Thesis for doctoral degree (Ph.D.)
2018

Epidemiological and pathophysiological studies on diverticular disease in the colon

M. Ellionore Järbrink-Sehgal

Karolinska Institutet

From Department of Medicine, Solna
Karolinska Institutet, Stockholm, Sweden

EPIDEMIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON DIVERTICULAR DISEASE IN THE COLON

M. Ellionore Järbrink-Sehgal

Karolinska Institutet

Stockholm 2018

Published by Karolinska Institutet.
Printed by Arkitektkopia AB, 2018

ISBN 978-91-7831-208-5

Epidemiological and pathophysiological studies on diverticular disease in the colon

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

M. Ellionore Järbrink-Sehgal

Principal Supervisor:

Associate Professor Peter Thelin Schmidt
Karolinska Institutet
Department of Medicin, Solna
Division of Clinical Medicine

Co-supervisor(s):

Associate Professor Anna Andreasson
Karolinska Institutet
Department of Medicine, Solna
Division of Clinical Medicine

Professor Lars Agréus
Karolinska Institutet
Department of Neurobiology, Care and Science
Division of Family Practice and Primary Care

Professor Nicholas J. Talley
University of Newcastle
Department of Medicine
Division of Gastroenterology

Opponent:

Clinical Associate Professor David Humes
University of Nottingham
Department of Surgery
Division of Nottingham Digestive Diseases
Centre, School of Medicine

Examination Board:

Associate Professor Riadh Sadik
University of Gothenburg
Department of Internal Medicine
& Clinical Nutrition

Associate Professor Scott Montgomery
Örebro University
Department of Medical Sciences
Division of,Clinical Epidemiology
and Biostatistics

Associate Professor Monika Egenvall
Karolinska Institutet
Department of Molecular Medicine
and Surgery
Division of Colorectal Surgery

To my girls, Sofia and Bella

“If you only do what you can do, you’ll never be better than what you are.”
– Master Shifu from Kung Fu Panda

ABSTRACT

Background: Diverticular disease of the colon is common and is associated with a high and increasing societal burden with great economical and human costs. Prevalence increases with age and with an overall aging population, investigating risk factors are important. The pathogenesis is complex and poorly understood. Low-grade inflammation and gut dysbiosis have been suggested to play a role but population studies are lacking. While genetic and lifestyle factors have been associated with increased risk for complicated diverticular disease in adults, environmental risk factors are underexplored. The aim of this thesis was to investigate the prevalence of diverticulosis, its association with gastrointestinal symptoms and colonic inflammation in a general population, and to identify early lifestyle and environmental risk factors for developing future symptomatic diverticular disease, in a young population.

Methods and Main results: In **paper I**, we performed a population-based colonoscopy study of randomly selected adults born in Sweden (18–70 years old) assessing the association between abdominal symptoms, mental health, colonoscopy findings and diverticulosis (n=742). We found the prevalence of diverticulosis to be age-dependent and diverticulosis was associated with diarrhea across all age groups. In those older than 60 years of age, diverticulosis was further associated with abdominal pain and diarrhea-predominant IBS. In **paper II**, a nested case control study from paper I was performed (n=127 cases with diverticulosis and n=127 controls). The findings were that in a general community sample, neither asymptomatic nor symptomatic diverticulosis, were associated with serological or colonic mucosal inflammation. Other explanations for symptomatic colonic diverticulosis need to be identified. **Papers III and IV** were population-based cohort studies of Swedish male conscripts ages 18-20, investigating the association between lifestyle and environmental exposure variables, and symptomatic diverticular disease requiring hospitalization from 1969-2009 (n=49,321). In papers III and IV, we found that exposure to parental divorce, being overweight or obese, a smoker, a risk user of alcohol and/or having low cardiovascular fitness in late adolescence is associated with an increased risk of hospitalized diverticular disease later in life.

Conclusions: Diverticulosis is common, age-dependent and associated with diarrhea and age-specific symptoms but not inflammation. Early adulthood lifestyle and environmental factors such as obesity, smoking, risky alcohol use, physical inactivity and early adverse events such as parental divorce increase the risk for developing severe diverticular disease.

Future studies investigating alternate pathophysiologic mechanisms for diverticulosis are needed and prospective age-specific studies evaluating early life events and the role of modified lifestyle risk factors and course of diverticular disease are recommended.

LIST OF SCIENTIFIC PAPERS

I. M. Ellionore Järbrink-Sehgal, Anna Andreasson, Nicholas J. Talley, Lars Agréus, Jeong-Yeop Song, Peter T. Schmidt
Symptomatic Diverticulosis is Characterized By Loose stools.
Clin Gastroenterol Hepatol 2016;14(12):1763-1770

II. M. Ellionore Järbrink-Sehgal, Loui Rassam, Aws Jasim, Marjorie M. Walker, Nicholas J. Talley, Lars Agréus, Anna Andreasson, Peter T. Schmidt
Diverticulosis, Symptoms And Colonic Inflammation- A Population-Based Colonoscopy Study
Under revision

III. M. Ellionore Järbrink-Sehgal, Peter T. Schmidt, Filip Sköldberg, Tomas Hemmingsson, Hannes Hagström, Anna Andreasson
The Influence Of Environmental Factors In Late Adolescence On Future Symptomatic Diverticular Disease Requiring Hospitalization: A 39 Year Follow Up Study
Manuscript

IV. M. Ellionore Järbrink-Sehgal, Peter T. Schmidt, Filip Sköldberg, Tomas Hemmingsson, Hannes Hagström, Anna Andreasson
Lifestyle Factors in Late Adolescence Associate with Later Development of Diverticular Disease Requiring Hospitalization
Clin Gastroenterol Hepatol. 2018;16(9):1474-1480

CONTENTS

LIST OF ABBREVIATIONS

AGA	American Gastroenterology Association
BMI	Body Mass Index
CI	Confidence Interval
CT	Computerized Tomography
DNR	Diarie Nummer
GI	Gastrointestinal
GWAS	Genome-Wide Association Study
H&E	Hemtaoxylin and Eosin
HADS	Hospital Anxiety Depression Scale
HPA	Hypothalamic–Pituitary–Adrenal
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
IBS-C	Constipation predominant Irritable Bowel Syndrome
IBS-D	Diarrhea predominant Irritable Bowel Syndrome
ICD	International Classification of Diseases
IHC	Immunohistochemistry
IQR	Intraquartile Range
LLQ	Left Lower Quadrant
MRI	Magnetic Resonance Imaging
NPR	National Patient Registry
NSAID	Nonsteroidal Antiinflammatory drug
OR	Odds Ratio
PIN	Personal Identity Number
RCT	Randomized Controlled Trial
SCAD	Segmental Colitis Associated with Diverticulosis
SD	Standard Deviation
SES	Socioeconomic Status
SNP	Single Nucleotide Polymorphism
SUDD	Symptomatic Uncomplicated Diverticular Disease
TNF	Tumor Necrosis Factor
UK	United Kingdom
US, USA	United States, United States of America
USD	US Dollars

1 INTRODUCTION AND RATIONALE

Diverticular disease is a highly common gastrointestinal condition in the Western world (US, Europe and Australia). In the US, it represents the eighth most costly gastrointestinal disease with an estimated economic burden of 2.7 billion USD per year.(1) European data estimate diverticular disease to account for 786,000 hospital admissions per year and 23,605 deaths per year.(2) Comparable data exist in Sweden reports of rising rates of hospitalization for diverticular disease by 14% was noted between 2002 and 2014.(3)

Colonic diverticula are small outpouchings of mucosal and submucosal layers of the colonic wall. While the majority of persons with diverticulosis are asymptomatic, 15-20 % develops symptoms.(4) The clinical picture of diverticular disease ranges from an acute presentation with complicated diverticulitis, perforation, abscess, strictures or fistulas to a chronic presentation with recurrent abdominal pain and change in bowel habits. In addition, long-term complications such as recurrent episodes of diverticulitis(5), new onset irritable bowel syndrome (IBS) and mood disorders(6) after a diverticulitis event as well as reduced quality of life(4) have all been implicated in diverticular disease.

True incidence and prevalence of diverticulosis is unclear though since most affected individuals lack symptoms. Diverticulosis is however the most common colonoscopy finding and it has been estimated that in the US, slightly less than three thirds of the US population will be have diverticulosis by the age of eighty.(7)

The epidemiologic profile of diverticular disease is dominated by age and geography. For many decades diverticular disease has been considered a disease of Western civilization. (8) The countries with the highest prevalence rates are thus the Western countries, i.e. USA, Europe and Australia while it is rare in rural Africa and Asia. An inverse association with fiber intake is thought to play a role in the etiology and geographical variation.(8) Further, in these countries, diverticular disease is age prevalent, rarely affecting individuals younger than 40 years of age (<10%) but commonly (>70%) affecting elderly ages 70 and older.(7)

In spite of its worldwide socioeconomic impact and increasing prevalence of our aging and expanding population, the pathogenesis is not well understood. It is recognized to be multifactorial and complex. Twin studies have established a role for genetic factors increasing the risk for diverticular disease requiring hospitalization.(9, 10) Other factors such as lifestyle factors like diet, obesity, smoking, alcohol, physical inactivity and medications have also been found to play important roles.(11-16) The interaction and

interplay between genetic and non-genetic factors are thus suggested but the exact mechanisms are still unclear.

The main rationale for this project was to elucidate the prevalence of diverticulosis, its association with gastrointestinal symptoms and pathophysiology, namely, colonic inflammation, in a general population. Further it was to identify early lifestyle and environmental risk factors for developing future symptomatic diverticular disease in a young population.

2 BACKGROUND

2.1 Definition

Colonic diverticula are sac-like protrusions of mucosa and submucosa through the muscular colonic wall at weak points in the circular muscle where blood vessels, the vasa recta, enter to supply the mucosa. The size of a diverticulum is typically 3 -10 mm in diameter. Diverticula are really false diverticula as only the mucosa and submucosa, are involved. Diverticula may localize throughout the colon but sigmoid colon is the most commonly affected colonic segment.(17)

2.2 Terminology

The terminology used in the medical literature remains poorly defined. In the past, the term *diverticular disease* was often loosely used as an umbrella diagnosis including both diverticulosis regardless of symptom status and diverticulitis, while more recently it includes any type of symptomatic diverticulosis. Several propositions to nomenclature exist with aim to clarify diverticular terminology and add evolutionary linkages.(4, 18) In this thesis, I use the latter definition where diverticular disease is the umbrella diagnosis for clinically significant symptomatic diverticulosis. See nomenclature in Figure 1.

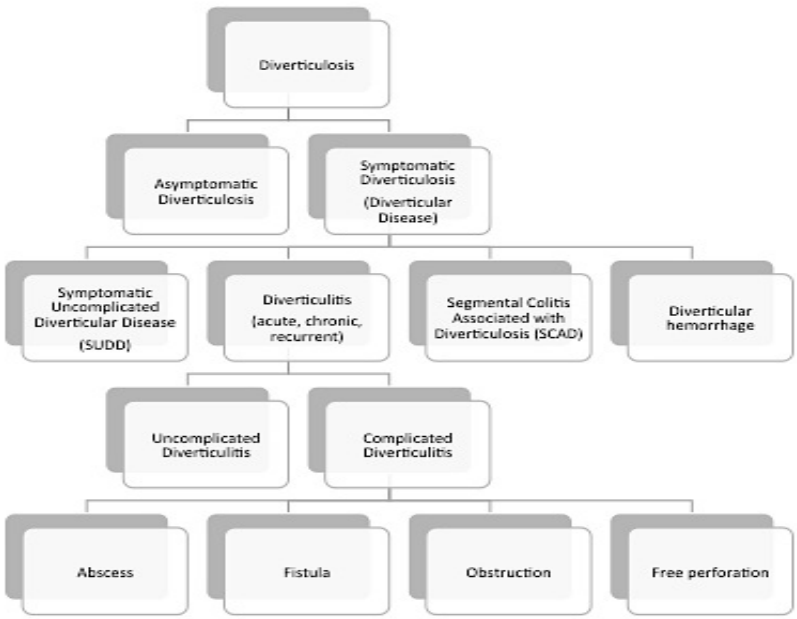

Figure 1. Nomenclature chart adapted and modified from Strate et al. Am J Gastroenterol 2012 (4)

Diverticulosis is the presence of diverticula in the colon and may be asymptomatic or symptomatic. While most individuals affected with diverticulosis are asymptomatic, 20% are symptomatic.

Diverticular Disease is defined as clinically significant and symptomatic diverticulosis, in which diverticulosis has escalated to an illness.(18)

Symptomatic Diverticular Disease, namely, symptomatic uncomplicated diverticular disease (SUDD) is a distinct clinical subtype of diverticular disease with persistent abdominal symptoms secondary to diverticula but without obvious colitis or diverticulitis.(19) The current definition though is controversial with wide range of included symptoms. While some define SUDD as the presence of abdominal pain *and* change in bowel habits attributed to diverticula in the absence of alternate etiologies(19-21) others define it as abdominal pain *or* change in bowel habits in the presence of diverticulosis and absence of alternate etiologies (4), or the presence of any symptoms in diverticular disease as symptomatic diverticular disease.(22)

Diverticulitis is the inflammation and/or infection of a diverticulum. The clinical picture is either acute or chronic and uncomplicated or complicated.

Complicated Diverticular Disease occurs when abscess, fistula, colonic obstruction or free perforation secondary to inflamed diverticula occurs. While small pericolic abscesses are secondary to microperforation, extensive abscesses, or fistula formations are from large perforations. Other complications include frank bacterial/ fecal peritonitis, which may be life-threatening.

Chronic or "smoldering" diverticulitis is defined as a subset of uncomplicated diverticulitis characterized by poor response to antibiotics, rebound symptomatology when stopping treatment and/or continued subclinical inflammation without complete resolution after the initial episode.(23)

Segmental Colitis Associated with Diverticulosis (SCAD) is a poorly understood but distinct type of diverticular disease characterized by macroscopic colonic mucosal inflammation in segments affected by diverticulosis.(24, 25)

Diverticular hemorrhage is the bleeding from a diverticulum. To date it is the most common cause of significant lower gastrointestinal bleeding (LGIB) in adults and accounts for approximately 33.1% of all lower GI bleeding etiologies in the Western countries.(26)

2.3 History

Diverticula have been discussed in the medical literature for centuries. In 1815 Fleischman introduced the term, “divertikel”(27) followed by a histopathological description of diverticula in 1849 by the French pathologist Jean Cruveilhier.(28) Diverticulitis was not described until 1899 in Germany by the surgeon Ernst Graser.(29) In the 20th century the medical literature on diverticular disease flourished. In 1904, Beer proposed the diverticulitis process with impaction of feces in the neck of diverticula causing inflammation and possible abscess and fistula.(30) Soon thereafter in 1907, reports of the first diverticulitis indicated surgical resection was published by Mayo and colleagues.(31) Diverticulosis case series with radiological images was published in 1914.(32) The proposed process in the diverticular disease was soon classified by Telling and Gruner (33) and Spriggs and Marxer(27) in 1917 and 1925, respectively.

Early recognition of age being an important key player in diverticular disease is well documented in literature.(34) In 1969, Parks published the first study on natural history of diverticular disease.(35) In his retrospective review of 455 inpatients out of a total 521 patients overall, during the years 1951-1965, he found a female predominance of diverticular disease requiring inpatient care but similar age of onset of symptoms among genders in the sixth to eighth decade of age, which holds true today. Similar to current data, diverticular disease was noted to be rare in individuals younger than 40 years of age.

2.4 Epidemiology

2.4.1 Prevalence and incidence

Since diverticulosis is predominantly asymptomatic, the true prevalence of colonic diverticulosis is difficult to determine. In contrast, data on diverticular disease, which by definition is symptomatic, exist.
Diverticular disease was recently reported to be the eighth most frequent outpatient gastrointestinal diagnosis in the US with diverticulitis accounting for approximately 157,000 cases of hospital admissions, a 31% increase compared to 2006.(1) In Sweden, data from the National Patient Registry (NPR), suggest similar trends as noted in the US. Based on ICD diagnosis for diverticular disease (K57), a 14% rise in discharge diagnoses for hospital admissions was noted between 2002 and 2014.(3)

Diverticular hemorrhage is estimated to occur in 3% to 5% of all patients with diverticulosis.(36) Temporal trend data from the US though, found diverticular hemorrhage to be the most frequent diagnosis of LGIB requiring hospital admission and was associated with a17% increase in hospital admissions between 2006 and 2012.(1) Similarly, a recent nationwide UK audit study found diverticular bleeding to be the most common diagnosis for LGIB (26.4%) in the UK.(37)
SCAD prevalence is reportedly 0.3% to 1.3% in the US population with diverticulosis, with a slight male predominance (58.7%) and mean age of 63.6 years.(38)

2.4.2 Age and gender

Within the spectrum of diverticular disease, the medical literature suggests existing age and gender differences. As described in the introduction age plays a key role in the prevalence and incidence of diverticulosis and diverticular disease.(1, 7, 8) Different and additional aspects will be discussed below.

While diverticulosis per se does not appear to have a gender difference (39, 40), diverticular disease does. In the US, complicated diverticular disease and diverticular bleeding incidence seem to be higher in men (5, 41), while women seem to suffer more diverticulitis episodes, more severe episodes requiring hospitalizations and recurrent diverticulitis.(5, 42, 43)

In regards to age some additional important epidemiological differences need to be mentioned. While diverticular disease is rare (2-5%) in individuals younger than age 40 years, a time trend population-based study from the US suggest a more significant increment in the incidence of diverticulitis in the younger population compared to the older population.(5) In the same study, the younger population affected by diverticulitis was noted to have a reversed gender difference with a male predominance. Other reported differences seem to exist in the natural history, where the severity, recurrence, complication rate of diverticulitis and need for urgent surgery, was noted to be higher in the younger population than in the older population.(44-46) Lastly, age also seems to associate with the progression of the diverticulosis by increasing number of diverticula with age. In a large US screening population colonoscopy-based study the proportion of patients with more than 10 diverticula was noted to increase with age: 8%, 15% and 30% in age categories: 50 years or younger; 51-60 years; older than 60 years, respectively.(47)

2.4.3 Geography

Prevalence studies over the years have time and again shown a Western-dominant prevalence of diverticulosis (e.g., the United States, Europe, and Australia) while being rare in rural Africa and Asia.(8) One postulated explanation is the low fiber diet in Western countries.(48) Migrant studies further support the importance of geography. A Swedish population-based migrant study found that immigrants from low prevalence countries in Africa, Asia and Middle East had increased rates of hospital admission from diverticular disease within 10 years of moving to Sweden.(49) In addition, an older autopsy study of Japanese-born immigrants to Hawaii, found immigrants to have a higher prevalence of diverticulosis than Japanese natives living in Japan.(50)

However, with an overall aging population worldwide, ongoing migration and globalization and assimilation to Western diet and lifestyle behaviors, a rising incidence of diverticular disease are expected. This notion is already supported by studies from non-Western countries, such as Israel, Korea, Japan, Kenya, Singapore, and Uganda where reports of increasing prevalence of diverticulosis compared to previous estimates have been noted.(51-55)

2.4.4 Risk Factors

2.4.4.1 Heritable Risk Factors

To date, two large Scandinavian population-based twin studies confirm the role of heritability in symptomatic diverticular disease. The first study is a Swedish twin study, which linked the Swedish National Patient Registry (NPR) to the Swedish Twin Registry.(9) The study included 104,452 twins born from 1886 to 1980, of which 2296 were hospitalized for diverticular disease. The authors found that monozygotic twins had an OR of 7.15 (95% confidence interval (CI) = 4.82–10.61) for developing the diverticular disease requiring hospital admission if the co-twin was affected. By contrast, the same gender dizygotic twins only had an OR of 3.20 (95%CI= 2.21-4.63). Given that monozygotic twins share 100% of genome and dizygotic twins only 50%(56), a heritability component was thus confirmed and calculated to account for 40% and non-shared environmental factors 60%. Comparable results were reported from the Danish twin study with linkage to the Danish NPR finding a relative risk for requiring hospitalization for diverticular disease of 2.92 (95% CI= 2.50–3.39) in siblings of cases, and heritability estimated to be 53% (95% CI= 45–61%), accordingly.(10)

More recent studies have explored heritability by association and genome wide association studies (GWAS). In 2014, the single nucleotide polymorphisms (SNPs) rs784647 on the

TNFSF15 gene was noted to be associated with diverticulitis requiring surgery in a small 21 patient study compared to controls with healthy colon, ulcerative colitis and Crohn's disease. The TNFSF15 gene has immunoregulatory and angiostatic properties and has been associated with IBD in GWAS studies.(57) Earlier, a coincidental finding of the association between a SNPs of the Reprimo gene (with cell proliferative regulatory properties) was found to associate with Caucasians patients with diverticular disease in a colorectal cancer association study.(58) But both studies were small in size. A third and large study (n=707) found another SNP linked with diverticulosis. A variant of COL3A1 gene (rs3134646) (associated with collagen disorders and herniation) was noted to be associated with colonic diverticulosis in white men in a German population even after adjusting for confounders(59), further supporting heritability and possible collagen alteration to play a role. However, these finding are only applicable to Caucasians of European decent.

The first GWAS study evaluating sequence variants affecting the risk of diverticulitis and diverticular disease was by Sigurdsson et al. on Icelandic and Danish patients.(60) The authors found an association of three introns variants in the genes *ARHGAP15* (Rho GTPase-activating protein 15) and *COLQ* (collagen-like tail subunit of asymmetric acetylcholinesterase) with diverticular disease and in *FAM155A* (family with sequence similarity 155A) with diverticulitis. Similarly, a more recent GWAS with 27,444 cases and 382,284 controls, found 42 loci to be linked with diverticular disease with 39 of these loci being novel.(61) Interestingly, the genes in these associated loci have roles in immunity, extracellular matrix biology, cell adhesion, membrane transport and intestinal motility.

The increased prevalence of diverticulosis and diverticular disease in the inherited conditions Ehlers-Danlos syndrome (EDS) type IV(62, 63), Willams-Beuren syndrome(64), and adult polycystic kidney disease(65-67) and possibly Marfan syndrome further support the role of heritability.(68)

Ethnicity

Ethnic differences also seem to exist within the spectrum of diverticular disease. For example, a large US screening population based colonoscopy study found different localization of diverticula depending on race and ethnicity. Among Caucasians the majority of diverticula (75%) were located in the sigmoid colon, while 11%, 6%, and 8% were located in the descending splenic, transverse and ascending or hepatic flexure, respectively. In contrast, while the sigmoid colon was still the most common location for diverticula in African Americans (64%), 20 % had diverticula localized to the ascending colon or hepatic flexure

and 8% and 7% located in descending colon or splenic flexure and transverse colon, respectively.(47)

Further, ethnic and racial differences seem to affect the natural history of diverticular disease as well. US data from a study including 347 patients hospitalized with acute diverticulitis reported discrepant need for surgery, where African Americans required surgery more frequently than Hispanics and Caucasians.(69) The precise reasons for the ethnic/ racial discrepancies in localization and natural history are unclear.

Similarly, in diverticular hemorrhage, while no gender predilection has been reported, race/ ethnicity disparities seem to exist. A recent report on trends in hospitalization in the USA between years 2000-2010 found that the incidence of diverticular disease has been highest in African Americans (34.4/100,000 in 2010) as well as for hospitalizations for diverticular bleeding compared to Caucasians.(41) Despite the predominantly left sided diverticular disease in the Western world, the most common site for diverticular hemorrhage is thought to be right-sided.(70, 71) Further, more extensive diverticulosis (pandiverticulosis vs. unilateral) seem to be associated with higher bleeding rates.(72)

2.4.4.2 Lifestyle Risk Factors

Diet

Diet is described to play a role in diverticular disease but it is controversial whether this is true for diverticulosis per se. In 1969, Painter and Burkitt examined differences in diet, stool weight and stool transit times between UK and Uganda nationals and found that UK population had longer stool transit time and lower stool weights. These findings gave rise to the idea that fiber intake inversely correlated with the prevalence discrepancy between the two countries, where Uganda and UK had a low and high prevalence of diverticular disease, respectively.(8) Since the 1970's, several UK and US epidemiological studies have confirmed that dietary fiber to be inversely linked with diverticular diseases.(73-75) Moreover, a vegetarian diet is reported to lower the risk of diverticular disease while high red meat consumption increases the risk of diverticulitis.(73, 76)

However, the role of diet in diverticulosis though is controversial. Peery et al. found in a cross-sectional study low-fiber diet not to be associated with an increased risk of asymptomatic diverticulosis.(77) Similarly, a South Korean cross-sectional colonoscopy-based study found no difference between participants with and without diverticulosis

(predominantly right sided) and consumption and amount of vegetables, fermented vegetables (kimchi), fruits, and fruit juices intake.(52)

Obesity

During the past decades the frequency of diverticular disease has paralleled the steady increasing incidence of obesity in the Western world. Multiple large prospective cohort studies have found obesity to associate with diverticulitis, diverticular bleeding and diverticular disease requiring hospitalization.(11, 12, 78) In addition, a recent meta-analysis evaluating BMI and the risk of diverticular disease risk, included 6 cohort studies with a total of 28,915 cases and 1,636,777 participants in which a 28%, 31% and 20 % increase in the relative risk of diverticular disease, diverticulitis and diverticular disease complications, respectively, was noted per each 5 unit increase in BMI.(79)

Conflicting results however exist on the association between obesity and diverticulosis. While Song and colleagues (52) and Strate et al.(13) did not find any association between obesity and diverticulosis, an Israeli study did.(80)

Physical inactivity

Several large population based studies have reported that high physical activity and/or vigorous exercise lowers the complication risk of diverticular disease including diverticulitis and diverticular bleeding.(12, 74, 81) Further, a recent systematic review and meta-analysis evaluating physical activity and risk of diverticular disease, included 5 adult prospective cohort studies with 2080 cases and in total 147,869 participants reported a 24% and 26% risk reduction of diverticular disease incidence and diverticulitis for the highest vs. lowest level of physical activity.(79)

In contrast though, Peery et al.'s study including 2104 participants found no significant association between physical activity and diverticulosis.(77)

Smoking

Several prospective studies have found an increased incidence of symptomatic diverticular disease in smokers.(15, 16, 73, 82) A current systematic review and meta-analysis evaluating the relative risk of diverticular disease and complications of diverticular disease among current, former and ever smokers, included 5 prospective studies with 6076 cases of incident diverticular disease (diverticulosis and diverticulitis) out of 385,291 participants and 3 studies with 1118 cases of complicated diverticular disease with abscesses or perforations out of 292, 965

patients exists.(83) The authors found a 36%, 17% and 29% increment of the relative risks of diverticular disease among current, former and ever smokers, respectively, and an increased risk for complicated diverticular disease.

By contrast, in diverticulosis only few studies have suggested smoking to be associated with diverticulosis, but have been limited by loss of statistical significance when adjusted for other factors(52), (84) or by cross-sectional design.(84, 85) It is also noteworthy that before mentioned studies included Asian populations, which predominantly harbors right-sided diverticulosis.

Alcohol

Current data on alcohol as a risk factor for diverticular disease is conflicting. In a large Danish National patient registry study, a 3-fold risk of requiring hospitalization for diverticulitis was noted in patients admitted for alcoholism compared to the general population.(86) In contrast, two prospective population-based studies were unable to find an independent association between alcohol consumption and self-reported symptomatic diverticular disease or diverticular disease requiring hospitalization.(73, 82)

In terms of diverticulosis though, a Lebanese cross-sectional study of 746 individuals undergoing screening colonoscopy and a Korean colonoscopy study found alcohol consumption to be associated with diverticulosis.(87),(52) However, recent systematic review and meta-analysis of 6 included studies with 53,644 subjects, found no association between alcohol consumption on a regular basis (OR=1.99; 95% CI 0.99–4.03) compared to subject who did not consume alcohol on a regular basis. While the overall number of subjects included had left sided predominance, four out of the 6 included studies were in Asian population and right-sided predominance in diverticula localization.(88)

Medications

Multiple studies have reported increased risk for complicated diverticular disease with opiates, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs).(89-91) A recent meta-analysis with 11 included studies found an increased pooled OR of 3.4 for diverticular perforation and 12 studies with an increased pooled OR of 2.7 for diverticular bleeding with NSAID use.(92) The largest study, the US Health Professional Follow-Up Study (HPFS) cohort included 47,210 adult men, reported NSAID use to be independently associated with a 25% and 72% relative risk increment for developing diverticulitis and diverticular bleeding.(93)

2.4.4.3 Environmental Risk Factors

To date, studies on environmental factors, such as geographical variability, urbanization and crowded living, and their influence on risk for diverticular disease are sparse, conflicting and only assessed in adult populations.(39, 73, 94) An early small Greek study found high socioeconomic status (SES) and urbanization to be associated with diverticulosis.(39) But two more recent large population-based studies have found conflicting results. While one study found that residency in small cities, or rural areas increased the risk for uncomplicated diverticular disease and diverticular disease requiring hospitalization, respectively, when compared to urban living(94) another Swedish adult population-based study found thought that SES, housing or residence did not influence the rate future diverticular disease requiring hospital admission.(49)

In the UK study a higher education level (higher secondary level and university degree vs. some secondary school) was noted to be protective against future hospitalizations from diverticular disease.(73)

2.5 Pathophysiology

The pathogenesis of diverticulosis is multifactorial and remains incompletely understood. Most studies have focused on structural features and alterations of the colonic wall with aging, abnormal motility, environmental factors and heritable factors. Their inter-relation in the pathogenesis of diverticulosis is unclear though.

2.5.1 Structural Changes

Both macroscopic and microscopic differences between colons with diverticulosis have been described in the literature. Macroscopically, a sigmoid colon with markedly thickened longitudinal and circular muscle layers and shortening of taeniae may be apparent. Microscopically, several studies support a colonic wall structural change. Specifically the increment in elastin deposition within the muscle fibers, which plays a role in the colonic elasticity, has been reported to possible contribute to the wall thickening.(95, 96) Whiteway et al. found in 25 surgical specimens of uncomplicated diverticular disease compared to 25 controls, structurally normal appearing muscle cells but a difference in elastin deposition between cases and controls and between layers as well. In cases the taenia had twice as much of elastin deposition between myocytes and was noted to be in an aberrant pattern supporting contraction and are thought to be the reason for subsequent thickening of the circular muscle by means of contracting and shortening the taenia when compared to controls.(95) Further, age-

related alterations in the smooth muscle with increased type III collagen in patients with diverticulosis compared to controls have been described to play a role.(97) In addition, an upregulation and increased concentration of a tissue inhibitor of metalloproteinases in diverticula-affected colons has been reported, possibly further explaining the increment elastin and collagen deposition.(98, 99)

In addition, the increased prevalence of diverticulosis in patients with Ehlers-Danlos syndrome, Marfan's syndrome and scleroderma, all connective tissue disorders, further support this postulated pathophysiologic mechanism.(68, 100, 101)

2.5.2 Motility Changes

Several explanatory motility disturbing pathogenic mechanisms in individuals with diverticulosis have been postulated over the years. Increased intraluminal pressures noted in patients with diverticulosis vs. controls (at rest, postprandial and post-neostigmine stimulation) have been reported and thought to contribute to altered motility.(48) (102) Adding to this notion, Painter et al. suggested that colonic contraction at the level of the haustral pleads could give rise to a series of discrete small bladders with consequently high intrasegmental pressures. He further suggested that the diverticula formation was linked to the low fiber diet increasing the intrasegmental pressures allowing the herniation. In terms of symptomatic diverticular disease though, specific aberrant motility patterns have been reported. For example, individuals with diverticulosis have been reported to have higher motility measurements when compared to asymptomatic patients (103), and higher magnitude and opposite direction waves in diverticula-affected colonic segments compared to diverticulosis-free segments, possibly explaining associated symptoms with diverticular disease.(104)

Other postulated explanatory pathophysiological mechanisms, for the motility changes and symptoms in diverticular disease, include reduced number of the enteric pacemaker cells, interstitial cells of Cajal but preserved number myenteric and submucosal plexus neurons noted in those with diverticulosis vs. those without(105) and imbalance between the normal excitatory and inhibitory influences (increased cholinergic nerves and a decreased activity of non-adrenergic, non-cholinergic inhibitory nerves) in colons with diverticulosis vs. those without with resulting augmented tonicity in diverticula affected colons.(106) In addition, diverticulosis affected sigmoid segments were noted to have reduced magnitude of electronically stimulated contraction suggesting possible circular smooth muscle

dysfunction(107), possibly leading to both development of diverticula and bowel symptoms in diverticulosis-affected patients.

2.5.3 Microbiome

Dysbiosis has been postulated to play a role in pathogenesis of symptomatic diverticular disease.(108) Gut microbiome has been reported to change in response to diets as well as to environmental and lifestyle factors like obesity, tobacco and alcohol use, all of which have been implicated in diverticular disease.(109) In addition, some disease-specific variations in the gut microbiome have been reported. For example, in a mucosa adherent microbiota study of surgical specimens those with surgery for diverticulitis had more Bifidobacterium longum and B. animalis abundant compared to patients with IBD and colon cancer.(110)

In addition, in SUDD patients a microbiome pattern with predominant *Firmicutes* strains over *Bacteroidetes* has been reported in fecal samples compared to controls.(111, 112) Further, patients with symptomatic diverticulosis have been found to have depletion of microbiota with anti-inflammatory properties such as *Fusobacterium and Lactobacillaceae* vs. asymptomatic patients in fecal samples.(113) Similarly, a recent study including patients undergoing elective colonoscopies for symptoms or due to family history of colon cancer, found that patients with diverticulosis had a higher amount of mucosal adherent *Enterobacteriaceae* compared to patients without diverticula but the symptomatology did not affect the amount of *Enterobacteriaceae*.(114) However, possible selection bias and heterogeneity in how the microbiome was measured, fecal samples vs. mucosa-associated microbiome, makes interpretation difficult.
In terms of diverticulosis though, a recent screening colonoscopy study found no significant association between diverticulosis and mucosal adherent microbiota overall, or by the number or location of diverticula, suggestive of a nonsignificant role of mucosal adherent microbiome in the development of diverticulosis.(115)

2.5.4 Inflammation

Inflammation plays without a doubt a role in the acute setting of diverticulitis but also in the setting of chronic smoldering diverticulitis and SCAD where overt macro- and microscopic evidence of inflammation exist. However, the role of inflammation in diverticulosis and SUDD is unclear.

In diverticulitis, an intradiverticular obstructing fecalith with low-grade inflammation, bacterial overgrowth and, mucosal breach with or without transmural extension leading to

perforation has been postulated as a pathogenic mechanism.(116) Histologically, features with mucosal lymphoid tissue hyperplasia with apical lymphoid aggregation of the involved diverticulum have been reported.(117) By the same token, as the name implies, SCAD is an inflammatory condition. SCADisper definition a segmental colonic mucosal inflammation, macroscopically evident on endoscopy in the colonic segments harboring diverticula.(118) Histologically features are similar to IBD including chronic infiltration of lymphocytes, crypt abscesses, cryptitis and granulomas.(119)

However, conflicting evidence exist on the pathophysiological role of inflammation in diverticulosis and symptomatic diverticular disease, namely SUDD.(120-124) For example, in the surgical specimens of patients who underwent sigmoid resection for symptomatic uncomplicated diverticular disease and not diverticulitis, Horgan et al. found evidence of chronic inflammation present both peri- and intradiverticularly. However, no correlation between the amount of inflammation and symptom intensity was noted.(122) On the other hand, Simpson and colleagues found evidence of post inflammatory damage to the enteric nervous system after recent diverticulitis associating with symptom persistence.(125)Further, Humes and colleagues found that chronic low-grade inflammation might alter motility and sensation by influencing the function of epithelial cells, smooth muscle and enteric nerves. (121) Similarly, Böttner et al. observed significant attenuation in serotonin transporter levels, which are a primary trigger of gut motility, in patients with history of acute diverticulitis.(126)

In terms of the coexistence of symptomatic diverticulosis, diverticulosis *per se* and mucosal inflammation though published data is conflicting.(121, 127, 128) For example, patients with SUDD were found to have an increased expression of inflammatory modulators including TNF(127), galanin and tachykinins(121), and fecal calprotectin(129) comparison to controls. Recently though, a study of 619 outpatients undergoing screening colonoscopy, found no evidence of mucosal inflammation measured as mRNA expression of tumor necrosis factor, CD4+ cells, CD8+ cells, and CD57+ cells in sigmoid biopsies of normal appearing mucosa in subjects with diverticulosis and/or abdominal pain and IBS compared to controls without diverticulosis.(130) Similar results were noted by Elli and colleagues in a smaller study.(128)

2.6 Natural History

Colonic diverticulosis is most commonly a benign and incidental finding. In fact, in most individuals affected with diverticulosis are and remain asymptomatic throughout their

lifespan. However, while only a small percentage actually develop diverticulitis, recurrence and associated complications and long-term sequela are possible. In a US retrospective study of patients with colonoscopy confirmed diverticulosis development of diverticulitis only occurred in 1-4 % of subjects during11 years follow up.(131) However, the risk of recurrent diverticulitis after an initial episode is significant. In a population-based study from the Olmstead County in Minnesota, USA the recurrence risk was observed to be 8% at 1 year, 17 % and 22% at 5 and 10 years respectively. A second recurrence risk was even higher at 19%, 44% and 55% at 1, 5 and 10 years, respectively. Further, being female and young posed an increased risk for any recurrence, while being male and elderly was associated with an increased risk of a recurrence complicated by obstruction, fistula, stricture, or peritonitis.(5) In addition, long-term sequela after the initial acute episode of diverticulitis is plausible. Apart from chronic symptoms such as abdominal pain and change in bowel habits, an increased 4- and 2-fold increased risk of new onset IBS and mood disorders after the initial diverticulitis event have been reported.(6) Moreover, lower health related quality of life in patients with chronic diverticular disease vs. controls is being increasingly recognized.(4)

In contrary, SCAD tend to have a benign and self- limited clinical course (132) with no apparent increased risk of diverticulitis or colon cancer.(25)

Diverticular hemorrhage is thought to differ from the other diverticular diseases in pathogenesis. Although not well understood, intimal thickening and medial thinning of the supplying vessel, vasa rectum, leading to weakening of the vessel, is thought play a role.(133) As the diverticulum forms the blood vessel is stretched with only the mucosal layer of the colon separating from the colonic lumen. When the vessel then ruptures mild to life-threatening hemorrhage may occur. The natural history studies on diverticular hemorrhage estimate that bleeding spontaneously stops in up to 80% of patients but with a 30-day rebleeding rates and emergency surgery rates as high as 53% and 35%, respectively.(36, 70)

2.7 Diagnosis

2.7.1 Asymptomatic Diverticulosis

Asymptomatic diverticulosis is commonly an incidental finding during colonoscopy or radiology imaging done with other indications and is the most common finding on colonoscopy.(7)

2.7.2 Symptomatic Diverticular Disease

SUDD is clinically similar to IBS apart from the time criteria in the Rome criteria for diagnosis. Studies with aim to differentiate the symptom profiles in SUDD and IBS exist.(21, 134) Purported differences include prolonged, less frequent, moderate to severe left lower quadrant (LLQ) abdominal pain (>24 hours), without relief by defecation, and family history of a first-degree relative with diverticular disease in those with SUDD vs. IBS.(21, 134) However the studies have been limited by selection bias hence leaving it unclear how symptoms in the community are related to diverticulosis.(21) Although laboratory tests should be normal a small case-control study reported fecal calprotectin to be higher in SUDD patients than in healthy controls and IBS patients.(129)

Diverticulitis is usually diagnosed by history and physical exam. The classic presentation includes LLQ pain, fever and leukocytosis. However, despite a "classic" presentation clinical diagnosis can be inaccurate with a misdiagnosis rates as high as 34-68%.(135) Andeweg and colleagues investigated predictive factors to improve diagnostic accuracy and found 7 features (age, number of episodes, LLQ symptom localization, pain on movement, absence of vomiting, LLQ tenderness, and elevated CRP > 50 mg/L) to be independent predictors of acute left-sided diverticulitis. A nomogram constructed from these predictors gave a diagnostic accuracy of 86%.(135)

Additional diagnostic testing includes laboratory and radiologic tests. Suggestive findings on laboratory tests may be an elevated C reactive protein (CRP) and/or leukocytosis with or without left shift, indicating active inflammatory reaction and infection. Blood cultures may help to streamline antibiotic choice. Similarly, radiological evaluation can be helpful to diagnose, identify complications and guiding management.

CT scans has a good sensitivity and specificity (up to 97%)(136), and include advantages such as readily availability, informative on disease severity and possible complications as well as being therapeutic in abscess drainage for example. Characteristic CT findings in diverticulitis include diverticula, pericolic fat stranding and segmental bowel wall thickening. Phlegmons, abscesses, fistulas and obstruction are findings suggestive of complicated diverticular disease. ***Ultrasound*** though is associated with low cost, great convenience and no ionizing radiation risk. However, although sensitivity and specificity is acceptable, at a reported 84-98% and 80-93 % respectively(137, 138), the operator dependency is a possible shortfall.(139) In contrast, ***MRI*** (magnetic resonance imaging) is radiation free, with excellent sensitivity and specificity of 100%(140) but is limited by limited

availability and potential motion artifact.

Endoscopic diagnostic modalities such as ***colonoscopy,*** is the gold standard diagnostic test in for diverticulosis and diverticular hemorrhage. However, it is not currently recommended in the acute setting given concern for worsening diverticulitis or perforation. Albeit widely advocated, the recommendation is not based on RCTs. In fact, one study found no increased risk for perforation in the acute setting if air and water technique used.(141) Similarly, it is widely accepted and followed to pursuit a colonoscopy after the episode of diverticulitis. In fact, US guidelines recommend performing colonoscopies 6-8 weeks after the diverticulitis episode, if no prior screening colonoscopy has been done, with purpose to exclude colorectal cancer. This recommendation however is based on limited data. More recent studies are challenging the rationale and cost effectiveness. For example, a recent systematic review of studies in which patients with CT diagnosis of acute diverticulitis undergoing follow up colonoscopy found only a slightly higher pooled prevalence of colorectal cancer (2.1%) compared to a population of comparable age.(142)

SCAD is diagnosed by endoscopic evidence of overt mucosal inflammation with erythema, friability and mucosal erosions, only within the diverticula-bearing colonic segment while sparing the rectum. Histology and clinical features are suggestive but not conclusive and are similar to IBD.(25)

Diverticular hemorrhage usually presents as abrupt and painless and self-limited hematochezia. The initial diagnostic and therapeutic test is an urgent colonoscopy within 24 hours of presentation.(143)

2.8 Management

2.8.1 Asymptomatic Diverticulosis

While asymptomatic diverticulosis does not need any management, prevention of progression to symptomatic diverticular disease is recommended. Several guidelines currently recommend lifestyle modifications such as weight loss, exercise, increase high fiber diet and reduce red meat intake, avoid smoking and NSAIDs to prevent future risk of a first episode of diverticulitis.(144-147)

2.8.2 Symptomatic Diverticular Disease

Treatment modalities for symptomatic diverticulosis can be divided into treatment options for SUDD, acute uncomplicated diverticulitis, complicated diverticulitis, SCAD and diverticular hemorrhage.

SUDD: Different treatment options targeting postulated pathophysiological mechanisms such as diet, dysbiosis, inflammation and dysmotility have been considered in the management of SUDD. First, increased fiber intake has been recommended. However, this is based on old and observational uncontrolled data limited by high placebo response rates. Secondly, antibiotic treatment with Rifaximin (a poorly absorbable oral broad spectrum antibiotic covering Gram-positive and negative bacteria including anerobes) is another option. In a meta-analysis of 4 included RCTs, comparing the effect of Rifaximin combined with fiber vs. placebo on symptom relief in SUDD patients, Rifaximin was 29% more effective than placebo in symptomatic relief.(148) Similarly, probiotics have been studied. However, the results and potential benefits are inconclusive due to open-label design and heterogeneity in probiotic strains studied.(149-151) Thirdly, the anti-inflammatory agent, mesalazine has been studied as a possible treatment for SUDD targeting the postulated inflammation. Three recent double blind placebo controlled studies support symtomatic relief from mesalazine when compared to placebo in patients with SUDD.(152-154) Lastly, anticholinergics and antispasmodics targeting featured hypermotility in diverticulosis have been used but no adequate controlled therapeutic trials have documented benefits.

Diverticulitis: Treatment modalities for acute uncomplicated diverticulitis include outpatient vs. inpatient treatment. Inpatient treatment is typically reserved for patients with inability to tolerate oral intake, excessive emesis, fever or if lack of improvement on outpatient therapy or complicated features such as peritonitis. Traditionally, outpatient management including bowel rest, liquid diet and oral antibiotic treatment with colon bacteria coverage has symptom resolution in 94-97%. However, recently the standard antibiotic practice has been challenged. Evidence from a large multicenter RCT in Sweden and Iceland found when comparing antibiotic vs. no antibiotic treatment arms in 623 patients with acute uncomplicated left sided diverticulitis, no clinical difference in terms of symptoms, mean hospital stay, complications such as perforation or abscess, or recurrence needing hospital re-admission during the first year (16% in both arms).(155) Authors concluded that close observation without antibiotics may suffice as treatment in selected patients with uncomplicated diverticulitis.

Consequently, several guidelines and recommendations on diverticulitis management have changed. For example in Scandinavia, the Danish national guidelines do not recommend antibiotics in the management for uncomplicated diverticulitis.(146) In the US however, the AGA guidelines while still recommended the use of antibiotics it now advocates selective and not routine use of antibiotics in acute diverticulitis. While AGA guidelines acknowledged the findings of Chabbas et al. to be important, the concern for possible imbalance between comparative groups in terms of prior diverticulitis (44.8% in the antibiotic groups vs. 35.6% in the non-antibiotic group, p =0.02) resulted in more cautious recommendations.(147)

In contrast, inpatient treatment includes intravenous antibiotics, fluids and bowel rest. In addition, complicated diverticular disease with pericolic or pelvic abscesses usually requires percutaneous drainage as additional treatment. Surgical drainage is otherwise reserved if refractory to percutaneous drainage. Surgical management is otherwise needed for perforated acute complicated diverticulitis but the optimal surgical strategy is still being debated.(156, 157)

SCAD: Currently, there are no guidelines for its management, which is usually based on the administration of salicylates and antibiotics, with surgery being reserved for refractory cases.

Diverticular Hemorrhage: An urgent colonoscopy within 24 hours of presentation, with rapid laxative bowel preparation (143) may achieve hemostasis. Existing endoscopic interventions include epinephrine injection therapy (1:10,000 dilution with saline),with thermal or mechanical therapy.(143) If high-risk clinical features and ongoing bleeding with refractory to hemodynamic resuscitation efforts are present then angiography should be considered If high-risk clinical features and ongoing bleeding with refractory to hemodynamic resuscitation efforts are present then angiography should be considered.(143) Surgery should be considered as last resort and partial colectomy is favored over subtotal colectomy whenever possible.(158)

3 AIMS OF THE THESIS

Study I

- To describe the prevalence of diverticulosis in the general population
- To assess if diverticulosis is associated with abdominal discomfort or other gastrointestinal symptoms

Study II

- To examine if low-grade inflammation is present in the colon mucosa in individuals with diverticulosis

Study III

- To examine the role of environmental determinants in late adolescence and the risk of diverticular disease requiring hospitalization

Study IV

- To examine if late adolescent lifestyle factors influence the risk of diverticular disease requiring hospitalization

4 METHODS

Table 1. Overview of study designs, number of participants, data collection, main outcome variables and statistical analysis methods.

Stud	Study Design	Number of Participants	Data collection	Main outcome	Analysis Methods
I	Cross sectional	742	Questionnaires Colonoscopy	Diverticulosis Gastrointestinal symptoms	Logistic regression
II	Nested Case Control	254	Questionnaires Histopathology	Mucosal and serological inflammatory markers Gastrointestinal symptoms	Logistic and Linear Regression
III	Cohort	45 952	Questionnaires Register data Physical assessment	Diverticular disease requiring hospitalization	Cox Regression
IV	Cohort	43,772	Questionnaires Register data	Diverticular disease requiring hospitalization	Cox Regression

4.1 Study design and Study populations

4.1.1 The PopCol Study Population

Papers I and II were both part of the larger PopCol study. The aim of the PopCol study was to survey colonic pathology and its association with gastrointestinal symptoms in a normal population and was carried out between 2000 and 2006. The design is a population-based cross-sectional study in which the study population was selected by using the official Swedish National Population Register. A random sample of 3556 Swedish born individuals, aged 18 to 70 years, out of the existing 38,646 inhabitants of the parishes Katarina and Sofia (parishes surrounding Ersta Hospital where the study took place) in Södermalm, Stockholm, Sweden in the year 2000, were selected and contacted. The official Swedish National Population Register includes all inhabitants without exception. Individuals not born in Sweden were excluded a priori.

The study population was representative of the whole native Swedish adult population (11% born abroad were excluded) except in gender. A unique identification number was given to each individual. The original study population received the validated Abdominal Symptom Questionnaire (ASQ) with questions on troublesome gastrointestinal symptoms over the past three months by mail.(159) While all responders were telephoned and scheduled for a preparation hospital visit with a gastroenterologist if agreeable, the non-responders underwent structured interview over the phone. During the gastroenterology visit all the participants completed an extended and validated questionnaires (ASQ, Rome II Modular Questionnaire and Hospital Anxiety Depression Scale (HADS)) and underwent blood and fecal sample collection. The colonoscopy procedure was offered during this visit.

In total, 2293 were questionnaire responders, of which 1244 out of 1673 were reached by telephone and scheduled for a gastroenterologist consultation. Overall, 745 out of

1244 participants (426 women and 319 men) accepted and consented to proceed with subsequent ileo-colonoscopy. See flowchart in Figure 2.

Ileo-colonoscopy with biopsies

Seven experienced endoscopists all colonoscopies were performed in Ersta Hospital between June 2002 and October 2006. Bowel preparation for the colonoscopy procedure included bowel cleansing with 45 ml Phosphoral taken orally twice within 4-hour interval and clear liquid diet the day prior to the colonoscopy. All colonoscopies followed Swedish standard of care and included administration of sedation and analgesics (inhaled nitric oxide, intravenous midazolam and/or alfentanyl) on an as needed basis. Colonic biopsy sampling from all colonic segments (cecum, transverse, sigmoid and rectum) using standard endoscopic forceps (Boston Scientific, Boston, USA) was performed in all participants. The endoscopists were blinded to participants' past medical history and questionnaires results but aware of the study's general aims and protocol. All adverse events were recorded. The location and presence of diverticula was diagnosed and recorded at time of colonoscopy.

Paper II is based on a nested case-control study derived from the PopCol study population. Cases were those with diverticulosis diagnosed during the colonoscopy. The cases were matched 1:1 to gender and age (+/- 2 years) with controls (those without diverticulosis) from the remaining 615 participants who underwent a colonoscopy. Missing data on localization of diverticula left a total of 127 cases and 127 controls for analysis. Participants with inflammatory bowel disease and/or microscopic colitis were excluded *a priori*. See flowchart in Figure 2.

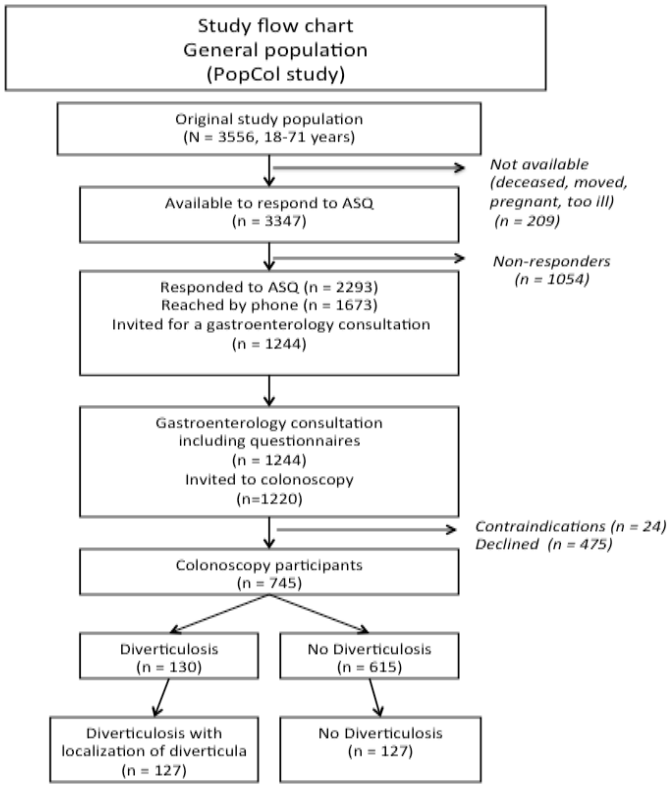

Figure 2. Flow chart for paper I and II

4.1.2 The Swedish Conscript Cohort

Paper III and IV are both based on the nationwide, population-based cohort study of 49,321 male Swedish conscripts, age 18-20 conducted during 1969-1970. During the time of the study conscription was compulsory in Sweden. Exemption only occurred in 2-3% of men, mainly due to severe disabilities or diseases. Data was prospectively collected with extensive psychological and physical examinations including face-to-

face interviews, questionnaires on lifestyle behaviors, alcohol, smoking and use of recreational drug consumption and self-rated health at times of conscription.

In **paper III,** 46,171 men out of the total 49,321 men had complete data on environmental and adjusting lifestyle factors of interest. See flowchart in Figure 3.

In **paper IV,** 43,772 out of the total 49,321 men had complete data on all the lifestyle factors of interest. Loss to follow up during the study period included 421 emigrations and 3019 deaths before 1987. Flowchart can be seen in attached **paper IV.**

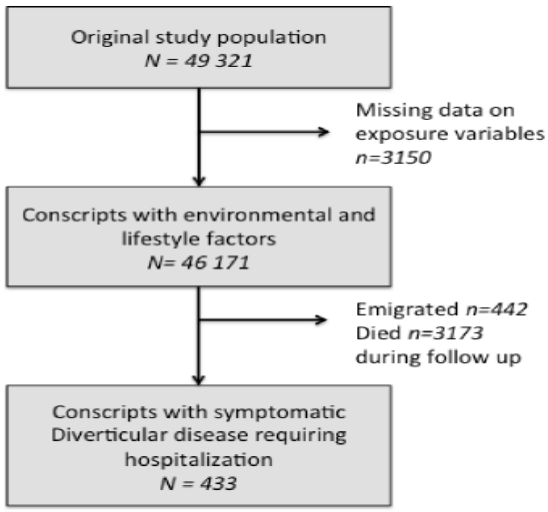

Figure 3. *Flowchart paper III.*

4.2 Outcomes of Diverticular Disease

4.2.1 Paper I and II

The outcome of interest was the presence of Diverticulosis, which was diagnosed during the colonoscopy.

4.2.2 Paper III and IV

The outcome of interest was Symptomatic Diverticular Disease requiring hospitalization.

The dataset from the Swedish Conscript Cohort study was linked to the Swedish NPR by using the unique Personal Identity Number (PIN), which all Swedish citizens obtain after birth or immigration. To identify the primary discharge diagnoses (outcome of interest) in the NPR the following *International Classification of Diseases* (ICD) codes for Diverticular Disease (ICD-8: 562.10-11; ICD-9: 562.10-13; ICD-10: K57.2-5, K57.8-9) were used. The NPR includes all information on hospitalization including discharge diagnoses classified into ICD codes, dates of hospital admission and discharges. While the NPR was established in1964, nationwide coverage was not obtained until 1987. Approximately 99% of all somatic discharge diagnoses are covered in the NPR and the validity of hospital discharge diagnoses is between 85-95% depending on diagnosis. In Sweden, ICD-10 codes have been used since 1997 and ICD codes 8 and 9 since1969 to 1996. Secondary discharge diagnoses in NPR of gastrointestinal hemorrhage (ICD-8: 578.9; ICD-9: 578.9; ICD-10: K92.2) were excluded *a priori* to minimize the risk for misclassification of diverticular bleeding being included in the outcome of interest.

4.3 Variables/ Covariates

4.3.1 Paper I and II

Background variables were derived from the face-to-face interview and examination during the gastroenterology visit and at the time of colonoscopy and verified using the PIN number and with the electronic medical records. These included *age, gender, body mass index (BMI)* (defined as weight in kilograms divided by the square of the height in meters (kg/m^2), *smoking ((**paper II only)*** obtained at the time of

gastroenterology consultation and defined as non- or current smoker) and the use of *laxatives and antibiotics*. Recent antibiotic use was defined as any antibiotic use 3 months prior to visit or colonoscopy and was in addition to self- report at the gastroenterology consultation interview also verified from electronic medical record using ATC codes.

Gastrointestinal symptoms were obtained from the validated Rome II Modular questionnaire and included; abdominal pain or discomfort (located anywhere in the abdomen for at least 3 weeks, at least one day in each week, in the past 3 months); mushy stools; high frequency defecation (> 3 bowel movements a day); lumpy stools; low frequency defecation (one bowel movement less than every three days); bloating, urgency: straining during defecation: sensation of incomplete bowel movement; passage of mucus during defecation and fecal incontinence.

Irritable Bowel Syndrome (IBS) and IBS subtype diagnoses were derived from the Rome II Modular questionnaire using the Rome II symptom-based criteria. IBS was defined as having abdominal pain or discomfort for at least 3 weeks (at least one day in each week) in the past 3 months with at least two out of three of the following: pain or discomfort improved or relieved after a bowel movement, onset of pain or discomfort associated with a change in the usual number of bowel movements, or onset of pain or discomfort associated with a change in stool consistency. Similarly, IBS-Diarrhea (IBS-D) was defined as having IBS and reporting loose, mushy or watery stools but not hard or lumpy stools at least 25% of the time for the last three months and IBS-Constipation (IBS-C) as having IBS and reporting hard or lumpy stools but not loose, mushy or watery stools at least 25% of the time in the last 3 months.(160, 161)

Localization of abdominal pain or discomfort (paper I only) was derived from the ASQ and defined as presence of "trouble- some" abdominal pain/ discomfort in the preceding 3 months specified to epigastrium, periumbilical, suprapubic area, right

quadrant, left quadrant or the whole abdomen. Left lower quadrant included the suprapubic and left quadrant areas. Separate analysis of all localizations was performed.

Anxiety, depression (paper I only) diagnoses were made if the HADS score for respective condition was 8 or above.(162)

Self-rated health was assessed with the question: "In general, would you say your health is: excellent, very good, good, fair or poor".

Inflammatory Bowel Disease (IBD) and Microscopic Colitis diagnoses were either established (by past medical history of Crohn's disease, ulcerative colitis or microscopic colitis obtained from the questionnaires, gastroenterology visit or at the time of colonoscopy) or newly diagnosed (by histopathology review by expert pathologist of the colonic biopsies obtained during the colonoscopy).

History of diverticulitis by self- report was derived from questionnaires and the face-to-face interview at time of the gastroenterology visit.

4.3.2 Paper II

Serological and colonic mucosal inflammation was assessed by serum levels of *C Reactive Protein (CRP)* collected during the gastroenterology visit and histological examination of the colonic biopsies obtained during the colonoscopy. The biopsies were routinely processed with formalin-fixed paraffin-embedded tissue blocks, sectioned and stained with Hematoxylin & Eosin (H&E) and stored. For this study, in collaboration with Professor Marjorie M. Walker, the biopsy slides belonging to the study population in Study II were shipped to the Hunter Area Pathology Service Department at the University of Newcastle, NSW, Australia, for histological analysis. Two GI pathologists blinded to the case-control status performed the analysis and concordance of pathology between pathologists was calculated.

Assessment of the H&E stained biopsies included the presence or absence of markers of histological inflammation, specifically, intact surface epithelium, mucin depletion, Paneth cell metaplasia, cryptitis, crypt abscesses, apoptosis of epithelium, normal architecture/ crypt branching, intact chronic inflammatory gradient (no expansion of chronic inflammatory cells from base to surface), basal plasmacytosis and granulomas. Further, the number of lymphoid aggregates, follicles and neutrophils were counted in the lamina propria, and intraepithelial lymphocytes were counted/ 100 colonocytes. Other present pathology was noted and recorded.

4.3.3 Paper III and IV

Environmental and lifestyle factors were derived from the questionnaires completed by all conscripts at time of conscription. The questionnaires included questions on upbringing conditions such as residence, living conditions, social background, school and personal relationships and parents' marital status and social groups as well as questions on lifestyle behaviors such as alcohol, tobacco, and recreational and narcotic drug use. The initial assessment at time of conscription also included rigorous physical and psychological assessments.

Environmental factors (Study III only)

Residency was derived from the conscripts' zip code at time of conscription and defined as the region of upbringing and geographical location of residency at time of conscription. As defined by Statistics Sweden (a governmental statistical department established in 1858 with accurate validated information) the geographical residency was classified into categories dependent on the number of inhabitants: *Large cities* were areas with a population of >200,000; *large towns* with >50 000 inhabitants, *small towns* with <50 000 inhabitants, and *rural localities* were areas with 50–199 inhabitants in a contiguous built-up area with no more than 150 meters between

houses. The fifth category, *abroad*, included conscripts who had been living abroad prior to time of conscription.

Living conditions was derived from the questionnaires and included where the conscript lived most of the time; both parents, mother, father or with another person, and whether the living condition was crowded or non-crowded. As defined by the Swedish National Board of Housing, Building and Planning during the years 1965- 1974 (corresponding to the study period when data was prospectively collected) crowded living was present if >2 individuals lived per room, excluding kitchen, bathroom and living room.

Parental marital status was derived from the questionnaires and answered as divorced or not divorced.

Parental socioeconomic status (SES) was based on the paternal socioeconomic status, which was categorized in to 7 categories dependent on the occupation of the head of the household (father) when the conscripts were age10 (years 1959-1960). The 7 SES categories included (1) unskilled workers, (2) skilled workers, (3) assistant non-manual employees, (4) non-manual employees at intermediate level, (5) non-manual employees at higher level, (6) farmers and (7) unclassified, which were those fathers not classified into a socioeconomic group. The highest SES belonged to fathers' who were non-manual employees at higher levels. The paternal SES data was derived from the Statistics Sweden Register linked through the conscripts' PIN obtained at birth.

Lifestyle factors (Study III and IV)

BMI was calculated from the weight and height obtained at the physical exam at time of conscription (kg/m^2). BMI was categorized into 4 categories: underweight (<18.5 kg/m^2), low normal (18.5-<22.5 kg/m^2), high normal (22.5-<25 kg/m^2) and overweight and obese (⩾25kg/m^2). For study IV, the reference category was the low

normal category (BMI 18.5-<22.5 kg/ m^2). Given the low number of obese conscripts (BMI ⩾30) men (0.8%) the obese category was combined with overweight category into one category.

Cardiovascular fitness was derived from a stanine scale, which was obtained from the conscripts' maximum work capacity on an ergometer cycle divided by the body weight. The stanine scale ranged from 1 to 9, where a higher score indicated a better result. (163)

Use of recreational drugs (other than alcohol and tobacco) was derived from the questionnaires at time of conscription and was defined as present if the conscript had ever tried or was actively using any recreational drug.

Smoking status and amount was derived from the questionnaires completed at time of conscription and classified into 5 categories: absent, 1–5 cigarettes per day, 6–10 cigarettes per day, 11–20 cigarettes per day or > 20 cigarettes per day.

Alcohol consumption derived from the questionnaires was defined per weekly amount and categorized to; absent, 1–100 g of pure alcohol per week, 101–250 g per week or > 250 g per week.

Risky alcohol use was defined as present if apprehension for drunkenness and/or being drunk often and use of alcohol to alleviate a hangover was reported.

4.4 Statistical analysis

All statistical analyses were performed in STATA (versions 11.0, 13.1 or 14. StataCorp, Texas). Results were considered significant when the two-sided *p* value was < 0.05.

4.4.1 **Logistic and Linear regression** (Paper I and II)

To assess the differences in dichotomous (present or absent) background variables, IBS and gastrointestinal symptoms between participants with and without diverticulosis logistic regression was used. These were presented as crude and multivariate analysis by adjusting for age and gender. In **paper I**, an interaction analysis was performed to evaluate interaction between diverticulosis and antibiotic use and gastrointestinal symptoms with an interaction term diverticulosis *use of antibiotics.

In **paper II**, the nested case control study, gender and age (+/-2 years) matching was done with the purpose to enhance comparison between cases and controls and reduce variability and to ultimately use McNemars' analysis to evaluate association between diverticulosis and inflammatory markers. However, due to the unexpected and unfortunate loss of multiple slides during shipping, loss of multiple pairs occurred explaining the reasoning for choosing unpaired statistical analysis (logistic and linear regression adjusted for age and gender) to preserve sample power. Hence, in **paper II** diverticulosis status and symptom status was used as explanatory variables for practical reasons, and logistic regression or linear regression with bootstrap with X repetitions were used depending on whether the tested variable was dichotomous (presence of histopathology finding) or continuous (number of cells).

All analyses were age and gender adjusted.

4.4.2 Cox Regression (Paper III and IV)

To calculate the association between lifestyle factors and symptomatic diverticular disease requiring hospitalization, cox regression analysis was done. Hazard ratios (HR) were used to present estimates. The data was presented in a crude model per lifestyle factors and as multivariate model including all lifestyle factors. The lifestyle factors included in the analysis were: BMI (continuous and categorical), cardiovascular fitness, smoking, use of recreational drugs, alcohol consumption and

risky alcohol use were calculated. The multivariate models BMI was presented as both a continuous and categorical variable. Proportionality testing using Schoenfeld residuals was done in all models, with no evidence of violation. Risk time was defined as the time from conscription until the time of death of any cause, emigration, the first registered discharge diagnosis of symptomatic diverticular disease or the end of the follow-up period (31 December, 2009), whichever came first. The men were considered lost to follow-up after emigration but contributed with the time until emigration to the analysis.

4.5 Ethical considerations

For studies I and II the ethical approval was obtained from the regional ethics committee at Karolinska Institutet (Forskningskommitte Syd, DNR 394/01).

For study III and IV, the regional ethics committee at Karolinska Institutet (DNR 2004/5:9 – 639/5) approved the studies. Due to the character of the database and the data being anonymous, no written informed consent was needed.

5 RESULTS

Below is a summary of results. For the detailed results please see the appended papers.

5.1 Paper I

Prevalence and localization of diverticulosis

During the study period a total of 745 participants underwent ileo-colonoscopies, but missing data on the presence of diverticulosis left 742 for analysis. Out of the 742 participants 130 had diverticulosis (17.5%, 95% CI: 14.95-20.4). The prevalence of diverticulosis increased with age as seen in Figure 5 and was similar among gender (men=18.6%, women=16.7%). Consequently age differed among those with and without diverticulosis (mean age=60, range 37-71 years vs. mean age 51, range 19-70 years, respectively, $p< 0.001$). Overall, older participants (>60 years of age) reported less gastrointestinal symptoms than younger participants.

Diverticula was localized in the sigmoid colon in all affected participants while the cecum, ascending, flexures with transverse colon and descending colon were only involved in 3.2%, 4.0%, 13.6% and 12.7%, respectively.

Diverticulosis and gastrointestinal symptoms, IBS and IBS subtypes

Missing data on gastrointestinal symptoms and BMI, left a total of 122 and 577 participants with and without diverticulosis for analysis of gastrointestinal symptoms, respectively. Overall, results were noticeable for a significant association between the presence of diverticulosis and diarrhea symptoms, namely, mushy and high frequency stools (OR: 1.88, 95%CI: 1.20-2.96, p=0.006; OR: 2.02, 95%CI: 1.11-3.65, p=0.02, respectively) and urgency and passage of mucous (OR: 1.64, 95%CI: 1.02-2.63

p=0.04; OR: 2.26, 95%CI: 1.08-4.72, p=0.03, respectively) in all participants regardless of age.

Age stratification further showed that in those older than 60 years of age vs. those 60 years and younger, diverticulosis was significantly associated with abdominal pain (OR: 2.10, 95%CI: 1.01-4.37, p=0.047) and IBS-D (OR: 9.55, 95%CI: 1.08-84.08, p=0.04) in addition to diarrhea symptoms. Similar results were noted when excluding participants with colitis and recent antibiotic exposure.

In terms of anxiety, depression or self-rated health there was no difference among participants with diverticulosis vs. those without or when age was stratified.

In the analysis of localization of abdominal pain using the ASQ, missing data on pain localization left 703 participants for analysis. Overall, pain was reported by 55 of 122 participants with diverticulosis and 286 of 581 participants without and a trend was noted for left lower quadrant (LLQ) localization of the abdominal pain/discomfort (OR: 1.83; 95%CI: 0.92-3.64, p=0.09). However, when age stratified, the abdominal pain was significantly associated to the LLQ localization in participants older than age 60 years with diverticulosis vs. those without (OR: 6.78, 95%CI: 1.80-25.56, p=0.005).

Lastly, recent antibiotic exposure was present in 21 out of 127 (16.5%) in those with diverticulosis compared to 70 out of 610 (11.5%) in those without diverticulosis. Antibiotic exposure was significantly higher in those older than age 60 than in those age 60 years or younger (14.1% (95%CI: 13.8-14.4) vs. 11.5% (95%CI: 11.4-11.6), p<0.001, respectively), regardless of diverticulosis status. Results of the interaction analysis between diverticulosis and recent antibiotic use on GI symptoms showed a positive interaction effect between the presence of diverticulosis and recent antibiotic use indicating that participants with diverticulosis and recent antibiotic use were more symptomatic, namely GI symptoms, than those with diverticulosis without recent

antibiotic use, or participants without diverticulosis with recent antibiotic use.(Figure 6) The GI symptoms mushy stools, high frequency stools and urgency were the specific symptoms associated with a positive interaction.

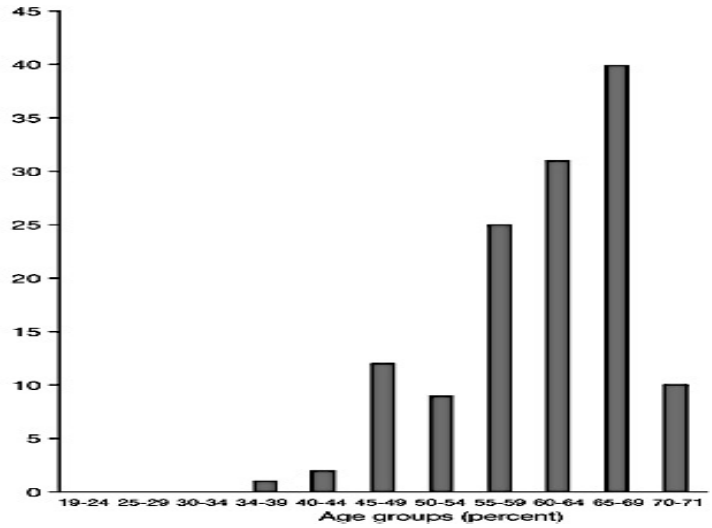

Figure 4. *Prevalence of diverticulosis per age group presented as a percentage.*

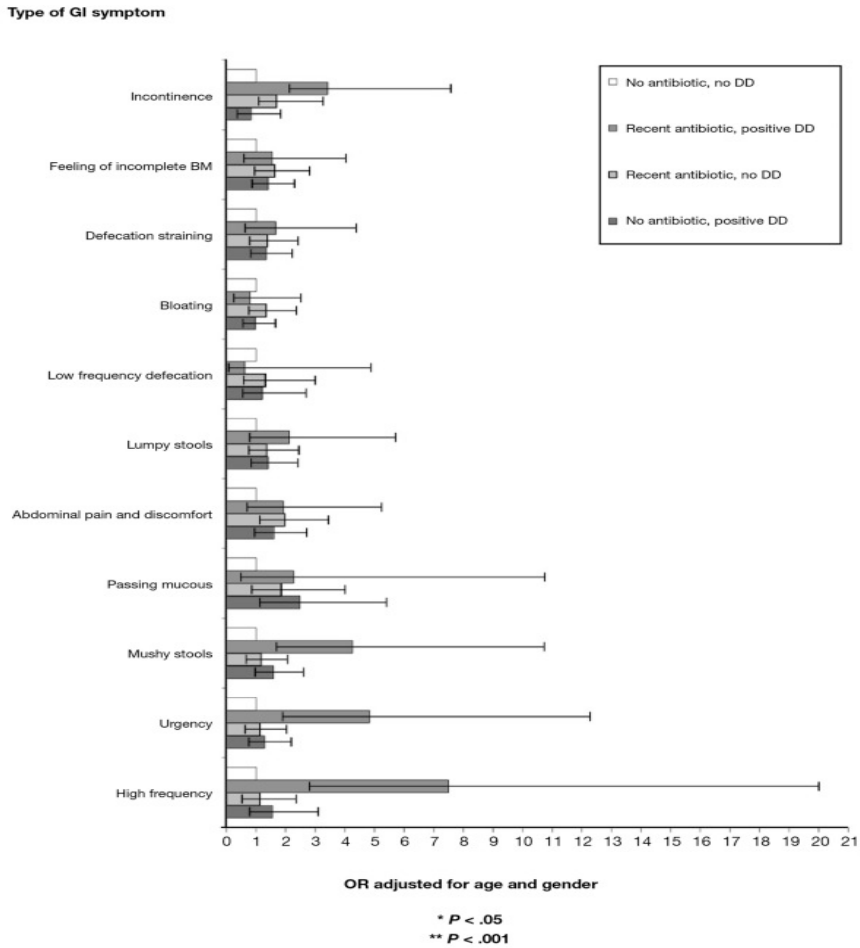

Figure 5. *Adjusted OR with 95% CI for each gastrointestinal symptom evaluating the interaction of antibiotics and diverticulosis in all 4 different groups. The reference group was "no antibiotics, no diverticulosis", with an OR of 1.00. The other groups were as follows: "recent antibiotics, positive diverticulosis", "recent antibiotics, no diverticulosis", "no antibiotics, positive diverticulosis".*

5.2 Paper II

Overview

A total of 242 participants were included in this 1:1 nested case control study. Age was similar among cases and controls (60.8 years (7.5) vs. 60.7 years (7.4), p=0.92) and the gender distribution was equal (45.7% males, p=1.00). Similarly, background variables such as BMI (p=0.71), smoking (p=0.34) or recent antibiotic exposure (p=0.68) were similar between cases and controls. Cases with diverticulosis differed from controls in terms of reported symptoms such as mushy and high frequency stools and abdominal pain (p=0.01, p=0.03, p=0.04, respectively). GI symptoms were otherwise similar among the groups. As previously reported in Paper I all participants with diverticulosis had sigmoid colon involvement while only 8 (6.3%) had both the right and left colon affected.

Diverticulosis, Symptomatic Diverticulosis and Inflammation

Overall, median CRP levels were similar between cases and controls (1.05 (0.3, 2.7) vs. 0.8 (0.4, 2.2), p=0.53). Missing data on mucosal inflammatory markers on histology left a total of 170-215 participants for analysis. Mucosal inflammatory markers such as surface epithelium and chronic inflammatory gradient were intact in all participants' and basal plasmacytosis, granulomas and mucin depletion were absent in all samples. Logistic and linear regression analysis models showed no association between mucosal inflammatory cells and diverticulosis throughout the colonic segments on the histology analysis. Only a trend of increased numbers of cecal lymphoid aggregates in cases vs. controls (p=0.07) was noted.

In the sub-analysis evaluating the association between symptomatic diverticulosis and serological and mucosal inflammation, missing data on GI symptoms left 241

participants for analysis, of which 45 (38%) cases and 30 (25%) controls reported diarrhea and 34 (29%) cases and 21 (17%) controls reported abdominal pain.

Cases with diarrhea were similar in background variables compared to asymptomatic controls except for recent antibiotic use, which was two-fold more likely in cases with diarrhea compared to asymptomatic controls (OR 2.50, 95% CI: 1.01, 6.15, p=0.047). Median CRP levels (p=0.23) and mucosal inflammatory markers were similar among symptomatic cases, asymptomatic cases and symptomatic controls when compared to asymptomatic controls.

Cases with abdominal pain had a trend to be active smokers (OR 2.51, 95%CI: 0.93, 6.72, p=0.068) but were otherwise similar when compared to asymptomatic controls. Median CRP levels did not differ significantly among cases with abdominal pain and asymptomatic controls (p=0.19). Similarly, no association between mucosal inflammatory markers and cases with abdominal pain compared to asymptomatic controls was noted except for a significantly less number of rectal lymphoid aggregates present than asymptomatic controls (p=0.022). Interestingly though controls with abdominal pain were 16 times more likely to have cryptitis present in the transverse colon in comparison to asymptomatic controls (OR 16.12, 95%CI: 1.31-197.96, p=0.03); an analysis adjusted for smoking and recent antibiotic exposure gave similar results (OR 17.38, 95%CI: 1.29-233.24, p=0.03).

5.3 Paper III

Overview

During the study period 3150 out of 49,321 men had incomplete data for any of the exposure variables and leaving 46,171 observations for analysis. The mean follow-up time was 37.9 years (SD ± 4.7, range 0-39), or 1,749,037 person-years. During the follow up period a total of 433 men (0.9%) required hospitalization for symptomatic

diverticular disease, 442 men emigrated and 3173 men died. Mean time to the first primary diagnosis of symptomatic diverticular disease requiring hospitalization was 29.9 years (SD ± 6.3, range 2-39).

In terms of geographical location of residence most conscripts were brought up in rural areas (38.8%) and small towns (29.8%). The most common type of living conditions was non-crowded (79.4%) and most conscripts lived with both parents (89.6%) at time of conscription. The most common conscripts' paternal occupations were of unskilled and skilled worker category (33. 2 % and 21.4 %, respectively) while only 11.1% were farmers. Parental divorce was only reported by 4728 (10.2%) of all conscripts.

Environmental Factors and Risk of Symptomatic Diverticular Disease requiring hospital admissions

The only environmental factors found to be associated with the risk of hospital admission for symptomatic diverticular disease was parental divorce. Parental divorce was independently associated with a 49% increased risk of hospitalization for symptomatic diverticular disease later in life when compared to those with married parents (HR 1.49, 95%CI: 1.02-2.17, p=0.04). No other environmental factor was associated with hospital admissions for symptomatic diverticular disease.

5.4 Paper IV

Overview

In total, the study included 49,321 men and incomplete data on any of the exposure variable left 43,772 observations for analysis. Emigration and death accounted for 421 and 3019 losses to follow up, respectively, during the study period. The mean follow-up time was 37.8 years (SD +/- 4.8 years; range, 0– 39 years), or 1,657,659 person-years. The mean time to the first primary diagnosis of symptomatic diverticular disease requiring hospitalization was 30.0 years (SD, +/- 6.26 years; range, 2– 39

years) and was received by a total of 444 men during the follow up period. Readmission for the same diagnosis occurred in 184 out of 444.

In terms of lifetime factors the mean BMI at conscription was 21.0 kg/m^2 (SD: 2.6 kg/m^2), equivalent of normal BMI range. Very few (0.8%) conscripts classified as obese (BMI >30). Alcohol consumption was common (70.7%) but in adequate amount of less than 100 g/wk. At the time of conscription, 58.6% were smokers and 11.6% reported ever having used recreational drugs.

Lifestyle Factors and Risk of Diverticular Disease

First, BMI was independently associated with an increased risk of diverticular disease as a continuous variable by 9% per unit increment in BMI (HR: 1.09, $p< 0.001$) and as a categorical variable. A 2- fold increased risk for developing symptomatic diverticular disease was noted in overweight and obese conscripts (BMI >25) (HR: 2.02, $p< 0.001$) when compared to conscripts with low normal BMI (Figure 9). Similarly, smokers was had a significantly higher risk of developing symptomatic diverticular disease compared to nonsmokers, across all smoking categories except for the highest. Risky alcohol use was also independently associated with a 43% increased risk of developing symptomatic diverticular disease (HR: 1.43, $p= 0.01$). In contrast, higher cardiovascular fitness independently reduced the risk of development of diverticular disease (HR: 0.94, $p= 0.02$) compared to lower cardiovascular fitness, Alcohol consumption per se and the use of recreational drugs were not associated with increased risk of development of symptomatic diverticular disease ($p=0.19$, $p=0.76$; respectively).

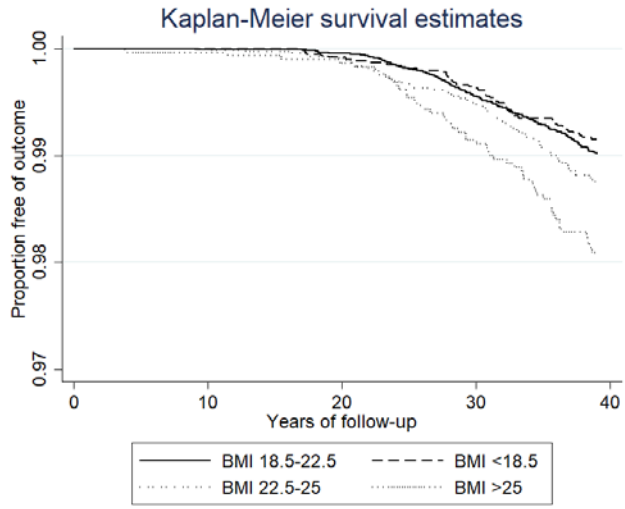

Figure 6. Kaplan-Meier curve for the development of symptomatic diverticular disease requiring hospitalization per BMI category

6 METHODOLOGICAL CONSIDERATIONS

6.1 Study design

All four studies in this thesis are observational. The study in **Paper I** is cross-sectional, which unavoidably inherits certain limitations per design. One limitation is the lack of consideration of temporal aspects. Hence, while inference on associations between outcome of interest and variables can be made, no inference on causality can be made. The other limitations include possible selection bias, decrease external validity as well as the presence of possible confounding factors affecting the associations.(164)

Paper II is a nested case-control study from the same PopCol study population in Study I. In our study, we identified subjects by the outcome of interest (diverticulosis) at the initiation. Generally, methodological considerations for case control studies include the importance of study population selection to minimize selection bias and improve generalizability.(165) Our study population was obtained from the PopCol study population, which is a representative sample of a Swedish born urban population, minimizing selection bias and improving generalizability to Swedish urban populations. Other shortfalls of case control studies include susceptibility to recall bias or information bias, all of which are addressed below.(165) Another important thing to recognize is that case –control studies provides approximate estimates of relative risk, which may or may not be inaccurate, and not valid estimates of risks or odds.(165)

Papers III and IV are retrospective cohort studies with prospectively collected exposure data. All individuals were disease-free when the exposure status was established correlating with the beginning of the observation period. The time of exposure was measured at initiation of the study, and the outcome of interest was studied along the follow up period, with other words a single baseline design. The

difference between exposed and unexposed groups was then calculated. Although is a good approach when assessing multiple risk factors, one shortfall is that distribution of the risk factors cannot be controlled, possibly leading to different numbers in the factor and nonfactor groups.(164) Another is the withdrawals by loss to follow up, but in our study this was very low (<1%) given the existing mandatory conscription law in Sweden at time of the study and access to register data using the PIN. Lastly, residual confounding factors are an important threat, which I address below.

In **papers III and IV** given the single baseline design with exposure variables only collected at baseline, making inference on the effect of modifications of lifestyle and environmental factors over time on the outcome of diverticular disease requiring hospitalization is not possible.

6.2 Bias

All research is subject to the risk of error. One differs between random errors, which can usually be dealt with increasing the sample size of a studied population, and systematic errors (bias). Bias must be considered and dealt with either in the design of the study, or in its interpretation and include selection bias, information bias and confounding.(165)

6.2.1 Selection bias

Selection bias arise when the selection of the study population, either by selection procedures or factors, influence the inclusion and/or exclusions of study participants.(165)

The PopCol-population in **papers I and II** is a random sample from the adjacent parishes in Stockholm, which minimizes selection bias and improves generalizability as participants are less likely biased by medical attention or secondary gain behavior.

Further, it has a high participation rate and a wide age range. The voluntary participation without financial compensation further helped minimizing any potential risk of selection bias. In addition, an earlier study of the PopCol population showed in a comparative analysis similarity in measured variables between questionnaire responders and non-responders, suggesting good generalizability of the general population.(166) Similarly, we performed a comparative analysis between the colonoscopy participants and the non-colonoscopy ASQ responders and although no difference in gender or education was noted, those undergoing colonoscopy were older and reported more gastrointestinal symptoms (abdominal pain), reflecting possible response bias. However, the main finding was the association between diverticulosis and diarrhea, and hence unlikely to have impacted the results. Further, the older participants were less symptomatic overall. Hence, although an overestimation in the younger participants is possible, diverticulosis was very rare in the younger individuals. Lastly, the underrepresentation of younger participants in study I, especially men despite the random sampling process of participants need to be recognized. A noticeable lower participation rate was noted at all levels including response rate of the mail questionnaire and the nonresponse analysis. Although the precise reason is unclear, one may speculate that younger individuals are less likely to respond to questionnaires due to frequent residency changes compared to the older participants.

In **paper II** cases from study I was age (+/-2 years) and gender matched with controls from the same population. This nested case control study was performed to optimize comparisons between cases and controls and reduce risk of confounding. However, due to unfortunate damage of several slides during the transportation between Karolinska University Hospital, Sweden and the Pathology Department in Australia, it consequently resulted in the loss of multiple pairs, decreasing the power, explaining the reasoning behind using unpaired statistical analysis (logistic and linear regression)

instead of McNemars' analysis as initially planned. However, given the random damage of slides, it is unlikely to have biased the results apart from reducing power in the analysis. The statistical analyses were thus adjusted for age and gender.

An obvious strength in **papers III and IV** was the inclusion of around 97% of the total Swedish male population in the relevant cage categories at the time as well as the very low (1%) loss to follow up. This significantly minimizes the risk of selection bias. Missing data on covariates excluded 5549 individuals (12.7%) from the cohort and final analysis. The proportion of hospitalization due to symptomatic diverticular disease was similar (1.1%) compared with the final group (1.0%).

6.2.2 Information bias/ Misclassification bias

Information bias may result from erroneous or inexact sampling of information.(165) Misclassification occurs if a participant is wrongly classified in to a wrongful category (i.e. light drinker instead of heavy drinker). Non differential vs. differential misclassification further differentiates if the misclassification is unrelated to other study variables vs. differs according to the value of other study variables, such as exposed or unexposed or if they reach the study outcome or not. (165)

In **papers I and II,** our diagnostic method for identifying diverticulosis was colonoscopy, which is considered the gold standard. In addition, experienced endoscopists performed the colonoscopies. Further, we used clearly defined variables and validated GI symptom and questionnaires such as the ASQ and Rome II modular questionnaires, minimizing risk of misclassification of GI symptoms and/or IBS.(159) Similarly, in **paper I** we used the validated HADS questionnaire to assess depression and anxiety. While HADS is not the gold standard screening tool for depression and anxiety, it is a validated tool to assess prevalence and symptom severity in the general population.(162)

Any study using questionnaires will have potential for recall bias but it arguably depends on the questions asked. In **paper I and II,** the gastrointestinal symptoms and variables were assessed in two questionnaires at different times (the mail questionnaires and then at time of the gastroenterology visits), which helps minimizing the potential risk for recall bias. Concordance data from a previous study on presence or absence of IBS in the ASQ questionnaire (mailed) and the Rome II Modular questionnaire (visit), showed a concordance of 86.8%.(166) Medication use though was verified with detailed questioning of all medication use during the initial gastroenterology visit. However, the time limit of recent antibiotic use was 3 months, minimizing the potential for recall bias. Also in Sweden antibiotic prescription is tightly regulated and requires a visit with a healthcare provider, further minimizing the potential risk for recall bias and thus unlikely to have affected our results.

To minimize misclassification of mucosal inflammation, biopsies were obtained in standard uniform fashion from each colonic segment and not limited to the location of diverticula. Further, histology analyses were performed by two independent pathologists with good inter-concordance reliability, blinded to both diverticulosis and symptomatology status. In addition, CRP was measured and recorded. A possible limitation may be the lack of measurement of a correlating mucosal inflammatory marker such as fecal calprotectin. Fecal calprotectin was not readily available in Sweden at the time of the study though. Moreover histology remains the gold standard for evaluating mucosal inflammation.

Papers III and IV included data from the NPR, where primary ICD codes were used to identify the outcome of interest (diverticular disease). Although potentially being a shortfall, the ICD codes are based on a physicians' discharge summary and thought to be accurate. In an earlier review examining the accuracy of ICD-10 coding for the discharge diagnosis of symptomatic diverticular disease (K57.2-9 codes) in 528

consecutive admissions at a single center in Sweden, found coding and classification to be accurate in 95.8 % of cases with.(16) However, given the inclusion of ICD 8 and 9 codes in our study the possibility that diverticular hemorrhage may have been included within the ICD codes of interest is still possible. Thus, in an effort to further minimize the risk of misclassification, all cases with secondary discharge diagnosis of gastrointestinal hemorrhage (K92.2, 578.9) were excluded. Another possible limitation of using the NPR, is the possibility of missing cases with outcome before 1987, which is when the NPR attain nationwide coverage. Although this may possibly explain why only a few cases were diagnosed with diverticular disease in non-covered areas before that time, in 1987 the conscripts would still be younger than age 40, an age when diverticulosis and diverticular disease is very rare as reported in **paper I.**

Other important considerations include the possible misclassifications on exposure variables such as parental SES used in **paper III**. The data was derived from Statistics' Sweden which is a central statistical office established in 1858, with reliable data on geographical residency and household income minimizing risk for SES misclassification. Similarly, **paper IV** has the potential of misclassification of high BMI due to large muscular mass in muscular athletic men.(167) This risk was minimized though by adjusting for cardiovascular fitness.

6.2.3 Confounding

Confounding is a frequent issue in epidemiological studies and must always be prevented or handled. Per definition, a confounder is linked with both outcome and exposure. A confounder though is not an effect of the exposure.(165)

In **studies I and II**, inflammatory bowel disease and microscopic colitis were excluded *a priori* to minimize risk of potential confounding on the presence of diverticulosis, GI symptoms and presence of mucosal or serological inflammation.

While individuals born abroad, in total 11 % of the two parishes' total inhabitants, were excluded a priori, minimizing possible confounding by genetics or difference in gut microbiome it does so at the cost of the external validity.

In **study II**, we further performed a sensitivity analysis to evaluate confounding by smoking, recent antibiotic use and BMI, and the outcomes were essentially unchanged.

One possible limitation in **paper III** was that the reason for and perception of divorce, which might be perceived as either a positive or negative life event, were not asked. Similarly, the family environment preceding parental divorce/separation was unknown. Hence, stress and possible unknown stress related confounders might be possible. Early adverse events have been reported to increase the risk for future IBS.(168) IBS like symptomatology in a young population may lead to an increase use of colonoscopy despite current Rome based diagnostic criteria, which are entirely based on symptom-based diagnostic criteria. This may arguably lead to possible detection bias and confounding bias.

Other possible confounders such as level of hygiene, susceptibility to infections and antibiotic use etc., were not measured in this study and may have played a role. Longitudinal and in-depth studies on early life stressors including parental divorce, over time, should be studied to evaluate causality.

In **paper IV**, one potential limitation is the lack of information on dietary factors, which is a known risk factor and may affect some of the measured exposure lifestyle factors.

6.3 External validity

External validity measures the applicability of the results in a particular study population to a larger population.

Papers I and II includes a representative sample of a Swedish urban population. A slight difference in education was noted in our study population compared to the Swedish average but more importantly and arguably the greatest limitation is that only Swedish born participants were included. Although the reasoning was to limit confounding from possible difference in microbiome and lifestyle behaviors, this affects the external validity making the results only applicable to native Swedes. Otherwise, no main differences were noted among investigated variables between the included and excluded participants indicating it to be a good representation of the overall Swedish population.

Papers III and IV were population-based studies from the same cohort hence improving the external validity to young male populations with similar genetic background yet limited in the generalizability to women given the exclusively male population.

7 DISCUSSION

In this thesis, diverticulosis and diverticular disease was studied from different perspectives. Pathophysiological and epidemiological aspects of the disease were addressed.

7.1 Prevalence and Symptoms

In spite of the worldwide socioeconomic impact and increasing prevalence of our aging and expanding population that diverticular disease poses, true prevalence of diverticular disease is uncertain. Current prevalence data has mostly been extracted from early autopsy series, hospital admissions, barium radiological studies and more recently endoscopic series but of symptomatic subjects.(7) In addition, Swedish prevalence data and population-based colonoscopy studies on diverticular disease have been lacking.

This is to my knowledge the first large population-based colonoscopy study evaluating the true prevalence of diverticulosis in a community that includes a young population. Our findings confirm the current evidence that diverticulosis increases with age, but adds that this holds true also in a general community sample.(2, 169-171) One differentiating strengths in our study is the random population-based study design not biased by medical attention and secondary gain seeking individuals. Consequently selection bias was minimized and external validity improved. Further, the wide age range and high participation rate strengthens the external validity. Moreover, colonoscopy performed by experienced endoscopists was our diagnostic test of choice. Above differences have been major limitations in prior studies, possible explaining the difference in overall prevalence of diverticulosis.(8, 72, 171, 172)

It is unclear if diverticulosis per se causes gastrointestinal symptoms and namely if there is a link between diverticular disease and IBS. (7, 171, 173) Prior studies have

had issues with selection bias, leaving the question unanswered. Another problem is the differentiation between SUDD and IBS. SUDD, by definition includes abdominal pain and/or change in bowel habits due to diverticula in the absence of macroscopic colitis or diverticulitis. However, the strong IBS resemblance makes differentiation difficult. Although some studies have attempted to differentiate these two conditions by clinical characteristics the results have not been validated.(21, 134, 174) While this study was not designed to tackle how to differentiate between SUDD and IBS, we assessed the prevalence, differences and similarities of gastrointestinal symptoms overall among participants with and without diverticulosis.

Similar to the findings in two population-based non-colonoscopy studies and one recent colonoscopy study, we found that diverticulosis is associated with diarrhea-like symptoms.(171, 175) In addition, we found that abdominal pain and diarrhea-predominant IBS was associated with diverticulosis only in participants older than 60 years of age. This is interesting, as it suggests possible age-specific variations in symptomatic diverticulosis. Our study population had comparable IBS prevalence to the Swedish community (14.7% vs.6-18%, respectively), suggesting good generalizability and confounding by laxative use, microscopic colitis or IBD was unlikely given the similar results despite exclusion of possible confounders. However, despite the strong association between diverticulosis and diarrhea-predominant IBS evident by an almost 10 -fold increased OR, given the wide confidence intervals caution in interpretation is warranted and confirmation is needed.

The exact pathophysiological mechanisms for diverticulosis-associated diarrhea remain unclear but some plausible mechanisms exist. First, age-related alterations in the smooth muscle or neuronal functions are possible. However, it is unlikely to alone explain the diarrhea.(97) At the time of study one another plausible mechanism thought was low-grade inflammation by influence on epithelial cells, smooth muscle and enteric nerves function leading to changes in motility and

sensation.(121, 123, 125, 176) However, in paper II we found no evidence in this study population to support the low-grade inflammation theory. Another hypothesis though is possible dysbiosis causing alteration in motility. In our study, 21 out of 130 participants with diverticular disease reported recent antibiotic use. Participants with diverticulosis and reported recent antibiotic use had a significant 4 to 7-fold higher likelihood of increased stool frequency, urgency and looser stools. Known and accepted mechanisms of antibiotic-associated diarrhea include alteration of the gut microbiome as well as direct luminal gastrointestinal irritation of the antibiotic.(177) Interestingly though, diarrhea was not observed in participants with recent antibiotic use but no diverticulosis, suggesting an alternative explanation. While cause-or-effect relationship cannot be established, we hypothesized that heightened sensitivity to disturbances in the gut microbiome in patients with diverticulosis may be possible.

Another interesting finding in **paper I** is the predominant LLQ localization of abdominal pain/discomfort found in older participants (above age 60) with diverticulosis seen in the sub-analysis derived from the ASQ. While the literature is controversial on the definition of SUDD this raises the question whether this indeed is SUDD, since a purported difference is the LLQ abdominal pain,(134) and if so perhaps the prevalence of SUDD is underestimated. However, the wide confidence intervals warrant caution in the interpretation and larger studies to confirm this association.

Lastly, in **paper I** we found a lack of association between diverticulosis and mood disorders. In fact, our participants reported as good self-rated health as those without diverticulosis and without an association with anxiety or depression. These findings are in contrast to a recent large retrospective chart review of patients with acute symptomatic diverticulitis who were found to be 4.7 fold more likely to develop IBS after an episode in comparison to controls and 2.2 fold more likely to be diagnosed

with mood disorders.(6) Some differences exist. First, while our study is a random, wide age range sample of a population, Cohen's study population was multicultural and predominantly a male veteran population, with a mean age of 62.2 years. Secondly, while we used the validated HADS questionnaire to evaluate depression and anxiety, Cohen et al. used ICD codes from chart review, possibly introducing misclassification. HADS while not the gold standard for screening depression and anxiety, it is a validated tool to evaluate prevalence and symptom severity in the general population.(162)The main and most important difference though is that our population did not have a history of acute diverticulitis while patients in Cohen's study did. Hence, it is possible that acute inflammation may be the key trigger for developing mood disorder. Nevertheless, prospective studies are warranted to confirm this association.

7.2 Inflammation

Conflicting literature exists on the role of inflammation in diverticulosis with or without symptoms. Kealy et al. described early a microscopically evident increased density of lymph node aggregates in necropsied colons of patients with diverticular disease when compared to those from patients without diverticular disease, suggesting lymphoid follicles may be weak points in the mucosa, and diverticula could develop at these points.(178) These findings suggested the possibility of a relationship between diverticulosis and inflammation.

The largest body of evidence for this theory though, is the presence of macroscopic colitis in the areas with diverticulosis seen in SCAD. These patients have rectal sparing and similarities with IBD, ischemic colitis and infectious colitis histologically, with presence of crypt abscesses, crypt distortion and granulomas.(179) (180) Diverticular disease without segmental colitis has also been found to have chronic inflammation. For example, in resected colon segments for symptomatic

uncomplicated diverticular disease without diverticulitis, Horgan and colleagues reported the finding of peridiverticular chronic low-grade inflammation and within the diverticula in 75 % of 930 resected sigmoid specimens but the inflammation degree did not correlate with symptom intensity.(122) Similarly, Tursi and colleagues found persistent low-grade inflammation and increased expression of tumor necrosis factor alpha in patients with diverticular disease after an episode of diverticular disease. (127) However, these studies were not population-based, and included patient populations with symptomatic uncomplicated diverticular disease (SUDD), history of diverticulitis or significant symptoms requiring surgical resection as symptomatic treatment, raising concern for selection bias. Furthermore, pathologists were not blinded to the symptom status in all the studies.

In addition, several studies exist with possible explanatory pathophysiological mechanism explaining the link between chronic inflammation in diverticular disease and symptoms but results remain unclear. Simpson et al. noted damage to the enteric nervous system after recent diverticulitis, correlating with symptom persistence.(125) Humes and colleagues found that chronic low-grade inflammation could alter the motility and sensation by influencing the function of epithelial cells, smooth muscle and enteric nerves.(121) Furthermore, patients with history of acute diverticulitis have significant attenuation in serotonin transporter levels, which are a primary trigger of gut motility.(126) However, all these studies included subjects with history of diverticulitis in contrast to our study population who lacked history of diverticulitis.

In **paper II** we did not find any association between diverticulosis per se and serologic or mucosal inflammation, in any colonic segment, regardless of location of diverticula. Moreover, there was no association between symptomatic diverticulosis with abdominal pain or diarrhea and serological or mucosal inflammation. The population-based study design minimizes selection bias and improves the

generalizability. GI symptoms were further well characterized using validated modified Rome II questionnaires and the gender and GI symptom distribution was similar between included and excluded participants' support that the study population was a good representation of the overall population. Further, the diagnostic method for identifying diverticulosis was colonoscopy. While biopsies were not targeted to the diverticula per se, the biopsies were obtained in standard uniform fashion from each colonic segment and not limited to the location of diverticula. Histology analyses were further performed by two independent pathologists with good inter-concordance reliability, blinded to both diverticulosis and symptomatology status. Lastly, we measured and accounted to for known and possible confounders in our analysis.

Our study complements the recent findings by Peery et al. demonstrating absence of colonic mucosal inflammation in diverticulosis or symptomatic diverticulosis.(130) While both studies were colonoscopy-based and included study populations with absence of past diverticulitis, our study was population-based and assessed the whole colon for inflammation, regardless of localization of diverticula, while Peery et al. only assessed the sigmoid colon. Furthermore, while Peery et al. measured the presence of active immune response by TNF-α messenger RNA, interleukins-6 and interleukin-10 levels, we evaluated the actual presence of inflammatory cells, changes and gradients.

Arguably, some limitations need to be mentioned. None of the study participants had history of diverticulitis. We can thus not exclude a severe disease subgroup, which suffer recurrent episodes of acute diverticulitis where colonic inflammation plays a role. Another possible limitation is the lack of a correlating colon mucosal inflammatory marker such as fecal calprotectin but it was not readily available in Sweden at the time of the study and histology remains the gold standard to evaluate mucosal inflammation.

The main issue with **paper II** was missing data. While matching to age (2+/-) and gender was done a priori to minimize risk for confounding, missing data by damage of slides during transportation between Sweden and Australia occurred, leaving discordant pairs and ultimately loss of power. This was the main reason for proceeding with logistic and linear regression adjusted for age and gender instead of McNemar's analysis. However, it is unlikely to have affected the results as the damage occurred at random with no significant difference when comparing included and excluded cases in terms of age, gender, or symptoms. Other possible limitations include, underreporting of over the counter NSAID use possibly underestimating the presence of mucosal inflammation. However, the detailed questioning of all medication use twice and on two different occasions (during the initial gastroenterology visit and at time of endoscopy) minimizes the risk for potential recall bias and hence unlikely to have altered our results.

In the symptomatic diverticulosis subanalysis, there was no evidence of association between symptomatic diverticulosis with abdominal pain or diarrhea and serological or mucosal inflammation throughout the colon. This further extends both Peery et al. and Elli et al.'s recent findings of an absence of sigmoidal colonic mucosal inflammation, measured by levels of serological immune markers and histological cytokine levels in subjects with symptomatic diverticulosis (IBS or abdominal pain) and SUDD compared to controls without diverticulosis.(128, 130)

In conclusion, the findings in **paper II** suggest that alternate pathophysiological mechanisms need to be explored as we found no association between diverticulosis and inflammation regardless if symptomatic or not and thus questions the rationale of mesalazine use (an anti-inflammatory agent) in symptomatic diverticulosis without history of diverticulitis.

7.3 Risk Factors

In spite of emerging data suggesting an increment in incidence of diverticular disease in younger individuals and gap of knowledge exists on predictive risk factors in the young populations. In adults, epidemiological studies have identified obesity, smoking, NSAID use and diet to be risk factors for complicated diverticular disease, diverticular bleeding and diverticulitis (12, 13, 16, 90) and low socioeconomic status has been linked with increased hospitalization risk for both complicated and uncomplicated diverticular disease.(94) The influence of environmental determinants during upbringing and late adolescence, such as socioeconomic status, residency geography (rural vs. urban) on diverticular disease are unknown and longitudinal studies in a young population are lacking.

Papers III and IV help close this knowledge gap. In this large cohort study of young late adolescent males, we found exposure to parental divorce to be associated with a 49% risk increment for future hospital admission for symptomatic diverticular disease compared to conscripts with married parents. While both smoking and risky alcohol use was more prevalent in conscripts with divorced parents compared to those with married parents, the association between having divorced parents and future risk of diverticular disease was not explained by the these lifestyle factors.

The mechanism by how parental divorce influences future diverticular disease is unclear. Considering that parental divorce is among the most commonly endorsed adverse and stressful childhood events but also associated with known health implications such as adopting risk behaviors in lifestyle, mental health disease and substance abuse conditions(181) it is difficult to delineate whether it directly or indirectly (as a surrogate marker for stress) influences the risk of future hospital admission for symptomatic diverticular disease. Stress per se, may affect gut inflammation via the hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system, stimulating production and activation of proinflammatory cytokines

and macrophages and altering intestinal permeability and the gut microbiota.(182) One shortcoming in paper III is that family environment preceding parental divorce/separation and other early life events were unknown, leaving the role of stress and possible stress related confounders unclear. Hence, longitudinal studies assessing multiple early life stressors including parental divorce are warranted to establish causality.

The influence of geographical residence on diverticular disease is unclear. In adults, an early study found urbanization to be associated with diverticulosis(39) while recent large population-based studies found an increased risk for diverticular disease (uncomplicated and diverticular disease requiring hospitalization) in residents of small cities or rural areas when compared to urban residents.(49, 94) In contrast, early exposure of rural residency in the pediatric IBD literature, at diagnosis and at birth, has been protective.(183) Similarly, reduced risk for developing IBD have been reported with early pet exposure, childhood contact with farm animals and sharing a home and beds.(184) However, since diverticular disease is an age dependent disorder in difference from IBD, it is plausible that geographical residency plays a role in the pathogenesis if exposed late rather than in early life, closer to onset of the disease, consequently explaining our results. Other factors such as hygiene, infection susceptibility and antibiotic use etc., were not measured in this study, and need to be considered as well.

In **paper IV,** we found that lifestyle factors high BMI, low cardiovascular fitness, smoking and risky alcohol use were all significant and independently associated with an increased risk of developing symptomatic diverticular disease requiring hospitalization.

Several epidemiological cohort studies exist with similar findings but this is the first study to report data from an exclusively late adolescent cohort.

While the causative mechanisms for obesity to increase the risk of symptomatic diverticular disease are unknown, some possible mechanisms will be discussed below. First, adipose tissue-driven secretion of inflammatory cytokines have been linked with immune cell infiltration in muscle and adjacent tissues in obesity (185, 186) and thus possibly playing a role in symptomatic of diverticular disease development. Secondly, obesity associated gut microbiome disturbance is possible.(187) Although the association is complex and poorly understood (188), a predominance of *Firmicutes* over *Bacteroidetes* has been reported in obese individuals, with opposite pattern in lean individuals.(189) Similarly, in SUDD patients similar microbiome patterns (predominant *Firmicutes* strains over *Bacteroidetes)* have reported when compared to controls.(111, 112) Alternatively, the duration of the exposure to being overweight/ obesity (a potentially proinflammatory condition) may influence muscular integrity of the colon and gut microbiota balance, increasing the risk for developing diverticular disease over time. However, this would need confirmation with a longitudinal study.

Comparable to existing adult data(81), we found that high cardiovascular fitness in late adolescence was independently protective against developing symptomatic diverticular disease requiring hospitalization.

In adults, while tobacco use has been associated with increased risk of symptomatic and complicated diverticular disease, the dose-response relationship between smoking and diverticular disease is unclear. Compared to nonsmokers, Humes and colleagues found a dose dependent risk increment in patients smoking >15 cigarettes/ day for developing symptomatic diverticular disease. In contrast, while Hjern et al. 24 % increase risk of symptomatic diverticular disease in current smokers vs. nonsmokers, a dose response effect was not noted.(15, 16) Similar to Hjern et al., we found no dose-response effect in study IV, and the risk increment in for developing symptomatic diverticular disease was similar across smoking categories except for the highest category in the multivariate analysis, which is likely explained by the small number of

heavy smokers among cases (N=21). Although the precise explanatory mechanisms on how smoking influences the pathogenesis and symptomatic diverticular disease are unknown, altered colonic structural, decreased blood circulation, imbalance in immune cell infiltration, altered colon transit times and gut microbiome, are possible

Patients admitted for alcoholism were found to have a nearly 3-fold higher risk of being hospitalized for diverticulitis when compared to the general population in a Danish National Registry study.(86) However, data on alcohol and risk for diverticulosis and diverticular disease is conflicting. Two adult prospective population-based studies found no independent link between alcohol and diverticular disease. (73, 82) In **paper IV,** late adolescent risky alcohol use but not alcohol per se, was found to be independently associated with a 43% increased risk of requiring hospital admission for diverticular disease. One possible explanation may be a link between risky alcohol use and overall risk behaviors. The lack of association between use of recreational drugs and development of diverticular disease however, argues against the possible explanation that risk behaviors overall are increased in conscripts with risky alcohol use. Alternatively, risky alcohol use may be associated with increased risk for comorbidities overall.(190)

The main limitation in **papers III and IV** is that the data on variables were only collected at baseline and lack of information on dietary factors, Hence, inference on whether changes in lifestyle factors and diet impact, and if so and to what extent, on developing clinically significant symptomatic diverticular disease requiring hospitalization, cannot be made. Thus, studies assessing the impact of lifestyle factor modification early and later in life on future symptomatic diverticular disease requiring hospital admission are warranted.

8 CONCLUSIONS

Referring to the described aims of the study the following conclusions can be formulated:

1. Diverticulosis is common, and the prevalence is age-dependent and similar among women and men.
2. Diverticulosis is associated with diarrhea and in those older than 60 years of age abdominal pain and diarrhea-predominant IBS.
3. In a general community sample, neither asymptomatic nor symptomatic diverticulosis, are associated with colonic mucosal inflammation. Other explanations for symptomatic colonic diverticulosis need to be identified.
4. Exposure to parental divorce in early life is associated with an increased risk of hospital admission for symptomatic diverticular disease even after adjustment for lifestyle risk factors.
5. A high BMI, poor cardiovascular fitness, risky alcohol use and smoking in late adolescence are associated with an increased risk of developing diverticular disease later in life.

9 CLINICAL AND SCIENTIFIC IMPLICATIONS

9.1 Implications for Clinical Practice and Future Studies

Paper I

- Identifying the true prevalence of diverticulosis and its association with gastrointestinal symptoms in a general population gives us much needed insight on the impact and spectrum of the condition.
- We confirm that diverticulosis is common, increases with age and has no gender predilection in the general population.
- Further, the overall link and age-specific association between diverticulosis and diarrhea, abdominal pain and diarrhea-predominant IBS should direct future age-specific studies aimed at uncovering the mechanisms underlying the development of diverticular disease and possible help identify high risk populations.

Paper II

- No evidence of serological or colonic inflammation in diverticulosis and/or the symptoms of diarrhea, abdominal pain or IBS was found.
- These findings suggest a different pathophysiologic mechanism for developing diverticulosis and question the current use of mesalamine in SUDD, which purportedly is the result of chronic low grade inflammation.
- This notion invites longitudinal population-based microbiome studies to further study pathophysiological mechanisms.

Papers III and IV

- We found that exposure to parental divorce influences the risk for development of diverticular disease later in life.
- This encourages future studies investigating early life events on the development for symptomatic diverticular disease
- It further fuels the current evidence suggesting that adolescence is a risky period for developing longstanding behaviors and lifestyle risk factors into adulthood.
- We conclude that being overweight, a smoker, poorly cardiovascular fit or a risky alcohol user in late adolescence are independantly associated with an increased risk for develeopingt of clinically signficant diverticular disease requiring hospital admission later in life.
- Having identified these early life risk factors should fuel future studies to evaluate to the effect of modifying these factors on the outcome possibly as preventable measures.

10 POPULÄRVETENSKAPLIG SAMMANFATTNING

Divertikelsjukdom (tarmfickor) i tjocktarmen är vanligt förekommande och är orsak till en stigande samhällsbelastning med höga sjukvårdskostnader. Divertikelsjukdom är ovanlig innan 40 års ålder men ökar i förekomst med stigande ålder. Den kliniska bilden spänner från ett symtomfritt tillstånd till svårt akut sjukdom som kräver sjukhusvård, intravenös antibiotika och vid behov kirurgi. Med en åldrande befolkning är kunskap om riskfaktorer för att utveckla divertikelsjukdom viktig. Orsaken till divertikelsjukdom är komplext och bristfälligt utforskad. Låggradig inflammation är en potentiell underliggande orsak till symtomatisk divertikulos, men befolkningsstudier saknas. Kända riskfaktorer att utveckla divertikelsjukdom inkluderar genetiska- samt livsstilsfaktorer, men endast vuxenstudier har utförts.

Syftet med denna avhandling var att kartlägga förekomsten av divertikulos och dess samband med mag-tarmsymtom i normalbefolkningen. Vidare var syftet att undersöka om låggradig inflammation i tjocktarmen har samband med divertikulos samt undersöka om tidiga livsstils- och miljöfaktorer ökar risken att utveckla symptomatisk divertikelsjukdom inklusive divertikulit.

I delarbete I utförde vi en befolkningsbaserad koloskopiundersökning av slumpmässigt utvalda vuxna födda i Sverige (18-70 år), där sambandet mellan mag-tarmsymtom, psykisk hälsa, koloskopi och divertikulos undersöktes. Studien visade att förekomsten av divertikulos är åldersberoende samt att divertikulos är associerat med diarré samt buksmärta och irritabel tjocktarm (IBS) hos äldre individer över 60 år. Delarbete II är en fallkontrollstudie från samma normalbefolkning som i delarbete I. Vi fann att divertikulos med eller utan mag-tarmsymtom är inte förknippat med låggradig inflammation vare sig i tjocktarmens slemhinna eller i blodet.

Delarbetena III och IV var stora befolkningsbaserade kohortstudier, där vi under- sökte sambandet mellan livsstils- och miljöexponeringsvariabler och de följande 39 års risk

för inneliggande symtomatisk divertikelsjukdom hos unga Svenska män som mönstrade år 1969-2009 (n=49 321). I delarbete III, fann vi att unga mönstrade män med skilda föräldrar hade ökad risk för framtida behov av sjukhusinlägg för behandling av divertikelsjukdom. Vidare fann vi i delarbete IV att övervikt, fetma, rökning, riskfyllt alkoholbruk samt dålig fysisk kondition i sen ungdom är förknippat med en ökad risk för framtida behov av sjukhusinläggning för behandling av divertikelsjukdom.

Sammanfattningsvis så visar denna avhandling att divertikulos är vanligt förekommande och åldersberoende samt ofta förknippat med diarré, buksmärta och irritabel tjocktarm hos normal befolkningen, men inte med låggradig inflammation i tjocktarmen. Livsstilsfaktorer som fetma, rökning, riskfyllt alkoholbruk och dålig fysisk kondition ökar risken för att utveckla sjukhuskrävande divertikelsjukdom även om föräldrar är skilda.

Framtida studier med fokus på vikten av stressfyllda situationer i barndom och framtida sjuklighet i divertikelsjukdom samt behandlingsstudie livsstilsintervention i riskgrupper är rekommenderat.

11 ACKNOWLEDGEMENTS

I would like to acknowledge everyone who has, in one way or another, contributed to all the hard work behind the four articles and also express my profoundest gratitude to all of you who have supported me while working on my thesis. In particular I would like to express my gratitude to:

All the participants in the studies included in this thesis. Without their participation this book would have been empty.

Associate Professor Peter Thelin Schmidt, my principal supervisor and friend, for your genuine and constant assistance given throughout the project. You not only shared your knowledge but also scientific enthusiasm and gave me independence even during times when progress was slower. You are a role model far outside the reach of research.

Associate Professor Anna Andreasson, my co-supervisor, you have been my rock and pillar throughout this journey. You infused your infectious enthusiasm that propelled me to such great heights. It is rare to have a mentor who surpasses all the makings of a true laureate, great teacher and friend, who has been by my side throughout this long journey. In times of scientific or statistical despair you have always been just one phone call away. I am beyond words in gratitude.

Professor Lars Agreus, my co-supervisor, for your contagious scientific enthusiasm, wisdom, sharp mind and extensive contributions to this project and for leading such welcoming and outstanding research group.

Professor Nicholas J. Talley, my co-supervisor, for being a brilliant researcher and eager to share your vast experience and knowledge. Thank you for your inspiration, attention to detail and invaluable constructive feedback on my scientific writing and career.

Annika Bergquist, previous head of the center of Digestive Diseases at Karolinska University Hospital, for recruiting me and for your support, vision and for creating a welcoming and research-oriented atmosphere.

Jan Björk, my external mentor, for encouragement and helpful career advice during the beginning.

Marjorie M. Walker, a special thanks to this amazing world-renowned GI pathologist, who

has been instrumental not only in study II but throughout my PhD studies. For the mentoring during my research visit Newcastle, Australia and beyond, for teaching me the art of histopathology, for your invaluable feedback on manuscripts and lastly, for opening my eyes to eosinophils.

Loui Rassam, co-author, for your patience and invaluable teaching in histology reading skills.

Jeong-Yeop Song, Aws Jasim, Hannes Hagström, Tomas Hemmingson and Filip Sköldberg, co-authors, for being inspirational researchers and/or clinicians. A special thanks to Tomas for allowing me to partake in the studies of the conscript cohort.

Leanne Tarrant, thank you for being instrumental in arranging the visit to Newcastle and making it a wonderful experience. The discussions about life over a "long blacks coffees" are fond memories.

I would also like to thank *Anders Ekbom and Maria Altman* and teachers at the KI's Research School in Epidemiology for Clinicians, for an outstanding education.

Hashem El-Serag and successor *Fasiha Kanwal,* head of Digestive Disease Center at Baylor College of Medicine for their support, vision and academically stimulating environment at Baylor College of Medicine.

Rhonda Cole, Associate head of Gastroenterology and *Clark Hair,* Chief of Endoscopy, at Michael E. Debakey VA Medical Center for supporting me and providing an amazing work environment.

Thank to my wonderful, former *colleagues and staff at Gastrocentrum Karolinska Universistetssjukhus,* for great support, enthusiasm and a great work environment.

To my wonderful *colleagues at Michael E. Debakey VA Medical Center (Rhonda Cole, David Y. Graham, Maria Velez, Clark Hair, Avinash Ketwaroo, Yamini Natarajan, Nisreen Husain, Ruben Hernaez, Rajesh Shah and Khozema Hussain)* for support, helping when needed and for making work something to look forward to everyday.

To the wonderful *staff of Endoscopy at Michael E. Debakey VA Medical Center* and Gastroenterology department at Baylor College of Medicine for continuously creating a great work environment and making work a true pleasure.

To *Bengt Curman,* who indirectly introduced me to the mesmerizing world of Gastroenterology.

To my parents, *Anders Järbrink and Nina Vazquez de Järbrink*, for their unconditional love, support, guidance, encouragement and just being the best parent a person can have. Words are not enough to say thank you.

To my second set of parents, *Sudarshan and Avnashi Sehgal,* for always being there for us, your invaluable support, wisdom, love, encouragement, and of course delicious meals and heartfelt cups of chai.

To *Patty Valenzuela, Pili Hernandez* and *Tia Eugenia,* for being my role models in life, for your support, complete faith in me and help with the girls. You have all taught me skills of love, strength, will-power, independence, perseverance by example and I am lucky to have you in my life.

Ajay, for support and for giving me the best thing in my life, my daughters.

To *Andres and Martin Järbrink,* my dear brothers, for your unconditional love, support, inspiration and laughs throughout this thesis and in life.

Marie Sundlöf, Sumita Mehta, and Saad Haque, friends and colleagues, for your encouragement, support and dark humor in times of gastroenterological, scientific despair in general

To the Rileys (*Magnus, Anna, Christina, Ray*) second cousins, for support, inspiration and help with Sofia and schooling at Tanto School. Without you, completing my studies would not have been possible.

To *Evelyn Vanegas,* for the early mornings, late nights, the overnights and the weekends. Without your tremendous support at home none of this would have been possible. You gave my girls love, support and warmth in my absence. And thank you Jaden and Marvin Parada for your patience in having your mom and wife away.

In memoriam, *Mormor Margit Järbrink*, who celebrated my every scientific, professional and personal endeavor with either champagne or a cup of Earl Grey tea.

And last but not least thank you, *Sofia,* love of my life, for always being so wonderful, studious, supportive, patient, loving and believing so completely in me. Without your support this would not have been done. *Bella,* the second love of my life, for making me smile, always keeping me busy and realizing that sleep is overrated. I love you both to the moon and back.

The studies included in this thesis were supported by grants from: Magtarmförbundet, Bengt Ihre Stiftelsen, Stockholms County Council, Ersta Hospital, Astra Zeneca, Stockholm, Sweden.

12 REFERENCES

1. Peery AF, Crockett SD, Barritt AS, Dellon ES, Eluri S, Gangarosa LM, et al. Burden of Gastrointestinal, Liver, and Pancreatic Diseases in the United States. Gastroenterology. 2015;149(7):1731-41 e3.
2. Delvaux M. Diverticular disease of the colon in Europe: epidemiology, impact on citizen health and prevention. Aliment Pharmacol Ther. 2003;18 Suppl 3:71-4.
3. Official Statistics of Sweden. The National Board of Health and Welfare. 2002-2014.
4. Strate LL, Modi R, Cohen E, Spiegel BM. Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. Am J Gastroenterol. 2012;107(10):1486-93.
5. Bharucha AE, Parthasarathy G, Ditah I, Fletcher JG, Ewelukwa O, Pendlimari R, et al. Temporal Trends in the Incidence and Natural History of Diverticulitis: A Population-Based Study. Am J Gastroenterol. 2015;110(11):1589-96.
6. Cohen E, Fuller G, Bolus R, Modi R, Vu M, Shahedi K, et al. Increased risk for irritable bowel syndrome after acute diverticulitis. Clin Gastroenterol Hepatol. 2013;11(12):1614-9.
7. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part II: lower gastrointestinal diseases. Gastroenterology. 2009;136(3):741-54.
8. Painter NS, Burkitt DP. Diverticular disease of the colon: a deficiency disease of Western civilization. Br Med J. 1971;2(5759):450-4.
9. Granlund J, Svensson T, Olén O, Hjern F, Pedersen NL, Magnusson PK, et al. The genetic influence on diverticular disease--a twin study. Aliment Pharmacol Ther. 2012;35(9):1103-7.
10. Strate LL, Erichsen R, Baron JA, Mortensen J, Pedersen JK, Riis AH, et al. Heritability and familial aggregation of diverticular disease: a population-based study of twins and siblings. Gastroenterology. 2013;144(4):736-42.e1; quiz e14.
11. Rosemar A, Angerås U, Rosengren A. Body mass index and diverticular disease: a 28-year follow-up study in men. Dis Colon Rectum. 2008;51(4):450-5.
12. Hjern F, Wolk A, Håkansson N. Obesity, physical inactivity, and colonic diverticular disease requiring hospitalization in women: a prospective cohort study. Am J Gastroenterol. 2012;107(2):296-302.
13. Strate LL, Liu YL, Aldoori WH, Syngal S, Giovannucci EL. Obesity increases the risks of diverticulitis and diverticular bleeding. Gastroenterology. 2009;136(1):115-22.e1.
14. Crowe FL, Balkwill A, Cairns BJ, Appleby PN, Green J, Reeves GK, et al. Source of dietary fibre and diverticular disease incidence: a prospective study of UK women. Gut. 2014;63(9):1450-6.
15. Humes DJ, Ludvigsson JF, Jarvholm B. Smoking and the Risk of Hospitalization for Symptomatic Diverticular Disease: A Population-Based Cohort Study from Sweden. Dis Colon Rectum. 2016;59(2):110-4.
16. Hjern F, Wolk A, Håkansson N. Smoking and the risk of diverticular disease in women. Br J Surg. 2011;98(7):997-1002.

17. Stollman N, Raskin JB. Diverticular disease of the colon. Lancet. 2004;363(9409):631-9.

18. Barroso AO, Quigley EM. Diverticula and Diverticulitis: Time for a Reappraisal. Gastroenterol Hepatol (N Y). 2015;11(10):680-8.

19. Elisei W, Tursi A. Recent advances in the treatment of colonic diverticular disease and prevention of acute diverticulitis. Ann Gastroenterol. 2016;29(1):24-32.

20. Tursi A, Papa A, Danese S. Review article: the pathophysiology and medical management of diverticulosis and diverticular disease of the colon. Aliment Pharmacol Ther. 2015;42(6):664-84.

21. Annibale B, Lahner E, Maconi G, Usai P, Marchi S, Bassotti G, et al. Clinical features of symptomatic uncomplicated diverticular disease: a multicenter Italian survey. Int J Colorectal Dis. 2012;27(9):1151-9.

22. Spiller R. Is it diverticular disease or is it irritable bowel syndrome? Dig Dis. 2012;30(1):64-9.

23. Fox JM, Stollman NH. Chapter: Diverticular Disease of the Colon. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. Philadelphia: Saunders; 2010.

24. Rezapour M, Ali S, Stollman N. Diverticular Disease: An Update on Pathogenesis and Management. Gut Liver. 2018;12(2):125-32.

25. Freeman HJ. Segmental colitis associated diverticulosis syndrome. World J Gastroenterol. 2016;22(36):8067-9.

26. Strate LL, Ayanian JZ, Kotler G, Syngal S. Risk factors for mortality in lower intestinal bleeding. Clin Gastroenterol Hepatol. 2008;6(9):1004-10; quiz 955-.

27. Spriggs EI, Marxer OA. An Address on Intestinal Diverticula. Br Med J. 1926;1(3395):130-4.

28. Cruveilhier J. Traite d'anatomie pathologique generale 1849.

29. Graser E. Uber multiple faslsche darmdivetikelin der fleura sigmoida. Munch Med Wochenschr 1899;46:74.

30. Beer E. Some pathological and clinical aspects of acquired (false) diverticula of the intestine. Am J Med Sci. 1904;128:125-45.

31. Mayo WJ, Wilson LB, Giffin HZ. Acquired diverticulitis of the large intestine. Surg Gynecol Obstet. 1907;5:8-15.

32. Case JT. The roentgen demonstration of multiple diverticula of the colon. Am J Roentgenol. 1914;2:654.

33. Telling WHM, Gruner OC. Brit J Surg. 1917;4:468.

34. Kocour EJ. Diverticulosis of the colon: Its incidence in 7,000 consecutive autopsies with reference to its complications. Am J Surgery. 1937;37(3):433-436,439.

35. Parks TG. Natural history of diverticular disease of the colon. A review of 521 cases. Br Med J. 1969;4(5684):639-42.

36. Zuckerman GR, Prakash C. Acute lower intestinal bleeding. Part II: etiology, therapy, and outcomes. Gastrointest Endosc. 1999;49(2):228-38.

37. Oakland K, Guy R, Uberoi R, Hogg R, Mortensen N, Murphy MF, et al. Acute lower GI bleeding in the UK: patient characteristics, interventions and outcomes in the first nationwide audit. Gut. 2018;67(4):654-62.

38. Mann NS, Hoda KK. Segmental colitis associated with diverticulosis: systematic evaluation of 486 cases with meta-analysis. Hepatogastroenterology. 2012;59(119):2119-21.

39. Manousos O, Day NE, Tzonou A, Papadimitriou C, Kapetanakis A, Polychronopoulou-Trichopoulou A, et al. Diet and other factors in the aetiology of diverticulosis: an epidemiological study in Greece. Gut. 1985;26(6):544-9.

40. Jun S, Stollman N. Epidemiology of diverticular disease. Best Pract Res Clin Gastroenterol. 2002;16(4):529-42.

41. Wheat CL, Strate LL. Trends in Hospitalization for Diverticulitis and Diverticular Bleeding in the United States From 2000 to 2010. Clin Gastroenterol Hepatol. 2016;14(1):96-103.e1.

42. Kang JY, Hoare J, Tinto A, Subramanian S, Ellis C, Majeed A, et al. Diverticular disease of the colon--on the rise: a study of hospital admissions in England between 1989/1990 and 1999/2000. Aliment Pharmacol Ther. 2003;17(9):1189-95.

43. McConnell EJ, Tessier DJ, Wolff BG. Population-based incidence of complicated diverticular disease of the sigmoid colon based on gender and age. Dis Colon Rectum. 2003;46(8):1110-4.

44. Guzzo J, Hyman N. Diverticulitis in young patients: is resection after a single attack always warranted? Dis Colon Rectum. 2004;47(7):1187-90; discussion 90-1.

45. Konvolinka CW. Acute diverticulitis under age forty. Am J Surg. 1994;167(6):562-5.

46. Pautrat K, Bretagnol F, Huten N, de Calan L. Acute diverticulitis in very young patients: a frequent surgical management. Dis Colon Rectum. 2007;50(4):472-7.

47. Peery AF, Keku TO, Martin CF, Eluri S, Runge T, Galanko JA, et al. Distribution and Characteristics of Colonic Diverticula in a United States Screening Population. Clin Gastroenterol Hepatol. 2016;14(7):980-5 e1.

48. Painter NS, Truelove SC, Ardran GM, Tuckey M. Segmentation and the localization of intraluminal pressure in the human colon, with special reference to the pathogenesis of colonic diverticula. Gastroenterology. 1968;54(4):Suppl:778-80.

49. Hjern F, Johansson C, Mellgren A, Baxter NN, Hjern A. Diverticular disease and migration--the influence of acculturation to a Western lifestyle on diverticular disease. Aliment Pharmacol Ther. 2006;23(6):797-805.

50. Stemmermann GN, Yatani R. Diverticulosis and polyps of the large intestine. A necropsy study of Hawaii Japanese. Cancer. 1973;31(5):1260-70.

51. Levy N, Stermer E, Simon J. The changing epidemiology of diverticular disease in Israel. Dis Colon Rectum. 1985;28(6):416-8.

52. Song JH, Kim YS, Lee JH, Ok KS, Ryu SH, Moon JS. Clinical characteristics of colonic diverticulosis in Korea: a prospective study. Korean J Intern Med. 2010;25(2):140-6.

53. Ogutu EO, Okoth FA, Lule GN. Colonoscopic findings in Kenyan African patients. East Afr Med J. 1998;75(9):540-3.

54. Kiguli-Malwadde E, Kasozi H. Diverticular disease of the colon in Kampala, Uganda. Afr Health Sci. 2002;2(1):29-32.

55. Toda S, Ito Y, Mizuno M, Suzuki Y, Ito I, Hiramatsu H, et al. Asymptomatic diverticulosis identified by computed tomography is not a risk factor for enteric peritonitis. Nephrol Dial Transplant. 2012;27(6):2511-6.

56. Reichert MC, Lammert F. The genetic epidemiology of diverticulosis and diverticular disease: Emerging evidence. United European Gastroenterol J. 2015;3(5):409-18.

57. Connelly TM, Berg AS, Hegarty JP, Deiling S, Brinton D, Poritz LS, et al. The TNFSF15 gene single nucleotide polymorphism rs7848647 is associated with surgical diverticulitis. Ann Surg. 2014;259(6):1132-7.

58. Beasley WD, Beynon J, Jenkins GJ, Parry JM. Reprimo 824 G>C and p53R2 4696 C>G single nucleotide polymorphisms and colorectal cancer: a case-control disease association study. Int J Colorectal Dis. 2008;23(4):375-81.

59. Reichert MC, Kupcinskas J, Krawczyk M, Jüngst C, Casper M, Grünhage F, et al. A Variant of COL3A1 (rs3134646) Is Associated With Risk of Developing Diverticulosis in White Men. Dis Colon Rectum. 2018;61(5):604-11.

60. Sigurdsson S, Alexandersson KF, Sulem P, Feenstra B, Gudmundsdottir S, Halldorsson GH, et al. Sequence variants in ARHGAP15, COLQ and FAM155A associate with diverticular disease and diverticulitis. Nat Commun. 2017;8:15789.

61. Maguire LH, Handelman SK, Du X, Chen Y, Pers TH, Speliotes EK. Genome-wide association analyses identify 39 new susceptibility loci for diverticular disease. Nat Genet. 2018.

62. Lindor NM, Bristow J. Tenascin-X deficiency in autosomal recessive Ehlers-Danlos syndrome. Am J Med Genet A. 2005;135(1):75-80.

63. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N Engl J Med. 2000;342(10):673-80.

64. Partsch CJ, Siebert R, Caliebe A, Gosch A, Wessel A, Pankau R. Sigmoid diverticulitis in patients with Williams-Beuren syndrome: relatively high prevalence and high complication rate in young adults with the syndrome. Am J Med Genet A. 2005;137(1):52-4.

65. Scheff RT, Zuckerman G, Harter H, Delmez J, Koehler R. Diverticular disease in patients with chronic renal failure due to polycystic kidney disease. Ann Intern Med. 1980;92(2 Pt 1):202-4.

66. Pourfarziani V, Mousavi-Nayeeni SM, Ghaheri H, Assari S, Saadat SH, Panahi F, et al. The outcome of diverticulosis in kidney recipients with polycystic kidney disease. Transplant Proc. 2007;39(4):1054-6.

67. Lederman ED, McCoy G, Conti DJ, Lee EC. Diverticulitis and polycystic kidney disease. Am Surg. 2000;66(2):200-3.

68. Suster SM, Ronnen M, Bubis JJ. Diverticulosis coli in association with Marfan's syndrome. Arch Intern Med. 1984;144(1):203.

69. Bose KP, Khorshidi I, Southern WN, Brandt LJ. The impact of ethnicity and obesity on the course of colonic diverticulitis. J Clin Gastroenterol. 2013;47(2):160-4.

70. McGuire HH. Bleeding colonic diverticula. A reappraisal of natural history and management. Ann Surg. 1994;220(5):653-6.

71. Wong SK, Ho YH, Leong AP, Seow-Choen F. Clinical behavior of complicated right-sided and left-sided diverticulosis. Dis Colon Rectum. 1997;40(3):344-8.

72. Yamada A, Sugimoto T, Kondo S, Ohta M, Watabe H, Maeda S, et al. Assessment of the risk factors for colonic diverticular hemorrhage. Dis Colon Rectum. 2008;51(1):116-20.

73. Crowe FL, Appleby PN, Allen NE, Key TJ. Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. BMJ. 2011;343:d4131.

74. Aldoori WH, Giovannucci EL, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, et al. Prospective study of physical activity and the risk of symptomatic diverticular disease in men. Gut. 1995;36(2):276-82.

75. Strate LL, Keeley BR, Cao Y, Wu K, Giovannucci EL, Chan AT. Western Dietary Pattern Increases, and Prudent Dietary Pattern Decreases, Risk of Incident Diverticulitis in a Prospective Cohort Study. Gastroenterology. 2017;152(5):1023-30.e2.

76. Cao Y, Strate LL, Keeley BR, Tam I, Wu K, Giovannucci EL, et al. Meat intake and risk of diverticulitis among men. Gut. 2018;67(3):466-72.

77. Peery AF, Barrett PR, Park D, Rogers AJ, Galanko JA, Martin CF, et al. A high-fiber diet does not protect against asymptomatic diverticulosis. Gastroenterology. 2012;142(2):266-72 e1.

78. Strate LL. Lifestyle factors and the course of diverticular disease. Dig Dis. 2012;30(1):35-45.

79. Aune D, Sen A, Leitzmann MF, Norat T, Tonstad S, Vatten LJ. Body mass index and physical activity and the risk of diverticular disease: a systematic review and meta-analysis of prospective studies. Eur J Nutr. 2017;56(8):2423-38.

80. Kopylov U, Ben-Horin S, Lahat A, Segev S, Avidan B, Carter D. Obesity, metabolic syndrome and the risk of development of colonic diverticulosis. Digestion. 2012;86(3):201-5.

81. Strate LL, Liu YL, Aldoori WH, Giovannucci EL. Physical activity decreases diverticular complications. Am J Gastroenterol. 2009;104(5):1221-30.

82. Aldoori WH, Giovannucci EL, Rimm EB, Wing AL, Trichopoulos DV, Willett WC. A prospective study of alcohol, smoking, caffeine, and the risk of symptomatic diverticular disease in men. Ann Epidemiol. 1995;5(3):221-8.

83. Aune D, Sen A, Leitzmann MF, Tonstad S, Norat T, Vatten LJ. Tobacco smoking and the risk of diverticular disease - a systematic review and meta-analysis of prospective studies. Colorectal Dis. 2017;19(7):621-33.

84. Wang FW, Chuang HY, Tu MS, King TM, Wang JH, Hsu CW, et al. Prevalence and risk factors of asymptomatic colorectal diverticulosis in Taiwan. BMC Gastroenterol. 2015;15:40.

85. Yamamichi N, Shimamoto T, Takahashi Y, Sakaguchi Y, Kakimoto H, Matsuda R, et al. Trend and risk factors of diverticulosis in Japan: age, gender, and

lifestyle/metabolic-related factors may cooperatively affect on the colorectal diverticula formation. PLoS One. 2015;10(4):e0123688.

86. Tonnesen H, Engholm G, Moller H. Association between alcoholism and diverticulitis. Br J Surg. 1999;86(8):1067-8.

87. Sharara AI, El-Halabi MM, Mansour NM, Malli A, Ghaith OA, Hashash JG, et al. Alcohol consumption is a risk factor for colonic diverticulosis. J Clin Gastroenterol. 2013;47(5):420-5.

88. Jaruvongvanich V, Sanguankeo A, Upala S. Association between Alcohol Consumption and Diverticulosis and Diverticular Bleeding: A Systematic Review and Meta-analysis. Hawaii J Med Public Health. 2017;76(8):211-9.

89. Jansen A, Harenberg S, Grenda U, Elsing C. Risk factors for colonic diverticular bleeding: a Westernized community based hospital study. World J Gastroenterol. 2009;15(4):457-61.

90. Humes DJ, Fleming KM, Spiller RC, West J. Concurrent drug use and the risk of perforated colonic diverticular disease: a population-based case-control study. Gut. 2011;60(2):219-24.

91. Hjern F, Mahmood MW, Abraham-Nordling M, Wolk A, Håkansson N. Cohort study of corticosteroid use and risk of hospital admission for diverticular disease. Br J Surg. 2015;102(1):119-24.

92. Kvasnovsky CL, Papagrigoriadis S, Bjarnason I. Increased diverticular complications with nonsteriodal anti-inflammatory drugs and other medications: a systematic review and meta-analysis. Colorectal Dis. 2014;16(6):O189-96.

93. Strate LL, Liu YL, Huang ES, Giovannucci EL, Chan AT. Use of aspirin or nonsteroidal anti-inflammatory drugs increases risk for diverticulitis and diverticular bleeding. Gastroenterology. 2011;140(5):1427-33.

94. Nikberg M, Ji J, Leppert J, Sundquist K, Chabok A. Socioeconomic characteristics and comorbidities of diverticular disease in Sweden 1997-2012. Int J Colorectal Dis. 2017;32(11):1591-6.

95. Whiteway J, Morson BC. Elastosis in diverticular disease of the sigmoid colon. Gut. 1985;26(3):258-66.

96. Watters DA, Smith AN. Strength of the colon wall in diverticular disease. Br J Surg. 1990;77(3):257-9.

97. Whiteway J, Morson BC. Pathology of the ageing--diverticular disease. Clin Gastroenterol. 1985;14(4):829-46.

98. Mimura T, Bateman AC, Lee RL, Johnson PA, McDonald PJ, Talbot IC, et al. Up-regulation of collagen and tissue inhibitors of matrix metalloproteinase in colonic diverticular disease. Dis Colon Rectum. 2004;47(3):371-8; discussion 8-9.

99. Rosemar A, Ivarsson ML, Börjesson L, Holmdahl L. Increased concentration of tissue-degrading matrix metalloproteinases and their inhibitor in complicated diverticular disease. Scand J Gastroenterol. 2007;42(2):215-20.

100. Leganger J, Søborg MK, Mortensen LQ, Gregersen R, Rosenberg J, Burcharth J. Association between diverticular disease and Ehlers-Danlos syndrome: a 13-year nationwide population-based cohort study. Int J Colorectal Dis. 2016;31(12):1863-7.

101. Compton R. Scleroderma with diverticulosis and colonic obstruction. Am J Surg. 1969;118(4):602-6.

102. Arfwidsson S, Knock NG, Lehmann l, Winberg T. Pathogenesis of multiple diverticula of the sogmoid colon in diverticular disease. Acta Chir Scand Suppl. 1964;63(Suppl 342) 1-68.

103. Cortesini C, Pantalone D. Usefulness of colonic motility study in identifying patients at risk for complicated diverticular disease. Dis Colon Rectum. 1991;34(4):339-42.

104. Bassotti G, Battaglia E, Spinozzi F, Pelli MA, Tonini M. Twenty-four hour recordings of colonic motility in patients with diverticular disease: evidence for abnormal motility and propulsive activity. Dis Colon Rectum. 2001;44(12):1814-20.

105. Bassotti G, Battaglia E, Bellone G, Dughera L, Fisogni S, Zambelli C, et al. Interstitial cells of Cajal, enteric nerves, and glial cells in colonic diverticular disease. J Clin Pathol. 2005;58(9):973-7.

106. Tomita R, Fujisaki S, Tanjoh K, Fukuzawa M. Role of nitric oxide in the left-sided colon of patients with diverticular disease. Hepatogastroenterology. 2000;47(33):692-6.

107. Maselli MA, Piepoli AL, Guerra V, Caruso ML, Pezzolla F, Lorusso D, et al. Colonic smooth muscle responses in patients with diverticular disease of the colon: effect of the NK2 receptor antagonist SR48968. Dig Liver Dis. 2004;36(5):348-54.

108. Fric P, Zavoral M. The effect of non-pathogenic Escherichia coli in symptomatic uncomplicated diverticular disease of the colon. Eur J Gastroenterol Hepatol. 2003;15(3):313-5.

109. Conlon MA, Bird AR. The impact of diet and lifestyle on gut microbiota and human health. Nutrients. 2014;7(1):17-44.

110. Gueimonde M, Ouwehand A, Huhtinen H, Salminen E, Salminen S. Qualitative and quantitative analyses of the bifidobacterial microbiota in the colonic mucosa of patients with colorectal cancer, diverticulitis and inflammatory bowel disease. World J Gastroenterol. 2007;13(29):3985-9.

111. Lopetuso LR, Petito V, Graziani C, Schiavoni E, Paroni Sterbini F, Poscia A, et al. Gut Microbiota in Health, Diverticular Disease, Irritable Bowel Syndrome, and Inflammatory Bowel Diseases: Time for Microbial Marker of Gastrointestinal Disorders? Dig Dis. 2017.

112. Tursi A, Mastromarino P, Capobianco D, Elisei W, Miccheli A, Capuani G, et al. Assessment of Fecal Microbiota and Fecal Metabolome in Symptomatic Uncomplicated Diverticular Disease of the Colon. J Clin Gastroenterol. 2016;50 Suppl 1:S9-S12.

113. Barbara G, Scaioli E, Barbaro MR, Biagi E, Laghi L, Cremon C, et al. Gut microbiota, metabolome and immune signatures in patients with uncomplicated diverticular disease. Gut. 2017;66(7):1252-61.

114. Linninge C, Roth B, Erlanson-Albertsson C, Molin G, Toth E, Ohlsson B. Abundance of. World J Gastrointest Pathophysiol. 2018;9(1):18-27.

115. Jones RB, Fodor AA, Peery AF, Tsilimigras MCB, Winglee K, McCoy A, et al. An Aberrant Microbiota is not Strongly Associated with Incidental Colonic Diverticulosis. Sci Rep. 2018;8(1):4951.

116. Williams R, Davis I. Diverticular Disease of the colon.5th edn Philadelphia: Saunders, 1995.

117. Rhatigan RM, Saffos RO. Mucosal hyperplasia in clonic diverticula. Histopathology. 1979;3(2):153-60.

118. Schembri J, Bonello J, Christodoulou DK, Katsanos KH, Ellul P. Segmental colitis associated with diverticulosis: is it the coexistence of colonic diverticulosis and inflammatory bowel disease? Ann Gastroenterol. 2017;30(3):257-61.

119. Lamps LW, Knapple WL. Diverticular disease-associated segmental colitis. Clin Gastroenterol Hepatol. 2007;5(1):27-31.

120. Spiller R. How inflammation changes neuromuscular function and its relevance to symptoms in diverticular disease. J Clin Gastroenterol. 2006;40 Suppl 3:S117-20.

121. Humes DJ, Simpson J, Smith J, Sutton P, Zaitoun A, Bush D, et al. Visceral hypersensitivity in symptomatic diverticular disease and the role of neuropeptides and low grade inflammation. Neurogastroenterol Motil. 2012;24(4):318-e163.

122. Horgan AF, McConnell EJ, Wolff BG, The S, Paterson C. Atypical diverticular disease: surgical results. Dis Colon Rectum. 2001;44(9):1315-8.

123. Böttner M, Wedel T. Abnormalities of neuromuscular anatomy in diverticular disease. Dig Dis. 2012;30(1):19-23.

124. Golder M, Burleigh DE, Belai A, Ghali L, Ashby D, Lunniss PJ, et al. Smooth muscle cholinergic denervation hypersensitivity in diverticular disease. Lancet. 2003;361(9373):1945-51.

125. Simpson J, Sundler F, Humes DJ, Jenkins D, Scholefield JH, Spiller RC. Post inflammatory damage to the enteric nervous system in diverticular disease and its relationship to symptoms. Neurogastroenterol Motil. 2009;21(8):847-e58.

126. Böttner M, Barrenschee M, Hellwig I, Harde J, Egberts JH, Becker T, et al. The enteric serotonergic system is altered in patients with diverticular disease. Gut. 2013;62(12):1753-62.

127. Tursi A, Elisei W, Brandimarte G, Giorgetti GM, Inchingolo CD, Nenna R, et al. Musosal tumour necrosis factor α in diverticular disease of the colon is overexpressed with disease severity. Colorectal Dis. 2012;14(5):e258-63.

128. Elli L, Roncoroni L, Bardella MT, Terrani C, Bonura A, Ciulla M, et al. Absence of mucosal inflammation in uncomplicated diverticular disease. Dig Dis Sci. 2011;56(7):2098-103.

129. Tursi A, Brandimarte G, Elisei W, Giorgetti GM, Inchingolo CD, Aiello F. Faecal calprotectin in colonic diverticular disease: a case-control study. Int J Colorectal Dis. 2009;24(1):49-55.

130. Peery AF, Keku TO, Addamo C, McCoy AN, Martin CF, Galanko JA, et al. Colonic Diverticula Are Not Associated With Mucosal Inflammation or Chronic Gastrointestinal Symptoms. Clin Gastroenterol Hepatol. 2018;16(6):884-91.e1.

131. Shahedi K, Fuller G, Bolus R, Cohen E, Vu M, Shah R, et al. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. Clin Gastroenterol Hepatol. 2013;11(12):1609-13.

132. Imperiali G, Terpin MM, Meucci G, Ferrara A, Minoli G. Segmental colitis associated with diverticula: a 7-year follow-up study. Endoscopy. 2006;38(6):610-2.

133. Meyers MA, Alonso DR, Gray GF, Baer JW. Pathogenesis of bleeding colonic diverticulosis. Gastroenterology. 1976;71(4):577-83.

134. Tursi A, Elisei W, Picchio M, Giorgetti GM, Brandimarte G. Moderate to severe and prolonged left lower-abdominal pain is the best symptom characterizing symptomatic uncomplicated diverticular disease of the colon: a comparison with fecal calprotectin in clinical setting. J Clin Gastroenterol. 2015;49(3):218-21.

135. Andeweg CS, Knobben L, Hendriks JC, Bleichrodt RP, van Goor H. How to diagnose acute left-sided colonic diverticulitis: proposal for a clinical scoring system. Ann Surg. 2011;253(5):940-6.

136. Rao PM, Rhea JT, Novelline RA, Dobbins JM, Lawrason JN, Sacknoff R, et al. Helical CT with only colonic contrast material for diagnosing diverticulitis: prospective evaluation of 150 patients. AJR Am J Roentgenol. 1998;170(6):1445-9.

137. Verbanck J, Lambrecht S, Rutgeerts L, Ghillebert G, Buyse T, Naesens M, et al. Can sonography diagnose acute colonic diverticulitis in patients with acute intestinal inflammation? A prospective study. J Clin Ultrasound. 1989;17(9):661-6.

138. Zielke A, Hasse C, Nies C, Kisker O, Voss M, Sitter H, et al. Prospective evaluation of ultrasonography in acute colonic diverticulitis. Br J Surg. 1997;84(3):385-8.

139. Laméris W, van Randen A, Bipat S, Bossuyt PM, Boermeester MA, Stoker J. Graded compression ultrasonography and computed tomography in acute colonic diverticulitis: meta-analysis of test accuracy. Eur Radiol. 2008;18(11):2498-511.

140. Öistämö E, Hjern F, Blomqvist L, Von Heijne A, Abraham-Nordling M. Cancer and diverticulitis of the sigmoid colon. Differentiation with computed tomography versus magnetic resonance imaging: preliminary experiences. Acta Radiol. 2013;54(3):237-41.

141. Lahat A, Yanai H, Menachem Y, Avidan B, Bar-Meir S. The feasibility and risk of early colonoscopy in acute diverticulitis: a prospective controlled study. Endoscopy. 2007;39(6):521-4.

142. Sai VF, Velayos F, Neuhaus J, Westphalen AC. Colonoscopy after CT diagnosis of diverticulitis to exclude colon cancer: a systematic literature review. Radiology. 2012;263(2):383-90.

143. Strate LL, Gralnek IM. ACG Clinical Guideline: Management of Patients With Acute Lower Gastrointestinal Bleeding. Am J Gastroenterol. 2016;111(5):755.

144. Pietrzak A, Bartnik W, Szczepkowski M, Krokowicz P, Dziki A, Reguła J, et al. Polish interdisciplinary consensus on diagnostics and treatment of colonic diverticulosis (2015). Pol Przegl Chir. 2015;87(4):203-20.

145. Cuomo R, Barbara G, Pace F, Annese V, Bassotti G, Binda GA, et al. Italian consensus conference for colonic diverticulosis and diverticular disease. United European Gastroenterol J. 2014;2(5):413-42.

146. Andersen JC, Bundgaard L, Elbrønd H, Laurberg S, Walker LR, Støvring J, et al. Danish national guidelines for treatment of diverticular disease. Dan Med J. 2012;59(5):C4453.

147. Stollman N, Smalley W, Hirano I, Committee AICG. American Gastroenterological Association Institute Guideline on the Management of Acute Diverticulitis. Gastroenterology. 2015;149(7):1944-9.

148. Bianchi M, Festa V, Moretti A, Ciaco A, Mangone M, Tornatore V, et al. Meta-analysis: long-term therapy with rifaximin in the management of uncomplicated diverticular disease. Aliment Pharmacol Ther. 2011;33(8):902-10.

149. Tursi A, Brandimarte G, Giorgetti GM, Elisei W. Mesalazine and/or Lactobacillus casei in maintaining long-term remission of symptomatic uncomplicated diverticular disease of the colon. Hepatogastroenterology. 2008;55(84):916-20.

150. Annibale B, Maconi G, Lahner E, De Giorgi F, Cuomo R. Efficacy of Lactobacillus paracasei sub. paracasei F19 on abdominal symptoms in patients with symptomatic uncomplicated diverticular disease: a pilot study. Minerva Gastroenterol Dietol. 2011;57(1):13-22.

151. Lahner E, Bellisario C, Hassan C, Zullo A, Esposito G, Annibale B. Probiotics in the Treatment of Diverticular Disease. A Systematic Review. J Gastrointestin Liver Dis. 2016;25(1):79-86.

152. Tursi A, Brandimarte G, Elisei W, Picchio M, Forti G, Pianese G, et al. Randomised clinical trial: mesalazine and/or probiotics in maintaining remission of symptomatic uncomplicated diverticular disease--a double-blind, randomised, placebo-controlled study. Aliment Pharmacol Ther. 2013;38(7):741-51.

153. Kruis W, Meier E, Schumacher M, Mickisch O, Greinwald R, Mueller R, et al. Randomised clinical trial: mesalazine (Salofalk granules) for uncomplicated diverticular disease of the colon--a placebo-controlled study. Aliment Pharmacol Ther. 2013;37(7):680-90.

154. Stollman N, Magowan S, Shanahan F, Quigley EM, Group DI. A randomized controlled study of mesalamine after acute diverticulitis: results of the DIVA trial. J Clin Gastroenterol. 2013;47(7):621-9.

155. Chabok A, Påhlman L, Hjern F, Haapaniemi S, Smedh K, Group AS. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg. 2012;99(4):532-9.

156. Galetin T, Galetin A, Vestweber KH, Rink AD. Systematic review and comparison of national and international guidelines on diverticular disease. Int J Colorectal Dis. 2018;33(3):261-72.

157. Andeweg CS, Mulder IM, Felt-Bersma RJ, Verbon A, van der Wilt GJ, van Goor H, et al. Guidelines of diagnostics and treatment of acute left-sided colonic diverticulitis. Dig Surg. 2013;30(4-6):278-92.

158. Gralnek IM, Neeman Z, Strate LL. Acute Lower Gastrointestinal Bleeding. N Engl J Med. 2017;376(23):e50.

159. Agréus L, Svärdsudd K, Nyrén O, Tibblin G. Reproducibility and validity of a postal questionnaire. The abdominal symptom study. Scand J Prim Health Care. 1993;11(4):252-62.

160. Drossman DA. Rome II. The functional gastrointestinal disorders. 2nd ed. McLean,VA: Degnon Associates; 2000.

161. Drossman DA. The functional gastrointestinal disorders and the Rome II process. Gut. 1999;45 Suppl 2:II1-5.

162. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.

163. Aberg MA, Nyberg J, Toren K, Sorberg A, Kuhn HG, Waern M. Cardiovascular fitness in early adulthood and future suicidal behaviour in men followed for up to 42 years. Psychol Med. 2014;44(4):779-88.

164. Woodward M. Epidemiology-Study Design and Data Analysis. 2nd ed. Boca Raton, FL, USA: Chapman & Hall/CRC; 2005.

165. Rothman KJ. Epidemiology- An introduction. 2nd ed. New York, NY, USA: Oxford University Press; 2012.

166. Kjellström L, Molinder H, Agréus L, Nyhlin H, Talley NJ, Andreasson A. A randomly selected population sample undergoing colonoscopy: prevalence of the irritable bowel syndrome and the impact of selection factors. Eur J Gastroenterol Hepatol. 2014;26(3):268-75.

167. Rothman KJ. BMI-related errors in the measurement of obesity. Int J Obes (Lond). 2008;32 Suppl 3:S56-9.

168. Alander T, Heimer G, Svärdsudd K, Agréus L. Abuse in women and men with and without functional gastrointestinal disorders. Dig Dis Sci. 2008;53(7):1856-64.

169. Painter NS. Diverticular disease of the colon--a disease of the century. Lancet. 1969;2(7620):586-8.

170. Hughes LE. Postmortem survey of diverticular disease of the colon. II. The muscular abnormality of the sigmoid colon. Gut. 1969;10(5):344-51.

171. Jung HK, Choung RS, Locke GR, Schleck CD, Zinsmeister AR, Talley NJ. Diarrhea-predominant irritable bowel syndrome is associated with diverticular disease: a population-based study. Am J Gastroenterol. 2010;105(3):652-61.

172. Manousos ON, Truelove SC, Lumsden K. Prevalence of colonic diverticulosis in general population of Oxford area. Br Med J. 1967;3(5568):762-3.

173. Parks TG. Natural history of diverticular disease of the colon. Clin Gastroenterol. 1975;4(1):53-69.

174. Köhler L, Sauerland S, Neugebauer E. Diagnosis and treatment of diverticular disease: results of a consensus development conference. The Scientific Committee of the European Association for Endoscopic Surgery. Surg Endosc. 1999;13(4):430-6.

175. Yamada E, Inamori M, Uchida E, Tanida E, Izumi M, Takeshita K, et al. Association between the location of diverticular disease and the irritable bowel syndrome: a multicenter study in Japan. Am J Gastroenterol. 2014;109(12):1900-5.

176. Simpson J. Perception and the origin of symptoms in diverticular disease. Dig Dis. 2012;30(1):75-9.

177. Högenauer C, Hammer HF, Krejs GJ, Reisinger EC. Mechanisms and management of antibiotic-associated diarrhea. Clin Infect Dis. 1998;27(4):702-10.

178. Kealy WF. Lymphoid tissue and lymphoid-glandular complexes of the colon: relation to diverticulosis. J Clin Pathol. 1976;29(3):245-9.

179. Makapugay LM, Dean PJ. Diverticular disease-associated chronic colitis. Am J Surg Pathol. 1996;20(1):94-102.

180. Peppercorn MA. The overlap of inflammatory bowel disease and diverticular disease. J Clin Gastroenterol. 2004;38(5 Suppl 1):S8-10.

181. Amato PR. The Consequences of Divorce for Adults and Children. Journal of Marriage and Family. 2000;62(4): 1269-87.

182. Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. Gastroenterology. 2013;144(1):36-49.

183. Benchimol EI, Kaplan GG, Otley AR, Nguyen GC, Underwood FE, Guttmann A, et al. Corrigendum: Rural and Urban Residence During Early Life Is Associated with a Lower Risk of Inflammatory Bowel Disease: A Population-Based Inception and Birth Cohort Study. Am J Gastroenterol. 2017;112(9):1485.

184. Cholapranee A, Ananthakrishnan AN. Environmental Hygiene and Risk of Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2016;22(9):2191-9.

185. Paeschke A, Erben U, Kredel LI, Kühl AA, Siegmund B. Role of visceral fat in colonic inflammation: from Crohn's disease to diverticulitis. Curr Opin Gastroenterol. 2016.

186. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. J Clin Invest. 2011;121(6):2111-7.

187. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444(7122):1027-31.

188. Arora T, Backhed F. The gut microbiota and metabolic disease: current understanding and future perspectives. J Intern Med. 2016;280(4):339-49.

189. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006;444(7122):1022-3.

190. Rehm J. The risks associated with alcohol use and alcoholism. Alcohol Res Health. 2011;34(2):135-43.

Karolinska Institutet

Arkitektkopia AB, Bromma, 2018