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EPIDEMIOLOGICAL STUDIES ON DIVERTICULAR DISEASE OF THE COLON

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EPIDEMIOLOGICAL STUDIES ON DIVERTICULAR DISEASE OF THE COLON
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Objective: The aims of this thesis were to evaluate if there is an association between diverticular disease and colorectal cancer (Paper I), to assess any genetic contribution to the occurrence of diverticular disease (Paper II), determine how common hospitalization and surgery for diverticular disease are in measures of admission rates, incidence rates and lifetime risk (Paper II), and to estimate mortality in diverticulitis patients, needing hospital care (Paper IV).

Methods: Swedish national registries were cross-linked through individual personal identification numbers. Data on admissions for diverticular disease and diverticulitis were retrieved from the National Patient Register. In Paper I, 41,037 colon cancer cases, registered in the Swedish Cancer Registry, were compared to matched colon cancer-free controls in concern of preceding admission for diverticular disease. In Paper II, including 104,452 twins in the Swedish Twin Registry, diverticular disease admissions were compared between monozygotic and dizygotic twins. Admission rates, incidence rates and lifetime risk for hospital admission for diverticular disease and diverticular disease surgery were analyzed in 95,049 individuals with diverticular disease admissions in Paper III, by using data from the Total Population Register in estimating risk sets. Survival analyses were used when comparing mortality in 83,461 patients with a first admission for diverticulitis with matched disease-free individuals, in Paper IV.

Results: Within the first 6 months after admission due to diverticular disease, odds ratios of having a colon cancer were up to 31.49 (95% CI 19.00-52.21). After the first year, there was no association between diverticular disease and colon cancer (Paper I). Odds ratio for diverticular disease admission given that the co-twin was affected/not affected, was higher in monozygotic twins compared to same-sex dizygotic twins (7.15 [95% CI 4.82-10.61] vs. 3.20 [95% CI 2.21-4.63]). Heritability was estimated to 40% (Paper II). Incidence rates for diverticular disease admission were 47.4 (95% CI 47.1-47.4) and for diverticular disease surgery 8.4 (95% CI 8.2-8.5) per 100,000 person-years. Corresponding admission rates were 70.8 (95% CI 70.4-71.2) and 8.7 (95% CI 8.6-9.9). Following an increase 1990-1994, rates remained rather constant thereafter. The estimated remaining lifetime risk for diverticular disease admission at the age of 30 was 3.1% in men and 5.0% in women (Paper III). Diverticulitis patients had a four times higher mortality compared to disease-free individuals in short term; the first 100 days after initial admission, Hazard Ratio (HR) 4.44 (95% CI 4.26-4.63). Within this time, 11.4% of patients receiving surgical treatment died. Among all diverticulitis patients, long term mortality, from day 101 to five years, was increased 11% (HR 1.11, 95% CI 1.09-1.13).

Conclusions: Hospitalization for diverticular disease is not associated with colon cancer after one year. The first 12 months after initial hospitalization is however highly associated with colon cancer. Therefore, colon cancer should be excluded after a first episode of suspected diverticulitis, due to the risk of misdiagnosing colon cancer as diverticulitis. Genetic influence is of importance in diverticular disease occurrence. The continuous increase of diverticular disease hospitalizations found in other studies are not present in Sweden. Diverticulitis patients have a significantly reduced survival compared to disease-free individuals, both in short- and long term.

LIST OF SCIENTIFIC PAPERS

I. Diverticular disease and the risk of colon cancer - a population-based case-control study
II. The genetic influence on diverticular disease -a twin study.
III. Incidence and lifetime risk of hospitalization and surgery for diverticular disease - a nation-wide cohort study
IV. Mortality in patients hospitalized for diverticulitis in Sweden - a national population-based cohort study

CONTENTS

LIST OF ABBREVIATIONS

CI	Confidence Interval
CT	Computed Tomography
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
OR	Odds Ratio
SCAD	Segmented Colitis Associated with Diverticulitis
SUDD	Symptomatic Uncomplicated Diverticular Disease

1 BACKGROUND

1.1 HISTORY

Diverticula of the colon have been recognized for the last 300 years. In 1700, a French surgeon named Alexis Littre described a diverticulum at a post mortem examination (1). The herniation of colonic mucosa through the rest of the colonic wall was further described by three pathologists: Matthew Baillie, who was Kings George IIIs and Georges IVs physician, authored in 1793 *The Morbid Anatomy of Some of the Most Important Parts of the Human Body*, which is considered the first systematic study of pathology (2, 3); Jean Cruveilhier, most known for his contribution in describing the nervous system and particulary multiple sclerosis, wrote in his monumental book *Traité d'anatomie pathologique*, in 1849:

> We not infrequently find between the bands of longitudinal muscle fibers in the sigmoid a series of small, dark, pear-shaped tumours, which are formed by herniae of the mucous membrane through the gaps in the muscle coat (4).

Rudolf Virchow, famous also for being the first describing leukemia, embolism and thrombosis, described the inflamed diverticula as "chronic adhesive peritonitis" in 1854 (5).

Having been so far a curiosity among pathologists, Graser was the first to write a paper that caught the medical communities' interest. In 1899, he pointed out that diverticula were far from uncommon and that they could become life-threatening if inflamed (6). In the beginning of the 20th century, x-ray machines were rapidly getting popular and Carman was the first in 1915 to show diverticula with this new imaging technique (7). At this time, complications of diverticula such as perforation, abscess formation and fistula were known (8) but since colonic resection carried a 10 % mortality, treatment was kept conservative as long as possible (9). As advances in anesthesia, development of antibiotics and better supportive therapy followed, mortality of colon resection dropped to an acceptable level (9).

In the 1960's and 1970's, Neil S Painter argued that it was a deficiency disease of dietary fiber, after having compared the incidence in Western countries, where we eat less fiber, to the one in rural Africa and having estimated intra-luminal pressure in the colon. Diet of less fiber alters the role of segmentation of the colon, which has a function of transporting faeces. Stagnating faeces would cause higher intraluminal pressure and development of diverticula (10). This way of describing the pathogenesis has been established for the last decades but has been questioned the last few years.

1.2 ANATOMY AND PHYSIOLOGY OF THE COLON

The colon, with its length of 1-1.5 meters, is the longest part of the large intestine, which also involves caecum, appendix vermiformis, rectum and the anal canal. Its main functions are propulsion, storage and to absorb water and electrolytes. Sodium is actively transported from lumen to blood, with the accompanying osmotic absorption of water. There is normally also a net movement of potassium from blood into the lumen. As food enters from the caecum, most breakdown is already finished but some digestion is made from the many bacteria living there. By them, undigested polysaccharides (fiber) are metabolized to short-chain fatty acids, which are then absorbed (11). In this process flatus (gas) is formed. The colon secretes bicarbonate that neutralizes the short-chain fatty acids, and in this way stabilizing pH in lumen. The bacteria also produce small amounts of vitamin K that can be absorbed (11). About 1500 ml content enters the large intestine each day and it stays there for 12-24 hours. Most is absorbed and less than 200 grams remains in the stool.

As most walls of the entire gastrointestinal tract, the colon wall consists of four layers: 1) the innermost mucosa, comprising of an epithelium, lamina propria, and muscularis mucosae, 2) the submucosa, 3) the muscularis externa, consisting of inner circular and outer longitudinal layers and 4) the serosa (12). The internal surface of the colon is lined by simple columnar epithelium including goblets cells that secrete large amounts of lubricating mucus, and absorptive cells that resorbs water and electrolytes. Stem cells at the bases of the intestinal crypts replace the epithelial cells every week (12). Compared to the rest of the gastrointestinal tract, the lamina propria in the colon contains more lymphoid tissue, reflecting the extensive bacterial flora here (12). The teniae coli are thickenings of the longitudinal layer of the muscularis externa, formed as three longitudinal stripes spaced at intervals of the colon. Tension in these muscles cause the colon to pucker into sack-like haustra (12). Colon motility has been described as three different types of contractions; 1) rhythmic phasic contractions (RPC) in the circular smooth muscle, which occurs two times per hour, in order to mix food and propels the content slowly forward, 2) giant migration contractions (GMC) occurring three to four times a day, generally following a meal, in where a wave of intense contractions causes mass movement forward and 3) tonic contractions which aid RPC in its function (11, 13)

The proximal colon is supplied by the superior mesenteric vessels while the distal part is supplied by the inferior mesenteric vessels. Small branches, vasa recta, penetrate the circular muscle layer and continue in the submucosa. Arteries, veins and lymphatic vessels follow each other into the colon.

The innervation of the gastrointestinal tract is complex. The speed at which the colon operates is set by the balance between the sympathetic innervation (via superior mesenteric and celiac ganglia plexuses in proximal colon, and inferior mesenteric and hypogastric plexuses in distal colon, respectively) and the parasympathetic innervation (via the vagus nerve in proximal colon and pelvic splanchnic nerves in distal colon, respectively).

Within the colon wall, as well as the rest of the gastrointestinal tract, a large number of nerve cell bodies and nerve fibers constitute the enteric nervous system, divided into the myenteric nerve plexus between the circular and longitudinal muscle layers and submucosal nerve plexus within mucosa. The enteric nervous is connected to the central nervous system through both parasympathetic and sympathetic nerves (12).

1.3 DEFINITION AND CLASSIFICATION

Diverticulosis of the colon is defined as presence of diverticula, protrusions of mucosa through the muscular layers of the bowel wall (14), usually considered asymptomatic. *Diverticulitis* is defined as inflammation in and around diverticula. There is no international agreement on *diverticular disease* definition or classification (272) but the term diverticular disease is mostly used expressing a symptomatic state, excluding it from diverticulosis. Although, in some literature, especially American, diverticular disease is used as a general term for both diverticulosis and diverticulitis (14).

Several different classifications have been used describing the different variations with focus on clinical symptoms, imaging findings or operative findings. There is still no internationally used classification that covers all variations which has led to conflicting terminology in literature (15). The most important classifications are described below.

In this text, the term diverticular disease is used as a general term including all states of the disease, also asymptomatic diverticulosis. When excluding asymptomatic diverticulosis this will be declared.

Hinchey's classification (16) from 1978 was intended to stratify surgical procedures in the presence of perforated diverticulitis and is still used (Table 1). When computed tomography became more widely used, with ability to provide more information, Sher et al. modified the Hinchey's classification to distinguish between a pericolic abscess (stage 1), distant abscesses that might be possible to treat with percutaneous drainage (stage IIa), and complex abscesses associated with a possible fistula (stage IIb) (15, 17) (Table 1). Wasvary et al. published another modification of Hincheys classification in 1999. In this modification clinical mild disease was included (stage 0) and a difference was made between

confined pericolic inflammation or phlegmon (stage Ia) and a confined pericolic abscess (stage Ib) (15, 18) (Table 1). Kaiser defined later specific CT findings for this classification (15, 19) (Table1).

Table 1. Hinchey classifications and Kaiser radiological classification (16-19)

Hinchey classification		Modified Hinchey classification by Sher		Modified Hinchey classification by Wasvary		CT findings by Kaiser
				0	Mild clinical diverticulitis	Diverticula ± colonic wall thickening
I	Pericolic abscess or phlegmon	I	Pericolic abscess	Ia	Confined pericolic inflammation or phlegmon	Colonic wall thickening with pericolic soft tissue changes
				Ib	Pericolic or mesocolic abscess	Ia changes + pericolic or mesocolic abscess
II	Pelvic, intraabdominal, or retroperitoneal abscess	IIa	Distant abscess amenable to percutaneous drainage	II	Pelvic, distant intraabdominal, or retroperitoneal abscess	Ia changes + distant abscess (generally deep in the pelvis or interloop regions)
		IIb	Compex abscess associated with fistula			
III	Generalized purulent peritonitis	III	Generalized purulent peritonitis	III	Generalized purulent peritonitis	Free gas associated with localized or generalized ascites and possible peritoneal wall thickening
IV	Generalized fecal peritonitis	IV	Fecal peritonitis	IV	Generalized fecal peritonitis	Same findings as III

The European Association of Endoscopic Surgeons published a classification consensus statement in 1999, differentiating symptomatic uncomplicated disease, recurrent symptomatic disease and complicated disease with sub-classifications (Appendix Table A1) (15, 20).

In Germany, the most popular classification has been the one published by Hansen/Stock in 1998 (Appendix Table A2) (15, 21). It has been considered useful in clinical practice but has not won acceptance internationally (15). Another German classification is the one published by Siewert et al in 1995 which is similar in differentiating aspects of acute complicated diverticulitis (15, 22) (Appendix Table A2).

Neff et al suggested about the same time a simple classification that has been used widely (23). This classification has been modified too, adding a substage —Ia— localized pericolic pneumoperitoneum without abscess (24) (Table 2). Tursi et al introduced a simple clinical classification of uncomplicated and complicated diverticulitis in 2008, based on findings as inflammatory markers in blood, and imaging (25).

Table 2. Modified Neff Classification (24)

Stage	Findings
0	Uncomplicated diverticulitis. Diverticula, thickening of the wall, increased density of the pericolic fat .
I	Locally complicated diverticulitis
a	Localized pneumoperitoneum in the form of air bubbles
b	Abscess (< 4 cm)
II	Complicated diverticulitis with pelvic abscess. Abscess > 4 cm in pelvis
III	Complicated diverticulitis with distant abscess. Abscess in abdominal cavity (outside pelvis)
IV	Complicated diverticulitis with other distant complications. Abundant pneumoperitoneum and/or intra-abdominal free liquid

Another classification that is strictly based on CT-scan findings is the one from Ambrosetti, which is often used internationally (Table 3) (26).

Table 3. Ambrosetti classification (26)

Moderate diverticulitis	Localized sigmoid wall thickening (≥5 mm)
	Pericolic fat stranding
Severe diverticulitis	Abscess
	Extraluminal air
	Extraluminal contrast

In an attempt to combine the classifications above and also include post-inflammatory changes like fistulas or stenosis, Klarenbeek et al, from the Netherlands, published a sophisticated classification in 2012 differentiating between a) uncomplicated, b) chronic complicated and c) acute complicated disease. For each classification, clinical findings, radiological findings and treatment modalities are presented (Appendix Table A3) (15).

Since then, new German guidelines, accepted by the German Societies of Gastroenterology and of Visceral Surgery have been published, named Classification of Diverticular Disease (CDD). In this classification, one is not tied to a specific diagnostic preference and the definitions are not stated as severity stages, but as different types of the disease (27, 28) (Table 4). Gastrointestinal bleeding is included as well as the rather new term symptomatic uncomplicated diverticular disease (SUDD). Asymptomatic diverticulosis is included (type 0), but not stated as a disease.

Table 4. Classification of Diverticular Disease (CDD) (28)

Type	Definition	Symptoms
0	Asymptomatic diverticulosis	Random finding; asymptomatic; not a disease per se
1	Acute uncomplicated diverticulitis	
1a	Diverticulitis without peridiverticulitis	Symptoms attributable to diverticula; signs of inflammation (laboratory tests): optional; typical cross-sectional imaging
1b	Diverticulitis with phlegmonous peridiverticulitis	Signs of inflammation (laboratory tests): mandatory; cross-sectional imaging: phlegmonous diverticulitis
2	Acute complicated diverticulitis	Signs of inflammation (laboratory tests): mandatory; typical cross-sectional imaging
2a	Microabscess	Concealed perforation, small abscess (≤1 cm); minimal

Type	Definition	Symptoms
		paracolic air
2b	Macroabscess	Paracolic or mesocolic abscess (>1 cm)
2c	Free perforation	Free perforation, free air/fluid; generalized peritonitis
2ci	Purulent peritonitis	
2cii	Fecal peritonitis	
3	Chronic diverticular disease	Relapsing or persistent symptomatic diverticular disease
3a	Symptomatic uncomplicated diverticular disease (SUDD)	Localized symptoms; laboratory test (calprotectin): optional
3b	Relapsing diverticulitis without complications	Signs of inflammation (laboratory tests): present; cross-sectional imaging: indicates inflammation
3c	Relapsing diverticulitis with complications	Identification of stenoses, fistulas, conglomerate tumor
4	Diverticular bleeding	Diverticula identified as the source of bleeding

Advances in imaging techniques and changes in treatment, as well as different focuses for surgeons, gastroenterologists and radiologists, have steadily demanded modified classifications but is a problem when comparing studies and making guidelines.

1.4 EPIDEMIOLOGY

1.4.1 Incidence and prevalence

Many patients with diverticulosis will never have any disease-related symptoms why incidence and prevalence studies are difficult. It has been showed in United States that about 30% of individuals aged 50–59 years and 70% of those aged ≥80 years at colonoscopy or sigmoidoscopy are diagnosed with the condition (29). These findings should not have been influenced by symptoms or other indications for the procedure according to the authors and could therefore be considered prevalence in the American population. Comparably, in a population-based study from Sweden, where participants underwent colonoscopy, the prevalence of diverticulosis in the age group 60–69 years was >30% and similarly increasing with age (30). It was also shown that the prevalence of diverticulosis in women and men are similar, which is in accordance to other studies (30, 31). The incidence has been estimated to 634/100,000 person-years in a retrospective study including 2,222 patients having for various reasons undergone colonoscopy (32).

Regarding incidence of symptomatic diverticular disease, including diverticulitis, reports are scarce. Since symptomatic diverticular disease has a variety of symptoms, some patients do not seek health care, others visit their general practitioner and others need emergency care. This makes it difficult to study incidence, also because patient visits often are registered in different health registries depending on level of care. In the literature, focus is usually on diverticular disease demanding hospital inpatient care, probably because most register-data are available in this group of patients. Most recent studies have reported admission rates rather than incidence rates, which are not exactly the same

since a patient can have a recurrent disease with several readmissions. Also, primary data sources are usually not covering the whole population. See Table 5 for studies on admission rates and incidence rates, including our own (paper III). Incidence rate has reported to be 16-188/100.000 person-years and is increasing with age. There is a female predominance (sex ratio commonly reported to 1.5:1) which is more pronounced with increasing age (33, 34). In the last decades, incidence seem to be rising in the Western world, especially in younger age groups (33, 35, 36). In African and Asian countries, diverticular disease has traditionally been rare but seems to have become more common when influenced by westernized culture last decades (37). As in studies of admission rates, studies of incidence rates have not covered the whole nation-wide population and generalizability can therefore be problematic.

Another way of describing the impact of a disorder is to estimate the risk of developing the disease during the remaining lifespan. This is a quantity that is usually easier to communicate to patients in clinical practice. This has been done on several other diseases, but before our study (Paper III) not with diverticular disease (38, 39).

Table 5. Studies on incidence and admission rates of diverticular disease

Study	Study period	Primary data sources	No. of events	Main measure(s)	Rate estimate(s)
Kang 2003 (34)	England 1989/1990–1999/2000	Hospital Episode Statistics (Department of Health)	Not specified	Admission rates with diverticular disease at National Health Service hospitals (excluding day case admissions)	25.1 (1989/1990)–28.2 (1999/2000) admissions per 100,000 inhabitants (Standardized to the European standard population)
Warner 2007 (40)	Ontario Canada 1988–2002	Discharge Abstract Database (Canadian Institute for Health Information)	133,875 admissions	Admission rates with diverticular disease	94 (1988)–105 (2001) admissions per 100,000 inhabitants
Jeyarajah 2009 (41)	England 1996–2006	Hospital Episode Statistics (Department of Health)	560,281 admissions	Admission rates with diverticular disease at National Health Service hospitals (including day case admissions)	56 (1996)–120 (2006) admissions per 100,000 inhabitants

Study	Study period	Primary data sources	No. of events	Main measure(s)	Rate estimate(s)
Etzioni 2009 (35)	USA 1998–2005	Nationwide Inpatient Sample (representative sample of approximately 20% of the hospital discharges within the United States)	267,000 admissions	Admissions rates with acute diverticulitis, length of stay >0 day, excluding patients with a diagnosis of colorectal cancer	58.9 (1998–1999)–71.0 (2004–2005) admissions per 100,000 inhabitants (Standardized to the 1998–1999 US population)
Humes 2009 (42)	United Kingdom 1990–2005	General Practice Research Database (diagnostic and prescription data for over 13 million people of the general population in the United Kingdom, with 3.4 million active patients contributing high-quality validated data)	953 incident cases	Incidence rates of perforated diverticular disease	1.75 (1990–1995)–3.27 (2001–2005) incident cases per 100,000 person-years (Excluding the population denominators for those under 45 years of age)
Nguyen 2011 (33)	USA 1998–2005	Nationwide Inpatient Sample	323,097 admissions	Admissions rates with acute diverticulitis, length of stay >1 day	61.8 (1998)–75.5 (2005) admissions per 100,000 inhabitants (Standardized to the US standard population from 2000)
Jamal 2014 (43)	Levanger Hospital (serving a defined population), Norway	Hospital patient administrative system and individual review of medical records	851 admissions in 650 patients	1) Admissions rates with acute diverticulitis 2) Incidence rates with acute diverticulitis	1) 17.7 (1988–1992)–51.1 (2008–2012) admissions per 100,000 person-years 2) 15.6 (1988–1992)–38.6 (2008–2012) incident cases per 100,000 person-years
Bharucha 2015 (36)	Olmsted County USA 1980–2007	Rochester Epidemiology Project database	3,222 cases with an initial (index) diagnosis of diverticulitis	Incidence rates of acute diverticulitis, outpatients and inpatients combined	115 (1980–1989)–188 (2000–2007) incident cases per 100,000 person-years (Standardized to the United States white population in 2000)
Sköldberg 2018 (Paper III)	Sweden 1987-2010	The National Patient Register	144,107 admissions in 95,049 patients	1) Admission rates with diverticular disease 2) Incidence rates of admission with diverticular disease	1) 70.8 admissions per 100,000 person-years 2) 47.4 incident cases per 100,000 person-years (Standardized to the European standard population from 2013)

1.4.2 Association to colon cancer

Colon cancer and diverticular disease share several characteristics. They are diseases mainly situated in the left colon. They have both increased admission rates the last decades and are more common in Western world and in elderly individuals (41, 44, 45). Several studies have suggested the typical Western diet of low fibre and high intake of fat as major etiological factors for both diseases (46-49). Other inflammatory conditions in the gastrointestinal tract, such as ulcerative colitis, Crohn's disease and helicobacter pylori infection, have been shown to increase the risk of malignancy (50-52). Therefore, an association between diverticular disease and colon cancer has been hypothesized. Despite several studies, mainly cross-sectional endoscopy- radiological- and surgical specimen analyses but also register-based studies, the association has been unclear due to contradictory results (44). Since it, in the acute state, can be difficult to distinguish diverticulitis and colon cancer and due to the unclarity regarding diverticulitis as a factor for future development of colon cancer, diverticular disease patients have in some centres been monitored repeatedly by various modalities for colon imaging. However, these routines have not been evidence-based.

Table 6 shows a summary of current findings of association between diverticular disease and colorectal cancer and adenomas, including our study (paper I).

Table 6. Main studies on association between diverticular disease and colorectal cancer and/or adenomas

Study	Patients	Study design, type of examination, type of diverticular disease	Association to			p<0.05
			colorectal cancer	adenomas	advanced adenomas	
Sim 1982 (53)	1,118	Cross-sectional Contrast barium enemas Diverticular disease	None	None	N/A	No
McCallum 1988 (54)	119	Case-control Contrast barium enemas Diverticulosis	Negative	N/A	N/A	not published
Morini 1988 (55)	150	Case-control Colonoscopy Symptomatic diverticular disease	None	Positive	Positive	yes
Stefansson 1993 (56)	7,159	Cohort Hospital discharge diagnoses Diverticular disease	Positive (only left side)	N/A	N/A	yes
Morini 2002 (57)	630	Case-control Colonoscopy Diverticulosis	None	Positive	Positive	yes (not for colorectal cancer)

Study	Patients	Study design, type of examination, type of diverticular disease	Association to			p<0.05
			colorectal cancer	adenomas	advanced adenomas	
Loffeld 2002 (58)	6,827	Cross-sectional colonoscopy Diverticulosis	Negative	Positive -polyps	N/A	yes
Kieff 2004 (59)	502	Cross-sectional Colonoscopy	Positive only when comparing women with extensive distal diverticulosis with women with none or few diverticula, all other analysis showed no association	N/A	N/A	yes
Rajendra 2005 (60)	410	Cross-sectional Colonoscopy Diverticulosis	None	Positive	N/A	yes
Krones 2006 (61)	1,838/ 512	Retroperspective Colonoscopy, barium enema, histopathology Diverticulosis/diverticulitis	Negative	N/A	Negative	yes
Soran 2006 (45)	1,561	Retroperspective Histopathology Diverticulosis	Positive to rectosigmoid cancers (no control group without colorectal cancer)	N/A	N/A	yes
Stefansson 2004 (62)	7,159 (diverticulosis and diverticulitis) 64 colorectal cancer 123 colorectal cancer-free controls	Nested case-control Hospital discharge diagnoses + medical chart review Diverticulitis compared to diverticulosis	Positive - diverticulitis-	N/A	N/A	yes
Meurs-Szojda 2008 (63)	4,241	Cross sectional Colonoscopy Diverticulosis/diverticulitis	Negative - diverticulosis None -diverticulitis	N/A	Negative - diverticulosis None - diverticulitis	yes
Lam 2010 (64)	288	Retroperspective cohort Hospital discharge diagnoses +CT-scan or surgery Diverticulitis	Negative	Negative	N/A	yes
Granlund 2011 (Paper I)	41,037	Nationwide population-based case-control Hospital discharge diagnoses	None after 1 year (positive first 12 months)	N/A	N/A	yes

Study	Patients	Study design, type of examination, type of diverticular disease	Association to			p<0.05
			colorectal cancer	adenomas	advanced adenomas	
Huang 2014 (65)	41,359	Nationwide population-based cohort Hospital discharge diagnoses	None after 1 year (positive first 12 months)	N/A	N/A	yes

1.5 MORTALITY

Of the spectrum of disorders of diverticular disease, diverticulitis has gained the most attention when studying mortality, probably because of its impact on patients in term of severe symptoms and complications. One way of examining mortality is by calculating standardized mortality ratios in where one compares the number of subjects that died per year to the expected number dead in the general population with the same sex and age distribution. In Scotland, this was calculated by Paterson et al. for first-time emergency admitted diverticulitis patients 2010-2010, using mortality rates in the general population in groups of sex and 10-year bands of age. Increased standardized mortality ratio was found to be 2.81 (95% CI 2.63-3.00) for surgically treated patients and 1.78 (95% CI 1.73-1.82) for conservative treated patients. Increased standardized mortality ratios were associated with female gender and younger age when surgically treated, and socio-economic deprivation for conservative and surgically treated patients (66). Regarding follow-up time, when investigating mortality in diverticulitis patients, mainly short-term mortality after hospitalization has been studied, usually as in-hospital death proportion or ditto within 30 days. These have been reported to be 0.5-2.1% in conservative managed patients (67, 68, 69). Regarding surgically treated patients, Haas and colleagues reported in 2016 an up to 30-days mortality of 3.05% (95% CI 1.73-5.32) after reviewing 59 studies (70). Long-term mortality is not as well studied, regarding death/survival proportion. Diverticulitis patients with first abscess formation (modified Hinchey Ib-II) has been studied as 5-year survival proportion from Kaplan-Meier statistics by Gregersen et al. in a Danish register-based cohort study including 3,148 patients and was found to be 66.0% (95% CI 63.9-68.0) in conservative treated patients and 66.7% (59.0-73.3) in surgically treated patients (71). Mortality was associated with male sex and glucocorticoid use. In Ontario, Canada, the 5-year death proportion was 14.1% in first time diverticulitis hospitalized patients that were treated conservative, when starting observation period 30 days after discharge (72). Bharucha et al found, in a register-based cohort study, a 5-year survival proportion of 65-71% in different calendar time periods 1980-2007 in 1,502 diverticulitis patients in Olmsted county and considered the overall survival over the study period not significantly different from expected in a similar (white Minnesota) population. Mortality was higher in older people, in women and in the most recent calendar periods

(36). However, those results were not adjusted for comorbidity or social factors. There is no nation-wide study published comparing diverticulitis patients, neither on short-term mortality nor long term mortality, to a sex- and age-matched disease-free group of individuals adjusted for comorbidity or social factors. Humes et al have published the only study so far comparing long-term mortality in a cohort of diverticulitis patients with an individually matched disease-free comparison group. This cohort of 953 individuals was however a subgroup of diverticulitis patients, including only those with perforated colon. They found a first-year HR of 5.63 (95% CI 4.68-6.77) (42).

1.6 ETHIOLOGY AND PATHOGENESIS

1.6.1 Diverticula structure and formation

Diverticula are herniations of mucosal and serosal layers at sites where the blood supply via vasa recta penetrate the colon wall. Sometimes, they are referred to as false diverticula, since no muscle layer is included in the herniation. They are mainly located in the distal colon in the Western world (>90% in the sigmoid) and can vary from solitary findings to many hundreds in an individual. They are usually 5-10mm in diameter but can exceed 2 cm (73).

The ethiology and pathogenesis of diverticular disease is still not fully understood. Painter and Burkitt proposed a theory in the 1970's suggesting that the Western diet of low fiber reduce stool volumes and slower transit time which promotes constipation that causes hypersegmentation (by increased tension of circular muscle layers and teniae coli). Hypersegmentation would narrow the lumen and generate higher intraluminal pressure according to Laplace's law (wall tension=pressure x radius), which would favor formation of diverticula at weakest point of the wall (where vasa recta enter, in connective tissue clefts in the circular muscle layer) (74). This causality theory, between low fiber content diet and colon wall changes, has been quite well established, but recently being questioned, as described further below.

There are several studies supporting different types of structural changes in colon wall in diverticular disease patients. Thickening of circular muscle and shortening of coli teniae have been shown in necropsy studies (75-77). Imbalances in the extracellular matrix, which has an important role in the integrity, strength and flexibility of the colon wall might lead to changes in motor activity and herniation when exposed to increased intraluminal pressure, argues several authors (73, 78-80). A recent study has shown that thickening of the longitudinal muscle layer was associated with increased fractions of connective tissue located within the circular and longitudinal muscles. Additionally, other differences in smooth muscle architecture were shown, as irregular muscle bundle orientation (81, 82).

Some researchers suggest that smooth muscle dysfunction may result from vagal attrition associated with ageing (83). Tighter collagen crosslinking has also been found in diverticulosis patients, which might reduce submucosal compliance (= degree of elasticity), thereby increasing the risk for herniation (82, 84, 85). Ulmer et al showed that diverticular disease patients had lower collagen I/III quotients and decreased glial cell (involved in the intrinsic ganglia part of peripheral nervous system, they are thought to have functions related to maintaining epithelial barrier integrity and regulate colonic motility (86, 87)) density. The authors found indices of increased proliferation and apoptosis in patients with complicated diverticular disease. This was however compared to a group of disease-free colectomy samples from colon cancer patients (that might have an underlying inflammatory component) (78, 79). Also comparing to disease-free colectomy samples from colon cancer patients, Basotti et al found similarly decreased amounts of glia cells but also that interstitial cells of Cajal (the gut pacemaker cells) were decreased in diverticulosis patients (88, 89). Several studies have actually suggested that diverticulosis might be an enteric neuropathy (90-93). A derangement of the myenteric nerve plexus was first reported by Macbathe and Hawthorne in 1965 (91). Milner et al. found that the neurotransmittor vasoactive intestinal polypeptide (found in the myenteric plexus and appears to inhibit peristalsis) levels in sigmoid colon wall was increased in diverticular disease patients (89, 94). Other neurotransmittors associated with colon motility as serotonin, acetylcholine and nitric oxide have also been suggested to play a role in development of diverticular disease (95). Elastin, which is a highly elastic protein in the connective tissue that allows mass to resume its shape after stretching or contraction, has shown to be increased up to 200% in taeniae coli in surgical specimens of uncomplicated diverticular disease. It was however no alternation of elastin content in the circular muscle. The authors concluded that this "elastosis" may be responsible for the shortening of coli teniae (which in turn leads to changes in circular muscle tension and hypersegmentation) (96, 97). Interesting is, that diverticulosis is more common in patients with connective tissue disorders, as Ehler Danlos syndrome and Marfan syndrome (98-100).

Colonic transit studies show conflicting results. Both delayed and increased transit times have been found in diverticular disease patients (101-103). Studies of myoelectrical activity recordings in vivo through catheters in the colon of diverticular disease patients have showed unaltered or increased activity but the relevance of any changes in relation to mechanical events remains uncertain (95, 104-109). Manometry studies over 24 hours have showed an overall increase in basal motility in segments harboring diverticula, an abnormal motor activity response after eating and an abnormal forceful propulsive activity (92, 95). Some authors regard the increased intraluminal colonic pressure being a major

pathogenetic factor of diverticula formation while others have suggested, that these increased pressures are only detectable when symptoms occur (90, 110-112). An explanation of why diverticula are more common in the sigmoid could be that this part of colon has the smallest diameter and therefore least elasticity, which would contribute to highest intraluminal pressures (113, 114).

In summary, pathogenesis of diverticula formation is yet unclear but structural changes in the colon wall, including abnormalities in muscle composition and changes in the enteric nervous system associated with altered motility seem to be essential elements. Environmental and genetic factors that are associated with presence of diverticula are described below.

1.6.2 Inflammation in diverticula

When macroscopically signs of inflammation are seen in a diverticulum together with raised inflammatory parameters and typically symptoms (described below), it is called diverticulitis. The inflammation often engages a part of the adjacent bowel and peridiverticular mesenteric fat, but can also spread diffusely along the peritoneal surface, form abscesses and involve nearby organs (14). A diverticulum can also perforate into the peritoneal cavity and lead to rapidly spreading purulent or faecal peritonitis (14). As described earlier, Hincheys classification (Table 1) is used to differentiate stages of perforated diverticulitis (16). Another complication is fistula to other pelvic organs as the urine bladder or vagina (14). Inflammation can also lead to formation of scar tissue which might cause strictures of the affected bowel segment, resulting in obstructive symptoms (14). In addition, a diverticulum can erode the arterial wall of the vasa recta and cause gastrointestinal bleeding (inflammation not required) (14, 115, 116). The bacteria involved in abscesses and peritonitis secondary to diverticulitis typically originate from the normal colon flora (14). Anaerobes as bacteroides fragilis, Escherchia coli, Klebsiella enterobacteria and Enterococcus species are commonly seen (14, 117-119).

Entrapment of faecoliths within a diverticulum causing microperforation and abscess formation, or ischemia or mechanical injury at the neck of the diverticula, has been explained as the pathogenesis behind diverticulitis (27). Recently, several other mechanisms of pathogenesis have been suggested, described below. Furthermore, the last few years, a new subclass of diverticular disease has been suggested, Symptomatic Uncomplicated Diverticular Disease (SUDD). It is defined as diverticulosis with associated chronic abdominal pain in the absence of acute symptoms of diverticulitis or overt colitis (89). This condition might have a different pathogenesis than diverticulitis. Chronic low-grade inflammation localized in the mucosa has been suggested as a factor (120). Increased

number of mast cells in all the layers of the colonic wall has been shown in these patients as well as microscopic infiltrates with lymphocytes and neutrophils (121-124). Some authors even conclude that low-grade macroscopic inflammation could be evident in these patients. There seem, however, to be different diagnostic criteria used in studies when including patients with SUDD, from "presence of abdominal pain and change in bowel habits attributed to diverticula in the absence of alternate etiologies" to presence of any symptoms in diverticular disease (and excluding diverticulitis) (30). Low-grade mucosal inflammation has also been described in irritable bowel syndrome (IBS) (125). There have also been studies showing signs of visceral hypersensitivity in SUDD, as well as in inflammatory bowel disease (IBD), which might explain some of the symptoms (125-127).

The gut microbiome in diverticulosis, SUDD and diverticulitis has been studied by some authors, as it has been found that a disruption of the homeostatic microbial balance (dysbiosis) being associated with other gastrointestinal diseases, as inflammatory bowel disease (82, 128-133). Some of the studies analyzed fecal bacteria while others mucosal bacteria. The first mentioned could be different from those inside the diverticulum because of the anatomically limited communication with the lumen (82). Several species of bacteria have been found to be either increased or decreased compared to controls but because of small sample sizes, different bacterial identification methods and use of control groups that might harbor a confounding dysbiotic microbial composition, it is difficult to identify common bacteria that influence disease (82). The host immune response has also been investigated in diverticulitis using RNA-sequencing of resected sigmoid colon tissue from patients with quiescent disease. Although examination of the tissue did not show gross inflammation, both the innate and the adaptive immune system pathways were enriched compared to in non-diverticulosis individuals (82, 134).

Segmented colitis associated with diverticulitis (SCAD), is currently considered a separate disorder (135). It is described as non-specific segmental inflammation in the sigmoid colon surrounded by multiple diverticula (135, 136). The diverticular orifices do not need to be involved (135, 137). SCAD shares several features of IBD and infectious and ischemic colitis. Cryptitis, crypt abscesses and granulomas have been described in SCAD-patients. (89, 138). It appears to be a mainly benign and self-limiting condition (135, 136) but some authors suggest that it might develop into IBD in a small subset of patients (139).

1.6.3 Genetic susceptibility

Until our twin study in 2012, based on data from Swedish Twin registry, little research had been published regarding genetic susceptibility (Paper II). Several case reports describing diverticular disease among siblings and twins had been published (140-145), including

European and African patients, and several genetic diseases as Ehlers Danlos syndrome, William-Beuren syndrome, Coffin-Lowry syndrome and polycystic kidney disease have been associated with higher risk of diverticular disease which could imply a genetic component (146-151).

Diverticula are more common and mainly located in the left part of the colon in the western world compared to in the right part of the colon in Asians (152). Furthermore, it had been shown that incidence and prevalence of diverticulosis and diverticulitis differ widely between different ethical groups in the same geographical area (153-158). Burkitt and Painter suggested this difference might be due to lifestyle factors as the typical Western diet of low fiber (10). It was indeed shown in the 1970's that prevalence of diverticular disease was higher among Japanese that migrated to Hawaii compared to those staying in Japan, which could support the theory of altered lifestyle habits as a cause of the disease (159). Hjern et al. found, in accordance, in a Swedish registered based study, lower risk of hospitalization for diverticular disease for non-western immigrants compared to natives, and that the risk increased the longer they lived in Sweden (160). More intriguingly, Miura et al. found that the increase incidence in diverticulosis in Japan (analyzed as review of medical chart of barium enema examinations) in the 1980's and 1990's, a time when the country was increasingly influenced by western culture, was only apparent for right side and not left side diverticulosis (161).

Our study from the Swedish Twin Registry was based on 104,452 twins, including 2296 with diverticular disease, demonstrating an estimated heritability of 40% (Paper II). Strate et al published the following year a study based on the Danish twin registry but also in a separate analysis including siblings to an index case. The twin analysis included 923 twins with diverticular disease (diagnosed at hospitalization, or in the later time period, at outpatient visits) of 60,644 twins. Results were similar to our study, with an estimated heritability of 53% (95% CI 45-61%). The sibling analysis showed an increased relative risk for diverticular disease in siblings of 2.92 (95% CI 2.50-3.39) (162).

Since 2014, several gene candidate driven studies have been performed searching for single nucleotide polymorphisms (SNPs) and other variants in DNA that could be associated with diverticular disease. The first SNP that was associated with diverticular disease was rs7848647 on the TNFSF15 (Tumour necrosis superfamily 15)-gene. This gene has earlier been associated with IBD and is involved in T-receptor maturation. It was found that diverticulitis patients requiring surgery to a greater extent had genotypes including the nucleotide guanine, compared to IBD patients and healthy controls (163). In a follow-up haplotype analysis on TNSFS15-gene including the above-mentioned SNP, an association with diverticulitis was found (164). An exome sequencing study identified a rare

single nucleotide variant in the laminin β 4 gene (LAMB4) in diverticulitis patients. This gene is involved with laminins which are constituents of the extracellular matrix and play a role in functions of the enteric nervous system (165). This might support the role of dysmotility as part of the pathogenesis of diverticular disease. Another SNP, (rs3134646) in collagen type III alpha 1 chain (COL3A1) gene was associated with diverticulosis in white men. This finding might support the role of collagen vascular system in the pathogenesis (82, 166).

In 2017, the first genome-wide association study (GWAS) was made on diverticular disease patients from Iceland and Denmark. Common sequence variants in introns (part of the nucleotide sequence that are removed in the final RNA product) of the genes ARHGAP15 (involved in cell proliferation apoptosis, attachment and motility), COLQ (encodes a molecule that is associated with acetylcholinesterase) and FAM155A (unknown function but close SNPs have been associated with increased fat mass in children and anorexia) was found in these patients. These sequence variants do not overlap with other known signals in other diseases or traits found in other GWAS. However, no significant differences were seen in expression of the target genes or nearby genes, therefore these differences are of unknown functional impact (82, 167).

1.6.4 Environmental factors

1.6.4.1 Diet

As described in chapter 1.6.1 "Diverticula Structure and Formation", Painter and Burkitt suggested in the 1970's that diet with low fiber content is an important cause of diverticula formation (10). This hypothesis originated from their discovery that prevalence of diverticulosis in African countries, where high consumption of fiber is common, was much lower than in Western countries with a deficiency in fiber intake.

Aldoori et al found in a prospective cohort study that low fiber intake was associated with risk of symptomatic diverticular disease (168). In a follow-up study, they suggested that the insoluble component of fiber, particularly cellulose, was negatively associated with symptomatic diverticular disease (169). Crowe at al found in a prospective cohort study, that consuming a vegetarian diet and a high intake of dietary fiber were both associated with a lower risk of admission to hospital and death from diverticular disease (170). The same authors concluded in a follow-up study that cereal and fruits had the strongest negative association for these events (171). Mahmood et al found that high intake of dietary fiber from fruit and vegetables decreased the risk of hospitalization for diverticular disease, in two major cohorts, The Swedish Mammography Cohort and the Cohort of Swedish Men. In their study, intake of cereals did not influence the risk (172). Strate et al

studied incidence of diverticulitis in diverticulosis-free men (no earlier known diagnose of diverticulosis) with Western diet (high in red meat, refined grans, and high-fat dairy) compared to prudent diet (high in fruits, vegetables, and whole grains). The highest quintile of western dietary pattern score had a HR 1.55 (95% CI 1.20-1.99) of diverticulitis compared to ones in the lowest quintile. High vs low prudent scores were associated with decreased risk of diverticulitis (HR 0.74, 95%CI 0.60-0.91) (173).

However, recent studies on diverticulosis show different associations of dietary fiber. In 2013-2014, Peery et al published two articles of cross-sectional analyses of individuals that underwent outpatient colonoscopy and found that asymptomatic diverticulosis was associated with high intake of dietary fibers. Moreover, they reported that these patients had increased and not decreased frequency of bowel movements. They suggested that the diet recommendations of higher fiber intake should be reconsidered since they were of low scientific quality (174, 175). There might be different risk factors concerning dietary fiber for diverticula per se and development of symptomatic disease. Based largely on these data, the recent American Gastroenterology Association (AGA) guidelines on diverticulitis suggest a high dietary fiber intake in patients with explicitly a history of acute diverticulitis (176, 177).

Other dietary factors that have been studied are red meat/fat, alcohol, nuts/corn/popcorn and caffeine intake. High red meat and high fat diets have been associated with symptomatic diverticular disease (168) and red meat with incidence of diverticulitis in men (178). Intake of nuts, corn or popcorn did have an inverse association to diverticulitis and diverticular bleeding, the controversy of earlier common beliefs, as it has been thought that these small food particles could get caught in the diverticula and cause inflammation (179). Studies of alcohol use and diverticulosis respectively symptomatic diverticular disease show conflicting results (175, 180-182). Caffeine intake did not substantially increase risk for symptomatic diverticular disease in a prospective cohort study (180).

1.6.4.2 Vitamin D

Among patients with diverticulosis, higher pre-diagnostic levels of vitamin D (25(OH)D) were associated with a lower risk of diverticulitis (183). In a follow-up study, the authors found that low UV (ultraviolet) light exposure was associated with an increased rate of diverticulitis admissions and higher seasonal variation. Since UV light exposure determines a large part of the vitamin D status, they conclude that these findings support a role for vitamin D in the pathogenesis of diverticulitis (184).

1.6.4.3 Smoking

Smoking has been associated with an increased risk of diverticulosis, hospitalizations for diverticular disease and diverticulitis as well as more complications and increased rate of recurrent diverticulitis episodes after surgical treatment of diverticulitis (175, 185-188).

1.6.4.4 Obesity/Physical activity

A pro-inflammatory state is thought to be the mechanism through which obesity could contribute to diverticular disease (79). Obesity has been found to increase the risk for diverticulosis, hospitalization for diverticular disease and diverticulitis as well as diverticular bleeding (175,185, 189-191). Pilgrim et al concluded in a systematic review of 23 clinical case series that the majority of diverticulosis patients aged <40 years were obese (192). Hjern et al found that obese (BMI ≥30) women had a twofold (RR 2.00, 95% CI 1.08-3.73) risk of complications as perforation and abscess (191). The same authors showed that low physical activity, defined as exercise ≤ 30 min/day, increased the risk for hospitalization for diverticular disease with 42% (RR 1.42, 95% CI 1.18-1.69) compared to exercise >30 min/day, in women (191). Strate et al found similarly decreased risk of diverticulitis and diverticular bleeding with physical activity, in a cohort of men from the Health Professionals Follow-up study (193). Just recent, Järbrink-Sehgal et al. published a Swedish register-based study including 43,772 men aged 18-20 years conscripted to military service and followed for a period of 39 years. It was found that overweight and obese men had a 2-fold increased risk of hospitalization for diverticular disease compared to normal-weight men; HR 2.02, (95% CI 1.50-2.73) (194).

1.6.4.5 Drugs

Corticosteroids are known to alter responses to inflammation and infection and their chronic use reduces collagen turnover (195). Several authors have reported that use of corticosteroids may weaken the colon wall and increase risk of perforation in diverticulitis (188, 196). Hjern et al found in a population-based cohort study of 37,000 middle-aged women that use of oral and inhaled corticosteroids also increased the risk for hospitalization of diverticular disease with 37% (RR 1.37, 95% CI 1.06-1.78) and 71% (RR 1.71, 95% CI 1.36-2.14), respectively. A significant dose-response relationship, with the risk increasing the longer duration of inhaled corticosteroids was seen (195). Patients with perforated diverticulitis had a two-fold increased risk of dying when using corticosteroids compared to non-users, but no dose-response relationship was apparent (197).

Non-steroid inflammatory drugs (NSAID) are thought to induce mucosal damage due to its reduction of prostaglandin synthesis (198). They have in some studies been found to increase the risk for diverticulitis, diverticular bleeding and diverticulitis perforation (196,

198, 199) while others have not found any significant increased risk of hospitalization for diverticular disease or diverticulitis perforation (188, 195).

Opioids have shown to double the risk for diverticulitis perforation in a case-control study of Humes et al (188) and similarly in a study by Morris et al (196).

Strate et al reported increased risks for both diverticulitis and diverticular bleeding in the Health Professionals Follow-up Study cohort of men with Aspirin (198) whereas Humes et al (188), and Morris et al (196) did not find any influence of Aspirin use on perforated diverticulitis. In addition, Hjern et al found no increased risk of diverticular disease hospitalization in their cohort of women (195).

Calcium blockers show no influence in perforated diverticulitis but might increase the risk for diverticular bleeding according to a systematic review (200).

Statin use did not affect the development of symptomatic diverticular disease but was associated with a reduced risk of emergency surgery for diverticulitis in a nation-wide population-based case-control study by Sköldberg et al (201).

1.7 CLINICAL FEATURES AND HEALTH CARE MANAGEMENT

1.7.1 Diverticulosis

Diverticulosis, is commonly found *en passant* when patients are investigated with endoscopy or radiological modalities for different indications. Recent studies have shown that presence of diverticula represent the most common non-neoplastic finding during screening colonoscopy (202, 203) There is no routine follow-up for these patients as most of them will not develop any symptoms related to diverticulosis. However, healthy lifestyle (regular physical exercise, maintaining ideal body weight, abstention from smoking) has been recommended to prevent progression to a symptomatic state (170, 202). The recommendation of a high-fiber diet in these patients is still under debate (170, 176, 177).

1.7.2 Symptomatic uncomplicated diverticular disease (SUDD)

When a patient with diverticula develop chronic gastrointestinal symptoms such as abdominal pain, bloating or change of bowel habits without any clinical sign of acute inflammation, the term SUDD has lately been used. The incidence of SUDD and other problems in patients with diverticulosis is not well studied, but may occur in 15% of diverticulosis patients according to a health questionnaire study (202, 204). In a population-based study of 745 randomly selected adults, including 130 with diverticulosis (none with an earlier diverticulitis episode), Järbrink-Sehgal et al found that diverticulosis patients were more likely to report loose stools, urgency, passing mucus, and a high stool

frequency than diverticulosis-free individuals. Diverticulosis was associated with abdominal pain and diarrhea-predominant IBS in participants older than 60 years (30). Symptoms of IBS and SUDD widely overlap (205). An Italian survey found that 59% of SUDD patients fulfilled the Rome III criteria for IBS (206). The age distribution is however different between the two conditions, SUDD is most common in older individuals while IBS is predominantly diagnosed in younger ages (202). Several studies have been conducted trying to discriminate symptoms of the two diseases (206, 207, 208). Some authors have suggested that a positive fecal-calprotectin test can differentiate SUDD from IBS (207, 209, 210). It has also been found that patients have an increased risk of being diagnosed with IBS after an episode of diverticulitis (211). Whether this post-diverticulitis condition should be classified as SUDD instead is discussed. Many still consider SUDD as a coincidence of diverticular disease and IBS (212).

Several drugs, including rifaximin (a poorly absorbed antibiotic used in treatment of small intestine bacterial overgrowth and related disorders) and mesalazine (an anti-inflammatory and antioxidant substance used in treatment of ulcerative colitis), as well as probiotics have been suggested as new therapies in SUDD but there is still no strong recommendation for such use (202).

1.7.3 Diverticulitis

1.7.3.1 Clinical findings

Diverticulitis develops in an estimated 4-25% of patients with diverticulosis (32, 213). After a first episode of diverticulitis, 9-30% of patients have at least one recurrence (214-216, 67) and the risk of recurrence increases with the number of episodes (36).

Symptoms of diverticulitis are typically abdominal pain in the left lower quadrant, and temperature >38 degrees centigrade. Diarrhea or constipation, bloating, nausea and vomiting and an increased urge to urinate are common. Palpation tenderness in the left lower quadrant is a classical sign of diverticulitis. On physical examination, peritoneal signs such as défense musculaire, rebound tenderness or Rovsing's sign can be apparent while signs of generalized peritonitis as rigid abdominal wall, non-localized tenderness, absent bowel sounds can appear in patients with perforation to free abdominal cavity. In severe cases with free perforation, patients become hemodynamically instable.

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are usually increased.

Cross-sectional imaging is recommended in most international guidelines and computed tomography (CT) is routinely used in Scandinavia (212). It has a good diagnostic accuracy with reported sensitivity of 93-98% and specificity of 75-100% (73) and therefore has

replaced contrast barium enema, which earlier was the investigation of choice. Patients with diverticulitis have CT findings including (217):

- pericolic stranding, often disproportionately prominent compared to amount of bowel wall thickening,
- segmental thickening of bowel wall,
- enhancement of colonic wall (usually inner and outer high-attenuation layers, with a thick middle layer of low attenuation)
- extravasation of air and fluid into the pelvis and peritoneal cavity seen at diverticular perforation
- abscess formation that may contain fluid, gas or both
- fistula formation with gas in the bladder or with direct visualisation of a fistulous tract (in the case of colovesical fistula)

In some countries, ultrasound is frequently used instead of CT (212).

1.7.3.2 Treatment of uncomplicated diverticulitis

Uncomplicated (absence of perforation, abscess, fistula, obstruction or bleeding) acute diverticulitis has been regarded as accounting for 75% of the diagnoses of symptomatic diverticular disease (218). If the patients have mild clinical symptoms and known diverticulosis they can be managed in primary care but often patients visit the emergency department at the hospital. The traditional care of uncomplicated diverticulitis is antibiotics, sometimes fluid, and bowel rest in hospital (219, 220). Antibiotics include trimetoprim-sulfametoxazol, metronidazol, ciprofloxacin and imipenem/cilastatin. In recent years, this management has been questioned as the guidelines mainly rely on uncontrolled studies (221, 222). Some studies, including multicenter randomized trials, have shown that antibiotics have no additional beneficial effect in these patients (223-226). Also, it has been found that patients with uncomplicated acute diverticulitis with or without antibiotics can be treated safely in an outpatient setting (221, 227). Thus, many patients with uncomplicated disease, being able to maintain hydration themselves at home, are now managed as outpatients, and antibiotics are no more routinely used in Swedish hospitals (212).

1.7.3.3 Treatment of complicated diverticulitis

Diverticulitis with abscess formation (Hinchey I and II) is usually treated with antibiotics only if of small abscess size (<3 cm) while larger abscesses are percutaneously drained when possible. Operative drainage is considered for very large abscesses (>5 cm) if percutaneous drainage is not feasible (212).

Diverticulitis with perforation (Hinchey III and IV) is often diagnosed by extraluminal air or fluid on CT-scan. Some hospitals routinely perform diagnostic laparoscopy in cases with these findings while others reserve operative treatment to patients with clinical findings of diffuse peritonitis and hemodynamically unstable patients (212). The more conservative management has been regarded as safe in two recently published cohort studies (228, 229). Purulent peritonitis is treated surgically. Hartmann's procedure (primary resection of the affected bowel segment and proximal colostomy), primary resection with anastomosis or the rather new technique laparoscopic lavage (230) are the main options. Angenete et al found in the randomized controlled trial DILALA, that laparoscopic lavage was safe in these patients (231). Other similar studies have shown different results but inclusion criteria have varied, including also additional Hinchey grades (232, 233). Feculent peritonitis (Hinchey IV) is most commonly treated with Hartmann's procedure (212).

Earlier international guidelines recommended elective sigmoid resection following two episodes of medically treated diverticulitis (213, 234, 235). Lately, this has been questioned and most guidelines now recommend elective sigmoid resection on an individual basis and preferably on patients with recurrent disease with difficult complications (236-239). Laparoscopic resection is preferred in most cases (240). A recent study found that the first occurrence of diverticulitis is the most complicated in a majority of cases and subsequent readmissions are often milder (241). It has been thought that young individuals have a more aggressive disease course than older individuals. Shahedi et al found that younger patients with diverticulosis had an increased risk of diverticulitis in a retrospective health registry study on veterans in Los Angeles, US (>97% males) (32). However, a in recent review article Pilgrim et al found that younger diverticulitis patients had lower rate of complicated disease than older (cut-off age 50 years) (192).

1.7.3.4 Follow-up

In most hospitals in Scandinavia, a colon examination is routine after an episode of acute diverticulitis (except if this is recently done), usually with colonoscopy and sometimes with CT colonography. The purpose is to rule out a missed colorectal cancer since the conditions may be difficult to distinguish in the acute clinical setting (212). Recent review articles have found that the risk of a misdiagnosed colorectal cancer is higher in complicated diverticulitis than uncomplicated disease (242, 243).

1.7.4 Diverticular bleeding

Bleeding from diverticula is the most common cause of acute lower gastrointestinal bleeding (244). In a study of hospitalizations of diverticulitis and diverticular bleeding, it was found that the prevalence of diverticular bleeding was approximately one third of that

of diverticulitis and that older patients are over-represented (with a peak prevalence in the age of 80+) (245). About 10% of diverticular bleeding patients without definite therapy will experience a recurrence within one year (246). 70-80% of cases of diverticular bleeding will resolve spontaneously (247). Scintigraphy, angiography and colonoscopy can be used to localize the bleeding vessel and the two-last mentioned also for therapeutic interventions (248).

1.7.5 Segmental colitis associated diverticulosis syndrome (SCAD)

SCAD is a rare condition in patients with diverticula and is currently included in some diverticular disease classifications. It is defined as a non-specific segmental or localized inflammatory process around diverticula and rectum is not involved. At endoscopy inflammation can be present within the inter-diverticular mucosa without necessarily involving diverticular orifices (136). It occurs predominantly in older males, usually discovered following an initial presentation with rectal bleeding (>70%) (136). It is many times self-limited and also responsive to oral 5-aminosalicylate (5-ASA). Sometimes however, chronically and symptomatic disease develop or recurrent separate episodes follow. If so, corticoids can be used and eventually surgical resection (136).

2 AIMS

The overall aim is to acquire deeper epidemiological knowledge of diverticular disease. Specific aims are to contribute in answering the following questions:

1. Is hospitalization for diverticular disease associated with an increased risk of colorectal cancer? (Paper I)
2. Is heretability contributing to the occurence of diverticular disease? (Paper II)
3. What are the admission rates and incidence rates of hospitalizations and surgery for diverticular disease? What is the risk of hospitalization and surgery during the remaining lifespan? (Paper III)
4. How deadly is diverticulitis needing hospital care? (Paper IV)

3 PATIENTS AND METHODS

The present thesis comprises four quantitative studies. Patients and controls were derived from the Swedish national quality registries described below in details. Table 7 shows an overview of the number of patients, study periods and study designs used.

Table 7. Overview of studies

	Paper I Association to colon cancer	Paper II Heritability	Paper III Incidence - Lifetime risk	Paper IV Mortality
Study design	Register based case-control	Register based twin study	Register based cohort	Register based cohort with comparison group
Number of individuals included	41,037 cases with colon cancer from Swedish Cancer Registry 82,074 colon cancer-free controls	104,452 twins from the Swedish Twin Register of which 2,296 with diverticular disease in the National Patient Register	95,049 with diverticular disease in the National Patient Register	83,461 with diverticulitis in the National Patient Register 812,942 diverticulitis-free in the comparison group
Study period	1987-2006	1969-2009	1987-2010	1990-2010

3.1 DESCRIPTION OF THE SWEDISH NATIONAL QUALITY REGISTERS

In Sweden, all citizens are assigned a unique identifier, the national registration number, at birth. The national number is registered together with other relevant personal information in the national quality registries. By record-linking the national quality registries through the national registration number, large quantities of data can be attained for research projects. Below is a description of the national quality registries used in this thesis.

3.1.1 Register of the Total Population

The *Register of the Total Population* was initiated 1968, after the Swedish population data had been computerized and is maintained by the government agency Statistics Sweden ("Statistiska Centralbyrån"). Data is updated daily from the Tax Agency. It contains information of birth, death, civil status, name changes, family relationships, and place of residence of all Swedish citizens. Nearly 100 per cent of births and deaths, 95 per cent of immigrations and 91 per cent of emigrations are registered within 30 days and with a higher proportion over time. It is estimated that there is over-coverage to 0.25-0.5 per cent of the total population, including missed registered emigration and deaths abroad (249).

3.1.2 National Patient Register

The *National Patient Register* was established in 1964 and is maintained by government agency Swedish National Board of Health and Welfare, "Socialstyrelsen". Its main part, the Inpatient Register, contains all discharges from hospitals. By year 1977, 19 of 26 counties were represented, including all great city regions, and from 1987, all hospitals in Sweden were included. It includes up to eight discharge diagnoses; patient's place of residence; and hospital, clinic and surgical procedures. The coverage of this part of the register is estimated to 99 per cent (250, 273). Another part of the register covers patients treated in day surgery (not admitted to hospital, from 1997) and specialized open care (from 2001).

3.1.3 Swedish Twin Register

The *Swedish Twin Register* was founded at Karolinska Institutet in 1961 and is considered to be the largest of its kind in the world. It contains close to 200 000 twins born in Sweden, covering all same-sexed twin births since 1886, and all twin births since 1906. Zygosity has predominantly been assigned based on questions about intrapair similarities in childhood. This method has been validated repeatedly with DNA as having 98% or higher accuracy. The database is updated regularly with information about cancer diagnoses, hospital discharges and inpatient diagnoses, conditions during birth, cause of death and vital status by record-linkage from relevant national health care registries (251, 252)

3.1.4 Swedish Cancer Registry

The *Swedish Cancer Registry* was established in 1958 and is maintained by the government agency Swedish National Board of Health and Welfare, "Socialstyrelsen". It is compulsory for every health care provider in Sweden to report new cancer cases to the register. This includes cases diagnosed at clinical-, morphological-, other laboratory examinations, as well as cases diagnosed at autopsy. Six regional registries associated with the oncological centres in each medical region of the country do the registration, coding, major check-up and correction work. The regionalization enables a close contact between the registry and the reporting physicians which simplifies the task of controlling data. The coverage is estimated to be 96% of all diagnosed cases (253, 254).

3.1.5 Swedish Cause of Death Register

The *Swedish Cause of Death Register* was originally established in 1749 and registers all deaths in Swedish inhabitants. The recent register is maintained by the government agency Swedish National Board of Health and Welfare, "Socialstyrelsen" and contain data from 1961 and is updated every year. The death cause diagnoses are registered as the international version of the World Health Organisation's ICD (International Classification of Disease). Both all diagnoses contributing to death and underlying death cause are

registered. It is mandatory for physicians to report death causes to the register, which is done in > 99 per cent of all deaths (255).

3.1.6 Total Registry of Educational Participation

The *Total Register of Educational Participation* was established in 1985 and is maintained by government agency Statistics Sweden, "Statistiska Centralbyrån". The register comprises achieved education in all Swedish citizens aged 16-74 years old. From 2007, citizens aged over 75 years of age are also included. Highest education attained and completion year are the main variables. Educations covered are primarily secondary school education, adult education, undergraduate education and postgraduate education. It is updated yearly (256).

3.2 STUDY DESIGN

3.2.1 Paper I -Association to colon cancer

In this nationwide register-based case-control study, associations between diverticular disease and colon cancer were examined. We included 41 037 patients (cases) (52% females, median age females 75, and men, 73 years), diagnosed with their first colon cancer in the *Swedish Cancer Registry* from 1992-2006. The cases were divided into subgroups according to the localization of the tumor (left- or right-sided). All cases were individually matched by gender, age and calendar year of diagnosis with two controls, not having had any diagnose of colon cancer in *The Swedish Cancer Registry* up until the time for the cases' diagnoses.

The exposure was hospitalization for diverticular disease, registered in the *National Patient Register* (ICD-9 code 562B 1987-1996 and ICD-10 K57.2-K57.9 1997-2006 as main or secondary diagnoses) prior to the dates the cases were diagnosed with colon cancer. As an indicator of severity of diverticular disease, the number of hospitalizations for diverticular disease, before the time of colon cancer diagnosis, was calculated and categorized. For comparison over time, the study period was divided into three calendar time intervals, according to the cases date of colon cancer diagnoses. The time between diagnose of diverticular disease and colon cancer was categorized as 0-6, 7-12, 13-18, 19-24 and 25+ months. In separate analyses, outcome of death (of all causes and caused by colon cancer) was compared between cases that had been admitted for diverticular disease and those who had not.

3.2.2 Paper II -Heritability

To assess heritability in diverticular disease, we performed a national twin study. Twin studies take advantage of the fact that monozygotic twins share 100% of their genome,

whereas dizygotic share on average 50%. With the traditional twin study design, it is possible to estimate the relative importance of genes and environmental factors to the development of a disease.

Twins with known zygosity, in the *Swedish Twin Registry* born between 1886 and 1980 and not dead before 1969 were included. Twins with diagnoses of non-infectious colitis and coeliac disease were excluded to avoid misclassification (for diagnose codes, see Appendix Table A4). Since we in in Paper I had found that there seems to be a proportion of patients with colon cancer initially being misdiagnosed as diverticular disease, we excluded twins diagnosed with colon cancer (ICD-7 codes 1530-1533 and 1538-1539) in *The Swedish Cancer Registry* before, and 2 years after diagnosis of diverticular disease.

Outcome in this paper was hospitalization for diverticular disease in the *National Patient Register* (primary and secondary diagnoses ICD-8 [1969-1986]: 562,10, 562,11, 562,18 and 562,19. ICD-9 [1987-1996]: 562B. ICD-10 [1997-2009]: K57.2-K57.9). In order to analyze the severity of disease, we also analyzed primary diagnoses for diverticular disease separately.

Twins were divided into groups of monozygotic, same sex dizygotic and opposite sex dizygotic pairs. Concordant pairs were twin pairs in which both twins had been hospitalized or not hospitalized for diverticular disease, while in discordant pairs, one of the twins had been hospitalized with diverticular disease.

3.2.3 Paper III -Incidence and lifetime risk

In this nation-wide register-based cohort study, incidence and lifetime risk of hospitalization and surgery for diverticular disease was assessed. All Swedish residents during 1987-2010 constituted the study base.

The events of interest in this study was 1) hospitalization for diverticular disease and 2) surgery for diverticular disease. These two events were identified by use of ICD codes and procedure codes recorded in the *National Patient Register* (Please refer to Appendix Table A5 for codes). Further definitions of the events are described below:

3.2.3.1 Hospitalization for diverticular disease

All records since 1970 of hospitalization with a primary diagnostic code for diverticular disease in the *National Patient Register* were identified. Some adjustments were made to minimize classification bias. Patients that received a primary diagnostic code for peritonitis, abscess or fistula together with a secondary diagnostic code for diverticular disease were also included, with the additional criterion that no concomitant secondary diagnoses of colorectal cancer, Crohn's disease or ulcerative colitis, appendicitis or

mesenteric ischemia were present. Furthermore, any hospitalization with a procedure code for endoscopy in the colon were excluded, in order to reduce the number of patients who received a diagnostic code for diverticular disease merely as a result of in-hospital investigation (possibly reflecting presence of diverticula rather than symptomatic diverticular disease). To avoid including colon cancer misclassified as diverticular disease, any hospitalization with a concomitant diagnosis of colon cancer in the *Swedish Cancer Registry*, were excluded from the analyses. In this paper, individuals with concomitant diagnosis of lower gastrointestinal bleeding were tallied, but not excluded.

3.2.3.2 Surgery for diverticular disease

For the analyses of diverticular disease treated by surgery, only hospitalizations with any of the procedure codes for colorectal resection or stoma formation were included. Since endoscopy is occasionally performed per-operatively, hospitalizations with surgery and a concomitant procedure code for endoscopy were also included.

3.2.4 Paper IV -Mortality

In this nationwide register-based cohort study, mortality among hospitalized diverticulitis patients was investigated. Any individuals, aged ≥30, diagnosed 1990-2010 with a first-time hospitalization for diverticular disease as primary diagnosis code, or as secondary diagnosis code together with primary diagnostic code for peritonitis, abscess or fistula in the *National Patient Register*, were included (257). Type of treatment during hospitalization, surgical (colorectal resection or stoma formations) or conservative (no colorectal resection or stoma formations), was registered by procedure codes in the same register. Please refer to Appendix Table A5 for codes.

Several exclusions were made to obtain a cohort that was hospitalized for diverticulitis. Similarly, as we did in papers II and III, any individual with a diagnosis of colorectal cancer, according to the Swedish Cancer Registry, registered within a year after the hospitalization for diverticulitis, were excluded, to avoid misclassification. Furthermore, we excluded any individual with a primary or secondary diagnosis of gastrointestinal bleeding during hospitalization for diverticulitis. Diverticula commonly bleed without obvious inflammation or any other symptoms of diverticulitis. Any individual with a procedure code for endoscopy but no procedure code for colorectal resection or stoma formation, at the admission, were excluded for the same reasons as in Paper III.

Among patients with a primary diagnosis of peritonitis, abscess or fistula and a secondary diagnosis of diverticular disease, any individuals were excluded if they had a concomitant diagnostic code for colorectal cancer, inflammatory bowel disease, vascular disorder of the

intestine or appendicitis in *National Patient Register* during the same hospitalization, as in Paper III. Please see Appendix Table A5 for codes.

The diverticulitis cohort defined above, was compared to a disease-free cohort without any prior history of diverticulitis (same criteria as for cases) recorded in the *National Patient Register* since 1970. For each patient with incident diverticulitis, up ten individuals were randomly selected from the *Register of the Total Population* and assigned the same index date, with matching for sex and age at the date of corresponding diverticulitis admission.

Covariates included were education level, civil status and comorbidity. Information about education level and civil status, was obtained from the *Total Registry of Educational Participation* and the *Register of the Total Population*, respectively. Information about comorbidity was obtained from the *National Patient Register* and the *Swedish Cancer Registry*. Please refer to Appendix Table A6 for comorbidity disease groups and codes.

The event of interest in this study was death, registered in the *Register of the Total Population*, throughout the study period.

3.3 STATISTICAL ANALYSES

3.3.1 Paper I -Association to colon cancer

The risk of preceding admission for diverticular disease in cases (colon cancer patients) was estimated by odds ratios with corresponding 95% confidence intervals. Colon cancer mortality and overall mortality were compared in cases with and without a preceding admission for diverticular disease, using Cox regression and presented as hazard ratios with 95% confidence intervals. Calculation were made with the statistical software SAS 9.2 (SAS institute, Inc, Cary, NC, USA).

3.3.2 Paper II -Heritability

Prevalence of diverticular disease was calculated as the percentage of individual twins that were hospitalized in the entire twin cohort as well as within zygosity.

Probandwise concordance was defined as 2 x hospitalized concordant pairs / (2 x hospitalized concordant pairs + discordant pairs. This was calculated for all zygosity groups and is a measure of the probability of one twin to have been hospitalized with the disease given that the co-twin has been hospitalized (258).

Co-twin odds-ratio (OR) was estimated for monozygotic and same-sex dizygotic twins. This is a measure of relative increase in odds of hospitalization of diverticular disease for one twin given the presence/absence of hospitalization in the co-twin.

Tetrachoric correlation was calculated for all zygosity classes. It is a measure to estimate a correlation between two dichotomized variables and is commonly used in twin studies. Higher tetrachoric correlation in monozygotic compared to dizygotic groups would indicate the presence of genetic effects (259). These calculations were made with the statistical software SAS 9.2 (SAS institute, Inc, Cary, NC, USA).

Mx, a software package designed for structural equation modeling used in twin studies, was used to estimate the relative importance of shared genetic effects (A), shared environmental effects (C) and non-shared, individual specific environmental effects (E) for the development of diverticular disease. First, we fitted all components (ACE) in the model estimating those proportions, and then tested if we could omit the C component in the model without reduction of model fit (260, 261).

3.3.3 Paper III -Incidence and lifetime risk

Statistics on population size and mortality during 1987-2010, stratified by sex, attained age, and calendar year, was retrieved from the *Register of Total Population*. For the calculation of admission rates, the mid-year population (calculated as the mean of the population at the beginning and end of the calendar year) in each stratum was used as the denominator. Similarly, the number of population person-time in each age/sex stratum per calendar year was approximated to the mean of populations in the beginning and the end of the calendar year (262). For the estimation of incidence rates and lifetime risk, person-time of individuals no longer at risk of an incident event was calculated for each age/sex/calendar-year stratum, using individual dates of birth admission and death, respectively, and subtracted from the total population person-time to yield an estimate of person-time at risk in each stratum.

3.3.3.1 Lifetime risks

In order to use relatively current information, we used data from the period 2000-2010 for lifetime risk analyses. Lifetime risk for the two events of interest were estimated using cumulative incidence functions based on Poisson regression models, treating death as a competing event (38).

3.3.4 Paper IV -Mortality

The cohort was followed until the first in order of these events:

- event of death
- migration
- first time admission with diverticulitis in corresponding disease-free individuals
- end of study period

In the last three events above, the individual became censored. Individuals in the disease-free cohort were moved to the diverticulitis cohort at date of admission for diverticulitis, if this occurred, and from that date no longer included in the disease-free cohort.

For comparison over time, the study period was divided into two calendar time intervals, years 1990-1999 and 2000-2010.

Cumulative mortality was calculated as Kaplan-Meier 1-survival estimates for the whole study period. Cumulative death proportions at 100 days and five years of follow-up were noted. Information about in-hospital mortality and hospital length of stay at diverticulitis hospitalization was also registered.

Cox regression models stratified on the matched sets were used to calculate hazard ratios (HR). Adjustments were made for education level, civil status, year of diagnosis, and comorbidity. Separate analyses were performed after stratification for sex, age group (30-49, 50-69, ≥70 years), calendar time period (1990-1999, 2000-2010) and whether diverticulitis patients were treated by surgery or conservatively. Follow-up time was divided into i) day 0 to day 100 (for short term mortality) and ii) day 101 to 5 years (for long term mortality) after index date. This time band was used as an interaction term with exposure, which allowed for different hazard ratios in the different time periods. Attributable risk percentage (ARP) was calculated from Cox regression. All statistical analyses were performed with Stata SE, version 14.2 (Stata Corp, College Station, TX, USA)

3.4 ETHICAL ASPECTS

Permission to compile and to publish these data was obtained from the Stockholm regional research ethics review board (dnr 2007/1335-31/4, 2010/322-31/2, 2010/1111-31/2, 2010/1114-32, 2011/1317-32). Data have been managed according to the Karolinska Institutet regulations for keeping and analyzing research information. Data was anonymized by Swedish National Board of Health and Welfare and Statistics Sweden before delivered to us. The code keys for linking data to persons has been kept at Swedish National Board of Health and Welfare and Statistics Sweden.

4 RESULTS

Below are summaries of results. For the complete results, please see the appended papers.

4.1.1 Paper I -Association to colon cancer

The first year before a diagnosis of colon cancer, the proportion of patients that was hospitalized for diverticular disease was significantly higher among cases than controls. Odds ratios were highest the first six months (up to 31.49 [95% CI 19.00-52.21]), independent of calendar time period. After the first year there was no general pattern of increased risk (Table 8).

Table 8. Odds ratios (OR) by time intervals from preceding admission for diverticular disease to diagnosis of colon cancer in cases (N=41 037) and controls (N=82 074) during three time periods in Sweden, 1992-2006

	Cases n, (%)	Controls n, (%)	OR (95% CI) 1992–1996	1997–2001	2002–2006
No diverticular disease	39,705 (96.8)	80,929 (98.6)	Reference	Reference	Reference
Diverticular disease before colon cancer (months)					
0–6	760 (1.9)	59 (0.1)	22.75 (14.06–36.82)	31.49 (19.00–52.21)	25.34 (16.72–38.39)
7–12	64 (0.2)	54 (0.1)	1.67 (0.88–3.18)	2.18 (1.21–3.93)	5.33 (2.48–11.47)
13–18	41 (0.1)	56 (0.1)	0.93 (0.42–2.06)	1.77 (0.90–3.46)	2.11 (1.05–4.26)
19–24	35 (0.1)	54 (0.1)	1.60 (0.75–3.42)	2.14 (1.03–4.44)	0.67 (0.30–1.49)
25+	432 (1.1)	922 (1.1)	0.85 (0.65–1.12)	1.14 (0.94–1.38)	0.88 (0.74–1.04)
Total	1,332 (3.2)	1,145 (1.4)			

The number of preceding hospitalizations for diverticular disease, showed no general relation to colon cancer.

Cases with left sided colon cancer were to a higher extent associated with previously hospitalization with diverticular disease than those with a right sided colon cancer, especially the first year but the confidence intervals coincide and were wide. The later time period the risk was higher for both sides. There was no general pattern of increased risk after one year, similarly to the findings in the all-colon analysis described above.

Cumulative mortality for death in colon cancer and overall death was similar in colon cancer cases with or without preceding hospitalization for diverticular disease. Cox

regression analyses did not show increased hazard ratios for death in colon cancer or all death causes in cases with preceding hospitalization for diverticular disease.

4.1.2 Paper II -Heredity

We identified 104,452 twins in the *Swedish Twin Registry*, after exclusions. Of these twins, 13 994 pairs were monozygotic, 20 073 pairs were same-sex dizygotic and 18,159 pairs were opposite sex-dizygotic. Of the monozygotic twins, 46% were of male sex and of the dizygotic-same sex, 47%.

In all, 2,296 (38% males) twins had been hospitalized with diverticular disease, as main or secondary diagnoses, in the *National Patient Register*. The prevalence for hospitalization for diverticular disease was 2.2%; monozygotic twins 2.0%, same-sex dizygotic twins 2.3% and opposite sex-dizygotic 2.2%. Distribution of zygosity in concordant and discordant twin pairs is presented in Table 9.

Table 9. Twin similarity and correlations of liability for diverticular disease (both primary and secondary diagnoses)

Zygosity		Concordant pairs with no DD*	Concordant pairs with DD*	Discordant pairs with DD*	Probandwise concordance	Tetrachoric correlation (95% CI**)
Monozygotic	Total	13,479	31	484	0.11	0.39 (0.30-0.47)
	Male	6,177	11	188	0.11	0.39 (0.25-0.53)
	Female	7,302	20	296	0.12	0.38 (0.27-0.49)
Dizygotic	Total	36,536	54	1,642	0.06	0.21 (0.15-0.27)
	Male	9,058	10	317	0.06	0.23 (0.10-0.37)
	Female	10,107	22	559	0.07	0.21 (0.11-0.31)
	Same sex	19,165	32	876	0.07	0.22 (0.15-0.30)

*DD=Diverticular disease **CI=Confidence Interval

When including both main and secondary diagnoses in analyses, we found higher probandwise concordance rates and tetrachoric correlations for monozygotic compared to corresponding dizygotic pairs (Table 9). The co-twin OR was 7.15 (95% CI: 4.82-10.61) for monozygotic twins compared to 3.20 (95% CI: 2.21-4.63) for same sex-dizygotic twins.

When including only twins with primary diagnoses, 1902 (37% males) twins were registered with hospitalizations for diverticular disease. Probandwise concordance and tetrachoric correlations, did not differ substantially from the combined primary and secondary diagnoses.

The results of structural equation model fitting to our data of both main and secondary diagnoses of diverticular disease are shown in Table 10. Since tetrachoric correlations were similar between sexes, the results are shown for sexes combined for monozygotic and dizygotic twins. In the model where A, C and E was included, the C parameter was not significantly different from 0. Therefore, we could omit the C parameter without any

significant reduction of model fit. The proportion of the variance in liability to diverticular disease attributable to additive genetic effects (parameter A), was then 40%, and the non-shared environmental influence (parameter E), 60%. When using only primary diagnoses in the analysis, results were similar (Table 10).

Table 10. Estimation of genetic and environmental effects for diverticular disease

Classification of diagnoses	Model	A: Genetic effects (95% CI*)	C: Shared environmental effects (95% CI*)	E: Non shared environmental effects (95% CI*)
Primary and secondary diagnoses	ACE	0.40 (0.18-0.47)	0.01 (0-0.15)	0.60 (0.53-0.69)
	AE (C set to 0)	0.40 (0.33-0.47)	-	0.60 (0.53-0.67)
Only primary diagnoses	ACE	0.43 (0.25-0.51)	0 (0-0.12)	0.57 (0.49-0.65)
	AE (C set to 0)	0.43 (0.35-0.51)	-	0.57(0.49-0.65)

*CI=Confidence Interval

4.1.3 Paper III -Incidence and lifetime risk

We identified in total 144,107 (66% females) hospitalizations for diverticular disease in 95,049 (63 % females) individuals with a median attained age at first hospitalization of 62 years in men and 67 years in women. There were 17,599 (60% females) hospitalizations with bowel resection or stoma formation with a diagnosis of diverticular disease in 16,824 individuals (60% females). The total number of person-years in the population years 1987-2010 was 213,949,897.

Overall, the standardized incidence rates during the study period were 47.4 and 8.4 per 100 000 person-years for hospitalization and surgery, respectively. The corresponding admission rates were 70.8 for hospitalization and 8.7 for surgery.

Incidence rates and admission rates for both hospitalization and surgery for diverticular disease were higher in females. In the years 1990-1994, there was an increase of hospitalizations in both sexes, but years before and after they were relative stable. Hospitalization and surgery with diverticular disease were more common with increasing age. Incidence rates for hospitalization were increasing in younger age groups of men over the different calendar time periods but there was no consistent change of the incidence of surgery in any age group over time of study.

Age-specific incidence rates of hospitalization were largely equal between sexes at ages 30-45, followed by higher rates in women with a peak between 80 and 90 years of age. The incidence of diverticular disease surgery was higher in women from approximately 55 years of age, compared to men.

The estimated remaining lifetime risk at age 30 being hospitalized for diverticular disease was 3.1% in men and 5.0% in women. Corresponding for surgery for diverticular disease was 0.5% and 0.8%.

4.1.4 Paper IV -Mortality

4.1.4.1 Cohort characteristics

The diverticulitis cohort consisted of 83,461 (9,510 surgically and 73,951 conservatively treated) patients after exclusions were made. Of these, 63.2% were female. The matched disease-free cohort comprised 812,942 individuals. Diverticulitis patients had a higher comorbidity compared to individuals in the disease free-cohort.

4.1.4.2 Cumulative mortality

During a maximum follow-up of 21 years, diverticulitis patients and disease-free individuals were monitored 623,918 and 6,438,357 patient years respectively. 27,382 and 226,007 deaths were observed, corresponding to mortality (rates) of 43.9 (95% CI 43.4-44.4) and 35.1 (95% CI 35.0-35.2) deaths per 1000 person-years.

The proportion of individuals who died in the first 100 days and 5 years was 4.1% (95% CI 4.0-4.3%) and 20.3% (95% CI 20.0-20.6%) for diverticulitis patients and 0.8% (95% CI 0.7-0.8%) and 14.5% (95% CI 14.4-14.5%) for disease-free individuals.

The cumulative mortality in diverticulitis patients was similar when comparing sexes. At 100 days, the death proportion was 4.1% in both males and females. At 5 years the proportion of men with diverticulitis who had diseased was 21.1% (95% CI 20.6-21.6%) compared to 14.7% (95% CI 14.6-14.9%) in disease-free individuals. Corresponding proportions for women were 19.8% (95% CI 19.5-20.2%) and 14.3% 95% CI 14.2-14.4%).

Surgical treatment in diverticulitis patients was associated with an almost four times higher death proportion after 100 days compared to conservative treatment, 11.4% (95% CI 10.8-12.1%) vs. 3.2% (95% CI 3.1-3.3%). In the comparison cohort, 0.8% (95% CI 0.7-0.8%) [conservative reference cohort] and 0.8% (95% CI 0.7-0.9%) [surgical reference cohort] were dead after 100 days. After 5 years, death proportion was 29.0% (95% CI 28.1-30.0%) in patients with initial surgical treatment, and 19.2% (95% CI 18.9-19.5%) in conservative treatment. This should be compared to 14.6% (95% CI 14.4-14.9%) and 14.4% (95% CI 14.4-14.5%) of the disease-free individuals, respectively.

Mortality during the hospital stay decreased slightly over time for conservative treatment, from 0.92% during years 1990-1999, to 0.79% 2000-2010, but increased for surgical

treatment, from 6.27% to 6.73%. The average hospital length of stay decreased over the two calendar periods, with about one day for both treatment groups.

4.1.4.3 Mortality from regression models

The diverticulitis cohort had over 4 times increased hazard rates for death the first 100 days after initial admission (HR 4.44 [95% CI 4.26–4.63]), compared to disease-free individuals. From day 101 to 5 years, hazard rates were increased by 11% (HR 1.11 [95% CI 1.09–1.13]).

Surgical treatment was associated with the highest hazard ratios, both in short term, HR 12.13 (95% CI 11.03–13.34) and long term, HR 1.40 (95% CI 1.32–1.47).

The first 100 days, the relative increase in hazard rates was slightly higher in female patients, HR 4.75 (95% CI 4.51–5.01), than in males, HR 3.99 (95% CI 3.72–4.27). Long term hazard ratios were similar between sexes. There was no apparent pattern of advancing age affecting hazard ratios.

The later calendar period (2000–2010) was associated with slightly higher hazard ratios compared to earlier calendar period (1990–2000) in the short term but they were similar in the long term.

The adjusted overall attributable risk percentage for diverticulitis was 77,5% the first 100 days and thereafter up to five years 9.8%. Corresponding figures for surgically managed hospitalization was 91.8% and 28.4% and for conservative 70.9% and 7.0%

5 DISCUSSION

5.1.1 Association to colon cancer

Four possible types of theoretical relationships between the diverticular disease and colon cancer have been described: 1) Both diseases are associated due to causal relationships 2) Both diseases are associated due to common risk factors and similar causes 3) Both diseases are separate entities and are unrelated 4) Separate diseases but somehow related (eg. one may cause diagnostic problems of the other) (263). Chronic inflammation, alterations in the extracellular matrix, dysregulated cell proliferation and dysbiosis in diverticular disease patients, promoting carcinogenesis, have been speculated as possible links between the disorders (263).

Our study (Paper I) of all registered colon cancer patients in Sweden during 1992–2006 showed an increased risk of colon cancer within the first year, and particularly the first 6 months, after hospitalization for diverticular disease. No association between hospitalization for diverticular disease and colon cancer was found thereafter.

The first-year association with colon cancer in our study was probably mainly caused by misclassification and surveillance bias. Since the two disorders can present with similar symptoms and it sometimes is difficult to distinguish clinical and radiological findings, a colon cancer can be misclassified as diverticulitis, where after a subsequent colon examination reveals the cancer (45, 264–266). Follow-up colonoscopy is recommended within the first two months after a first-time diverticulitis episode but in Sweden the waiting time might well exceed 6 months for patients with a stable clinical condition. Surveillance bias can be present as patients with diverticular disease might have symptoms leading to colon examination in a greater extent than diverticular disease-free individuals. There might be controls with unknown colon cancer that would be found if they were had their colon examined in the same extent as cases.

Our conclusion is that diverticular disease does not increase the risk of colon cancer *per se,* but that colon cancer should be excluded after a first hospitalization.

Most studies on the issue published before 1993, including cross-sectional studies of endoscopic findings did not find any association between diverticular disease and colon cancer except from Morini et al, who found a positive association between diverticulosis and colon ademonas in a case-control study (55). In 1993, Stefansson et al found an association between diverticular disease and the risk of colon cancer with a relative risk of 1.8 (95% CI 1.1–2.7) in all age groups and both in males and females in a Swedish register-based cohort study, including 7,159 patients hospitalized in Uppsala health care region for

diverticular disease, during the years 1963–1983. The increased risk of colon cancer was found to be only in left colon. Based on these results, many medical centres started surveillance programs for diverticular disease patients. In 2004, the same authors did a nested case–control follow–up study and hypothesized that it could be the inflammation in diverticulitis that was the driving force to formation to malignancy. An OR of 4.2 (95% CI 1.3–13.0) for developing colon cancer was found for diverticulitis patients compared to diverticulosis patients. However, these two studies of great impact included patients at a time when diverticulitis patients mainly were diagnosed by barium enema or solely clinically without radiological examination. In our study of patients hospitalized during 1992-2006, CT was most likely, widely used to enhance diagnostic accuracy, with sensitivity of 93-98% and specificity of 75-100% (213). Other later studies, including cross–sectional endoscopic findings and case–control studies in which colon cancer patients are compared to a colon cancer free group and incidence of diverticulosis is examined in surgical specimen or by endoscopic or radiological findings, have in some extent been contradictory (Table 6). In a review article from 2008, Morini described that studies so far had several limitations and that there was not enough evidence yet to recommend surveillance programs (44). After our study, another large register–based study was performed in Taiwan, including 41,359 patients. In this cohort study with a disease–free comparison group, diverticular disease patients were classified as having diverticulosis or diverticulitis. Results were similar to ours. The first year after diagnose the risk for colorectal cancer was increased (HR 4.54, 95 CI 4.19–4.91) but when excluding the first 12 months there was no increased risk for colorectal cancer, neither in diverticulosis nor diverticulitis group (65). They also concluded that diverticular disease is not associated with colon cancer after one year. This strengthens the fourth of the above–mentioned hypotheses, that diverticular disease and colon cancer are separate diseases but related in diagnosing. Regarding colonoscopy after initial hospitalization for diverticulitis, there is still an ongoing debate. Daniels et al compared findings of advanced colonic neoplasia at follow–up colonoscopy in patients with CT–proven uncomplicated diverticulitis to those in participants in a primary colonoscopy colorectal cancer screening program and found no significant differences in the groups (267). Updated guidelines internationally are still recommending routine follow–up colonoscopy after first episode of diverticulitis (267). Perhaps it will be possible in the future to differentiate the group of diverticulitis patients to those with lower and higher risk of colon cancer findings after a diverticulitis episode respectively, and to exclusively re–examine the colon on those who have the benefits of this extra investigation. This approach would need further research, preferably in prospective settings.

5.1.2 Heredity

Our twin study on diverticular disease patients we found that genetics contributes to disease occurrence. The results were similar when analyzing both primary and secondary diagnoses compared to analyzing primary diagnoses alone. This might indicate that inflammation in diverticulitis (which is considered predominant in primary diagnoses) does not differ in genetic susceptibility to that of diverticulosis (please see "5.2 Methodological considerations " for further discussion on this topic). The twin study model relies on some assumptions including equal environmental influences for monozygotic and dizygotic twins, random mating and no interaction between genes and environment. These assumptions might lead to an over- or underestimate of the genetic component. Lifestyle factors or use of drugs that are known to influence the risk of diverticular disease could differ in different zygosity groups and could influence the results, although this is unknown. The relative influence of genetic and environmental factors could also differ in different populations; therefore, the results might not be generalizable to all parts of the world.

One year after our study, Strate et al published a similar twin study from the Danish Twin Registry, including also outpatients in the latter part of the study period. In addition, they analyzed incidence of diverticular disease in siblings of a diverticular disease case compared to the incidence in the general population (standardized incidence ratios, SIR). Their twin study results resembled ours, with an estimated genetic susceptibility for diverticular disease occurrence of 53% (95% CI 45-61%). Their analyses of siblings revealed a relative risk for diverticular disease in siblings of diverticular disease patients of 2.92 (95% CI 2.50-3.39) compared to the general population. This strengthens our conclusion of the importance of a genetic factor. The pathophysiological pathways of genetic influence on diverticular disease have been suggested to include connective tissue alterations, neuromuscular abnormalities and differences in mucosal immunity, but is still unknown. (162).

5.1.3 Incidence and lifetime risk

Our nation-wide cohort study of admission rates, incidence rates and lifetime risk of hospitalization and surgery of diverticular disease, included 95,049 individuals, with 144,107 admissions. We found an increase of admission rates and incidence rates of hospitalization for diverticular disease during the first years of 1990's, but thereafter the rates were relatively constant. However, the rates of diverticular disease surgery remained essentially unchanged throughout the study period. We estimated that approximately one in 33 men and one in 20 women are likely to be hospitalized with diverticular disease during their lifetime, which corresponds to about six times their risk for diverticular disease surgery.

The observed increase of hospitalization with diverticular disease in the beginning of the study period is probably not reflecting an increase in the true incidence but might be related to other aspects as improved diagnostics (such as computed tomography becoming more frequent used (268)) or changes in coding practices. Before 1987, some hospitals in Sweden were not yet registering hospitalizations in the *National Patient Register* (see 3.1.2 *National Patient Register*) and therefor some cases in the beginning of the study period might not be incident. However, these false incident cases should then probably have occurred already in 1987.

In United States, increased admission rates, in the time period 1998–2001, have been found, which was not evident in our material of Swedish patients. However, admission rates were similar to ours in the time period 2002–2005 (35, 33). Admission rates in Sweden were noticeably lower than those reported from Ontario, Canada (40). Two English studies on admission rates, using somewhat different selection criteria than ours, have been published. Kang et al found lower admission rates than in Sweden between 1989/1990 and 1999/2000 and Jeyrajah et al revealed admission rates surpassing the Swedish ones between 1996 and 2006, probably largely due to an increase of included daycases (34, 41). In Levanger, Norway, both admission rates and incidence rates 1988–2012 were reported lower than ours, partly due to stricter selection criteria (43). Incidence rates including both hospitalizations and outpatient visits, in Olmsted County, Minnesota, were considerably higher than ours (36).

Differences in reported admission rates and incidence rates can result from somewhat different definitions of events. We have strived to use event definitions that would minimize the extent of misclassification but cannot distinguish the different sub-classifications. Also, our study is nation-wide covering all defined events in the population during the study period which is not the case with several of the other reports.

Some previous studies have reported an increased incidence of diverticular disease, most pronounced in the young (33, 35, 36). Our report presents a consistent increase only in the group of young men.

Our study is the first to investigate lifetime risk of diverticular disease. The estimates are dependent on incidence rates (which are dependent on the event definition used and the extent of misclassification), as well as the impact of mortality. We did only include hospitalizations for diverticular disease and since the disorder can also be managed in an outpatient setting, the overall risk of being treated for diverticular disease is probably higher. The expected future increase in lifetime will presumably lead to higher proportions of individuals developing symptomatic diverticular disease in their lifetime and possibly

even higher proportions needing hospital care (274). This scenario might add to the burden that diverticular disease poses on our health care systems.

5.1.4 Mortality

In our nation-wide cohort study of mortality in 83.461 hospitalized diverticulitis patients we found a 4 times increased mortality within the first 100 days and 11% increased mortality thereafter up to five years, compared to matched disease-free individuals. Surgical patients had 12 times respectively 40% increased mortality. Diverticulitis could thereby be regarded as a quite deadly disease, particularly when surgery is needed.

According to our results, death occur frequently up to several months after surgery. The *Accordion Severity Grading* System of surgical complications has lately recommended extending the general time period for postoperative deaths from the more common used 30 days to 100 days (269). Edna et al. found a death proportion at 7.5% 100 days after initial hospitalization of in a mix of 650 conservative and surgically treated patients with acute diverticulitis, in Levanger, Norway, which is higher than our proportion of 4.1%. They found an all in-hospital death proportion of 6.1%, compared to ours of 0.79-0.92% in conservative treated and 6.27%-6.73% in surgically treated patients. In their study 12.3% had surgical treatment compared to 11.4% in our study (270).

Studies of long-term mortality in diverticulitis, for comparison, are rare. 5-year death proportion has been reported to be 14.1% after discharge from initial conservative managed admissions (72). In our study, the 5-year death proportion of 19.2% in these patients also include deaths in-hospital. Humes et al. have investigated long-term mortality of 953 diverticulitis patients with perforated colon and found a HR of 5.63 (95% CI 4.68-6.77). Our results of a HR 1.40 (95% CI 1.32-1.47, p-value <0.001) in surgically treated patients, include a broader spectrum of disease severities and long-term follow up was defined differently, as from day 101 to 5 years after admission.

We found that diverticulitis patients have more comorbidity than matched disease-free individuals, which is accounted for in the regression models. Patients being hospitalized for any kind of disease are probably more disposed to comorbidities than the general population and also for this reason have a higher mortality. Therefore, this is important adjusting for.

Our study comprises the entire spectrum of disease severity in diverticulitis-patients and demonstrates the increased mortality in this disease-group. The results might be useful when comparing mortality to other disease-groups, evaluating new treatments and prioritizing health care resources. The individual altered risk of dying because of this

disease is probably mostly dependent on its severity and if surgery is needed, together with comorbidities and the patients' general condition.

5.2 METHODOLOGICAL CONSIDERATIONS

There are several methodological aspects that are related to all four studies that need to be discussed further as they are potential limitations.

Classification of diverticular disease is a limitation in our studies. Diverticular disease is a spectrum of conditions, from asymptomatic diverticulosis, to the presence of less severe symptoms without signs of overt inflammation (SUDD) to diverticulitis. Diverticular bleeding is in addition a common complication separated from those related to diverticulitis but might itself lead to hospitalization. The existence of diverticula is apparent at endoscopy (colonoscopy and sigmoidoscopy) and radiological examinations such as computed tomography, magnetic resonance imaging, barium enema x-ray and ultrasound. Since the prevalence of diverticulosis is high and most patients do not have symptoms related to the diverticulosis, findings of diverticula, *en passant,* at investigations aimed at other disorders than diverticula-related ones are common. The diagnoses in the Swedish health registries used in our studies are based on the World Health Organization's International Classification of Diseases (ICD). While the 8th version of ICD, used until 1986, separated diverticulosis and diverticulitis, the succeeding versions 9 and 10 (used years 1987-1996 respectively 1997-present) do not. In version 9 there is only one common code for diverticulosis and diverticulitis and in version 10 one can only differentiate disorders with or without perforation in the colon wall and/or the existence of an abscess. Diverticulitis without perforation and abscess and asymptomatic diverticulosis or SUDD can therefore not be distinguished only by knowledge of the registered codes. One can however take into account if the code is registered as a primary or secondary code. The primary code is mainly used for the disorder that causes the symptoms or is the most important in the clinical setting while secondary codes many times can be considered as not directly causing the symptoms or as comorbidity. Asymptomatic diverticulosis, we believe, is therefore most commonly registered as a secondary code and diverticulitis registered as a primary code. The condition SUDD has most recently, after the study periods, gained more attention and diverticula without diverticulitis have earlier generally not being considered as a cause of symptoms, minimizing its portion of primary codes in inpatient setting. Hospitalization for a gastrointestinal bleeding caused by diverticula is mainly registered with both a code for gastrointestinal bleeding and a code for diverticular disease of which gastrointestinal bleeding is probably often the primary code, but this might differ in different hospitals. In the four studies, we have used somewhat different definitions of the disease of study. This is partly due to different approaches, as we in

Paper II and Paper III aimed to "catch" as many patients in the broader disease spectrum as possible, when studying incidence, admission rates and heritability, while it was more important to narrow the disease definition to solely diverticulitis patients when studying this patient category's mortality, with the potential cost of missed patients (Paper IV). The different approaches are also a result of our effort to enhance the precision of disease definition over time, which can be seen in differences of definition in Study I and Study IV; in both studies we were most interested in patients hospitalized for diverticulitis. The diverticular disease diagnoses registered in the Swedish inpatient register have not yet been validated in a large study which is drawback. There are however some reports available on the issue. Rosemar et al. studied 112 men with diverticular disease registered as primary or secondary codes in the National Patient Register. The diagnosis was verified in all the 107 cases in which medical records could be retrieved. Of these, 16 were gastrointestinal bleeding, 5 were diverticulosis, and the rest were diverticulitis with or without complications (271). Erichsen et al. analyzed the version 10 of the ICD-codes of diverticular disease in a sample of 100 patients in the Danish National Registry of Patients and found a positive predictive value (PPV) for diverticular disease in general of 0.98 (95% CI 0.93-0.99). Combined PPV for codes including any complication (codes K572, K574, K578) was also satisfactory, at 0.91 (95% CI 0.71-0.99) but identification of uncomplicated disease was found inaccurate. This study included however also outpatients and there was no separation of primary and secondary diagnoses. Furthermore, in a study of Dr. F Hjern (parts of the results are unpublished), the medical records of 529 consecutive inpatients with primary ICD-10 codes K572-9, at Danderyd Hospital, Stockholm, in years 2000-2002, were re-evaluated for validation. In all, 96% were correctly classified. Eighty-eight per cent had acute diverticulitis (of these, 78% of diagnoses were supported by computed tomography and/or surgical findings), 4% had elective surgery due to diverticulitis, 2% had diverticular bleeding and 3% were hospitalized for bowel preparation preceding a colon examination showing diverticulosis. Misclassification was found in 4% (in 1% subsequent colon examination showed colon cancer, and in 3% miscellaneous diagnoses were found) (187). In study IV, in which we aimed at including only patients with diverticulitis, patients with codes of gastrointestinal bleeding and those with a later diagnose of colon cancer were excluded, in addition only first admissions were included. These modifications of disease definition might have led to a higher proportion of diverticulitis patients included.

Another shortcoming is that no strict diagnostic criteria exists for diverticulitis. The diagnoses in our studies are most probably based upon clinical features, together with X-ray, or surgical findings consistent with diverticulitis. The major change in diagnosing diverticulitis the last decades, which probably have had an impact on proportion correct diagnoses, is the switch of standard radiological modality from barium enema x-ray to a

trans-sectional imaging by computed tomography. This change did however mainly occur prior to our study periods and should therefore have little effect on the results over time. Most international guidelines recommend trans-sectional imaging, but in some countries, ultrasound is used in as high degree instead of CT, which in theory might affect generalizability since the two methods could lead to different degrees of misclassification. However, both modalities are shown to have high sensitivity and specificity (236).

Since diverticular disease can be managed by other health care options than as inpatients in hospitals, on which our studies are based, results cannot automatically be generalized to include all diverticular disease patients. As most individuals have no symptoms related to their diverticulosis, they will never seek health care due to this condition. In Paper II, in which heritability was investigated, we aimed to include as many individuals as possible in the diverticular disease spectrum, using both primary and secondary diagnose codes (primary diagnose codes were also analyzed separately) in order to also include some of the patients without diverticulitis. Some of these, diagnosed by secondary codes, were probably asymptomatic findings during an investigation for other reason while others had SUDD. These groups of patients are probably not completely covered in our study. Another group of patients, that we might have missed, is diverticulitis patients that are treated as outpatients or in primary care. These patients are likely to mostly have a less severe disease than those needing inpatient care. The majority of diverticulitis patients are however diagnosed with diverticula at some time, and this is done from radiological or endoscopic investigations, many times in an inpatient setting. Still, the patients that are diagnosed with diverticulosis in an outpatient examination and thereafter seek primary care for less severe diverticulitis symptoms without needing hospital care, are likely to be missed in our studies.

In the first paper, investigating colon cancer association, these missed patients of asymptomatic diverticulosis, SUDD and less severe diverticulitis might not be as important since the main hypothesis stated inflammation as the driving force in malignant transformation. In Paper III, only hospitalized patients were of relevance since hospital incidence, admission rate and lifetime risk of hospitalization were the subjects investigated. If in Paper IV, one could include all diverticulitis patients with less severe disease never being treated in hospital, mortality would probably be lower than we reported.

6 CONCLUSIONS

- Hospitalization for diverticular disease is not associated with colon cancer after one year. The first 12 months after initial hospitalization is however highly associated with colon cancer. Therefore, colon cancer should be excluded after a first episode of suspected diverticulitis, because the risk of misdiagnosing colon cancer as diverticulitis
- Genetic influence accounts for approximately 40% of the occurence in diverticular disease.
- Age standardized incidence rates for hospitalization with diverticular disease is 47 per 100 000 person-years and 8 for diverticular disease surgery. The corresponding admission rates are 71 och 9. The continous increase of diverticular disease hospitalizations found in other studies is not present in Sweden. The remaining lifetime risk for hospitalization at 30 years of age is 3% in men and 5% in women.
- Diverticulitis patients have a significantly reduced survival compared to disease-free individuals, both in short- and long-term. The first 100 days after initial admission, patients have a four times higher mortality than diverticulitis-free individuals. 11% of patients undergoing surgery and 3 % of the conservatively treated patients die during this time period. From day 101 to 5 years surgical treatment is associated with 40% increased mortality and conservative treatment 8%.

7 FUTURE RESEARCH

Ten-fifteen years ago, little was known about diverticular disease, despite its great impact on the Western world public health care systems. Much of the knowledge was based on studies from the 1970's. However, the last years, diverticular disease have gained interest in the research community and many earlier findings have been questioned. Therefore, in a way, more issues now need to be answered than ever before.

The World Health Organizations' International Classification of Disease classification, used in many health care institutions over the world, has since the 1980's been an inconvenience when doing epidemiological research on diverticular disease, due to its' inability to easily differentiate the disorder's sub-classifications. Apparently, the next version, ICD-11, is expected to become more refined, which will likely facilitate future studies using administrative data. Until we have the new classifications in use and have gathered several years of new data, there is a need for a large validation study on the current diverticular disease coding system. Such a validation study would need to include separate and combined codes, primary and secondary diagnoses.

Furthermore, we found that genetic influences are of importance in disease occurrence, but the pathophysiology behind the genetic effects are not known. The findings of DNA sequence variants found in candidate-driven studies and the GWAS need to be adressed in patophysiological studies.

We found that mortality in diverticulitis is high both when initially treated surgically and conservative. It would be interesting to acquire deeper knowledge on the causes of death and how different surgical techniques might affect mortality.

Lastly, patients treated as outpatients in either primary care or at hospital clinics are a group that probably will become larger as indications for inpatient care are getting stricter, at least in Sweden. These patients are often overlooked in diverticular disease studies and should be investigated further.

8 SWEDISH SUMMARY FOR LAYMEN

Avhandling för avläggande av medicine doktorsgrad vid Karolinska Institutet, Institutionen för medicin, Solna, 2018

Epidemiogiska studier på divertikelsjukdom i tjocktarmen

Divertikelsjukdom innebär förekomst av fickor (divertiklar) på tjocktarmen som kan bli inflammerade och orsaka problem. Tillståndet är mycket vanlig hos äldre människor, över hälften av de i 70-80-årsåldern drabbas. Det är betydligt vanligare i utvecklade länder och man tror att diet kan påverka risken att få sjukdomen. De flesta med tarmfickor får inga symtom men ifall de blir inflammerade (divertikulit) får man ont i buken och feber. Inflammationen kan spridas och leda till allvarliga komplikationer som förträngningar, onormala gångbildningar till andra intilliggande organ (som urinblåsa eller vagina) och till akut livshotande tillstånd om tjocktarmen brister.

Avhandlingen omfattar fyra epidemiologiska studier. Epidemiologi betyder läran om sjukdomars utbredning, orsak och påverkan i befolkningen. Studierna är baserade på de svenska befolkningsregister som håller en mycket hög internationell standard. Genom att länka samman registren via personnummer har vi fått ut anonyma data från Socialstyrelsen och Statistiska Centralbyrån där patienters inläggningar på sjukhus, behandlingar, samsjuklighet, dödlighet, utbildningsnivå, civilstånd och eventuella detaljer kring tvillingskap framgår.

I delstudie 1 undersöktes om divertikelsjukdom var kopplat till cancer i tjocktarmen. Det har funnits hypoteser kring att inflammation i tarmväggen hos patienter med divertikelsjukdom skulle kunna orsaka cancer, vilket är visat i andra inflammatoriska tillstånd i mag-tarmkanalen. Både divertikelsjukdom och tjocktarmscancer har blivit betydligt vanligare i befolkningen i västvärlden senaste årtiondena och de ökar med stigande ålder. Därtill tror man att liknande diet kan öka risken för båda tillstånden. Tidigare studier har visat olika resultat och eftersom man inte med säkerhet har kunnat utesluta att divertikelsjukdom kan leda till tjocktarmscancer screenar man på vissa sjukvårdsinrättningar patienter med divertikelsjukdom regelbundet med tjocktarmsundersökning. Studien gjordes genom att länka samman Patientregistret, Registret över totalbefolkningen och Cancerregistret. Samtliga individer som diagnosticerats med tjocktarmscancer i Sverige under åren 1987-2006 inkluderades i studien. Resultaten visade att det första året efter divertikelsjukdom fanns en hög risk för att diagnosticeras med tjocktarmscancer men att det därefter inte fanns någon koppling mellan sjukdomarna. Den ökade risken första året beror sannolikt inte på att divertikelsjukdom i sig leder till tjocktarmscancer utan bland annat på att

divertikelsjukdom i det akuta skedet är svår att skilja från tjocktarmscancer och att man först vid den uppföljandende kontroll upptäcker cancern. Vår rekommendation blev att tarmen bör kontrolleras efter ett förstagångsinsjuknande i divertikelsjukdom för att utesluta tjocktarmscancer.

I delstudie 2 undersökte vi om det fanns en ärftlighet i utvecklandet av divertikelsjukdom. Detta hade hittills varit okänd och outforskat. Svenska tvillingregistret på Karolinska Institutet är världens största tvillingregister och innehåller information om tvillingar sedan 1800-talet. Detta register samt Patientregistret användes i denna studie. Genom att undersöka om enäggstvillingspar i högre utsträckning än tvääggstvillingspar drabbades av divertikelsjukdom kunde vi förstå om det fanns en ärftlig komponent. Detta då enäggstvillingpar har samma genetiska material medan tvääggstvillingpar i genomsnitt har till hälften samma. Resultaten visade att det finns en betydande ärftlig komponent i utvecklandet av sjukdomen.

I delstudie 3 undersökte vi i vilken utsträckning individer läggs in på sjukhus för sin divertikelsjukdom samt hur vanligt det är med operation för divertikelsjukdom och om dessa saker har förändrats senaste årtiondena. Tidigare studier har visat olika resultat och det har saknats en studie som innefattar en hel befolkning. Vi använde oss i huvudsak av Patientregistret och Registret över totalbefolkningen i denna studie. I resultaten framkom förutom mått på ovanstående även att en frisk kvinna som är 30 år gammal har 5% risk att någon gång under sin förväntade kvarstående levnadstid läggas in på sjukhus för divertikelsjukdom. Motsvarande för män är 3%.

I delstudie 4 önskade vi undersöka hur dödlig inflammation i tarmfickor är jämfört med en kontrollgrupp. För denna studie användes Patientregistret, Registret över totalbefolkningen, Utbildningsregistret och Cancerregistret. Resultaten visade att opererade patienter har en 12 gånger ökad dödlighet första 100 dagarna och därefter 40% ökad dödlighet upp till 5 år efter första inläggningen på sjukhus. Under de första 100 dagarna dör över var tionde opererade patient. De patienter som har en mindre allvarlig sjukdom och inte behöver opereras har inte lika hög dödlighet men den är förhöjd jämfört med den i den friska befolkningen även efter lång tid.

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11 APPENDIX

Table A1. The European Association of Endoscopic Surgeons classification

Symptomatic uncomplicated disease
Recurrent symptomatic disease
Complicated disease (Hemorrhage, Abscess, Phlegmon, Fistula, Perforation, Stricture, Purulent and fecal peritonitis, Small bowel obstruction due to post-inflammatory adhesion)

Table A2. Hansen/Stock and Siewert classifications

Hansen/Stock			Siewert et al.	
0	Diverticulosis			
I	Acute uncomplicated diverticulitis			
II	Acute complicated diverticulitis			
	a	Phlegmon, peridiverticulitis	I	Pericolic abscess or phlegmon
	b	Abscess, sealed perforation	II	Pelvic, intraabdominal, or retroperitoneal abscess
	c	Free perforation	III	Free perforation
III	Chronic recurrent diverticulitis			

Table A3. Klarenbeek classification

Classifi-cation	Clinical presentation	Imaging	Treatment
A	Uncomplicated disease	CT scan or US	Conservative treatment
	-Pain in left lower quadrant	-Phlegmon	Treatment acute episode
	-Fever	-Small abscess in bowel wall	-Antibiotics[a]
	-Changes in relief pattern	Colonoscopy	-Low residue diet[a]
		-Diverticulosis	Prevention
		-Inflammation	-Fibers
			-Prevention of obesity
			-Treatment of comorbidity
			-Mesalazine[a]
B	Chronic complicated disease	CT scan	Elective Intervention
		-Stenosis	Sigmoid resection with primary anastomosis
		-Fistula	-Open
		Colonoscopy	-Laparoscopically
		-Stenosis	
		-Fistula	
		-Blood in diverticula	
C	Acute complicated disease		Acute intervention
1	-Fever	CT scan	Percutaneous drainage
	-Painful mass	-Large abscesses (<5cm)	
2	Ileus	CT scan	Sigmoid resection with primary anastomosis
3	Massive rectal blood loss	-Intestinal obstruction	Hartmann's procedure
		CT angio	Sigmoid resection with primary anastomosis
		-Contrast blush	-Open
		Colonoscopy	-Laparoscopically
		-Active diverticular bleeding	Endoscopic intervention[a]
			Endovascular coiling[a]
4	Generalized peritonitis	CT scan	Diagnostic laparotomy/laparoscopy
		-Pneumoperitoneum	-Resection with primary anastomosis
		-Extraluminal contrast	Hartmann's procedure
		-Free fluid	Lavage and drainage[a]

[a]Experimental or non-evidence-based treatment

Table A4. Paper II -Excluded diagnostic codes from the National Inpatient Registry

Disease	ICD 8	ICD 9	ICD 10
Non-infectious colitis	561.00-04, 561,08-09, 563,00, 563,10, 563,98-99, 564,10, 569,02	555B, 555C, 555X, 556-558	K50.0-1, K50.8-9, K51.0, K51.2-4, K51.8-9, K55.0-1, K55.9, K52.0-3, K52.8-9
Celiac disease	269,00, 269,98	579A	K90.0

Table A5. Paper III and IV - Diagnose and procedure codes

Diverticular disease of the colon		
ICD-8	562,10	Diverticulosis of the colon
	562,11	Diverticulitis of the colon
	562,18	Diverticulosis and diverticulitis of the intestine, other
	562,19	Diverticulosis and diverticulitis of the intestine, unspecified
ICD-9	562B	Diverticulitis and diverticulosis of the colon
ICD-10	K57.2	Diverticular disease of large intestine with perforation and abscess
	K57.3	Diverticular disease of large intestine without perforation or abscess
	K57.4	Diverticular disease of both small and large intestine with perforation and abscess
	K57.5	Diverticular disease of both small and large intestine without perforation or abscess
	K57.8	Diverticular disease of intestine, part unspecified, with perforation and abscess
	K57.9	Diverticular disease of intestine, part unspecified, without perforation or abscess
Peritonitis, abscess, fistula		
ICD-8	567,00	Pelvic abscess
	567,01	Subphrenic abscess
	567,02	Retroperitoneal abscess
	567,03	Localized peritonitis
	567,04	Diffuse peritonitis
	567,08	Peritonitis, other
	567,09	Peritonitis, unspecified
	569,00	Intestinal abscess
	569,01	Intestinal perforation
ICD-9	567C	Other suppurative peritonitis
	567X	Peritonitis, unspecified
	569F	Abscess of intestine
	596B	Intestinovesical fistula
	619B	Digestive - genital tract fistulae, female
ICD-10	K65.0	Acute peritonitis
	K65.9	Peritonitis, unspecified
	K63.2	Fistula of intestine
	N32.1	Vesicointestinal fistula
	N82.3	Fistula of vagina to large intestine
	N82.4	Other female intestinal-genital tract fistulae
	K63.0	Abscess of intestine
Colorectal cancer		
ICD-7	153	Malignant neoplasm of colon
	154	Malignant neoplasm of rectum
ICD-8	153	Malignant neoplasm of colon
	154,01	Malignant neoplasm of rectosigmoid junction
	154,11	Malignant neoplasm of rectum
ICD-9	153	Malignant neoplasm of colon
	154A	Malignant neoplasm of rectosigmoid junction
	154B	Malignant neoplasm of rectum
	154W	Malignant neoplasm of rectum, rectosigmoid junction and anus, other

ICD-10	C18	Malignant neoplasm of colon
	C19	Malignant neoplasm of rectosigmoid junction
	C20	Malignant neoplasm of rectum
Inflammatory bowel disease		
ICD-8	563,00	Regional enteritis (including Crohn's disease)
	563,10	Ulcerative colitis
	563,98	Chronic enteritis and ulcerative colitis, other
	563,99	Chronic enteritis and ulcerative colitis, unspecified
	569,02	Ulcerative proctitis
ICD-9	555	Regional enteritis (including Crohn's disease)
	556	Idiopathic proctocolitis (including ulcerative colitis)
ICD-10	K50	Crohn's disease
	K51	Ulcerative colitis
Appendicitis		
ICD-8	540	Appendicitis acuta
	541	Appendicitis NUD
	542	Appendicitis alia
ICD-9	540	Acute appendicitis
	541	Appendicitis, unqualified
	542	Other appendicitis
ICD-10	K35	Acute appendicitis
Vascular insufficiency of intestine		
ICD-8	444,20	Mesenteric thrombosis and embolism
ICD-9	557	Vascular insufficiency of intestine
ICD-10	K55	Vascular disorders of intestine
Lower gastrointestinal bleeding		
ICD-9	569D	Haemorrhage of rectum and anus
	578X	Haemorrhage of gastrointestinal tract, unspecified
ICD-10	K62.5	Haemorrhage of anus and rectum
	K92.2	Gastrointestinal haemorrhage, unspecified
Colorectal resection		
Procedure codes -1996	4640	Left hemicolectomy
	4641	Right hemicolectomy
	4642	Ileocaecal resection
	4643	Resection of transverse colon
	4644	Resection of sigmoid colon
	4648	Ileocolic resection
	4649	Other colonic resection
	4713	Hartmann's procedure
	4651	Colectomy with ileostomy
Procedure codes 1997-	JFB20	Ileocaecal resection
	JFB21	Laparoscopic ileocaecal resection
	JFB30	Right hemicolectomy
	JFB31	Laparoscopic right hemicolectomy
	JFB33	Other resection comprising small intestine and colon

	JFB34	Other laparoscopic resection comprising small intestine and colon
	JFB40	Resection of transverse colon
	JFB41	Laparoscopic resection of transverse colon
	JFB43	Left hemicolectomy
	JFB44	Laparoscopic left hemicolectomy
	JFB46	Resection of sigmoid colon
	JFB47	Laparoscopic resection of sigmoid colon
	JFB50	Other resection of colon
	JFB51	Other laparoscopic resection of colon
	JFB53	Resection of sigmoid colon with partial proctectomy
	JFB54	Laparoscopic resection of sigmoid colon with partial proctectomy
	JFB60	Resection of sigmoid colon with end colostomy
	JFB61	Laparoscopic resection of sigmoid colon with end colostomy and closure of distal stump
	JFB63	Other resection of colon with proximal colostomy and closure of distal stump
	JFB64	Other laparoscopic resection of colon with proximal colostomy and closure of distal stump
	JFB96	Other partial excision of intestine
	JFB97	Other laparoscopic partial excision of intestine
	JFH10	Total colectomy and ileostomy
	JGB00	Partial proctectomy and colorectal or coloanal anastomosis
	JGB01	Laparoscopic partial proctectomy and colorectal or coloanal anastomosis
	JGB03	Partial proctectomy with partial excision of mesorectum
	JGB04	Laparoscopic partial proctectomy with partial excision of mesorectum
	JGB10	Partial proctectomy and end colostomy
	JGB11	Laparoscopic partial proctectomy and end colostomy
Stoma formation		
Procedure codes -1996	4700	Ileostomy
	4710	Sigmoidostomy
	4711	Transversostomy
Procedure codes 1997-	JFF10	Loop enterostomy
	JFF11	Laparoscopic loop enterostomy
	JFF23	Transversostomy
	JFF24	Laparoscopic transversostomy
	JFF26	Sigmoidostomy
	JFF27	Laparoscopic sigmoidostomy
	JFF30	Other colostomy
	JFF31	Other laparoscopic colostomy
Endoscopic procedures		
Procedure codes -1996	4674	Sigmoidoscopy with polypectomy
	4674	Colonoscopy with polypectomy
	4685	Sigmoidoscopy with biopsy
	4688	Ileoscopy with biopsy
	4689	Colonoscopy with biopsy
	9011	Colonoscopy

	9012	Sigmoidoscopy
	9023	Ileoscopy
Procedure codes 1997-	UJF32	Colonoscopy
	UJF35	Colonoscopy with biopsy
	UJF42	Flexible sigmoidoscopy
	UJF45	Flexible sigmoidoscopy with biopsy
	JFA15	Endoscopic polypectomy in colon

Table A6. Paper IV -Comorbidity classification

Diagnose	ICD 8	ICD 9	ICD 10
Myocardial infarction	410	410, 412	I21, I22, I25.2
Congestive heart failure	427,00, 427,10, 428,99, 782,40	398X, 402, 404, 425E-X, 428	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43, I50
Peripheral vascular disease	440-445	093A, 437D, 440, 441, 443B-X, 447B, 557B-X, V43E	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	430-438	362D, 430–438	G45, G46, H34.0, I60–I69
Dementia	290	290, 294B, 331C	F00–F03, F05.1, G30, G31.1
Chronic pulmonary disease	490-493, 515-518	416W-X, 490-505, 506E, 508B 508W	I27.8, I27.9, J40–J47, J60–J67, J68.4, J70.1, J70.3
Rheumatic disease	712, 734, 446, 716	446F, 710A-E, 714A-C, 714W, 725.x	M05, M06, M31.5, M32–M34, M35.1, M35.3, M36.0
Liver disease	070, 571, 573, 456,00	070C-X, 456A-C, 570, 571, 572C-W, 573D/E/W/X, V42H	B18, K70, K71.1, K71.3–K71.5, K71.7, K72.1, K72.9, K73, K74, K76.0, K76.2–K76.9, Z94.4, I85.0, I85.9, I86.4, I98.2
Diabetes mellitus	250	250	E10, E11, E12, E13, E14
Renal disease	403, 404, 580-584	403, 404, 582, 583, 585, 586, 588A, V42A, V45B, V56	I12.0, I13.1, N03.2–N03.7, N05.2– N05.7, N18, N19, N25.0, Z49.0– Z49.2, Z94.0, Z99.2
Malignancy	140-209	140-208, 238G	C00-C97
Alcohol abuse	291, 571,00, 571,01, 303	265C, 291, 303, 305A, 357F, 425F, 535D, 571A-D, 980	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51, Z50.2, Z71.4, Z72.1
Pulmonary embolism	450	415B	I26.0, I26,9