer, peptic ulcer, esophagitis, pancreatitis, or gallstone may indicate undiagnosed underlying diseases causing chest/epigastric pain and prompting referral to upper endoscopy. Consequently, careful evaluation for these diseases early in the diagnostic process should be brought into focus. The increased long-term risk of IHD, pancreatitis and gallstone, could reflect a genuinely increased risk potentially implying that UCEP patients might need prolonged surveillance for subsequent development of these diseases.

10.0 Danish summary

Uforklarlige bryst- og epigastrie-smerter (unexplained chest/epigastric pain, UCEP) er et hyppigt forekommende symptom i baggrundsbefolkningen og beskrevet i litteraturen med en prævalens på op til 33%. Kroniske smerter og forringet livskvalitet er kendetegnende for patienter med UCEP-relaterede symptomer, hvorfor gentagen kontakt til sundhedsvæsenet er karakteristik, specielt med betydeligt ressourceforbrug i primærsektoren. Prognosen for disse patienter mht. død, årsagsspecifik død, iskæmisk hjertesygdom, cancer i mave-tarmkanalen og mavetarmlidelser er stort set ukendt.

Denne afhandling tager udgangspunkt i tre historiske kohorte studier baseret på identifikation af UCEP patienter, udvalgt efter nøje manuel gennemgang af 7272 endoskopi journaler fra Aarhus Universitetshospitals Endoskopiregister. Data fra disse endoskopi journaler er indtastet i en forskningsdatabase, som via CPR-numre efterfølgende er koblet til Landspatientregistret for Århus Amt (LPR), Cancerregistret, Dødsårsagsregistret og CPR registret. Vi definerede UCEP patienter som patienter med udelukkende bryst- og/eller epigastrie-smerter, førstegangs normal øvre endoskopi og ingen tidligere udskrivelsesdiagnose med iskæmisk hjertesygdom (myokardieinfarkt, angina og/eller hjertesvigt). For hver UCEP patient blev 10 kontroller (matchet på køn, alder og bopæls amt) tilfældigt udvalgt fra CPR-registret. Data svarende til de undersøgte outcomes (død og udvalgte sygdomme) og potentielle confoundere (co-morbiditet, alkohol- og ryge-relaterede lidelser) blev identificeret i LPR og Cancerregistret på baggrund af de internationale klassifikations diagnosekoder (ICD 7, 8 og 10).

De udvalgte outcomes blev undersøgt blandt UCEP patienter og sammenlignet med kontroller fra baggrundsbefolkningen. Vi estimerede i) kort- og langtidsrisiko for død og årsagsspecifik død (studie I), ii) kort- og langtidsrisiko for udviklingen af iskæmisk hjertesygdom (studie I), iii) risikoen for gastrointestinal cancer (ventrikel, lever, colorectal og/eller pancreas cancer) i forskellige tidsperioder (studie II), og iv) risikoen for øvre mave-tarm sygdomme (peptisk ulcus, esofagitis, pancreatitis og galdesten) i forskellige tidsperioder (studie III).
I studie I fandt vi en total mortalitets rate ratio (MRR) på **1.1 (95% CI, 0.9-1.5)** efter 10 års opfølgning blandt UCEP patienter sammenlignet med kontroller, hvor MRR var højest indenfor det første år efter øvre endoskopi (MRR=**2.4 (95% CI, 1.3-4.5**)). Svarende til årsagsspecifik død viste studiet en relativ overdødelighed

på 1.1 (95% CI, 0.5-2.2) for død af iskæmisk hjertesygdom, **1.5 (95% CI, 0.3-8.2)** for død af alkoholafhængigheds syndrom, **2.7 (95% CI, 1.4-5.2)** for død af lungebetændelse og **1.7 (95% CI, 0.6-4.4)** for død af lungecancer. Studiet viste også en relativ risiko for iskæmisk hjertesygdom blandt UCEP patienter på **1.6 (95% CI, 1.1-2.2)** efter 10 års opfølgning – denne risiko var højest indenfor det første år efter øvre endoskopi, men forblev høj mere end 5 år efter tidspunktet for endoskopien (relativ risiko=**1.5 (95% CI, 0.9-2.3)**).
I studie II fandt vi en samlet relative risiko for ventrikel, lever, pancreas og/eller colorectal cancer blandt UCEP patienter på 8.4 (95% CI, 2.6-27.5) indenfor det første år efter øvre endoskopi; en risiko som faldt til 1.2 (95%CI, 0.5-2.9) i den periode, som lå mere end 1 år efter endoskopien.
I studie III fandt vi blandt UCEP patienter, indenfor det første år efter øvre endoskopi, en relativ risiko for peptisk ulcus på 2.0 (95% CI, 0.2-18.4), for esofagitis 8.2 (95% CI, 1.2-59.2), for pancreatitis 9.2 (95% CI, 2.0-41.8) og for galdesten 14.1 (95% CI, 5.4-37.2). Mere end 1 år efter øvre endoskopi fandtes en vedvarende høj relativ risiko for pancreatitis og galdesten, henholdsvis 3.9 (95% CI, 1.4-10.5) og 3.3 (95% CI, 1.9-5.8).

Sammenfattende vurderes, at UCEP patienter, sammenlignet med baggrundsbefolkningen, ikke har nogen betydende overdødelighed efter 10 års opfølgning. UCEP patienter har ingen betydende overdødelighed af iskæmisk hjertesygdom, men en overdødelighed af alkoholafhængigheds-syndrom, pneumoni og lungecancer kan der imod ikke udelukkes. Den påviste øgede relative risiko for død, iskæmisk hjertesygdom, mave-tarm cancer, peptisk ulcus, esofagitis, pancreatitis og galdesten indenfor det første år efter øvre endoskopi kan være et udtryk for endnu ikke diagnosticeret underliggende sygdom, hvor bryst- og epigastrie-smerterne har ført til undersøgelse i form af øvre endoskopi. Udredning for disse måske tilgrundliggende sygdomme tidligt i forløbet bør derfor tillægges stor betydning. Derimod kan den vedvarende øgede risiko for iskæmisk hjertesygdom, pancreatitis og galdesten mere end 1 år efter øvre endoskopi betyde, at der foreligger en reel overrisiko. UCEP patienter bør, som konsekvens heraf overvåges for mulig senere udvikling af iskæmisk hjertesygdom, pancreatitis eller galdesten.

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Appendix 1

Discharge diagnoses, cause-specific mortality diagnoses, and cancer diagnoses according to the International Classification of Diseases (ICD) codes obtained from the Hospital Discharge Registry, the Causes of Deaths Registry and the Cancer Registry

	The Hospital Discharge Registry	
Discharge diagnoses	**ICD-8**	**ICD-10**
Ischemic heart disease		
Myocardial infarction	410	I21-23
Angina	411.09, 411.99	I20
Heart failure	402.99, 403.99, 425.99, 427.09, 427.19	I13.0, I25.5, I42.0, I42.6-9, I50.0, I50.1, I50.9
Peptic ulcer	530.91, 530.98, 531-534, 531.00, 531.01, 531.08, 531.09, 532.09, 533.09, 534.09, 531.90, 531.92, 531.95, 532.90, 533.90, 534.90, 417-422	K22.1, K25-28, K25.1, K25.2, K25.5, K25.6, K26.1, K26.2, K26.5, K26.6, K27.1, K27.2, K27.5, K27.6, K28.1, K28.2, K28.5, K28.6, K25.0, K25.4, K26.0, K26.4, K27.0, K27.4, K28.0, K28.4, KJDA-F, H, W.
Esophagitis	530.90, 530.91, 530.98	K20.9, K21.0.
Pancreatitis	577.00-577.09, 577.10, 577.11, 577.19	K85.9, K86.0, K86.1.
Gallstone	574.00, 574.09	K80.1-8
Alcohol-related diseases	303.09, 303.19, 303.20, 303.28, 303.29, 303.90, 303.99, 979, 980, 570.0, 570.9, 571, 571.09, 571.10, 573.00, 573.01, 577.10	F10.0-9, K70.0-9, K71.1-2, K86.0-9, Z72.1, R78.0, T51
Chronic obstructive pulmonary disease (COPD)	(none represented)	J42.9, J43.9, J44.8, J44.9, I27.9
	The Causes of Deaths Registry	
Cause-specific mortality		
Pneumonia	486	J18.0, J18.9
Arteriosclerosis	412.9	I25.1, I70.9
Stroke	I61.9, I64.9, I69.4	(none represented)
Lung cancer	162.1	C34.9
Alcohol dependence	(none represented)	F10.2
Chronic obstructive pulmonary disease (COPD)	(none represented)	J42.9, J43.9, J44.8, J44.9, I27.9
	The Cancer Registry	
Cancer diagnoses	**ICD-7**	
Esophageal cancer	150	
Stomach cancer	151	
Small bowel cancer	152	
Colorectal cancer	153, 154	
Liver/biliary tract cancer	155.0, 155.1	
Pancreatic cancer	157	

Appendix 2

The Charlson Comorbidity Index according to discharge diagnoses according to International Classification of Diseases (ICD) codes obtained from the Hospital Discharge Registry

	The Hospital Discharge Registry	
Discharge diagnoses	**ICD-8**	**ICD-10**
Myocardial infarction	410	I21;I22;I23
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430-438	I60-I69; G45; G46
Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28
Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes type1 Diabetes type2	249.00; 249.06; 249.07; 249.09 250.00; 250.06; 250.07; 250.09	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9
Hemiplegia	344	G81; G82
Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes with end organ damage Type 1 Type 2	 249.01-249.05; 249.08 250.01-250.05; 250.08	 E10.2-E10.8 E11.2-E11.8
Any tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	195-198; 199	C76-C80
AIDS	079.83	B21-B24