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Irritable bowel syndrome diagnosed in primary care - occurrence, treatment and impact on everyday life

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"Utan tvivel är man inte klok."

Tage Danielsson, Tankar från roten, 1974

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Paper I - V

Abstract

Background. Functional gastrointestinal disorders (FGD) are characterised as: absence of demonstrable biological markers or an organic disease. It is a functional disorder of the GI tract affecting relatively young people with chronic or episodic abdominal pain, bloating, constipation and diarrhoea or alternating periods of constipation and diarrhoea.

IBS is the most common FGD and affects approximately 10-20 % of the general population and is widespread in all societies and socio-economic groups. Although the disorder does not have a life-threatening course, it still seriously affects the patients in their everyday life. IBS as well as other FGD's are a significant but often overlooked public health problem in the general population today. The precise aetiology of IBS is multifactorial and treatment is often focused on relieving symptoms rather than curing the disease. IBS appears to affect women 2-3 times more frequently than men. The symptoms causing embarrassment and often interferes with the working and social life. IBS has been associated with a variety of psychosocial factors, like psychological distress, sleeping problems, sexual dysfunction and disturbance in social life, at work and impaired health related quality of life.

Aim. The general aims of this thesis were to estimate the occurrence of irritable bowel syndrome in the general population and to achieve a better understanding of present treatment of this disorder and impact on everyday life in those suffering from IBS.

Material and methods. The LIPS study comprises two parts. Part I was a retrospective register study where the data collection was based on computerised medical records at three selected Primary Health Care centres in a defined region. Part II was a population based case-control study. The identified IBS cases from part I constitute the cases, while their control groups were randomly selected from the population census register in the same area as the cases. Data in part II were collected by means of a postal questionnaire to cases and controls. The study was conducted in Linköping, a city located in the south-east of Sweden with 135 000 inhabitants. The PHC centres covered in total a catchment population of over 40 000 inhabitants and were responsible for practically all primary health care consultations for the population in their respective geographical areas.

Results: The female IBS patients reported lower influence on planning their work and working hours as well as fewer opportunities to learn new things at their work compared to their controls, even after adjustments in

multiple logistic regressions for potential confounders like; mood, sleeping problems and perceived health.

The female IBS patients had considerably lower HRQOL in all dimensions compared to their controls, even when compared to male patients. Younger female IBS cases (18-44 years) reported lower mental health on the SF-36 scale than the older IBS female cases (p=0.015). In the multivariate analysis these variables, lack of influence on planning the work, family history of IBS, anxiety and sleeping disturbance were associated with IBS in women. In men, lack of influence on working pace, family history of IBS was associated with an IBS diagnosis. The consultation incidence of IBS in this study was 3.4 (95% CI 3.20-3.70) per 1000 person-years for all IBS cases, among females; the incidence rate was 4.6 per 1000 person-years (95% CI 4.16-4.97) and males; 2.3 per 1000 person-years (95% CI 2.01-2.59). The dominating pharmacological treatment prescribed for abdominal complaints were fibre and bulking laxatives agents as well as acid suppressive drugs, separately or in combination. The following variables had an independent impact on the probability of a follow-up consultation; diagnosed co-morbidity besides the IBS diagnosis, rectoscopy ordered and laboratory tests ordered.

In an international comparative analysis it was shown that women from Crete with IBS scored especially low on the dimensions general health p=0.009 (mean score: 48.0 s.d: 20.3) and mental health p<0.0001 (mean score: 48.6 s.d: 24.9) in comparison with Swedish women with IBS (general health mean score: 62.3 s.d: 23.2 and mental health mean score: 71.0 s.d: 16.3).

Conclusions: IBS patients identified in primary care are significantly affected in their working life compared to individuals in the general population. In particular female IBS-patients report lower decision latitude at work and they also appear to have a impaired psychosocial functioning in their everyday life and impaired HRQOL. Factors associated with IBS diagnosis among females are anxiety as well as family history of IBS and lack of co-determination at work.

The incidence rate of IBS was 3.4 per 1000 person-years which increased with age and with an overrepresentation of females. IBS patients did not appear to be heavy utilisers of primary care and those who attended were treated by their GP without further consultation. The strongest predictors for having a follow-up consultation were diagnosed co-morbidity, recto-scopy and laboratory tests ordered.

List of papers

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

I. Faresjö Å, Grodzinsky E, Johansson S, Wallander MA, Foldevi M. Patients with irritable bowel syndrome in Swedish primary care. European Journal of General Practice 2006; 12:88-90.

II. Faresjö Å, Grodzinsky E, Johansson S, Foldevi M. Wallander MA. Patients with irritable bowel syndrome in primary care appear not to be heavy health care utilisers. Alimentary & Pharmacology and Therapeutics 2006; 23:807-814.

III. Faresjö Å, Grodzinsky E, Johansson S, Wallander MA, Timpka T, Åkerlind I. A population based case control study of work and psychosocial problems in patients with irritable bowel syndrome - women are more seriously affected than men. (Submitted 2006)

IV. Faresjö Å, Grodzinsky E, Johansson S, Wallander MA, Timpka T, Åkerlind I. Psychosocial factors at work and in everyday life are associated with irritable bowel syndrome. (Submitted 2006)

V. Faresjö Å, Anastasiou F, Lionis C, Johansson S, Wallander MA, Faresjö T. Health related quality of life among IBS patients in different cultural settings. Health and Quality of Life Outcomes 2006; 4:21.

Abbreviations

ANOVA - Analysis of variance

ASA - Acetylsalicylic Acid drugs

BC - Before Christ

CBC - Complete Blood cell Count

C-IBS - Constipation predominant IBS

CI - Confidence Interval

CRP - C-reactive protein

D-IBS - Diarrhoea predominant IBS

ENS - The Enteric Nervous System

ESR - Erythrocyte Sedimentation Rate

FAD - Food and Drug Administration

FD - Functional Dyspepsia

FGD - Functional Gastrointestinal Disorders

GERD - Gastro-oesophageal reflux

GI - Gastrointestinal

GP - General Practitioner

HAD - The Hospital Anxiety and Depression Scale

HRQOL - Health Related Quality of Life

5-HT - Hydroxytryptamine

IBS - Irritable Bowel Syndrome

ICD - International Classifications of Diseases

LIPS - The Linköping IBS Population Study

NSAID - Non-Steroid Anti-Inflammatory Drugs

OTC - Over-The-Counter drugs

PHC - Primary Health Care

SPSS - Statistical Package for the Social Sciences

TSH - Thyroid Hormone test

WHO - World Health Organization

Vs - Versus

Definitions

Co-morbidity:

Other diseases that the individual might have besides the disease in focus.

Incidence:

The number of new cases of a disease during a specified period of time, related to the number of people at risk for the disease. This can be measured as a rate or risk

Irritable bowel syndrome:

Occurs when muscles in the intestines contract faster or slower than normal, this causes pain, cramping, gassiness, diarrhoea, and constipation due to no organic disease.

Odds ratio (OR):

This is a measure of incidence that calculates the odds of disease to nondisease. Odds ratio is often used in case-control studies when it can also be considered as the odds of exposure to non-exposure, among the diseased compared to the non-diseased.

Prevalence:

This is the total number of persons with a disease at a single time, or over a defined period of time (the existing cases in a population) often expressed as a percentage of the total population.

Rectoscopy:

Examination of rectum, in this study done by the GP.

1. Functional gastrointestinal problems in the general population

1.1. Definition of functional gastrointestinal disorder

Functional gastrointestinal disorders (FGD) like irritable bowel syndrome (IBS), constipation, Functional dyspepsia (FD), Gastro-Oesophageal Reflux (GERD) are characterised by the lack of pathological or biological markers, and definition and classification rely so far solely on symptoms. According to an internationally accepted classification system (Rome classification) IBS are characterised by persistent or recurrent abdominal pain related to defecation or to chronic disturbance of bowel habits in the absence of demonstrable biological markers or an organic disease (1,2,3).

1.2 Historical perspective

Bowel problems have probably been treated since antiquity. Herodotus, the Greek historian (circa 485-424 B.C) wrote about physicians treating "the intestines" and also Hippocrates wrote "those whose intestine are relaxed, if they are young get over their illness better than those who are constipated, better than the old people (4). In the early 19th century, the first reports of patients with symptoms similar to IBS appeared in medical journals. One description of the three cardinal symptoms of IBS; abdominal pain," dearangement of digestion" and flatulence appeared in English as early as 1818 (5). In 1849, Cumming described IBS as follows:" The bowels are at one time constipated, at another lax, in the same person." How the disease has two such different symptom, I do not propose to explain" (6). Numerous terms have been used to describe IBS through the 19th and into the 20th century, including spastic colon (7), neutrogenic mucous colitis (8) and irritable colon syndrome (9). The term irritable bowel syndrome was probably first described in 1944 by Peters and Bargen and 1967, by DeLor as a functional enteropathy characterized by a combination of symptoms, including abdominal pain, diarrhoea, constipation and passage of mucus in stool (10,11). IBS remained a diagnosis of exclusion until Heaton et.al reported that six symptoms could distinguish people diagnosed with the disorder from those with documented structural bowel disease (12).

1.3. Clinical definition, diagnosing and health utilization 1.3.1 The etiology, pathophysiology and possible mechanism of IBS

The etiology of IBS is complex and in many ways still unclear and there is still a lack of understanding of the pathology of IBS. However, multiple sets of factors are likely to interact in the pathogenesis and clinical manifestations of IBS. This multifactorial etiological pattern is often found for many public health diseases in a complex contemporary society. Several attempts have been made to create biopsychosocial models to help bring some order of factors and to explain a complex etiological pattern including environmental, cultural, social, psychological and biological factors (13,14,15).

The dysfunctions that lead to or aggravate IBS are both biologic and psychological factors, some of which may be predominant. However, more than one factor is operating in individuals that suffer from IBS (12,16). Some putative connections are shown in **Figure 1** below.



Figure 1. Hypothetical relation between putative predisposing, genetic and psychological factors and subsequent development of IBS, according to Talley, 2002. (Reprinted with permission from Elsevier, from" The Lancet V360 (9332): 555-564, and the author Talley NJ & Spiller R: "Irritable bowel syndrome: a little understood organic bowel disease?" © The Lancet 2002). IBS occurs when muscles in the intestines contract faster or slower than normal. Signs and symptoms of IBS are often gastrointestinal pain, bloating and an altered bowel habit. Putative biological mechanisms include visceral hypersensitivity, altered motility, and abnormal transit of stool and gas. This causes pain, cramping, gassiness, diarrhoea, and constipation. However, structural and molecular abnormalities have begun to be recognized in subsets of patients with the irritable bowel syndrome (17). Nevertheless, IBS is a bio-psycho-social disorder in which altered motility or sensation in small bowel or the colon is modulated by participation from the central nervous system (16). The earliest hypothesis, suggested that IBS was purely a motor disorder, according to observations made of clustered contractions in the small bowel during abdominal colic (18,19). Other observations suggest that visceral sensitivity in terms of abnormal visceral perception has been observed in ballondistension studies, and that motility may also be involved in the pathopsychology of IBS (16,20) A recent hypothesis is that IBS is caused by a defect in the enteric nervous system (ENS). The ENS controls motility and secretory functions of the intestine. This system contains many neurotransmitters; including serotonin (5hydroxytryptamine, 5-HT). Defects in ENS may lead to the characteristic symptoms of IBS-visceral hypersensitivity and primary motility disorder of the GI-tract. 5-HT has received considerable attention lately because it is found mainly in the gut, with most of its receptors located within ENS, and mediates the reflexes controlling GI motility; secretions and visceral pain. The subtypes 5-HT₃ and 5-HT₄ appear to play a role in the pathopsychology of IBS (21).

Regarding the role of psychopathology in the etiology of IBS, Gwee et.al found that IBS was more likely to follow acute infection i.e. gastroenteritis if the patients had a pre-existing psychopathology. One possible causal mechanism could be that gut permeability is affected by both infection and stress (22). Factors that do not necessarily cause IBS, but may be involved, include luminal and psychological factors. The first include food allergen and intolerance to lactose. Fructose and sorbitol may lead to irritated gut (23) and the latter psychological factors may alter GI–motor function (24).

Several studies have shown that patients who report a family member with abdominal pain or bowel problems have an increased risk of reporting IBS-like symptoms themselves (25,26,27,28). This association may reflect both genetic associations and shared environmental exposure, including learned responses to visceral stimuli. Two previous twin studies of functional bowel symptoms suggest that genetic factors may contribute to the etiology of IBS. However, in one of these studies, having parents with IBS and social learning was an even stronger predictor of the disease than having a twin with the same disorder (29,30). After specific environmental exposure, genetic factors that affect pain signalling and disturbance in central processing of afferent nerves might predispose to IBS (12). More than one of these factors could contribute to IBS symptoms and in the end might lead to health care consultations.

1.4 Diagnostic criteria

There is disagreement as to whether IBS and other chronic syndromes such as FD, fibromyalgia and chronic fatigue represent a manifestation of one functional somatic syndrome or whether IBS is an individual disorder (31). Development of biological or other disease-specific markers may resolve this dispute. On the other hand, results from population-based studies from different countries suggest that IBS represents similar symptoms groupings (32,33). Hence, an overlap of different FGD symptoms was found in patients with conditions such as IBS, constipation, FD, GERD (34).

Even though the molecular mechanisms underlying the disease remain unknown (35), reports indicate associations with depression, stress and anxiety, suggesting connections to neurobiological factors (12,36). Consequently, definition and classification of IBS rely solely on symptoms described by the patients (1,37). The first attempt to classify all functional gastrointestinal disorders was made in 1979 by Thompson in his book The *irritable gut* (38). Various diagnostic criteria for IBS have been developed to distinguish between IBS and organic diseases. The Manning criteria were obtained from results of a questionnaire administered to outpatients in Bristol with abdominal pain and disordered bowel habit (39). They found six of fifteen symptoms that were more common in the IBS than organic gut disease, later recognized as the Manning criteria. In 1984, Kruis et al (40) reported a similar study, in which they confirmed Powell's observation from the 19th century of three cardinal symptoms of IBS; pain, bowel dysfunction and flatulence. In, an effort to improve these diagnostic criteria, mostly Manning criteria, the symptoms were refined in 1989 by a working group of gastroenterologists who developed new diagnostic criteria for IBS called Rome I criteria and about 10 years later the Rome committee proposed a new definition called Rome II and formulated as follows: "Irritable bowel syndrome comprises a group of functional bowel disorders in which abdominal discomfort or pain is associated with defection or a change in bowel habit, and with features of distorted defection"(1,3) (see **Figure 2**). IBS is divided into three main subgroups: Diarrhoea predominant IBS (D-IBS) and constipation predominant IBS (C-IBS) or IBS with alternating symptoms of both diarrhoea and constipation (41).

Manning/Kruis Criteria:

Recurrent abdominal pain and more of the following:

-Relief of pain with defecation. -More frequent stools at onset of pain

-Looser stools at the onset of pain -A sensation of incomplete evacuation

-Passage of mucus per rectum

- Visible abdominal distension
- -Flatulence

-Alternating constipation/diarrhoea

Rome I Criteria:

Continuous or recurrent symptoms of:

- Abdominal pain relieved with defecation or associated with change in frequency or consistency of stools-and/or

-Disturbed defecation (two or more)

-Altered stool frequency -Altered stool form (hard or

loose/watery)

-Altered stool passage (straining urgency or feeling of incomplete evacuation)

-Passage of mucus

- Bloating or feeling of distension

Rome II Criteria:

At least 12 weeks (need not to be consecutive) in the preceding 12 months of abdominal discomfort or pain that has 2 of 3 features:

-Relieved with defecation-Onset associated with change in frequency of stool.-Onset associated with change in form (appearance) of stool.

Symptoms that cumulatively support the diagnosis of IBS when using Rome II criteria:

-Abnormal stool frequency (lumpy/hard or loose/watery stool)

-Abnormal stool passage (straining, urgency or feeling of incomplete evacuation)

-Passage of mucus

- Bloating or feeling of abnormal distension.

Figure 2. Symptoms and criteria of IBS.

1.5 Diagnosis setting in primary care

IBS is a chronic recurring disorder with variable illness episodes that may continue for many years (39) and this FGD condition is quite commonly diagnosed in primary care. Thompson et.al (42,43) confirmed that functional gastrointestinal problems are common in primary care, one in twelve consultations, and that half of these were FGD with the most common condition being IBS. Although, general practitioners (GP) play a crucial role in the management of IBS because the vast majority of the patients are diagnosed and treated in primary care, the most widely used criteria and guidelines are developed and validated mainly by specialist working in the secondary care studying sub groups of the disease. So this may not be appropriate for most GPs and their patients. Several GPs are unaware of these guidelines; in fact, many GPs, as wells as some gastroenterologists consider them to be too complicated and suitable only for the secondary care and research. The GPs also regards these criteria to be excessively restrictive and are confident that they can make a correct diagnosis based on simpler and more practical criteria. It is important that this guidelines and criteria for IBS could be developed by GPs together with gastroenterologists (42,44,45,46,47).

According to Thompson et.al, despite GPs unfamiliarity with the diagnostic criteria for IBS, they are nevertheless quite able to detect the most important symptoms of IBS and their diagnoses are in close agreement with those made by gastroenterologist. The GPs have to treat and diagnose the patients based on to their long experience combined with vast knowledge (42,49,50,51). A patient's history is important because it affects the probability of a correct diagnosis, most patients do not need referral or tests for organic disease unless there are alarm indicators seen in **Figure 3**. Nevertheless, recommended initial laboratory tests in the evaluation of IBS and exclusion of other organic diseases are complete blood cell count (CBC), metabolic tests, erythrocyte sedimentation rate (ESR), thyroid hormone test (TSH) and stool examinations for occult blood and parasites as wells urine tests (52).

- Age of onset older than 50 years
- Progressive or very severe or non-fluctuating symptoms.
- Nocturnal symptoms (e.g. diarrhoea, pain) waking the patient from sleep.
- Persistent daily diarrhoea
- Rectal bleeding or evidence of anaemia
- Unexplained weight loss
- Recurrent vomiting
- Positive family history of colon cancer
- Fever
- Abnormal physical examination (apart from mild abdominal tenderness), e.g. skin rash, anaemia, mouth ulcers, rectal mass, pain on tensing abdominal wall muscles.

Figure 3. Alarm indicators that suggest an organic disease according to Talley (2002).

1.6 Health care utilization

A large number of persons with IBS or FGD symptoms do not seek health care for their complaints. For those who do, IBS is most commonly diagnosed and treated in primary care but also at specialist clinics. Even, though the majority of the IBS cases are diagnosed in primary care centres, the data on the rates of health care utilisation in primary care are deficient (53). The full burden of this illness is still in many ways unclear, possibly due to the fact that most research on IBS is performed in secondary care. Donker et.al (43) reported that patients with IBS utilized health care more frequently than the general population. Studies have also reported that only 25-60 % of individuals suffering from IBS symptoms see a physician for their illness and the proportion who do so varies between countries (54,55). The variation found in health care seeking behaviour is probably due to characteristics associated with a country's health care system, its organization and financing (56,57) Levy et. al found that children of IBS parents consulted the health care service more often than matched controls, which might be due to social learning early in childhood (58). IBS patients have a higher prevalence of stress and psychiatric diagnoses, such as

anxiety and depression, compared to the general population (59,60,61,62) However, psychological factors do not seem to entirely explain the use of health care in society of persons with IBS, other factors than psychological morbidity might be more important for both conventional and alternative health care seeking for functional gastrointestinal symptoms (63,64,65). Visceral pain is the most common type of pain produced by this disorder and also a frequent reason for individuals to seek health care (66). Heaton et.al noted in a study in the UK that abdominal pain was the strongest predictor for health care seeking in both women and men (67,68). However, individuals with IBS are more likely to seek health care when their symptoms interfere with their daily life and activities as wells as if this condition cause depression or anxiety (69).

Recent studies have also noted that increased use of health resources were for the most part explained by co-morbidity symptoms and disorders (70, 71). Another reason for health care seeking among individuals with IBS is often related to the fear of serious illness such as cancer (72,73).

2. Epidemiological perspective and impact on health

IBS is widespread in all societies and socio-economic groups affecting relatively young people. Although the disorder does not have a lifethreatening course, it still seriously affects the patients in their everyday life (74,75,76,77).

Studies of incidence rates for IBS are quite rare, maybe due to methodological and definition problems. An earlier Swedish study reported incidence rate for IBS of 2 per 1,000 person-years in the general population (78) and in a study from general practice in UK, an incidence rate of just below 3 per 1,000 person years was documented (79). Locke et. al have reported the incidence of clinically diagnosed IBS among adults in Minnesota USA, to be 2 cases per 1,000 person-years (80). On the other hand, prevalence studies in the general population based on postal questionnaires and surveys are available in several countries (42,78,81,82,83,84,85,86). The prevalence in the general population is estimated at 10% to 20% depending on which criteria used when diagnosing the disease and is similar for each of the three subtypes (16, 42,75,87,88). The prevalence of IBS in the elderly is only slightly reduced and according to Talley, IBS is often misdiagnosed in this group (12). In a recent study in primary care of FGD on Crete in Greece, it was found that the IBS diagnosis was slightly increased among males over 65 years of age (89).

IBS appears to affect women 2-3 times more frequently than men. The syndrome is not predominant in any human race (90,91,92). The natural history of IBS still remains to be defined properly and the symptoms wax and vane over time. Hahn et al showed that over a 12 weeks period, symptoms rose a mean of 12 times with maximum duration of five days and the patients were affected about 50 % of the day (93).

2.1 Public health perspective

According to World health Organization (WHO), public health is a social and political concept aimed at improving health, prolonging life and improving quality of life among whole populations through interventions such as health promotion and disease prevention (94). A public health perspective describes the distribution of symptoms, ill-health and diseases in the society. But the definition of public health problems around the world varies, due to the commonness and distribution of the disease, but also due to consequences for the individuals and the community. The practice of public health comprises the assessment and monitoring of the health of communities and populations at risk to identify health problems and priorities; to solve identified local and national health problems and access to appropriate and cost effective care, health promotion and disease prevention for the population.

The post-industrial society is often characterized of stressful life and psychosocial problems, which also may lead to a variety of increasing symptoms and health problems, not least functional gastrointestinal problems. According to the WHO's Global Burden of Diseases Survey, mental diseases and stress-related disorders will be the second leading cause of disabilities in 2020 (95). IBS as well as other FGD's are a significant but often overlooked public health problem in the general population today. For the individual, IBS is often a painful condition as well as having profound social consequences. The symptoms cause embarrassment and often interfere with the working and social life. Persons suffering from IBS reports difficulties in their relationships with family and friends, as well as in sexual functions (96,97,98). There are also wider social costs that might impact on the health care systems and results in absence from work (99). Physicians may often mainly focus on treating the biological aspects of different diseases, believing that this may be sufficient to alleviate any psychological distress (100). However, these measurements correlate poorly with functional capacity and well-being and are badly related to patients' perception of their disease impact. The suffers often focus on how the disease interferes with their ability to live a normal everyday life (101,102). Consequently, it is important to also to focus on health-related quality of life (HRQOL) and mental health as well as social life and working conditions when trying to manage the impact of IBS in everyday life.

2.1.1 Gender perspective

The gender perspective refers to the social constructions of roles, responsibilities, opportunities and expectations related to being a female or male. The concept of sexes refers to the biological difference. Today the impact of gender and sex on health is well known. Some decades ago, the writings on gender-linked aspects of women's health were mainly focused on health costs of domestic labour, sexual violence and the nature of women's work outside the home (103,104,105). Paid work, unpaid work in the home and social support are important factors of health and illness, since these combinations affect both sexes (106). Women are still less likely to be employed and are more likely to work part-time, have lower incomes and more economic problems and, most importantly, perform more unpaid domestic labour and housework than men, all of which with the exception of work outside home are associated with poor health (107). There are also suggestion of a link between sickness absence and sex segregation at different occupational levels (108,109).

Women's excess risk of FGD such as IBS likely involves both sex and gender differences (105). IBS as well as health care seeking behaviour for these conditions might also be associated with gender roles, there are suggestions that patients with IBS feel unclean and this condition is more difficult for women in terms of femininity. Women might also be more aware of the body and symptoms *"The result of this differential treatment of males and females is a paradigm in which women live their lives experiencing their bowel functioning as secret and shameful, whereas men lives their lives with greater acceptance of their bowel functioning" (110). This hypothesis may be in accordance with the overrepresentation of women with an IBS diagnosis. Some study even make a quite controversial statement that men with IBS have less* male characteristics, but it remains to be seen whether this hypothesis can be verified (111).

2.2 Psychosocial factors associated to IBS

IBS has been associated with a variety of psychosocial factors such as psychological distress, sleeping problems, sexual dysfunction and disturbance in social life and at work (112). Nevertheless, the causal directions and significance of these associations remain unclear.

There are a number of studies, which report increased self-rated mental complaints among IBS-patients comparing with the general population (113,114,115). Individuals suffering from IBS often report more anxiety and depression than i.e. organic bowel patients (116). Reports also show a strong relationship between FGD symptoms and anxiety and depression (62,114,115). IBS-patients suffering from mental complaints are more frequently referred for hospital investigations (114). A case-control study from India using The Hospital Anxiety and Depression Scale (HAD) reported that stressful life-event scores are significantly higher in IBS patients than in normal controls, but not all of these patients had anxiety and/or depression (117). Sleep disturbance and daytime fatigue has also been documented among patients with IBS and other GI complaints in population studies and by comparing IBS patients and other GI-patients with healthy controls (118,119,120,121,122,123).

In recent decades, much attention has been paid to associations between, on the one hand, the context in which salaried and domestic work is performed, and, on the other, indicators of health. Such relationships have been studied using, e.g., the demand-control or job-strain model (124).Here, high psychosocial demands in combination with low control in work is related to increased risk of cardiovascular and stress-related diseases (125,126). The job-strain hypotheses also state that high demands and low control result in the lowest well-being (127). Low control at work or in relation to the daily chores at home is related to an increased risk of developing depression and anxiety (128). Little is known about the link between psychosocial occupational exposures and the role of a stressful work environment in the etiology of FGD. Surprisingly, to our knowledge, no studies have analysed perceived psychosocial working conditions among patients with FGD-problems in comparison with controls from the general population. However, Janson et.al found possible interaction between stressful work environment and the individual's response to it and a moderately increased risk of oesophageal and gastric cardia cancers (129).

2.2.1 Coping with IBS

Coping strategies are used to manage conflict and illness and can have adaptive or maladaptive (self-control, self-blame and escape) effects on health status. Living everyday with functional gastrointestinal problems means that the individual has to develop a coping strategy. The symptoms of IBS may influence the individuals coping strategy. It is also likely that factors such as worry, fear and feeling of isolation regarding the illness may contribute to different coping strategies and mechanisms (115). Crane et.al have suggested that the use of passive behavioural coping strategy among IBS patients can be predicted. This might be a consequence of illness-related social learning occurring during childhood, which may influence the development of habitual illness behaviour and, because of the benign nature of IBS, make the suffers more reliant on passive coping strategies to adjust to this discomfort (130,131).

2.3 Health and health-related quality of life

2.3.1. The concept of Health and Health-Related Quality of Life

We all have different perceptions of what it means to be healthy. Most people would say that it means functioning in daily life, feeling strong and vital, the absence of pain and not being disabled or to being able to work and live and enjoy life (132). Many medical theoretical scientists from the days of Hippocrates and Galenos have presented their view of the nature of health and diseases. Galenos (circa 200 B.C) developed theories about how the elements and functions of the body should relate to each other to keep us in good health. This became the foundation of modern theories of health and disease. Nordenfelt has presented a holistic and action-theoretical definition of health that states that a person is in health if he or she has ability to reach his or her vital goals, given standard or acceptable circumstances.

The holistic perspective on health focuses on all aspects of Man and uses concepts such as action capability, adjustments, well-being, pain, anxiety and handicap. The source of the holistic view of health deals with the basic commitment and interest of the ordinary human being in his or her own health with questions such as; "How do I feel today?", "Am I still have in pain?", "Could I go to work today?" However, the inner functions of the body are of no interest to the human being, according to the holistic theory, unless one is able to directly point to some part of the organ functions as being responsible for the symptoms or ill-health and thereby have a chance to adapting to it. The holistic view is based on a point of view that human being takes action in social relations. Taking this point of view, one could consider, health and disease mainly as a phenomenon that interferes with the human being's ability to act or in other ways connect to his/her ability to act in social circumstances (133).

IBS is not a life-threatening condition, but it certainly has an impact on everyday life and thereby impairs health of the individual. According to a holistic health theory like Nordenfelt's, health is impaired when the individual can no longer reach or achieve his or her vital goals. From this perspective, IBS could be considered as a condition that actually make it more difficult for the individual to achieve his/ her of the individuals' vital goals concerning social and working life. IBS also clearly reduces quality of life and increases absence from work as well as restricting social life in the individuals affected.

Measurement of HRQOL provides valuable information to help to understand how the disease and pharmacological or non-pharmacological therapy affect daily life of a patient group or individuals. Recent studies have indicated that persons with IBS have an impaired health-related quality of life (HRQOL) (134,135,136). IBS patients also have been found to display lower HRQOL than patients with e.g. GERD and asthma and lower in some dimensions than patients with other chronic illness such as diabetes mellitus and end-stage renal disease (137,138). A study in the UK found that patients with IBS have considerably lower HRQOL than control groups without IBS matched for age, sex and social characteristics, concerning perceived physical role, bodily pain and a perceived general health (139). It has also been suggested that impaired HRQOL in FGD patients might be explained by psychological factors (140).

The studies of the associations between IBS and quality of life have either used generic health-related quality of life measurements, such as Short Form-36 (SF-36) or IBS-specific HRQOL-instruments (141,142,143,144). Disease-specific measures are especially used in clinical trials, while generic HRQOL measures are designed to evaluate aspects that are applicable across diseases, treatments and populations and can therefore provide a basis for comparisons with data from the general population (144,145). IBS has an obvious negative impact on patient's wellbeing and daily life and the US Food and Drug Administration (FAD) recommends the use of HRQOL measurement in trials of IBS treatment (146,147).

2.3.2 HRQOL in different cultures

A resemblance concerning IBS patient's reports of their symptoms has been revealed in the sense that the patterns of GI symptoms seem to be similar across the Western cultures (148). However, the question is how are these symptoms and discomforts perceived by those affected? What is the impact on quality of life in different social and cultural settings? Are there any socio-cultural differences in this respect? In a comparative study of HRQOL between the UK and the US it was found that IBS had a significant impact on quality of life in both countries, but it appeared to be greater in the UK than in the US (149). In a study in the US of racial differences of IBS, similar HRQOL was found between white and non-white IBS patients (150). In general, the effect across different cultures of IBS on daily activities and quality of life of the IBS patients has only scarcely been studied.

2.4 Treatment today

Since the precise etiology of IBS is still unknown, treatment is often focused on relieving symptoms rather than curing the disease (151). Managing this chronic condition requires a coordinated effort between patient and physician, as well as diagnosing IBS as early as possible so treatment can be initiated without delay to avoid unnecessary tests. Dietary treatment, lifestyle and behavioural changes as well as pharmacological therapy play an important role in treatment of IBS (151,152,153,154,155,156).

Treatment could be most successful when therapy is directed against predominant IBS symptoms, but so far no single drug has shown the ability to treat the multiple symptoms of IBS (151). The general recommendation for drugs in this respect is directed towards the most troublesome symptoms such as; constipation, diarrhoea, pain and spasm (157). Anti-spasmodic and motility-regulating agents used alone or in combinations with laxatives, anti-diarrhoeic or anti-depressants are frequently used in treatment of IBS today (158). Reports confirm that prescriptions for IBS cases are dominated by three drug classes: gastrointestinal motility agents, antispasmodics, absorbents and anti-flatulence agents in addition to laxatives (159). This trend is also seen in self–medications with over-the–counter (OTC) drugs, although the majority of IBS patients have prescribed medications (83,160). Studies also report that fibre therapy could benefit many IBS patients with true constipation but on the other hand, some patients may become more bloated or have an increase in other IBS symptoms while taking fibre (161,162,163).

5-hydroxytrytamine⁴ (5-HT⁴) has been recently introduced mainly in the US. These receptors, which are expressed in the gastrointestinal tract, play a key role in motility, because they are released by pressure from enteroendocrine cells and thereby stimulate the peristaltic reflex (164,165). Furthermore, the partial serotonin type 4 (5- HT⁴) agonist Tegaserod exhibits e.g gastric motility and shortening of colonic transit time, as well as softens stools. This agonist improves to some extend the symptoms of constipation-predominant IBS (166,167,168). Patients treated with Tegaserod also feel less bloating, less abdominal pain and more satisfaction with their bowel habits compared with placebo-treated patients (88,169). The 5-HT³ antagonist, Alosetron delays transit, relaxes the colon and decrease urgency and stool frequency as well as improves symptoms in diarrhoea predominant-IBS patients (170). Serotonin (5-HT3) receptor antagonist and 5-HT4 partial agonist drugs appear to be more successful in the case of bowel pattern disruption in women with IBS compared to men (171).

There are some suggestions that the use of certain type of behavioural therapy might improve individual symptoms of IBS as well as psychological symptoms (88,169,172). In the UK it has been suggested that it might be beneficial if specially trained nurses in primary care can provide cognitive behavioural therapy to IBS cases as a complement to other pharmacological treatment (173). In general, IBS patients tend to be dissatisfied with the overall efficiency of traditional IBS therapies, although they tend to be useful for some patients (77). IBS treatment today still involves a multicomponent approach that includes medical management of dominant symptoms, dietary modifications and possibly psychotherapy and even self-medication in terms of seeking information about IBS (174).

2.5 Referral

Less than 30 % of IBS patients in primary care are referred to specialist (42,175).Uncertainty about diagnosis or dissatisfied patients are the predominant reasons why some IBS patients are referred to hospital specialist (98). As a goal of referral from primary care should be to satisfy the management required for the patient in terms of confirming the diagnose or other organic diseases, some patients also need a second opinion. Other patient might benefit from seeing a dietician or psychotherapist (176). Studies have also reported that patients referred to a gastroenterologist have a severe chronic form of IBS and a high number of consultations during the year (159). However, a study in the UK shows that patients managed in primary care do not have less severe symptoms of IBS than those consulting specialist cares (159,177). Thompson et.al. also suggest that the probability of referral increases with the number of tests ordered and performed (42). Paterson WG et al suggest in their "*recommendations for the management of irritable bowel syndrome in family practice*" that most IBS cases can be managed at the primary care level (178).

3. Aims of the study

3.1 General aims

The general aims of this thesis were to estimate the occurrence of irritable bowel syndrome in the general population and to achieve a better understanding of present treatment of this disorder and impact on everyday life in those suffering from IBS. A further aim was to establish a populationbased database for research on functional gastrointestinal problems.

3.2 Specific aims

- to describe consulting pattern of patients with an IBS diagnosis and to estimate the consulting incidence of IBS in a well-defined Swedish primary care region.
- to explore the patterns of treatment and health care utilization of patients with IBS in a Swedish primary care setting.
- to analyse everyday working conditions and health-related psychosocial indicators among individuals suffering from IBS diagnosed in primary care compared to an age and gender matched control group.
- to analyse the association between psychosocial and behavioural factors as well as family history and irritable bowel syndrome in primary health care.
- to compare health-related quality of life, through the SF-36 questionnaire among individuals suffering from irritable bowel syndrome in two different European cultural settings.

4. Material and Methods

4.1 The Linköping IBS Populations Study (LIPS)

In different studies, various kinds of reference methods have been used when comparing the results obtained from the IBS patients. Either questionnaire-specific values for the general population or other disease groups have been used as reference. Few of these studies of HRQOL and selfreported mental health have compared their results with randomised and matched population-based control groups. After a systematic review of how to optimally measure the outcome in IBS and other FGD trials in terms of HRQOL measurements, the conclusion was that future studies should match, by age and gender, a sample of control subjects without IBS or FD (135,179).With regard to this and due to the fact that there are limited studies with a population-based control design, we have performed a register study in primary care and a population-based case-control study addressing; occurrence, treatment, and psychosocial factors such as HRQOL, self-rated mental health, sleeping disturbance and working conditions in IBS cases and controls entitled "The Linköping IBS Population Study" (LIPS).

4.2 Study design

The LIPS study comprises two parts. Part I was a retrospective register study where the data collection was based on computerised medical records at three selected Primary Health Care centres (PHC) in a defined region. Part II was a population based case-control study. The identified IBS cases from part I constitute the cases, while their control groups were randomly selected from the population census register in the same area as the cases. Data in part II were collected by means of a postal questionnaire mailed to cases and controls. The study was conducted in Linköping, a city located in the south-east of Sweden with 135,000 inhabitants. The PHC centres covered in total a catchment population of over 40,000 inhabitants and were responsible for practically all primary health care consultations for the population in their respective geographical areas. The patients could either attend an open surgery or visit their GP by appointment during the period studied. A pilot study at one PHC centre was performed to develop a data registration form. The medical records of fifty IBS cases with code number K-58-p according to ICD-10-P were used for this purpose.

4.2.1 Study population, part I (paper I, II)

All cases with a registered first diagnosis of IBS (N= 849) were identified from the computerised medical records over a 5-year period (1/1 1997 – 31/12 2001) at the three selected PHC centres. The ICD-10-P code K-58-p for IBS was used to identify the cases in the medical records.

Diagnosis, date of diagnosis, number of health care visits and reason for consulting and demographic data were retrieved from the medical records. All these data were documented by the GP, including records of telephone consultations. The information was extracted and further scrutinised by means of a registration form for the identified IBS cases by one researcher. For all cases, medical records were checked to ensure that there had not been any earlier IBS diagnosis. Data on the identified IBS cases comprise information from all GP consultations, where the IBS was registered, during the period studied. The actual study period for each individual could be from one year up to 5 years, depending on when the first diagnosis was made during the follow-up.

We excluded 115 cases with a prior confirmed diagnosis in the medical records before 1997. Furthermore, seven IBS patients (three male and four female) had died during the follow-up and four had a sheltered and nonaccessible medical record. Consequently, these 11 cases were excluded since there was no information available on earlier diagnosis or other related data. Remaining in the study were 723 IBS cases in all ages (**table 1**).

Age-groups	Women (n=487) n	Men (n=236) n	total n
0 - 14	5	9	14
15 - 24	43	17	6
25 - 44	173	80	253
45 - 64	143	71	214
65 -	59	123	182

Table 1. Identified IBS-cases (N=723) in part 1 of the study, divided into age-groups, men and women.

Data about mental complaints such as sleeping problems, tiredness, depression and anxiety together with worries and stress was retrieved from the medical records. All these complaints, except for worries were diagnosed and documented by the GP in the medical records. The occurrence of worries were not diagnosed but documented by the GP in the medical anamnesis.

4.2.2 Consulting incidence

The concept of consulting incidence used in this study refers to the fact that the data provided do not necessarily apply to the entire group of individuals with possible IBS disease or IBS symptoms in the community. They refer only to those seeking primary care during the period studied. PHC centres have an overall responsibility for the primary health care of all inhabitants in the community. Thus only a negligible part of the population might have visited other providers of primary care. Medical records in primary care in Sweden are generally regarded as a reliable source of such kinds of data collection since the primary health care centres have an overall responsibility for the primary health care in a catchment area, and therefore are required to regularly report morbidity patterns based on structured diagnoses.

4.3 Study population, Part II (paper III, IV, V)

The LIPS uses a case-control study design. The cases have been identified on the basis of diagnoses in primary care medical records in part I, while the control group was randomly selected from the population census register. All the IBS cases in this study were identified in Swedish and Greek primary care, not in hospital care, so the severity of the disease could vary from mild or moderate to severe. Data were collected by means of a postal questionnaire.

4.3.1. The LIPS cases and controls

The recruitment of IBS cases from part I was based on four criteria:

- Being a patient at one of three randomly selected PHC centres in Linköping
- Being 18-65 years of age
- Having a first-time diagnosis of irritable bowel syndrome (ICD-10-P code K-58-p)
- Being diagnosed during the 5-year period 1997-2001.

Analysis of the computerized medical records at the PHC centres identified 515 IBS cases fulfilling the study criteria. Through the local census population register, a control group of 4,500 individuals in the age-group 18-65 years were randomly selected from the same geographical area as the IBS cases. The number of individuals in the control group was chosen proportionally in accordance with the size of the actual population living in each of the three PHC areas, i.e. 2,100, 1,500 and 900 controls from the respective PHC area, as shown in **Figure 4**.



Figure 4. Flow-chart of the study population – "The Lips Study".

4.4 Postal questionnaire and instruments used in part II

For the data collection, we drew up a postal questionnaire using validated psychometric instruments and established questionnaires. Questions about medication and co-morbidity were also included as well as the GI-specific ROME II questionnaire. In addition, we elaborated some questions about occurrence of GI disorders in the family, own knowledge of the disease, recent changes in working and nutritional habits, exercise, meal habits, perception of daily stress, and impact on daily working life and long-term and short-term sick leave. The questionnaire also included demographic data such as sex, civil status, education level (primary school, secondary school, upper secondary school regarded as low and University College and University regarded as high) and occupation.

Prior to the postal survey, a test of the questionnaire was performed in order to explore whether the questionnaire had unclear instructions, was difficult to fill in, had an appropriate size (A5), had an overload of questions or whether some of the questions were too personal or intimate. The pilot questionnaire was sent to 17 randomly selected persons between the ages of 30 and 75 years. The response rate was 82% and provided valuable practical indications that led to some adjustments in the final questionnaire.

The final postal questionnaire was sent to the LIPS population (515 IBS cases and 4,500 controls). Despite a check prior to the postal questionnaire, some IBS cases (n=28) and some in the control group (n=73) had an unknown address and one had died, leaving 4,913 individuals (487 IBS cases and 4,427 in the control group) in the study. The questionnaire was sent by mail in June, 2003. All subjects were provided with written information about the study together with the postal questionnaire. After two reminders, the overall response rate was 64%, 63% (n=2,786) for the control group and 72% (n= 351) for the IBS cases. These numbers include 4 IBS cases and 59 in the control group who answered but refused to participate in the survey. There was no difference in terms of severity of the disease, defined as proportion of referrals, between responders and non-responders among the IBS cases. Prior to the survey, a check was made to ensure that individuals in the control group did not have any registered IBS diagnosis during the period studied. Prior to this analysis (paper III and IV) the controls were randomly matched by sex and age to the cases. Three controls per case were selected (n=1,041 controls and n=347 cases) in this analysis.
4.4.1. Questions on everyday work demands and control

Questions about working situation previously used in the Swedish Living Conditions Surveys of welfare and health (180), principally measuring demand and control at work were included in paper III, IV. These questions are in line with the demand-control or job-strain model introduced by Karasek (124) and further developed by Karasek & Theorell (181). This model is one of the most influential models in studies on health effects of psychosocial working conditions. In this study we focus on questions measuring decision latitude at work which were: influence on planning own work, influence on working pace, influence on working-hours, and on lunch at work, monotonous work, and opportunities for learning new things at work. The response alternatives for these questions were: no influence, some influence or large influence, and no, yes sometimes and yes often. For working conditions, "lack of influence" was defined as exposed and "some" or "large influence" was defined as unexposed.

4.4.2 Stress, sick leave and co-morbidity

Perception of daily stress questions had the response alternatives: never, seldom, now and then, very often or always. For perception of daily stress, "never/seldom/now and then" were defined as unexposed and "very often" and "always" were defined as exposed. The questions concerning whether daily working life was affected by GI problems and whether sick leave was caused by GI problems were both dichotomised.

Questions concerning chronic co-morbidity (coronary heart disease, hypertension, diabetes mellitus, asthma, allergy, rheumatoid arthritis, migraine, metabolic disturbance) had three response alternatives: no, yes previously and yes now, which were dichotomised into no or yes in the database. The questions about other chronic diseases such as fibromyalgia and muscoskeletal disorders were subsequently dichotomised in the database.

4.4.3 Health-Related Quality of Life questionnaire - SF-36

The generic health-related quality of life measure SF-36 used in paper III and V, has been used extensively in public health research, epidemiological studies and in clinical trails. The SF-36 includes eight multi-item scales (35 items) that evaluate the extent to which an individual's health limits his or her physical, emotional and social functioning: physical functioning (10 items), role limitations caused by physical health problems (4 items), role limitations caused by emotional health problems (3 items), social functioning (2 items), emotional well-being (5 items), pain (2 items), energy/fatigue

(4 items), and general health perceptions (5 items). All questions were asked in respect to the previous four weeks, with the exception of an additional item that assesses change in the respondent's health over the preceding year. Responses in the SF-36 were transferred to a standard scale, ranging from 0 (the worst possible score) to 100 (the best possible score) (182,183,184). Summary of what measured in SF-36 are shown in **Figure 5**. (185)

SF-36 scales:

Physical Functioning:

Limited a lot in performing all physical activities including bathing or dressing due to health.

Performs all types of physical activities including the most vigorous without limitations due to health.

Role Physical:

Problems with work or other daily activities as a result of physical health. No problems with work or other daily activities as a result of physical health.

Bodily pain:

Very severe and extremely limiting pain No pain or limitations due to pain.

General health:

Evaluates personal health as poor and believes it is likely to get worse. Evaluates personal health as excellent.

Vitality:

Feels tired and worn out all the time. Feels full of pep and energy all of the time

Social Functioning:

Extreme and frequent interference with normal social activities due to physical or emotional problems.

Performs normal social activities without interference due to physical or emotional problems.

Role Emotional:

Problems with work or other daily activities as a result of emotional problems. No problems with work or other daily activities as a result of emotional problems

Mental Health:

Feelings of nervousness and depression all of the time. Feels peaceful, happy and calm all of the time.

Figure 5. Summary of information about what measured in the SF-36 scales, lowest possible score (floor) and highest possible score (ceiling).

4.4.4 The Hospital Anxiety and Depression scale (HAD)

The HAD questionnaire is a self-administered questionnaire measuring anxiety and depression designed to provide a simple but reliable tool for use in medical practice. It consists of 14 items (7 items each for anxiety or depression) and uses a 4-graded Likert scale (0 to 3), where 0 represents the most positive option and 3 the most negative one. A mean value for the items in each dimension was calculated. A score of 7 or less on each subscale (out of a maximum of 21), denotes a non-case, 8-10 a doubtful case and 11 or higher a definite case of anxiety or depression (186,187,188).

4.4.5 Sleeping problems

Questions regarding perception of sleeping problems in the last six months were derived from regional surveys of welfare and health and standard of living (180) and asked for: difficulties in falling a sleep in the evening, difficulties in waking up in the morning, not thoroughly rested in the morning, waking up in the middle of night with difficulties getting back to sleep and nightmares or disturbed sleep. The following alternatives were merged: sleeping disturbances, "never/seldom" and "now and then" were defined as not having sleeping problems while "very often" and "always" were defined as having sleeping problems in the database (Paper IV).

4.5 Comparison of LIPS data and Greek data

The design of the study in paper V is a matched case-control study, with two different groups of cases, IBS cases from rural and semi-rural villages on Crete, Greece and IBS cases from the city of Linköping, Sweden. In addition, a Swedish control group of non-IBS cases from part II of this study was randomly selected from the general population as shown in **Figure 6**.



Figure 6. The Cretan IBS cases and the age and sex matched Swedish IBS cases and controls from the LIPS.

4. 5.1 The Greek IBS cases and controls

Thirty cases with a diagnosis of IBS in the age groups 18 and 65 years were identified through medical records at three health care centres on rural Crete. These 30 IBS cases constitute all the cases in the age-group 18-65 years in an IBS database with cases identified from a four-year retrospective survey of gastrointestinal problems of the rural population on Crete which is reported elsewhere (89). These 30 IBS cases were invited for an interview by a medical doctor concerning health-related quality of life (the SF-36 questionnaire), demographics, life style indicators and gastrointestinal co-morbidity.

4.5.2 The Swedish IBS cases and controls

The Swedish IBS cases and controls were matched for gender and age with the Cretan IBS cases. Each Cretan IBS case, were matched with three Swedish IBS cases and with 10 Swedish controls from the general population. The Swedish IBS cases were randomly selected and matched from a larger sample based on a five-year retrospective survey of diagnosed IBS cases identified through medical records at three health care centres in the city of Linköping located in the south-east region of Sweden (part II). The larger sample of Swedish IBS cases, was sent a postal questionnaire including SF-36, demographics, lifestyle indicators and gastrointestinal co-morbidity.

4.6 Statistical analysis

4.6.1 Paper I, II

All data was stored in a common database and statistically analysed using the SPSS version 13.0 and 14.0 programs (SPSS Inc., Chicago, IL, USA). In the statistical analysis, IBS occurrence rates were calculated as incidence rates per 1,000 person-years. The total number of person-years during the five year study period was 210,870 (104,030 person-years for men and 106,840 for women). The study period for each individual could be from one year up to 5 years, depending on when the first diagnosis was performed during the follow-up. For the analysis of seasonal variations, only the month of the visit when the person actually was diagnosed was chosen. Logistic regression analysis was used to estimate the relative risks and 95% confidence intervals of different mental complaints as dependent variables associated with age and gender as the independent variables.

A Cox proportional regression analysis was performed in order to reveal possible factors influencing the likelihood of a follow up consultation after the initial GP contact, regardless of entering time or endpoint for each participant. The endpoint was defined as follow-up consultation or not during the period studied. In the analysis, the number of months from the initial consultation to the first follow-up consultation (which varied from 1 to 56 months) was used as the time variable. Univariate analyses of the relations between potential independent variables and the endpoint variable were performed prior to the multivariate Cox analysis, to reveal variables to be included in the final model. Factors analysed in the Cox model were, in addition to the background variables age and sex, earlier GI problems documented before the IBS diagnosis, diagnosed co-morbidity besides gastrointestinal diagnoses, including all common complaints seen in

primary care (i.e. hypertension, influenza, allergy, back pain, infections etc.) as well as mental complaints, documentation of type of investigations and referrals. A merged variable entitled "mental complaints" was also included in the model. This variable was based on documented diagnoses in the medical records with reference to either depression, worries, anxiety or tiredness/sleeping disorders. The Wald test was applied to calculate pvalues for data obtained in the Cox multiple regression analysis.

4.6.2 Paper III, V

The significance of differences between cases and the control group for SF-36 scale was estimated using the ANOVA test. Odds ratios and 95% confidence intervals were also calculated. For categorical variables, Mann-Whitney U and the chi2-test was used and a p-value of <0.05 was considered statistically significant. The associations between working conditions and IBS risks identified in the univariate analyses were adjusted for possible confounding variables by using a multiple logistic regression analysis. These confounding variables adjusted for were "sleeping problems", "mood changes" and "perceived health". Sleeping problems was constructed from the questions regarding perception of sleeping problems, mood changes was merged from the HAD variables anxiety and depression, while perceived health was directly transferred from SF-36. This multiple logistic regression analysis was performed separately for men and women and only employed subjects were included, (senior citizens, students, unemployed and early retirees were all omitted in this analysis). Odds ratios and 95% confidence intervals were also calculated in these multivariate analyses.

4.6.3 Paper IV

Univariate correlations were first assessed by Spearman's correlations and then followed by multivariate logistics analysis. The diagnosis of IBS was used as dependent variable. A correlation matrix was initially drawn up for all independent variables. For those variables that were highly intercorrelated and represented the same factor, only the variables that were strongest correlated with the dependent variable remained in the further analysis. The univariate analyses of associations between the independent variables (educational level, exercise, lack of influence on work, mother or father with IBS, perceived daily stress, anxiety, depression, sleeping disturbance, present use of over-the-counter or prescribed non-steroide anti-inflammatory drugs (NSAID) or acetylsalicylic acid (ASA), and meal habits) and the dependent variable were performed prior to the multivariate analysis to identify the variables that were associated with IBS diagnosis. These were thereafter included in the multivariate analysis that produced a final model. The multivariate logistic regression analysis was performed for the entire study population and separately for males and females, respectively. Odds ratios and 95% confidence intervals were calculated in the univariate analysis and estimated for variables included in the multivariate logistics analysis.

Ethical approval

This study was approved in 2002 by the Ethical Committee at the Faculty of Health Sciences, Linköping University, Sweden.

5. Results

5.1 Paper I

In this five-year retrospective analysis of medical records at three PHC centres, 723 IBS cases were found after exclusion. The cases were evenly distributed over the 5-year study period, (1/1 1997 - 31/12 2001) at the three PHC centres. The number of cases identified per year was as follows: 1997 n=133 (18.4%), 1998 n=155 (21.4%), 1999 n=174 (24.1%), 2000 n=149 (20.6%) and 2001 n=112 (15.5%).

The consultation incidence of IBS in this study was 3.4 (95% CI 3.20-3.70) per 1,000 person-years for all IBS cases, among females; the incidence rate was 4.6 per 1,000 person-years (95% CI 4.16-4.97) and males; 2.3 per 1,000 person-years (95% CI 2.01-2.59). The incidence in females was more than double that of men in all age-groups except in the youngest age-group. The relative risk among females versus males was 1.99 (95% CI 1.70-2.31). Of all the IBS cases, 63% had abdominal discomfort documented as the main reason for consulting their GP. Abdominal discomfort in combination with other non-abdominal complaints was documented among 31% and only a small group of the IBS cases (6%) had other type of discomforts recorded as the main reason for the consultation. The proportion of individuals having abdominal discomfort in combination with other discomforts and symptoms as consulting reason increased with age (p<0.0001), there were no gender difference in this respect.

52 % of the IBS patients consulted their GP at an open surgery without an appointment. Planned consultations (40 %) were more common among the elderly while consultations without an appointment were more common among the younger patients (p< 0.0001). An additional 8 % of the IBS cases were diagnosed either when revisiting the PHC centre or through a telephone contact with their GP. There were no gender differences in this respect. A majority (61.5%) of the IBS cases had only one GP visit during the period studied, no gender difference was seen in this respect. The older IBS patients tended to have a larger number of GP visits (p= 0.02).

There appears to be some seasonal variation among the initial GP consultations. Two peaks were seen, although not statistically significant, in spring and autumn (especially October). This is shown in **Figure 7**, for all IBS cases, and also for a subgroup of only those attending an open surgery with abdominal discomforts as the sole consulting reason.



Figure 7. Seasonal variations in GP consultations for the IBS cases.

Documented mental complaints and symptoms were: stress in daily life (24 %), (**Figure 8)** worries (15 %), depression (8 %), tiredness (7 %), insomnia (5 %) and anxiety (4 %). Most of these mental complaints increased with age, although stress and tiredness, which decreased after retirement. Depression, tiredness and documentations of anxiety were more frequent among females.



Figure 8. Stress in daily life documented by GP in the medical records of the IBS cases in different age-groups.

5.2 Paper II

In the case of a majority of the IBS patients (80.4%), their GP initiated some kind of treatment (either medical or non-medical) during the initial consultation and 16.2% of these IBS patients received treatment in conjunction with every consultation they had during the follow-up. For a very small group (5.7%), treatment was not initiated until the follow-up consultations. The vast majority of the IBS patients (74%) were prescribed some medication for their GI-symptoms, of these 30% also had pharmacological treatment in combination with non-pharmacological treatment. Solely non-pharmacological treatment was given to 11% of the patients. Very few of the IBS patients (15%) had neither pharmacological nor non-pharmacological treatment documented in the medical records.

Pharmacological treatment prescribed for abdominal complaints took the form of fibre and bulking laxatives agents in addition to acid suppressive drugs, separately or in combination, where were the absolutely dominating medication prescribed.

Medication	All IBS patients		Sex			
	(N=723)		Men		Women	
	n	%	n	%	n	%
Fibre and bulking	450	62.2	149	63.1	301	61.8
laxative agents						
Acid suppressive	167	23.1	47	19.9	120	24.6
drugs						
Anti-flatulence	49	6.8	15	6.4	34	70
agents						
Anti-diarrhoeic	47	6.5	17	7.2	30	6.2
agents						
Motility-regulating	36	5.0	7	3.0	29	6.0
agents						
Anti-spasmodic	35	4.8	7	3.0	28	5.7
agents						
Alginat	16	2.2	3	1.3	13	2.7
Antacids	6	0.8	1	0.4	5	1.0
Antidepressants	47	6.5	9	3.8	38	7.8*
Anxiolytics	27	3.7	6	2.5	21	4.3

Table 2. Pharmacological treatment prescribed for abdominal complaints given.

Logistic regression adjusted for sex *p< 0.05

For a majority of the patients treated with laxatives, constipation was noted in the medical records. Similarly, for those patients given acid suppressing therapy, either GERD or heartburn was noted in the medical record at the same time as the IBS diagnosis. Other types of medications were anti-flatulence agents, anti-diarrhoeic and motility-regulating agents. Antidepressants and anxiolytics were also prescribed. However, all the IBS patients who received antidepressants and anxiolytics also had a diagnosis of depression or anxiety documented in their medical records. Logistic regressions showed an impact of age on the prescriptions of medications. All prescriptions increased with increasing age except for anti-diarrhoeic agents, which were more common among the youngest patients. Sex had an independent impact (p=0.03) on the prescription of antidepressants, being more frequent among women.

Sick leave as prescribed by the GP due to GI problems was documented for 4.3% of the IBS cases and tended to be predominant among the age group 45-64 years (data not shown). No gender difference was found in this respect.

Laboratory tests were performed for 73% of all the IBS patients and were more common (p=0.05) (adjusted for age) for men (78%) than for women (71%). The laboratory investigations of IBS patients in this follow-up comprised approximately twenty different recurring tests. Complete blood cell count (CBC), erythrocyte sedimentation rate (ESR), some metabolic tests and faecal occult blood were most frequently performed. In logistic regressions, these data were adjusted for the possible impact of age and gender. Age impact was observed in most of the tests performed. Most laboratory tests occurred within the two oldest age groups, except for C-reactive protein (CRP) and test for coeliac disease, which occurred more frequently among the youngest age group. A gender difference was revealed for thyroid hormone tests (TSH and thyroxin), which were more frequent among females.

Rectoscopy was performed in 17% of the cases and was more frequent among patients aged 45 years and older (p<0.0001) and among women (p=0.005). 24.7% were referred for complementary investigations in hospital and of these, 8.9% were sent for further investigation to a gastrointestinal specialist. In this latter group, a small number (3.9% of all cases) had gastroscopy / sigmoideoscopy. The most common referral was for colon Xray (12.4%) which was most frequent (p=0.01) among the middle-aged. Very few of all the IBS cases (1%), predominantly women (p=0.02) were referred to psychotherapy. However, the odds ratio for referral were higher (OR=1.55 95% CI 1.08-2.23) among the IBS cases with mental complaints documented in their medical records.

A majority of the IBS patients (63%) had only one single consultation with their GP during the period studied, while 37 % had one or several followup consultations. Of the IBS patients who had an another appointment, 19 % had their next appointment within a month, 11% had a next appointment within 6 months, 4.4 % within a year and 4.1 % more than a year after their first consultation.

Variable	Hazard Ratio	(95% CI)	p- value	
Gender:	1.02	0.87 - 1.17	0.85	
Age:	1.06	0.98 - 1.15	0.12	
Laboratory test ordered Rectoscopy ordered Diagnosed co-morbidity *)	1.27 1.33 1.45	1.07 - 1.51 1.09 - 1.69 1.24 - 1.70	0.006 0.005 <0.0001	

Table 3. Factors related to follow-up consultation among IBS patients in primary care, analysed by Cox regression.

*) Diagnosed co-morbidity besides gastrointestinal diagnoses known at first visit or earlier

Univariate correlation analysis of different independent variables and the probability of a follow-up consultation for the IBS cases were performed. To reveal the relative importance of these factors, a Cox proportional regression analysis was performed. The following variables had an independent impact on the probability of a follow-up consultation; diagnosed co-morbidity besides the IBS diagnosis, rectoscopy ordered and laboratory tests ordered. Age and sex had no significant impact in the final model.

5.3 Paper III

Of the 347 IBS cases between 18-65 years, 72 % were females and more than 50% were below age 45 (**Table 4**). More female IBS patients reported long-term sick leave (8.4 % vs. 2.4 %, OR 3.70; 95% CI 1.94-7.07) and receiving early retirement compensation/disability pension (14.1% vs. 9.4 %, OR 1.56 95% CI 1.01-2.41) as compared to their female control group. No differences were observed among males in this respect. The prevalence of chronic diseases did not differ between IBS cases and controls. Short term sick leave caused by gastrointestinal problems in the last 12 months was more common among all IBS cases (23.8 % vs. 9.9 %, OR 2.82; 95% CI 1.79-4.46).

	IBS cases		Control group		
	n	%	n	%	
Sex:					
Male	96	27.7	288	27.7	
Female	251	72.3	753	72.3	
Age groups:					
15 to 24	36	10.4	108	10.4	
25 to 44	147	42.4	441	42.4	
45 to 64	164	47.3	492	47.3	
Civil status:					
Living alone	56	16.3	160	15.5	
Married/cohabitant	258	75.0	787	76.4	
Divorced	26	7.6	65	6.3	
Widow/widower	4	1.2	18	1.7	
Educational level:					
Primary school (low)	57	16.6	149	14.5	
Secondary school	60	17.5	200	19.4	
Upper secondary school	80	23.3	229	22.2	
University College or	146	42.6	453	43.9	
University					

Table 5. Socio-demographic data for IBS cases (n=347) and sex and agematched controls (n=1041) in paper III and IV.

The female IBS patients reported less influence on planning their work and working hours as well as fewer opportunities to learn new things at their work compared to their controls. The male cases only reported less influence on their working pace in comparison to their male controls. However, all IBS cases (females and males) reported that their daily performance in working life was considerably affected by their gastrointestinal problems. In contrast to the males, the female IBS cases reported more daily stress than did their controls. The associations between working conditions and IBS risks were still evident, especially for females, after adjustments in multiple logistic regressions for potential confounders such as; mood, sleeping problems and perceived health.

Risk factors	p-value	OR	95% CI	
Women:				
Low decision authority				
regarding planning the work	0.022	2.29	1.13-4.64	
Perceived health	0.007	6.55	1.66-25.83	
Mood*	< 0.0001	2.29	1.45-3.65	
Sleeping problems	0.007	1.71	1.16-2.49	
Low decision authority				
regarding working hours	0.087	1.53	0.94-2.49	
Perceived health	0.007	6.55	1.65-25.55	
Mood*	< 0.0001	2.32	1.46-3.68	
Sleeping problems	0.010	1.65	1.12-2.42	
No further				
education at work	0.004	2.12	1.26-3.57	
Perceived health	0.004	7.44	1.89-29.22	
Mood*	< 0.0001	2.30	1.46-3.63	
Sleeping problems	0.010	1.65	1.13-2.42	
Men				
Low decision authority				
Regarding working pace	0.022	5.44	1.28-23.18	
Perceived health	0.287	2.54	0.46-14.1	
Mood*	0.287	1.61	0.67-3.86	
Sleeping problems	0.195	1.47	0.82-2.62	
1 01				

Table 5. Multivariate logistic regression analysis of confounding variables for associations between risk factors identified in univariate analyses and being diagnosed with IBS displayed for the women and men participating in LIPS.

*A merged variable comprising anxiety and depression.

Self-reported HRQOL was lower among the IBS cases compared with the control group for all dimensions of the SF-36. The foremost differences seen were in the emotional role limitation, general health perception and bodily pain dimensions. The smallest differences were in physical

functioning and mental health dimensions. The female IBS patients had considerably lower HRQOL in all dimensions compared with their controls, even when compared to male cases. Younger female IBS cases (18-44 years) reported lower mental health on the SF-36 scale than the older IBS female cases (p=0.015). Among men, there were no differences concerning physical functioning and physical and emotional role. In the remaining areas, the male IBS patients scored somewhat lower than their controls.

More female IBS patients than controls fulfilled the HAD criteria for a definite anxiety and depression case. Among the males, there was only a tendency to more anxiety in the IBS cases. Moreover, the female IBS cases, reported more sleeping disturbances in all the aspects measured, while no difference was seen for males. Long-term pain was more frequently reported by female IBS patients than their controls (14.1 % vs. 9.0 %, OR 1.65; 95% CI 1.06-2.57) in contrast to the male groups.

5.4 Paper IV

The total 1,388 participants in this study consisted of 347 IBS cases and 1,041 controls aged between 18 and 65 years. The univariate analyses of associations between IBS diagnosis and educational level, current use of NSAID or ASA, exercise level, and irregular meal habits did not display any significant correlations. However, lack of influence on planning the work (8.4 % vs. 3.3%) or working pace (8.8% vs. 5.2%) perceived daily stress (42.6% vs. 36.4%), family history of IBS (19.0% vs. 10.7%), anxiety (25.4% vs. 11.0%) depression (6.1% vs. 2.7%) and sleeping disturbance (53.3% vs 37.7%) indicated an association with having an IBS diagnosis. In the multivariate analysis, where only the latter group of variables was included, lack of influence on work planning, family history of IBS, anxiety, and sleeping disturbance remained independently associated with an IBS diagnosis.

In the separate univariate analyses of females, lack of influence on planning work (9.6% vs. 3.9%), perceived daily stress (46.0% vs. 38.3%), family history of IBS (20.0% vs. 12.0%), anxiety (28% vs. 11.7%) depression (8.0% vs. 2.8%) and sleeping disturbance (56.8% vs. 39.3%) displayed an association with being diagnosed with IBS. In the multivariate analysis of these variables, lack of influence on planning work, family history of IBS, anxiety and sleeping disturbance remained in the final model. In males, lack of influence on working pace (8.4% vs. 1.4%), family history of IBS (16.8% vs. 7.0%) was associated with the IBS diagnosis in the univariate analyses. However, in the multivariate analysis only lack of influence on working pace and family history of IBS remained independently associated with having an IBS diagnosis. Sleeping disturbance and anxiety displayed a tendency to be associated with an IBS diagnosis in males even though the association was not statistically significant.

5.5 Paper V

The total 420 participants in this study consist of n=30 Cretan IBS cases, n=90 Swedish IBS cases and n=300 Swedish controls. The Swedish cases and controls were matched for gender and age with the Cretan cases. The ages for the cases and controls were distributed in the age-groups 18-24 years: 3.3 % (n=14), age-group 25-44 years: 26.7% (n=112) and age-group 45-64 years: 70.0 % (n=294). The gender distribution was 76.7 % (n=322) female and 23.3 % (n=98) male in total.

Insomnia was most common among the Swedish IBS cases and also higher among the Swedish controls in comparison with the Cretan IBS cases. A significantly (p<0.0001) larger proportion of the IBS cases from both Crete and Sweden perceived daily stress often or very often in comparison with the Swedish control group.

A general tendency was that the Cretan IBS cases reported lower HRQOL on six of the eight dimensions of SF-36 in comparison to the Swedish IBS cases. These differences were most evident in the dimensions general health and mental health. After adjustments in multiple regressions for the differences in the distribution of educational level and occurrence of present or past co-morbidity (coronary heart disease, high blood pressure, rheumatoid arthritis and depression) the Cretan IBS cases nevertheless scored lower general health (p=0.05) and lower mental health (p<0.0001) than the age and sex matched Swedish IBS cases. A gender analysis revealed that Cretan women with IBS scored especially low on the dimensions general health p=0.009 (mean score: 48.0 s.d: 20.3) and mental health p<0.0001 (mean score: 48.6 s.d: 24.9) in comparison with Swedish women with IBS (general health mean score: 62.3 s.d: 23.2 and mental health mean score: 71.0 s.d: 16.3). The IBS cases from both countries, reported significantly lower scores on all quality of life dimensions in comparison with the Swedish controls.

6. Discussion

An essential issue for patients with long-standing physical problems is how well they are able to function in their everyday lives, i.e. how they cope on a daily basis with their dysfunction. In fact, the particular importance of the assessment of everyday functioning qualifies IBS to be established as a specific problem area in public health and general practice. IBS is not a life treating disease, but those who suffer are seriously affected in their everyday life (77).

Health care seeking and treatment

The natural history of IBS is not clearly defined. A common pattern for some IBS cases is a previous consultation for abdominal complaints before the actual IBS diagnosis is made. In about one third of the IBS cases in this study, documentation was found in the medical records of FGD symptoms that had occurred earlier in life, at least three years prior to the diagnosis. This indicates a pattern of natural history of the disease and that the population at risk of a first occurrence of IBS will comprise some people who have been suffering from the disease in the past, but had not yet had any diagnosis noted in the medical records when this study started.

The main reason, documented in the medical records, for consulting their GP was abdominal discomforts. This was evident for more than half of the identified IBS cases and no differences between sexes emerged in this respect. The majority of the patients consulted their GP without an appointment. These findings confirm other results that have shown that abdominal pain or discomfort or when feeling that these complaints interfere with daily life might be the main reason for health care seeking, rather than other co-morbidity (67,68,110).

For the majority of the IBS patients, some treatment (either pharmacological or non-pharmacological) and one or more investigations such as rectoscopy or laboratory test were instituted at the initial consultation. However in this study, approximately twenty different recurring laboratory tests were performed. The relatively high number of tests performed may partly be explained by concomitant co-morbidity and the aim of excluding other organic diseases. It is very important to follow up what these laboratory tests predict to avoid unnecessary and expensive laboratory test. It might be more beneficial for all parts if only more specific tests were done. This may to some extend explain the existence of only a single consultation in 63% of all the cases during the period studied. Some may actually have been helped and others may have felt that their complaints were not taken seriously by the GP (189), and both could result in no further health care visits or some IBS patients after becoming aware that IBS is not a life threatening disease, might search information i.e. on the Internet. Self-medication might be a one way of learning how to cope with the disease and establishing regular bowel habits, avoiding certain foods and stress that can be helpful to manage everyday life.

There could be some factors that might explain follow-up consultations. Several independent variables such as: age, earlier GI problems documented in the medical records, referrals as well as indications of "mental complaints" were significantly associated with more than one consultation in the univariate analysis, but were not found to be significant in the multivariate analysis. Since the design of this study permit cases to enter at any time during the five year follow-up, we used Cox proportional regression in order to analyse the probability of a follow-up consultation. In these analyses, we found three variables, which had an independent impact on follow-up consultation; diagnosed co-morbidity besides the IBS diagnosis, rectoscopy and laboratory tests, all of which were adjusted for age and sex. Surprisingly, sex and age were no predictors of follow-up consultation in this study, neither were mental complaints. A possible explanation is that the relative importance of this latter factor diminished in the multivariate analysis because it is included in diagnosed co-morbidity.

From a patient perspective, it is important that symptoms experienced are taken seriously so that treatment can be initiated early on to avoid unnecessary suffering (42,190). Providing information on the chronic course and benign nature of IBS is important parts of GP counselling. The most common pharmacological treatment prescribed in this study was fibres, bulking laxatives and acid suppressive drugs. This is in contrast to other studies stating that anti-spasmodic, motility-regulating, anti-diarrhoeic and anti-flatulence agents are most frequently prescribed to IBS patients (158,159). This might be due to the fact that most research so far on this issue have been conducted in secondary and tertiary care.

It is clinically well-known that many patients with chronic gastrointestinal disorders may find it difficult to discuss their symptoms with other per-

sons (115). Consequently, establishing a trusting doctor-patient relationship (191) is essential when assessing the impact of IBS on a patient's wellbeing. As mentioned earlier, our study showed that most IBS patients in primary care only had one consultation, which may reflect a certain type of doctor-patient relationship. In this patient group it might be beneficial for both patients and primary care if the GP or other trained persons could provide cognitive behaviour therapy.

Our findings indicate a possible seasonal pattern in the consultations for all IBS cases. For those IBS patients seeing the GP in an open surgery with abdominal discomforts as sole consulting reason, a peak is seen in October and a minor increase is seen in March and April. This pattern was seen despite there being no increase in access to GP or other health care service during these months. A study by Talley et. al (192) found that a subset of IBS patients reported moderate or greater seasonal change in bowel symptoms and this could be in part explained by somatisation and lifelong depression. Seasonal periodicity has also been reported in a Norwegian study of the occurrence of peptic ulcer disease (193). More research is required concerning seasonal variation and IBS problems.

Working Life and coping

We found that IBS patients are considerably more affected in their daily working life and have more sick leave due to GI problems than are controls. Other studies report that patients with IBS miss approximately 1-2 days of work per months due to their disease (60,136,139,149). IBS symptoms may reduce the self-estimated fitness to work through several mechanisms, including embarrassment of using toilets at work and fear of faecal soiling, according to Silk et.al. Even some IBS cases feel that their GI problems hold them back from seeking promotion at work, despite this, many IBS patients have developed measures to cope with the disease and that IBS symptoms are often accepted as a valid reason for absence from work (194).

Our findings show that female IBS cases have lower influence on planning their work and working hours, and fewer opportunities for new learning at work compared to female controls. For males, we only found a lower influence over working pace in comparison to their male control group. These associations were still evident even after adjustments in multiple logistic regressions for potential confounders such as; mood, sleeping problems and self-perceived health. Several causal directions and explanations of these findings are possible. Negative working conditions, such as low influence on planning the work, may lead to an increased risk for IBS through different mediating factors. Studies of other diseases have reported that high psychological demand in combination with low control at work is related to increased risk of cardiovascular and stress-related diseases (125,126,195). The demand-control theory underpinning this hypothesis is perhaps the most commonly used model for associating psychosocial factors at work to stress-related diseases (124,126,181,195). Another explanation is that IBS symptoms causes a secondary selection process where IBS patients and predominantly females more frequently get low-demand jobs where they have little influence on planning their work.

Coping strategies have so far not been thoroughly studied in the case of IBS (131). Nevertheless, many IBS patients develop personal measures to cope with the disease at work, even though the same IBS symptoms could be used by other individuals as a reason for absence from work (194). One ultimate coping mechanism could thus be long-term sick leave. Our findings that female IBS patients reported more long-term sick leave fits into such a hypothetical coping mechanism. Another hypothetical active coping strategy could be primary health care seeking by some individual with IBS and when the benign nature of the disease is revealed, the patients revert to passive coping. This theory is also in line with our findings that this patients group are not heavy utilisers of primary care.

Mental factors and HRQOL

Insomnia, anxiety, depression and stress and lower HRQOL are quit common among IBS patients and stressful life-event scores are often higher for IBS patients than for normal controls (113,114,115,117,134,135,136,140).The perception of daily stress was also higher for IBS patients than the controls in our study. Sleep disturbance is often reported in association with IBS (120,123). We found that sleeping disturbance was evidently more frequent among IBS cases, mostly women, in comparison with controls. This difference was found for all the sleeping aspects measured. Mental factors may also be involved since especially younger and middle aged women with IBS (under the age of 44) report significantly lower mental health scores on SF-36 in this study.

The results in paper V also tentatively indicate that there are differences in how persons with IBS on Crete, Greece, and in Linköping, Sweden, perceive their disease and how it affects their quality of life. This is especially noticeable as regards impaired mental health and reduced general health, where the Cretan IBS cases reported a lower HRQOL, even after adjustments for differences in the distribution of educational level and comorbidity. A plausible explanation of the differences found is that coping with IBS in everyday life might be more problematic in the Cretan environment than in Sweden and this represents the main finding. The outdoor living tradition and the warm climate with long and hot summers together with a higher risk of gastroenteritis in combination with the IBS disease might negatively influence their everyday quality of life. The disease might possibly also cause a feeling of being out of the ordinary when affected by a quite sensitive and slightly embarrassing condition. This might partly explain why the Cretan IBS cases, and especially the Cretan women, scored significantly lower on the mental health dimension.

Risk factors associated with IBS

In LIPS, we included a broad variety of potential factors associated with an IBS diagnosis. The main result (paper IV) of IBS patients in primary care is that they, more often than controls, have a mother or father with IBS symptoms and lack of co-determination at work. Other potential factors such as educational level, absence of exercise, irregularly meal habits and use of NSAID or ASA did not display a significant association with an IBS diagnosis. It is interesting to note that sleeping disturbances remained as an independently associated factor in the multivariate model. It is reasonable to expect that poor sleeping habits would have exposed co-variation with other psychological distress. However, there is some evidence suggesting a deprivation of sleep among IBS patients and that this could lead to deterioration in the IBS symptoms (121,122,196). A fundamental question regarding the results presented here concerns causality, i.e. whether the factors identified are a cause or an effect of the disease. These questions must be focused on further research. Potential risk factors such as life events, trauma or traumatic stress might play a role in the etiology or perceptions of IBS (197) as well as biological markers which were not addressed in the LIPS.

Gender perspective

To what extent does gender influence the development of IBS? Being a women might include being under greater stress as a result of gender stereotyping, increased risk of poverty, care responsibilities, the undervaluing of women's paid and unpaid work as wells as risk of sex and physical violence (198,199). IBS is more common among women (200). The principles of management do not differ due to gender, when an individual becomes an IBS patient; there are not so many distinctive sex differences between male and female cases. However, we found that more women than men had undergone a rectoscopy. This gender difference might possibly be explained by the increasing risk of bleeding haemorrhoids after childbirth. On the other hand, laboratory tests were significantly more frequently ordered for men in this study. There is no conceivable explanation for this gender difference, although it might possibly be due to fear of cancer. Nor were gender differences found concerning pharmacological or non-pharmacological treatment, referral or sick leave.

Female cases also had to some extend lower HRQOL in some dimension and in addition, the female patients report more anxiety and sleeping disturbances than male IBS cases. IBS-patients, and especially female patients, may feel embarrassed suffering from symptoms such as flatulence and diarrhoea (115). Consequently, it is important to understand the impact of a chronic disease like IBS on patient's especially women's, well-being when managing the disease (115). Our findings that the differences between sexes in HRQOL were most pronounced as regards physical and emotional role and physical functioning underline this conclusion.

For males, only lack of influence on working pace and family history of IBS remained as significant risk factors independently related to an IBS diagnosis. Accordingly, the female patients have a broader array of determinants (risk factors) which also include emotional problems. Female IBS patients are more seriously affected in their everyday life, which might be connected to culturally associated differences in the expectations on the physical and emotional role of female and male.

Benefits

The benefits of this study are a possibility of increasing the knowledge, and gaining a better understanding, of this common, but often overlooked, public health problem. In the long term, this knowledge could result in a better understanding and treatment of this disease. There is a growing awareness of the fact that a vital factor for patients with chronic diseases is how well they are able to function in their everyday lives.

Methodological discussion

LIPS study comprises two parts. Part I is a retrospective register study where the data collection were based on computerised medical records at three selected PHC centres in a defined region. Part II is a population based case-control study. The identified IBS cases from part I constitute the cases, while their control groups were randomly selected from the population census register in the same area as the cases. Data in part II were collected by means of a postal questionnaire mailed to cases and controls. Analysis of the computerized medical records at the PHC centres identified 515 IBS cases fulfilling the study criteria (part II). To minimize the number of excluded cases from the study, it is important to have a large number of initial cases, since some cases might be prevalent cases rather than new cases.

One of the main aims of this, and forthcoming studies, was to examine the burden of FGD in the general population using IBS cases from primary care and controls from the general population. A hypothesis might be: are there a large number of individuals in the general population with functional gastrointestinal complaints who have not so far consulted the PHC or other health care services for their complaints? How many new cases/individuals are there in the population with an undefined need of health care service? To study this group, one needs a large population-based group from the general population in the catchment area studied. This is why the control group from the general population was not sex and age matched with the cases as when the study was initiated. We calculated the number of controls to this study in accordance with the epidemiologically well-established principle: in a case-control study, every identified case should at least have two or preferably three controls each from the general population.

Our study has several strengths. On is that the study has a populationbased matched case control design. Further, prior to the survey, a check was made to ensure that individuals in the control group did not have any registered IBS diagnosis during the period studied. Another strength is that we used established and validated questionnaires and index like the SF-36, HAD and established specific questions derived from regional and national surveys of welfare and health and standard of living (180). A possible limitation when using diagnoses from medical records, as we have in LIPS, is the dependence on the general practitioner's ability to make the correct diagnosis. However, studies have shown that general practitioners rarely misdiagnose IBS (44,50,51). There could, on the contrary, be a tendency to under-diagnosing these complaints in primary care. Medical records in primary care in Sweden are generally regarded as a reliable source of such kinds of data collection since the primary health care centres have the overall responsibility for the primary health care in a catchment area, and are therefore required to regularly report morbidity patterns based on structured diagnosis. This weakness is the same in the case of most clinical research utilizing data from more than one health care provider (201,202). Another possible limitation could be the use of selfreported data from questionnaires. A well-known phenomenon to take into consideration when using self-reported data is recall-bias, but in general, self-reports are reliable and well established (203).

6.1 Conclusions

- The incidence rate found was 3.4 per 1,000 person-years which increased with age, which was slightly higher than the rate reported in other studies. This increases with age and the overrepresentation of females found is in line with prevalence studies.
- The majority of the patients consulted their GP without an appointment and had abdominal discomfort as sole consulting reason. IBS patients did not appear to be heavy utilisers of primary care and those who attended PHC were treated by their GP without further consultation.
- The strongest predictors for having a follow-up consultation were diagnosed co-morbidity, rectoscopy and laboratory tests ordered.
- IBS patients identified in primary care are significantly affected in their working-life compared to individuals in the general population. Female IBS patients in particular report lower decision latitude at work and they also appear to have a highly impaired psychosocial functioning in their everyday life and impaired HRQOL. Our study also confirms previous findings that anxiety, sleeping disorder and impaired HRQOL might be independently associated with IBS in women.
- Factors associated with IBS diagnosis among females are anxiety as well as family history of IBS and lack of co-determination at work. For males, lack of influence on working pace and a family history of IBS were independent associated with IBS.

6.2 Future research

There is a lack of research in the field of psychosocial working conditions and their causal relationships to functional gastrointestinal disorders. Prospective population-based studies in this area are warranted. Future research might focus on:

- The association between psychosocial working conditions and the risk of FGD.
- The gender perspective of stressful everyday life and risk of IBS.
- Health related quality of life, health care utilization and psychosocial factors among cases with FD and controls.
- The IBS patient satisfaction with the consultation and also this from the GP's perspective.
- Self-reported functional gastrointestinal symptoms and overlapping GI morbidity in the general population.
- Types of co-morbidity found among IBS cases and controls.
- Family history of different types of gastrointestinal disorders and diseases in the general population.
- Prescription of antidepressants and other medication among IBS cases and controls.
- Morbidity and healthcare utilization during follow-up of cases with IBS and controls.
- Characterization of patient with FD in general practice.
- Self-medication and coping with the disease among the IBS patients.
- Laboratory test performed on IBS patients in primary care. What do they predict?
- International comparative studies of how IBS patients are affected in their everyday life in different social and cultural environments.

Summary in Swedish

Bakgrund. Irriterad tarm eller IBS är en funktionell sjukdom i magtarmkanalen som drabbar relativt unga människor. Sjukdomens symptom är antingen kronisk eller uppträder periodvis med magvärk, uppspändhetskänslor i magen, förstoppning och diarré eller perioder med antingen det ena eller andra. IBS är den vanligaste formen av funktionella magtarmbesvär och omkring 10-20 % av befolkningen har dessa besvär. Sjukdomen förekommer i alla samhällen och bland alla socioekonomiska grupper. Trots att sjukdomen inte är livshotande blir det dagliga livet allvarligt påverkat för dem som drabbas. IBS är idag ett underskattad och ofta förbisett folkhälsoproblem i befolkningen. Etiologin bakom sjukdomen IBS är multifaktoriell och behandlingen är oftast fokuserad på att lindra symptomen snarare än att bota sjukdomen. IBS förefaller att drabba kvinnor i betydligt större utsträckning än män. Det har påvisats tydliga samband mellan sjukdomen IBS och en mängd psykosociala förhållanden som psykiska symptom, sömnproblem, sexuella problem och störningar i det sociala livet, på arbetet och nedsatt hälsorelaterad livskvalitet. Sjukdomens symptom kan för den drabbade ofta upplevas som genant och inverkar menligt på både dennes sociala liv och arbetsliv.

Syfte. Studien övergripande syfte var att studera förekomsten av sjukdomen irriterad tarm (IBS) i befolkningen och hur sjukdomen behandlas inom primärvården och vidare sjukdomens inverkan på det dagliga livet för de som drabbats av IBS.

Material och metoder. Föreliggande studie kallas LIPS (*"Linköping IBS Population Study"*) och består av två delar. Del I utgörs av en retrospektiv registerstudie där materialet insamlades från datoriserade medicinska journaler från tre Vårdcentraler i en definierad region. Del II är upplagd som en fall-kontroll studie. De identifierade IBS-fallen från studiens första del utgör fallen, medan deras kontroller var slumpmässigt utvalda från befolkningsregistret i samma geografiska område som fallen. Datainsamlingen i studiens del II baserades på ett frågeformulär som skickades med post till både fall och kontroller. Studien genomfördes i Linköping, en kommun med omkring 135 000 invånare i sydöstra delen av Sverige. De tre utvalda vårdcentralerna har ett upptagningsområde omfattande omkring 40 000 invånare och är ansvariga för praktiskt taget all primärvård till invånarna i sitt respektive geografiska område.

Resultat. För kvinnor var lågt inflytande i planeringen av arbetet och inflytande över arbetstiden liksom mindre möjligheter att lära nya saker i arbetet associerat med IBS risk, även efter att data justerats i en multipel logistiskt regression för tänkbara inverkande faktorer som; mentalt tillstånd, sömnbesvär och självrapporterad hälsa. Kvinnliga IBS patienter hade betydligt lägre hälsorelaterad livskvalitet i alla uppmätta dimensioner jämfört med kvinnliga kontroller liksom lägre livskvalitet jämfört med män med IBS diagnos. I en multivariat analys framkom att följande variabler var oberoende associerade med IBS risk för kvinnor; brist på inflytande i planeringen av arbetet, förekomst av IBS sjukdom i familjen samt självrapporterad ångest och sömnbesvär. I motsvarande analys för män, var bristande inflytande på arbetstempo och förekomst av IBS sjukdom i familjen oberoende associerat till IBS diagnos. Insjuknandefrekvensen av IBS var totalt i denna studie 3.4 fall (95% CI 3.20-3.70) per 1000 personår. För kvinnor var insjuknandefrekvensen 4.6 fall per 1000 personår (95% CI 4.16-4.97) och för män 2.3 fall per 1000 personår (95% CI 2.01-2.59). Den dominerande medicinska läkemedelsförskrivningen för funktionella magtarmbesvär var fiber och bulkmedel, laxeringsmedel liksom syrahämmande medel. De som söker vårdcentralen för sina IBS symptom behandlas som regel av allmänläkaren vid ett vårdtillfälle utan ytterligare konsultationer. Om IBS patienten också hade andra sjukdomar, liksom i de fall man utfört rektoskopi eller olika laboratorietester ökade sannolikheten att IBS patienten skulle få en ytterligare konsultation. I en internationell komparativ analys framkom att kvinnor från Kreta i Grekland med IBS rapporterade särskilt låga värden på livskvalitet vad gällde allmän hälsa och mental hälsa i jämförelse med Svenska kvinnor med IBS diagnos.

Konklusioner: I denna studie framkommer att IBS patienter är betydligt mer drabbade och påverkade i sitt dagliga yrkesliv jämfört med befolkningen i övrigt. Särskilt kvinnliga IBS patienter rapporterar lägre inflytande över sin arbetssituation och att deras psykosociala funktion i det dagliga livet är nedsatt liksom att de har en lägre hälsorelaterad livskvalitet. Faktorer som är associerat med en IBS diagnos bland kvinnor även efter justering för inverkan av andra tänkbara faktorer är självrapporterad ångest, tidigare IBS sjukdom i familjen liksom lågt inflytande i arbetslivet. Insjuknandefrekvensen för IBS var i denna studie 3.4 nya fall per 1000 personår med en generell överrepresentation av kvinnor. IBS-patienter verkar inte vara några storkonsumenter av primärvård.

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