

Per Olav Vandvik

Irritable bowel syndrome in Norway

Studies of prevalence, diagnosis and characteristics
in general practice and in the population

Doctoral thesis
for the degree of doctor medicinae

Trondheim, June 2006

Norwegian University of Science and Technology
Faculty of Medicine
Unit for Applied Clinical Research
Department of Cancer Research and Molecular Medicine
Innlandet Hospital Health Authority, Gjøvik
Department of Medicine



NTNU

Norwegian University of Science and Technology

Doctoral thesis
for the degree of doctor medicinae

Faculty of Medicine
Unit for Applied Clinical Research
Department of Cancer Research and Molecular Medicine
Innlandet Hospital Health Authority, Gjøvik
Department of Medicine

© Per Olav Vandvik

ISBN 82-471-7918-0 (printed version)
ISBN 82-471-7917-2 (electronic version)
ISSN 1503-8181

Doctoral theses at NTNU, 2006:83

Printed by NTNU-trykk

TABLE OF CONTENT

	PAGE
ACKNOWLEDGEMENTS.....	3
LIST OF PUBLICATIONS.....	5
ABBREVIATIONS AND DEFINITIONS	6
GENERAL INTRODUCTION	7
ABDOMINAL COMPLAINTS, ORGANIC DISEASES AND FUNCTIONAL GASTROINTESTINAL DISORDERS	7
WHAT IS IBS, A HISTORICAL VIEW AND THE ROAD TO ROME.....	7
CAUSES AND MECHANISMS IN IBS.....	9
PREVALENCE OF IBS.....	10
DIAGNOSIS OF IBS.....	11
CHARACTERISTICS OF SUBJECTS WITH IBS.....	11
<i>Different viewpoints of IBS.....</i>	<i>12</i>
<i>Comorbidity in subjects with IBS.....</i>	<i>12</i>
TREATMENT OF SUBJECTS WITH IBS.....	12
AIMS OF THE STUDY.....	15
MATERIALS AND METHODS	16
STUDY OF IBS IN GENERAL PRACTICE.....	16
<i>Study design</i>	<i>16</i>
<i>Patients.....</i>	<i>17</i>
<i>General practitioners</i>	<i>18</i>
<i>Measurement</i>	<i>18</i>
<i>Data-collection</i>	<i>19</i>
SURVEY OF IBS IN THE GENERAL POPULATION.....	20
<i>Study design and material.....</i>	<i>20</i>
<i>Measurement</i>	<i>21</i>
DATA ANALYSIS.....	22
ETHICAL ASPECTS.....	22
SUMMARY OF RESULTS.....	23
GENERAL DISCUSSION	26
PREVALENCE OF IBS IN THE GENERAL POPULATION (PAPER IV).....	26
ABDOMINAL COMPLAINTS AND IBS IN GENERAL PRACTICE (PAPER I).....	27
DIAGNOSIS OF IBS IN GENERAL PRACTICE (PAPER II).....	28
CHARACTERISTICS OF SUBJECTS WITH IBS IN THE POPULATION AND IN GENERAL PRACTICE (PAPER III -IV).....	29
COMORBIDITY OF IBS AND ITS IMPLICATIONS (PAPER III AND IV).....	30
METHODOLOGICAL CONSIDERATIONS.....	35
WHAT HAVE WE LEARNED AND WHERE DO WE GO?.....	38
REFERENCES	41
APPENDIX	48
A COMMENT ON SOME COMMONLY USED TERMS AND DEFINITIONS.....	48
SCREENING QUESTIONNAIRE IN THE WAITING ROOM.....	50
ROME II QUESTIONNAIRE FOR IBS TRANSLATED TO NORWEGIAN.....	51
SHC INVENTORY.....	52
PAPERS I-IV	53

ACKNOWLEDGEMENTS

I was lucky to meet Professor Per Farup one morning during spring 2000 in the corridors of Gjøvik Hospital. He wondered whether I was interested in clinical research and would consider a research project regarding patients with Irritable bowel syndrome in general practice. Being a young doctor with two years clinical experience in internal medicine, mostly occupied with patients with chest pain and dyspnoea, one might wonder why Farup succeeded in his request. In fact, I had almost no knowledge about Irritable bowel syndrome at that time. But, I had a particular interest in patients with medically unexplained symptoms and disorders. To my experience, these patients were often handled less successfully than those with well defined organic disease. Five years later, my interest in this group of patients has not diminished.

Clinical research is a challenging discipline and perhaps particularly so in a hospital where research is not considered a part of clinical practice. Again, I am indebted to Per Farup for his great skills in clinical research, and for endless patience, support and firm guidance through the slopes and hills of this thesis. This thesis rests completely on the massive support and encouragement offered by him. In addition, I thank Rolf Slaastad (recently retired head of my hospital department) for great enthusiasm and continuing support which made me dare this journey.

I have been lucky to meet a considerable number of always kind and enthusiastic researchers. Some deserve special acknowledgement: Ingvard Wilhelmsen, Lars Aabakken and Pål Kristensen for being supervisors with invaluable contributions and Hege Randi Eriksen with colleagues in Bergen for sharing their knowledge about subjective health complaints. My work with designing courses in clinical and epidemiological research at the University of Oslo introduced me to other skilled researchers. I must mention the epidemiologist Per Magnus who has taught me that no statistics can replace a clear thought, a well defined research question and proper choice of scientific methods.

Funding of the study has been a challenge since financial support from GlaxoSmithKline was withdrawn autumn 2000 (due to withdrawal of their drug Alosetron for IBS because of adverse events). Nevertheless, they generously funded the general practice study and my salary the first critical year for which I am very grateful. Endless applications for research grants have given mixed results. I thank the following for financial funding: Innlandet Hospital Health authority, Institute for Molecular and Cancer Research-NTNU, Novartis Norway, Research curriculum at the Faculty of Medicine-University of Oslo and the Norwegian Gastroenterology Association.

This thesis was carried out during the probably and hopefully busiest phase of life for my dear family Helene, Anders, Olav and Elida. Maybe the best part of this research project has been the flexibility allowing our family to prosper and enjoy life. Helene: Without you I would not have succeeded and best of luck with your thesis about abdominal complaints in children. To my parents Bodvar and Inger Helene: Thank you for letting me understand what being a true researcher and a good doctor is all about.

LIST OF PUBLICATIONS

The present thesis is based on the papers listed below, referred to in the text by their Roman number in brackets.

- I. Vandvik PO, Kristensen P, Aabakken L, Farup PG. Abdominal complaints in general practice: Diagnoses and characteristics of patients. *Scandinavian Journal of Primary Health Care* 2004;22: 157-162
- II. Vandvik PO, Aabakken L, Farup PG. Diagnosing Irritable Bowel Syndrome: Poor agreement between general practitioners and the Rome II criteria. *Scand J Gastroenterol* 2004; 39:448-453
- III. Vandvik PO, Wilhelmsen I, Ihlebaek C, Farup PG. Comorbidity of Irritable Bowel Syndrome in general practice: a striking feature with clinical implications. *Aliment Pharmacol Ther* 2004; 20: 1195-1203
- IV. Vandvik PO, Lydersen S, Farup PG. Prevalence, comorbidity and impact of Irritable Bowel Syndrome in Norway. In press, *Scand J Gastroenterol* 2006

ABBREVIATIONS AND DEFINITIONS

List of abbreviations

CI	Confidence interval
CBT	Cognitive behaviour therapy
CNS	Central nervous system
ENS	Enteric nervous System
EPQ-10	Eysenck personality questionnaire, 10 items version
FGID	Functional gastrointestinal disorders
FBD	Functional bowel disorders
FD	Functional dyspepsia
GERD	Gastroesophageal reflux disease
GP	General practitioner
IBD	Inflammatory bowel disorder
IBS	Irritable bowel syndrome
NHSS	National health screening service
OR	Odds ratio
SHC	Subjective health complaints
SCL-10	Symptom check list-10 items version
SF-12	Short form-12
UK	United Kingdom
SD	Standard deviation
US	United States of America

Terms and definitions

In the appendix, I comment on the following perhaps confusing terms and definitions:

- ✓ IBS; Disease, disorder or illness? Functional or organic?
- ✓ Aetiology, pathogenesis, causes and mechanisms
- ✓ Comorbidity of IBS, subjective health complaints, somatisation or medically unexplained physical symptoms (MUPS)?
- ✓ Consultation behaviour in IBS: Subjects with IBS, consulters/ non-consulters or patients/ non-patients?

GENERAL INTRODUCTION

Abdominal complaints, organic diseases and functional gastrointestinal disorders

Symptoms from the gastrointestinal tract occur so frequently in humans that it is probably abnormal not to experience symptoms such as heartburn, abdominal pain/ discomfort, bloating, constipation or diarrhoea.¹ Such symptoms do not necessarily represent diagnosable disorders or diseases, nor result in contact with health care. Yet, abdominal complaints constitute a frequent reason for consultation both in general practice and in secondary health care.² Doctors need to correctly diagnose disorders and diseases to provide effective treatment. A correct distinction between organic diseases (within or outside the gastrointestinal tract) and functional gastrointestinal disorders is of particular relevance in this context.

Organic gastrointestinal diseases such as gastroesophageal reflux disease (GERD), peptic ulcer disease, inflammatory bowel disorder, celiac disease, hepatobiliary disease and gastrointestinal cancer are characterised by structural lesions or biochemical abnormalities, which can be identified by additional investigations.

Symptoms of functional gastrointestinal disorders (FGID) are reported by 60%-70% of adults in the community and constitute about half of diagnoses for abdominal complaints in general practice and gastroenterology units.¹⁻⁴ FGID are defined as variable combinations of chronic or recurrent gastrointestinal symptoms attributed to all levels of the gastrointestinal tract that have no structural or biochemical explanation.⁵ To date, 20 different diagnostic entities have been defined, from the oesophagus to the anus. Irritable bowel syndrome (IBS) and functional dyspepsia (FD) are the most frequent FGID and have been the most studied. With regard to IBS, there is an abundant literature on patients with IBS referred to specialists but little is known about the nature of IBS in general practice, where most patients are cared for. Knowledge about the nature of IBS in community subjects and their differences from those who see doctors could increase our understanding of this frequent and for some very troubling disorder. The objective of this thesis was therefore to study the prevalence, diagnosis and characteristics of IBS in general practice and in the general population of Norway. Throughout the work with this thesis I have become increasingly interested in the comorbidity of IBS, which is reflected in paper III and IV.

What is IBS, a historical view and the road to Rome

IBS is a chronic disorder, characterised by abdominal pain/ discomfort associated with defecation or a change in bowel habit, and with features of disordered defecation (Rome II).⁶ Bloating and abdominal distension are typical, together with other supportive symptoms which cumulatively support the diagnosis of IBS (figure 1). Constipation and diarrhoea are the main

forms of bowel disturbances, and the supportive symptoms allow a division into constipation predominant IBS, diarrhoea predominant IBS and alternating IBS. The onset of IBS may occur in childhood or during all stages of adulthood and most will experience a waxing and waning course with combinations of altered bowel habits and great turnover of symptoms.⁷ On long term follow up, most patients with a diagnosis of IBS still have bowel symptoms but there is no increased risk of organic complications or mortality.^{8,9}

Described by Powell in a scientific paper already in 1818, IBS is not a disorder of modern living. Over 150 years ago, the heterogeneity of symptoms puzzled Cumming who wrote “the bowels are at one time constipated, another lax, in the same person...How the disease has two such different symptoms I do not profess to explain”.¹⁰ However, the first systematic look at the syndrome was the classic 1962 paper by Chaudhary and Truelove entitled “the Irritable colon”.¹¹ We now know that more than the colon is involved, hence the modern label the Irritable bowel syndrome, abbreviated IBS. Although IBS is an accepted label in both epidemiological and clinical research, we know little about how IBS is perceived or labelled by its sufferers or by health care providers. In Europe, only a minority of patients are formally diagnosed with IBS or its synonyms.¹² In Norway, other labels such as irritable colon, dyspepsia, gastritis (magekatarr) nervous stomach (nervøs mage), or “abdominal complaints” (mageplager) are probably just as frequently used by patients and doctors. Some authors argue that IBS must be considered a disease, at least when symptoms become persistent and severe.¹³

Irritable bowel syndrome was deemed a diagnosis of exclusion until the Manning criteria were presented in 1978.¹⁴ This first set of symptom based diagnostic criteria for IBS, identifying six symptoms able to discriminate IBS from organic disease, soon became used in epidemiological and clinical studies. New criteria were developed through the Rome working teams, resulting in the Rome I criteria in 1992 and the Rome II criteria in 1999 (figure 1).⁶ The work of the Rome committee, based on available evidence from research and a consensus expert approach, has resulted in a standardisation of entry criteria into clinical studies, allowing investigators to compare their results with greater confidence. The definitions used in this thesis are based on the Rome II consensus. However, the Rome II criteria are to be followed by the Rome III criteria during 2006.

Figure 1: Rome II diagnostic criteria* for IBS

At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:

- Relieved with defecation; and/or
- Onset associated with a change in frequency of stool; and/or
- Onset associated with a change in form (appearance) of stool.

Symptoms that cumulatively support the diagnosis of IBS

- Abnormal stool frequency (for research purposes “abnormal” may be defined as greater than 3 movements per day and less than 3 bowel movements per week);
- Abnormal stool form (lumpy/hard or loose/watery stool);
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation);
- Passage of mucus
- Bloating or feeling of abdominal distension

* In the absence of structural or metabolic abnormalities to explain the symptoms

Causes and mechanisms in IBS

Despite extensive research, little is known about the pathogenesis of IBS and even less of its cause. Over the past thirty years, there has been a pendular movement from considering IBS a psychosomatic condition to a “little understood organic disease”.^{13,15} Although this “organification” of IBS is welcomed by some, IBS is by most considered a “a brain-gut disorder”: The typical cluster of symptoms results from a complex interplay of peripheral, central and environmental factors interacting on the brain-gut axis, and they do so to different degrees across individuals and even for the same individual over time.¹⁶ This interplay involves both motor and sensory dysfunction and is consistent with an up-regulation in neural processing between the gut and the brain.¹⁷ The “brain-gut” theory embraces psychological as well as physical factors and respects the indivisibility of mind and body. It fits comfortably with the biopsychosocial model of disease which is frequently used to conceptualize the pathogenesis of IBS.¹⁸⁻²⁰

Biological factors likely to play a role in IBS include visceral hypersensitivity, infection, inflammation, disturbed motility, abnormal gas production or transit, altered intestinal secretion, abnormal gut flora and food intolerance/ allergy. Visceral hypersensitivity, defined as increased sensitivity to gut stimuli, is the biological factor most strongly associated with symptoms of IBS. Rectal hypersensitivity has been proposed to be a useful marker for IBS, but not all subjects with IBS exhibit sensory thresholds outside the normal range.²¹⁻²³ Furthermore, processing of visceral pain is complex and involves both the Enteric nervous system (ENS) and the Central nervous

system (CNS).²⁴ Emotional states may have important influences on sensitivity, as demonstrated by novel functional brain imaging techniques (functional MRI or PET-scan). For instance, fear of painful stimuli (anticipation) increases visceral hypersensitivity.²⁵ Altered CNS processing of visceral sensations, particularly pain, is demonstrated in patients with IBS. In particular, increased activity of the limbic system and impaired inhibition of pain pathways may contribute to visceral hypersensitivity in IBS.²⁶ With regard to infection, one third of IBS cases develop their symptoms after an infectious gastroenteritis.²⁷ Although this finding suggests an infectious aetiology, psychosocial stressors were the most important predictors of post-infectious IBS in a well designed prospective study.²⁸

Psychosocial factors have been widely studied in IBS. Recent reviews conclude with four general observations: 1) Psychological distress exacerbates symptoms of IBS, and more lifetime and daily stressful life events are reported and are strongly associated with symptom onset and severity, 2) Psychological and psychiatric comorbidity is common in patients with IBS, with 40-90% classifying for mood disorders in specialist health care. Other associated psychological features are personality style (e.g. neuroticism), psychological distress, altered health beliefs, cognitions and coping style. 3) Psychosocial features, such as abuse, stressful life events or psychiatric disorder affect health status and clinical outcome. 4) Psychosocial factors influence which patients consult physicians, which tends to overestimate the true prevalence of psychosocial disturbance.²⁹⁻³¹ Furthermore, psychological profiles in subjects with IBS who do not consult have been found to be identical to the normal population.^{32,33}

These observations have resulted in a prevailing opinion that psychosocial factors are not associated with IBS per se, but have an important role in modulating the illness experience and its clinical outcome.³⁰ However, the evidence is conflicting with two studies having demonstrated a higher prevalence of mood disorder also in subjects with IBS who do not consult.^{34,35}

Prevalence of IBS

IBS is a world wide and highly prevalent phenomenon with a female predominance which appears to affect about a billion adults. The first population survey of functional gut symptoms (1980) found IBS in 14% of adults in Bristol, UK.³⁶ Other studies from around the globe have demonstrated prevalences of IBS between 3% and 65%.⁹ This wide variation in prevalence seems to be more dependent on definitions and criteria used than geographical differences, with the Rome criteria providing the lowest prevalence estimates.^{9,37} In a population based survey of Norwegian adults (Tromsø, 1980), 8% of males and 13% of females reported symptoms

suggestive of IBS (e.g. cramping pain and bloating).³⁸ No studies have formally addressed the prevalence of IBS by the use of well defined criteria in a Norwegian adult population.

Diagnosis of IBS

Diagnosing IBS in clinical practice remains a challenge in the absence of a diagnostic marker. Yet, the importance of a precise diagnosis of IBS is underscored by its high prevalence both in primary and secondary health care. Since no diagnostic test is available, the diagnosis of IBS must be based on symptoms. Two highly different approaches are possible.

The diagnosis by exclusion approach permits the diagnosis only after extensive investigation has excluded all disease that could possibly cause the symptoms. In view of the complexity of IBS, it is understandable that this approach has been adopted by some doctors. However, this approach can result in extensive diagnostic testing which can cause unnecessary inconvenience and harmful complications to the patient and substantial strain on health care budgets. Pulling the diagnosis out of the “bottom drawer” when investigations have repeatedly proved negative is also unlikely to provide proper reassurance.

A positive symptom based approach is recommended as the preferred way of diagnosing IBS.^{6;39} Physicians can diagnose IBS by recognizing certain typical symptoms, checking for alarm symptoms, performing a physical examination, and undertaking individualised diagnostic testing. This approach permits a reliable diagnosis without extensive testing in most cases, and facilitates the explanation and reassurance which are cornerstones in the clinical handling of patients.

Symptom based criteria could facilitate a diagnosis based on symptoms and current guidelines recommend the use of the Rome II criteria.³⁹ However, the diagnostic criteria for IBS were developed primarily for clinical and epidemiological research and they have not been validated in clinical settings. Therefore, we do not know whether the criteria are applicable in clinical practice or whether current knowledge about IBS, based on studies employing strict criteria, can be transferred to patients diagnosed with IBS in clinical practice. Importantly, if data from research are to be applied in clinical practice, diagnoses in research and clinical practice must be comparable or, ideally, identical.⁴⁰

Characteristics of subjects with IBS

There is great variation in the clinical expression of symptoms from mild abdominal symptoms without apparent negative consequences for the individual to severe and disabling symptoms in a subset of patients. Patients with IBS are also characterised by somatic comorbidity, psychosocial problems, reduced quality of life and increased use of health resources.^{30;41;42} Health related quality of life in referred patients with moderate to severe IBS is markedly reduced and at level with

diseases such as heart failure, diabetes mellitus and depression.^{42,43} The burden of illness in IBS has been estimated to be \$1.6-10 billion in direct and \$19.2 billion in indirect costs.^{44,45} Thus, IBS is considered to represent a major burden for the individual patients and the community.

Different viewpoints of IBS

Perceptions about IBS and its characteristics are influenced by the viewpoints of health care providers and researchers. Only half of subjects with IBS consult physicians and less than ten percent of subjects with IBS are referred to specialists.² Consultation behaviour is influenced by demographic factors, symptom severity, psychological factors and organisation of health care.³⁰ Therefore, GPs, gastroenterologists, gynaecologists, surgeons and mental health care providers encounter different populations of patients with IBS. The majority of studies have been performed in subsets of referred patients willing to enter research. These studies have limited external validity and may have resulted in a distorted view on IBS.

Comorbidity in subjects with IBS

An intriguing feature of patients with IBS is that they are about twice as likely as comparison groups to be diagnosed with a variety of other somatic and psychiatric disorders. A recent systematic review of studies mainly performed in referred patients with IBS conclude that somatic disorders such as fibromyalgia, chronic fatigue syndrome, temporomandibular joint disorder and chronic pelvic pain are reported by 14%-35%, gastrointestinal disorders such as functional dyspepsia and GERD by 30%-60% and psychiatric disorders such as mood disorder by 40-90%.⁴¹ In contrast, IBS does not seem to be clearly associated with organic diseases such as cardiovascular disease, diabetes mellitus or other autoimmune diseases. These observations have raised questions whether IBS is part of a functional somatic syndrome and whether the diagnostic entity of IBS could be an artefact of specialisation.⁴⁶ The systematic review has addressed this issue by multivariate analyses and concludes that IBS most likely is a distinct symptomatic entity.⁴¹ However, the strong comorbidity suggests a common feature important to the expression of these disorders, which is most likely psychological. Moreover, the comorbidity of IBS has possible implications for aetiology, diagnosis and treatment and might be important in explaining the observed suffering associated with IBS (see discussion).

Treatment of subjects with IBS

Effective management of IBS presents major challenges. In the absence of a causative mechanism, symptomatic and supportive care can be the only realistic goal. Therefore, an effective doctor-patient interaction is considered crucial in the clinical handling of patients with

IBS.¹³ Given the large variation in patients' symptoms and disability, a graded general treatment approach is recommended.⁶ A confident diagnosis is considered the cornerstone in this approach and could be, through patient reassurance and education, a powerful therapeutic tool in IBS.^{6,47} Identification of psychosocial stressors such as fear of cancer, psychiatric disease or chronic negative stress has a positive effect on the course of IBS and consultation behaviour.⁸ In a Norwegian survey, a large proportion of patients with somatic reasons for consulting GPs reported psychosocial problems which influenced on their health, but less than half of these problems were detected by their GPs.⁴⁸ Patient education by self help guide books has recently been shown to reduce consultations for IBS and perceived symptom severity.^{49,50} Targeted treatment towards specific psychological or biological disturbances can be restricted to the few with severe and disabling symptoms where the general treatment approach and lifestyle interventions offer no significant relief.

Specific therapies for IBS are generally directed at gastrointestinal motor, sensory or central nervous system processing. Both drug and non-drug treatments are available. Dietary advice is also recommended although the evidence of efficacy is sparse.^{47,51-53} Alternative treatment such as acupuncture is probably widely used but the efficacy of such treatment is uncertain.^{54,55}

Drug treatment in IBS has been disappointing and is hampered by side effects. According to systematic reviews and a recent meta-analysis, placebo seems to be the most effective treatment in IBS with a 20-50% placebo response in clinical trials.⁵⁶⁻⁵⁸ Limited therapeutic gains of 15-20% are observed for the few drugs with proven efficacy in subsets of patients with IBS in high-quality randomised trials. These drugs include tricyclic antidepressants in low doses (amitriptylin, desipramine, clomipramine), serotonin agonists (tegaserod) or antagonists (alosetron).⁵⁹⁻⁶¹ Furthermore, Loperamide is effective in relieving diarrhoea and urgency in IBS.⁶² Bulking agents as well as antibiotics and probiotics lack evidence of efficacy in IBS.⁶³ A range of novel drugs targeted at the disturbed sensitivity or motility in IBS are in the pipeline.

Psychological treatment has been widely studied in IBS. As with drug therapies, the effects on IBS symptoms are most often moderate and limited to subgroups of patients.^{64,65} Gut focused hypnotherapy is a particularly effective treatment option in patients with severe IBS. Such psychological treatment has the potential advantage of exerting beneficial effects on more than specific symptoms of IBS. For example, gut focused hypnotherapy also reduces the psychiatric and somatic comorbidity of IBS which might contribute to the observed long lasting beneficial effects on quality of life and use of health resources.^{66,67} The mechanisms by which hypnotherapy works remains to be understood, but recent research suggests that it exerts

physiological effects on colonic motility, visceral hypersensitivity and central processing of painful stimuli from the gut.⁶⁸⁻⁷⁰ Cognitive behaviour therapy (CBT) is another treatment option with additional beneficial effects which has recently been shown effective also in patients with IBS in general practice.⁷¹ A major limitation of hypnotherapy, CBT and other psychological interventions is their demand of considerable resources and their current unavailability in clinical practice.

AIMS OF THE STUDY

The following aims correspond to the four publications in this thesis.

Paper I: To investigate the prevalence of abdominal complaints in general practice and the spectrum of diagnoses made by GPs, and to compare characteristics of patients diagnosed with functional gastrointestinal disorders (FGID) with those diagnosed with organic diseases.

Paper II: To assess the agreement between the GPs' diagnosis of IBS and the diagnosis of IBS according to the Rome II criteria. Furthermore, agreement was assessed for the diagnosis of functional bowel disorders (FBD), which is a generic term for IBS, functional diarrhoea, functional constipation and functional abdominal bloating, to investigate whether a broader definition of bowel disorders altered the agreement. Possible explanatory factors in cases of diagnostic discrepancy for IBS were also explored.

Paper III: To explore characteristics, and in particular to measure comorbid symptoms, in patients with IBS in general practice. Secondly, we aimed to answer the following research question: Do patients with low, intermediate and high levels of somatic comorbidity constitute subgroups with different characteristics, natural course of symptoms and health care seeking behaviour?

Paper IV: To measure the prevalence of IBS in a Norwegian adult population, as defined by the Rome II criteria, and to explore possible differences in characteristics between 1) subjects with IBS and subjects without IBS and 2) IBS consulters and IBS non-consulters, with emphasis on comorbid somatic and psychological symptoms. We specifically hypothesised (post hoc) that the observed associations between IBS and global health, working disability, use of health care and medications were confounded by comorbid symptoms and disorders.

MATERIALS AND METHODS

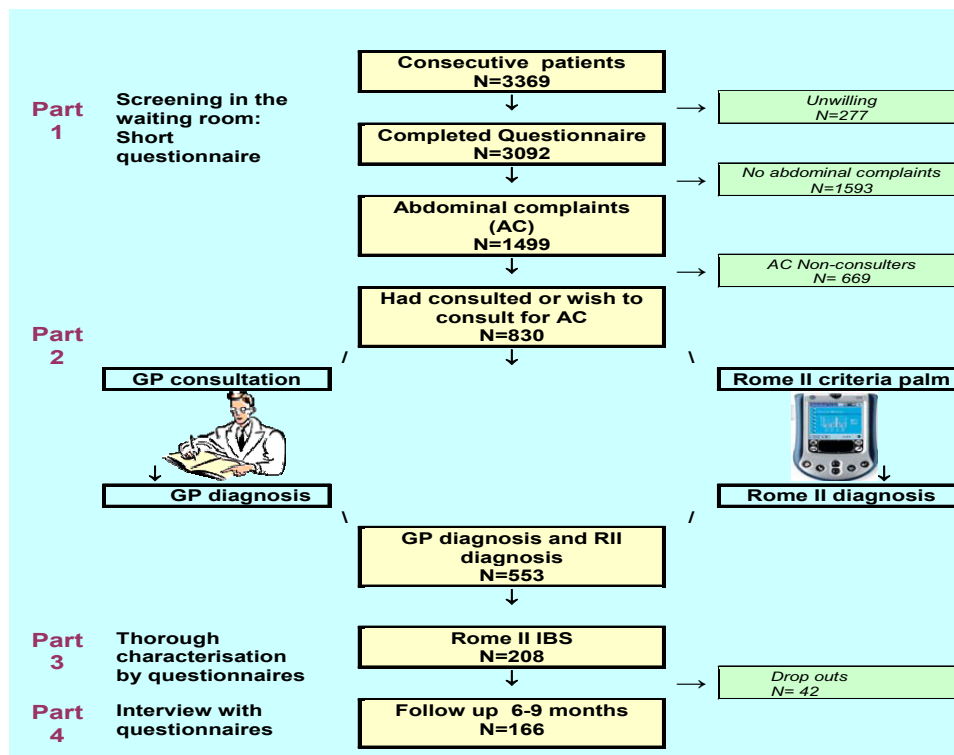
This thesis is based on two cross-sectional studies (of which one included a prospective design) performed during 2001 in the county of Oppland: The “Study of IBS in General Practice” (papers I-III) and the “Survey of IBS in the general population” (paper IV). The materials and methods used in these two studies are presented separately. Methodological limitations are mostly reserved for the general discussion.

Study of IBS in general practice

Study design

This observational prospective multi-centre study was designed to identify and follow up a representative sample of patients with IBS in Norwegian general practice. The study was carried out during 2001 in the western region of Oppland county, which comprises 110 000 inhabitants served by 99 GPs and one hospital (Innlandet Hospital Health Authority, Gjøvik). In Norway, patients must seek health care through their locally assigned GP. The study consisted of four parts (part 1-4) as outlined in figure 2.

Figure 2: Flow chart of the “Study of IBS in general practice”



Part 1 was performed during 10 days of practice for each participating GP. Consecutive patients consulting their GP were asked to complete a brief questionnaire in the waiting room (see appendix). Patients who reported abdominal complaints, for which they wished to consult or already had consulted, were invited to participate in part 2.

In part 2 of the study, patients completed an electronic questionnaire in the waiting room which assessed gastrointestinal symptoms based on the Rome II criteria for FGID. Patients then consulted their GP as planned. After the consultation, the GP reported their diagnoses of the abdominal complaints in the electronic questionnaire, blinded to the patients' answers. The GPs were instructed to manage their patients according to ordinary clinical practice, with no special attention to the study, and they received no formal information about IBS.

In part 3 of the study, patients with Rome II IBS were thoroughly characterised by questionnaires, completed immediately after the consultation.

In part 4 of the study, which had a prospective design, patients with Rome II IBS were invited to a follow up visit with practice staff after 6-9 months. Gastrointestinal symptoms were reported in the electronic questionnaire and use of health resources were assessed from the computerised health centre records. Patients received no specific attention during follow up.

Patients

The target population was adult consulters for abdominal complaints in Norwegian general practice, as opposed to non-consulters. We therefore recruited consecutive patients in selected general practices in the county of Vest-Oppland, with current abdominal complaints for which they had consulted or wished to consult their GP. Informed consent was required in all parts of the study. Exclusion criteria were acute disease requiring immediate attention by the GP, major psychiatric disease or language problems.

The material for paper I consisted of patients included in study part 2, who had consulted or wished to consult for abdominal complaints during the current consultation (main or additional problem).

The material for paper II consisted of patients in study part 2 with complete data in the electronic questionnaire (allowing a Rome II diagnosis) and with a diagnosis for the abdominal complaints made by their GP.

The material for paper III consisted of patients with IBS (Rome II) included in study part 3 and 4. Patients were excluded if the GP, based on all available information, had knowledge of organic disease to explain their symptoms.

The flow of patients in the different parts of the study is outlined in figure 2. More detailed flow charts are given in papers I-III.

General practitioners

Different practices in the county of Oppland were selected to obtain a variety of GPs, practice types and patient profiles. Only practices with available practice staff to perform the data-collection (see below) were invited to participate. In all 26 GPs, working in 9 (out of 12 invited) general practices participated in the study. Four practices had two GPs, three had three GPs, one had four GPs and one had five GPs. Two practices were located in a town with 18000 inhabitants (Gjøvik), seven were located in the countryside. Of the 26 participating GPs (20 M and 6 F, median age 45 years [range 26-68]), 15 were specialists in general practice and the median number of years in general practice was 10 (range 0-20).

Measurement

Patients completed questionnaires which assessed sociodemographic variables (such as adverse life events and working disability), gastrointestinal symptoms, comorbid symptoms, psychological factors and quality of life. GPs completed questionnaires of some patient-characteristics and diagnoses of abdominal complaints in their patients.

Gastrointestinal symptoms within the past three months were reported in the electronic questionnaire. Questions were based on the Rome II criteria (original criteria and the modular questionnaire, respondent form) for the following FGID: Functional heartburn, functional dyspepsia, IBS, functional diarrhoea, functional constipation and functional abdominal bloating.^{5,6} The Rome II criteria assess symptoms over the past year, but we used a three month time frame which is recommended for research purposes. The process of translating the questions into Norwegian included several revisions by experienced gastroenterologists and clinical researchers (see appendix for questions in Norwegian). The electronic questionnaire also assessed duration (more than one year), severity (mild/ moderate/ severe) and frequency (number of days per week) of abdominal pain/discomfort. An abdominal pain/ discomfort score was created by adding the severity and frequency of pain/ discomfort (range 0-12). Two questions assessed the relation between abdominal complaints and stress/ psychological factors (“stress-related symptoms”) and patients’ fear of cancer or other serious disease. GPs reported whether the patient was known from earlier consultations, whether a new consultation for abdominal complaints was scheduled, and the number of visits (0/1-5/>5) for abdominal complaints during the past two years.

A GP diagnosis for the abdominal complaints was reported. If the abdominal complaints had been sufficiently evaluated, the GPs reported their diagnosis by choosing one option from a list of clinically relevant diagnoses within three predefined categories (FGID, organic

gastrointestinal disease or other disease) (see diagnostic options in paper II). In order to evaluate the reliability of the diagnoses, the GPs were asked whether their diagnosis was considered to be verified or not. The GPs were instructed to interpret “verified” meaning that for the FGIDs, they had no evidence of organic disease, and for the organic diseases, that tests had confirmed organic disease.

Comorbid symptoms were assessed by the SHC (Subjective health complaints) inventory (see appendix). This questionnaire consists of 29 questions concerning severity and duration of subjective somatic and psychological health complaints during the preceding 30 days. The SHC does not map attributions or medical diagnoses for the complaints and is a systematic, easy and reliable way to score subjective health complaints.⁷² We created a somatic comorbidity score by adding the scores of 17 items concerning somatic symptoms (see paper III for more details). A reference material for the subjective health complaints assessed in patients with IBS was made available by SHC data from a Norwegian normal population, consisting of 1240 adults (53% females, mean age 41 years) included in a cross-sectional survey in Norway during 1996.⁷³

Psychological factors were assessed by validated questionnaires. Psychological distress was measured by a 10 item version of the Hopkins Symptom Check list (SCL-10) with the intensity of each symptom graded from “not at all” to “extremely”. The average item score is often used as a measure of psychological distress, with a cut off point of 1.85 recommended as a valid predictor of mood disorder (anxiety/ depression).⁷⁴ Health anxiety was measured with the Whitely index which consists of 14 questions, with the intensity of each symptom graded from “not at all” to “a great deal”.⁷⁵ The personality trait neuroticism was measured by ten items in the Eysenck Personality Questionnaire (EPQ-10).⁷⁶

Health related quality of life (HRQoL) was measured by Short form-12 (SF-12), with summary physical (PCS) and mental (MCS) component scores. The SF-12 appears to be a practical alternative to the widely used SF-36, with available population based results in Norway.⁷⁷

Data-collection

Challenges of conducting clinical research in general practice include recruiting representative samples and to avoid distorting the diagnoses or interventions given by occupying time and attention from GPs in their busy clinical settings.⁷⁸ In a meeting with GPs before the study, it became clear that successful data-collection in our study would require other study personnel than the GPs. Therefore, experienced members of the practice staff, who could be released from other duties during the study period, were made responsible for conducting the study in the participating centres. We emphasized detailed information, motivation and education of study personnel and monitoring of data-collection throughout the study period. All participating GP

and practice staff received specific education about the study protocol and practical procedures. Written instructions about the collection of data, including how to complete the electronic questionnaire, were distributed. Monitoring of data-collection was performed every second week by the project leader. At the monitoring visits, data from handheld computers were synchronised into a lap top computer data-base allowing control of insufficient data-entry. Screening lists and Case Report Forms (CRF) were also monitored and checked for missing data. Practice staff contacted the project leader by telephone immediately if technical or other problems occurred.

Data were collected by the above mentioned questionnaires. We chose to use an electronic questionnaire to facilitate data-collection and to permit the Rome II diagnosis to be available immediately after the consultation. This questionnaire was administered on a handheld computer (palm m100®), programmed (Pendragon Forms ®) to classify diagnoses according to the Rome II criteria for FGID. The questions were presented one by one on the screen, requiring an answer before the next question was presented. Patients entered their answers by touching the corresponding buttons on the screen, assisted by practice staff if necessary. Handheld computers have shown to be well accepted by patients, with good data quality and reliability in various clinical settings.⁷⁹

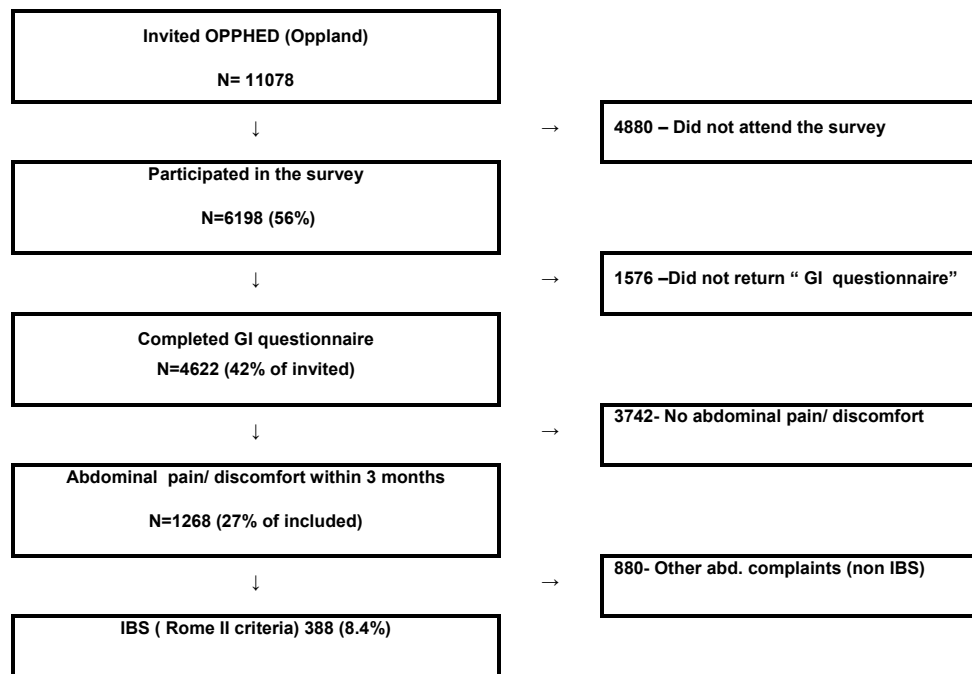
Survey of IBS in the general population

Study design and material

This cross-sectional population based survey was conducted as part of the OPPHED (Oppland and Hedmark) health study in 2001, performed by the National Health Screening Service (NHSS) of Norway. The NHSS have been responsible for similar surveys in different regions of Norway over the past 30 years. The director of the NHSS invited local research groups to participate with separate research projects in the OPPHED study. We participated with our questionnaire regarding IBS.

All men and women in selected age groups (born in 1970, 1960, 1955, 1940 and 1925) in the county of Oppland (180 000 inhabitants) were invited by mail to participate in the OPPHED survey. Subjects completed questionnaires in a bus located nearby their place of living. All subjects attending the survey were invited to answer our additional questionnaire regarding gastrointestinal symptoms. This questionnaire was completed at home and returned to the NHSS by mail. Non-responders received two reminders. Non-responders were compared with responders with regard to age-group and gender (the only available variables in non-responders). Of 11078 adults invited to the OPPHED survey, 4622 (42%) completed our questionnaire and 388 had IBS (8.4%) according to the Rome II criteria (figure 3).

Figure 3: Flow chart of subjects in the “Survey of IBS in the general population”



Measurement

Gastrointestinal symptoms were assessed in a paper questionnaire with 26 items regarding specific bowel symptoms, allowing a Rome II diagnosis for IBS as well as assessment of duration, severity and frequency of abdominal pain/ discomfort and earlier visits to physicians for abdominal complaints. The questions were similar to the questions used in the general practice study, as described above and shown in the appendix.

The original NHSS questionnaire, as well as a translated English version, is available at www.fhi.no/tema/helseundersokelse/oslo/index.html. Questions were asked about socio-demographic variables, including civil status, years of education, working status, current global health status (rated: poor, not quite good, good, very good) somatic and psychiatric comorbidity and use of health resources.

Somatic comorbidity was assessed by six questions regarding musculoskeletal complaints (MSC) within the last four weeks (neck/shoulder, arms/hands, upper back, lower back, hip/legs/feet and other locations) with the intensity of each complaint rated as none, some, severe. A MSC-score was calculated by summarising the scores of each item (range 0-12). Current or earlier presence of fibromyalgia/chronic pain syndrome was also reported.

Psychiatric comorbidity was assessed by the SCL-10 (as described above) and one question regarding presence of earlier or current mental problems for which the subjects had applied help.

Use of health resources was measured as the number of health care visits (0/1-3/ 4 or more) within the last year to general practitioners (GPs), psychiatrists/psychologists, other specialists and alternative health care providers, and the use of medications (analgesics over the counter and antidepressants) during the last month (none/ less than weekly/ weekly but not daily/ daily).

Data analysis

All statistical methods applied were performed in the SPSS statistical package v.10/v.11 and StatXact. Continuous variables were checked for distribution and results were given as mean with standard deviations (SD) or median with range. Categorical variables were presented as proportions, numbers or percentages. Comparisons between groups were performed with bivariate and multivariate analyses. Bivariate analyses were done by Chi-Squared, Mann-Whitney U, Student t or ANOVA tests. Multivariate analyses were performed by stepwise logistic regression, with variables with p-values <0.20 by bivariate analysis entered in the models. Results concerning differences between groups were preferably reported as Odds Ratios (OR) with 95% confidence intervals (CI) for categorical variables and with mean (SD) and p-values for continuous variables. For within group comparisons, we used the Kolmogorov-Smirnov test (or one sample t-test). Analysis of agreement was performed by kappa-statistics (paper II). Age and gender adjusted analyses of prevalence estimates were performed (paper IV). Correlation analyses of normally distributed continuous variables were performed by the Pearson r-test (paper III).

Ethical aspects

The studies were performed according to the Declaration of Helsinki, and approved by the Regional committee for Medical Research Ethics and the Data Inspectorate, Oslo, Norway.

SUMMARY OF RESULTS

Paper I- *Abdominal complaints in general practice: Diagnoses and characteristics of patients*

Abdominal complaints were reported by 1499 of 3092 consecutive patients. 460 patients (15% of screened) wished to consult for their complaints, of which 392 patients were further characterised. GPs diagnosed FGID in 167 (43%), organic disease in 145 (37%) and made no diagnosis in 80 (20%). IBS constituted the most frequent diagnosis (13%), followed by GERD (10%) and no malignant disease was diagnosed. 128 of the 312 diagnosed patients had a verified diagnosis. None of the 26 GPs used symptom based criteria to diagnose the FGID.

Although a common reason for consultation, the abdominal complaints were seldom of severe intensity (15%) and a minority (9%) had consulted their GP for such complaints more than five times during the last two years. Yet, 39% feared that abdominal complaints could be due to cancer/serious disease, independent of a diagnosis of FGID or organic disease.

We could largely not confirm our hypothesis that characteristics of patients could distinguish FGID from organic diseases. Stress-related symptoms was a predictor of a FGID diagnosis (OR 1.95[95% CI: 1.2-3.1]) and weight loss predicted in addition organic disease in the subset with verified diagnoses (OR=2.7[95%CI: 1.1-6.7]). No significant differences between FGID and organic diseases were observed with regard to age, gender, intensity or frequency of abdominal pain/ discomfort, number of visits for abdominal complaints, fear of cancer or alarm symptoms such as blood in stools, nocturnal symptoms or milk intolerance.

Paper II- *Diagnosing Irritable Bowel Syndrome: Poor agreement between general practitioners and the Rome II criteria*

In this study, 553 consecutive patients with abdominal complaints were diagnosed by their GP and had complete data in the Rome II electronic questionnaire. Of these patients, 107 had IBS according to the GPs and 209 had IBS according to the Rome II criteria (agreement 58%, kappa 0.01 [95%CI: -0.06; 0.09]). Similar levels of agreement were found for the diagnosis of FBD (49%, kappa 0.05[95% CI: 0.003; 0.13]). Agreement for the diagnosis of IBS and FBD remained poor in subgroups of patients without organic disease, without reflux or dyspepsia and in patients with a verified diagnosis (45%-58%, kappa -0.02 to 0.13). These subgroup analyses suggest that the poor agreement can not be explained by methodological issues. Unexpectedly, IBS and FBD cases were identified more often by the Rome II criteria than by the GPs in all these groups of patients. In patients with diagnostic discrepancy concerning IBS, stress-related symptoms predicted a diagnosis of IBS made by the GPs only (OR=2.2 [95% CI: 1.1-4.2]). Our findings

imply that current knowledge about IBS based on strict criteria is not necessarily transferable to patients diagnosed with IBS by their GP.

Paper III- *Comorbidity of Irritable Bowel Syndrome in general practice: A striking feature with clinical implications*

In this study, 208 patients with IBS (Rome II) were included and thoroughly characterised. Patients with IBS reported 20 of 22 comorbid symptoms significantly more frequent than a population based reference material of 1240 adults (odds ratios in the range 2-7, $p < 0.001$). Three groups of patients with low ($n=42$), intermediate ($n=100$) and high somatic comorbidity ($n=61$) were identified by a somatic comorbidity score (17 somatic symptoms in the SHC inventory). This score was normally distributed, significantly higher in patients with IBS than in controls (mean 13.0 [SD 8.1] and 5.8 [SD 5.1], $p < 0.001$) and correlated with psychological distress (SCL-10) ($R=0.46$, $r^2=0.22$, $p < 0.001$). Patients with high somatic comorbidity were characterized by high levels of psychological distress (mood disorder present in 63%), health anxiety, neuroticism and adverse life events as well as reduced quality of life and increased use of health resources, when compared to those with low and intermediate somatic comorbidity ($p < 0.05$ for all comparisons). The intensity of abdominal pain/ discomfort did not differ significantly between groups. Some other characteristics of patients with IBS can be noted: 13% of patients with IBS reported severe abdominal pain, 20% reported abdominal pain/ discomfort more frequent than five days per week and 7% had consulted for IBS more than five times within two years. Nine out of ten patients reported presence of abdominal pain/ discomfort after 6-9 months. The mean number of visits to GPs in the follow up period was 3.7 (SD 2.9) but only 20% had consulted their GP for IBS.

Paper IV- *Prevalence, comorbidity and impact of Irritable Bowel Syndrome in Norway*

388 of 4622 included subjects (8.4% [95%CI: 7.6-9.4%]) had IBS according to the Rome II criteria. The prevalence of IBS was higher in women and decreased with age. The proportion who had consulted for IBS (IBS consulters) increased with age, from 51% among 30 year olds to 79% in 75 year olds ($p=0.05$). IBS was associated with musculoskeletal complaints (OR= 2.4-3.4 for six different items), fibromyalgia (OR=3.6 [95% CI: 2.7-4.8]), mood disorder (OR=3.3 [95%CI: 2.6-4.3]), reduced global health (OR=2.6 [95%CI: 2.1-3.2]), working disability (OR=1.6 [95%CI: 1.2-2.1]), more frequent health care visits (OR 1.7-2.3) and use of medications (OR=2.3). When controlling for comorbidity, only reduced global health (OR=1.5[95%CI: 1.1-2.0]) and use of alternative health care (OR=1.7[95%CI: 1.3-2.4]) remained associated with IBS.

The severity of abdominal pain/ discomfort independently predicted earlier consultations for IBS (OR= 1.3[95%CI: 1.2-1.5]). This first formal community survey of IBS in Norway demonstrates that IBS is a common chronic disorder which leads to consultations for most in the long run. Somatic and psychiatric comorbidity are common features of IBS which play a main role in explaining the reduced health and increased use of health resources reported by subjects with IBS.

GENERAL DISCUSSION

Prevalence of IBS in the general population (paper IV)

IBS is truly a common disorder with an overall prevalence of 8.4% (95%CI: 7.6-9.2) in the county of Oppland, according to the strict Rome II criteria. The observed prevalence and its' age dependent decrease as well as the female predominance harmonise with findings from other countries.^{1,12,80,81} Prevalence estimates of Rome II IBS do however vary, with the lowest from Spain (2.9%) to the highest in Canada (12.1%) and intermediate estimates from eight European countries (9.6%), Finland(5.1%) and Australia (6.9%).^{3,12,37,82,83} The observed differences in Rome II prevalence estimates could represent geographical variations as suggested by the European study, or methodological aspects related to sampling procedures or translation of criteria.³ A methodological problem with the European study is that the reported prevalence rates comprised two populations of IBS subjects, those with a clinical diagnosis of IBS and those with IBS according to Rome II criteria. The problem with this approach is that a clinical diagnosis of IBS is not necessarily in agreement with a criteria based diagnosis, as shown in our general practice study (paper II).

Although widely recommended for epidemiological surveys of IBS, the Rome II criteria are not perfect. Some argue that they are too strict, supported by higher prevalence estimates obtained by the Rome I criteria and Manning criteria.^{82,83} This discrepancy highlights a major problem with defining disorders such as IBS. The intensity and frequency of IBS symptoms probably display normal distributions in the population which makes a meaningful cut-off point difficult to determine. Moreover, the selection of symptoms used to identify IBS also impact on prevalence estimates. This can be exemplified by the former population based survey of IBS in Norway (adults aged 20-55 years, Tromsø, 1980) which reported symptoms suggestive of IBS in 8% of men and 13% of women.³⁸ Since these estimates are strikingly similar to our age and gender adjusted prevalence estimates (see figure 1, paper IV) one could infer that the prevalence of IBS in Norway has remained unchanged since 1980. However, criteria used to identify IBS differ in these two surveys. In the Tromsø survey, the two questions used to diagnose IBS were as follows: "Do you often suffer from cramping abdominal pain?" and "Are you often bothered by bloating and abdominal rumbling?". All diagnostic criteria for IBS, including the Rome II criteria, require abdominal pain/ discomfort associated with a disturbed bowel habit (e.g. diarrhoea or constipation). The lacking assessment of a disturbed bowel habit, which is a main symptom feature in IBS, is a major limitation of the former Norwegian survey.

Most scientific papers and textbooks about IBS state that only a minority of subjects with IBS consult physicians.^{1,34} We found that more than half of subjects with IBS had consulted a physician for their abdominal complaints, increasing to 79% in the 75 year olds. Similar findings has been reported from Australia and contrasts with the general assumption that a minority will consult.³⁴ Whether our findings reflect geographical differences or a general increase in consultations for IBS remains unanswered. Differences in health care systems could be a major determinant of consultations for IBS. In Norway, the public health care system has high accessibility and low costs for the patient which might lower the threshold for consulting.

Abdominal complaints and IBS in general practice (paper I)

We confirm that patients presenting with abdominal complaints constitute a significant workload for GPs.^{2,85} Our finding that 15% of patients attending their GP consulted or wished to consult for these symptoms is higher than what has been reported from the UK.² In our study, abdominal complaints were not necessarily primary reasons for consultation which could explain some of the discrepancy with the UK study. Nevertheless, we demonstrate that many patients in general practice have a need to consult for abdominal complaints, supported by our finding that most adults with IBS in the population will consult in the long run (paper IV).

In those who consult for abdominal complaints, GPs need to correctly diagnose the various disorders and diseases to provide proper treatment. As reported by others, GPs diagnosed a wide range of non-malignant disorders and diseases with the FGID constituting half of diagnoses and IBS being the most frequent diagnosis.² The absence of malignant disease and the one percent with inflammatory bowel disorder in our study demonstrate what challenge it is for GPs to select patients for investigations such as colonoscopy. GPs might expect to see one new case and eight prevalent cases of IBS per week and one new case of colorectal cancer per year.^{2,86} In the UK study by Thompson, few patients were referred to specialists and GPs used other characteristics (e.g. polysymptomatic, unexplained symptoms and long lasting abdominal complaints) to separate FGID from organic diseases. In our study, a distinction between FGID and organic disease based on characteristics of patients proved difficult. Although stress-related symptoms predicted a GP diagnosis of FGID, the clinical significance of this finding is questionable in particular with regard to exclusion of organic disease (as discussed in paper I). A weakness of our study is the limited selection of patient characteristics which did not include a thorough characterisation of abdominal symptoms. Guidelines suggest that identification of the typical abdominal symptoms within the various FGID syndromes is the key to a correct and confident diagnosis.^{6,39} We do not know to what extent GPs use such characteristics in their daily

practice, but the observed poor agreement in the diagnosis of IBS between GPs and Rome II criteria (as shown in paper II and discussed below) does not support that GPs strictly rely on these characteristics in the distinction between FGID and organic disease.

Symptoms of colorectal cancer, celiac disease and inflammatory bowel disease (IBD) might mimic symptoms of IBS. In this context, alarm symptoms are recommended to identify candidates for further diagnostic evaluation.³⁹ However, most studies are based on referred patients and there is a lack of evidence with regard to the validity of alarm symptoms in general practice. We demonstrate that blood in the stools, abdominal complaints during night-time and intolerance to milk are reported as frequently by patients diagnosed with FGID as by patients diagnosed with organic diseases. The only alarm symptom which predicted organic disease was weight loss. However, this finding was only statistically significant in the subset with a verified diagnosis. A weakness of our study is the perhaps inaccurate distinction between FGID and organic disease, since different diseases have specific alarm symptoms attached to them. It has been suggested that questionnaires are suitable tools for assessment of alarm symptoms.⁸⁷ We propose that a detailed assessment by an experienced doctor is more valuable. Undertaking validity studies of alarm symptoms in general practice is a huge task but should nevertheless be performed to clarify this issue.

Diagnosis of IBS in general practice (paper II)

Although most patients with IBS are handled by their GP without referral to specialists, little is known about how GPs diagnose IBS. In the UK, GPs say they diagnose IBS with reasonable confidence and less difficulty than other common, painful disorders.⁸⁸ In the US, GPs were found to lack knowledge about the typical symptoms of IBS.⁸⁹ Moreover, in the large European survey, only a minority of IBS consulters had been formally diagnosed with IBS with significant differences between countries.¹² Our study provides further evidence that GPs are unfamiliar with diagnostic criteria for IBS, such as the Rome II criteria.²⁹⁰ We therefore explored whether GPs and Rome II criteria agreed on the diagnosis of IBS in a representative sample of patients with abdominal complaints.

Unexpectedly, we found poor agreement in the diagnosis of IBS between GPs and the Rome II criteria. Our finding is supported by others and implies that GPs and symptom based criteria identify different groups of patients with IBS.⁹¹ Importantly, current knowledge about IBS based on studies of patients who fulfil diagnostic criteria can not be transferred to patients diagnosed with IBS in general practice. This includes knowledge concerning characteristics of patients and efficacy of treatment.

Another unexpected finding was that the Rome II criteria identified nearly twice as many cases with IBS than did the GPs. The Rome II criteria have been criticized for being too strict for clinical practice.⁸³ We postulate that the Rome II criteria are more capable of identifying the typical symptoms of IBS than GPs, supported by the extensive body of research underlying the development of the criteria.⁶

If GPs lack knowledge about the typical symptoms of IBS, how can they succeed with the recommended symptom based approach? In this context, acquisition of such knowledge could represent the greatest challenge to overcome for physicians in general, and for GPs in particular. A fact easily forgotten by specialists is that GPs encounter the whole spectrum of human disorder and disease in their practices. This poses a restriction on how much we can expect GPs to know about IBS. Another issue is to what extent GPs consider a positive diagnosis of IBS important. As with other medically unexplained physical symptoms, little time is probably devoted to IBS in pre- and post-graduate medical education in Norway.⁹² Yet, since GPs diagnose and treat most patients without referral, they need to learn more about IBS if to succeed with a positive symptom based strategy. We also need to learn more about how GPs diagnose IBS.^{2,88}

The role of diagnostic criteria for IBS in clinical practice remains unclear. Apart from being valid, the criteria need to be applicable in busy clinical settings. The Rome II criteria are primarily developed for research purposes and might be too complicated and time consuming in clinical practice.⁴⁰ The Rome II committee offers no recommendations as to how the criteria should be applied in busy clinical practices.⁵ While criteria provide a platform for a positive IBS diagnosis, the clinical diagnostic process includes a complex mental search for structural disease. Therefore, questionnaires in clinical practice should probably be different from those employed in surveys or trials. It also remains unclear which criteria perform best in clinical practice. A Swedish group has evaluated a simple questionnaire for IBS which shows satisfactory agreement with Rome criteria.⁹³ Hopefully, the Rome III criteria to be published in 2006 will further clarify the role of diagnostic criteria in clinical practice. So far, GPs have not participated in the development of diagnostic criteria for IBS and they have not participated in the Rome III process. It therefore remains to be seen whether these criteria will be tailored to fit in a general practice setting.

Characteristics of subjects with IBS in the population and in general practice (paper III and IV)

Since most attention has been given to patients with IBS referred to specialists, our studies of subjects with IBS who do not consult and of patients seen by GPs provide a broader picture. The

overall impression is that most subjects with IBS have longstanding abdominal complaints of mild to moderate intensity which seldom disrupts daily activities. Although most will consult for symptoms of IBS in the long run, few had consulted their GP frequently for abdominal complaints. We confirm that symptom severity is a predictor for healthcare seeking in IBS (paper IV).³⁰ In general practice, the natural course of IBS was remarkably stable in the short term but less is known about the natural course of IBS in the long term.⁷ In the population based survey, we observed a male predominance of diarrhoea symptoms and female predominance of constipation. Similar patterns have been demonstrated in IBS consulters.⁹⁴⁻⁹⁶

We also found that IBS sufferers in the general population and in general practice were characterized by reduced global health, working ability and increased use of health care resources. In line with what is generally believed and published about IBS, we could have concluded that IBS leads to reduced quality of life and increased use of health resources.^{42,44} Such causal inferences are however vulnerable for confounding effects of unmeasured characteristics. Interestingly, patients consulted their GPs nearly four times during the following up period but only 20% had consulted for IBS. Our assessment of comorbid symptoms and disorders in IBS revealed a striking feature not to be overlooked.

Comorbidity of IBS and its implications (paper III and IV)

Prevalence

Although described twenty years ago as a common feature in IBS, comorbid symptoms and disorders are seldom taken into account in clinical or epidemiological research or in aetiological models to explain IBS.^{41,97} Again, most studies are based on referred patients. We provide novel evidence that somatic and psychiatric comorbidity is associated with IBS per se, and not merely a feature of its consulters.

In the general population and in general practice, the odds for reporting a range of somatic and psychiatric comorbid symptoms and disorders were two to seven times higher in subjects with IBS than in subjects without IBS. To give the reader an example of what the observed levels of somatic comorbidity means, the average patient with IBS in general practice reported severe intensity of headache, low back pain and dizziness and moderate intensity of neck pain and sleep problems. Two other studies of IBS in general practice support our findings.^{91,98} Patients with IBS in general practice also frequently reported comorbid gastrointestinal disorders such as heartburn and dyspepsia, in line with what has been found in referred patients.⁴¹

With regard to psychiatric comorbidity, mood disorder (as measured by the SCL-10) was reported by 38% of patients with IBS in general practice, by 25% of community subjects with

IBS and by 9 % of adults without IBS. The odds for reporting mood disorder was three times higher in subjects with IBS than in subjects without IBS. Our finding is supported by others and contrasts with the general assumption that non-consulters with IBS display similar psychological profiles as subjects without IBS.^{12;34;35;35} In a brain-gut disorder such as IBS, it should however not be surprising that psychology interplays with biology.

It is indeed common to experience somatic symptoms also in adults without IBS. In the Norwegian survey used as a reference material by us, headache was reported by 51% and low back pain by 40% of adults (paper III). Musculoskeletal symptoms along with mental disorders constitute the most frequent reasons for sick leave and disability pension in Norway, by far more frequent than symptoms of IBS.^{99;100} A reasonable question is what bothers patients with IBS the most: Their abdominal complaints or their comorbid symptoms and disorders?

Impact of comorbidity

We largely confirmed our hypothesis that the comorbidity of IBS confounds associations between IBS and reduced health and increased use of health resources. Our hypothesis emerged from the picture provided by our division of patients in general practice with different levels of somatic comorbidity (paper III). Patients with IBS with few or none somatic comorbid symptoms reported apparently normal quality of life (SF-12), infrequent use of health resources and mood disorder at level with the general population in Norway. Those with IBS and excessive somatic comorbidity were characterised by markedly reduced quality of life, high levels of mood disorder (present in 61%), neuroticism, health anxiety, adverse life events and more frequent GP visits in the follow up period. Contrary to what we expected, the severity of abdominal pain/discomfort did not differ significantly between patients with different levels of somatic comorbidity.

These observations made us specifically address the possible confounding effects of somatic and psychiatric comorbidity in IBS by multivariate analyses in the population based survey (paper IV). As expected, presence of fibromyalgia and mood disorder contributed to and was more important in explaining the reduced global health reported by subjects with IBS. Furthermore, the comorbidity solely explained the reduced working ability and increased use of health resources, except use of alternative health care. The increased use of alternative health care associated with IBS could imply insufficient public health care for this group of patients. Unfortunately, alternative treatment is costly to the patient and lacks documentation of efficacy.⁵⁵

An increasing number of studies support that much of the suffering hitherto associated with IBS can be explained by comorbid symptoms and disorders.^{33;101-105} We conclude that the

comorbidity of IBS should be taken into account as a possible confounder in future attempts to measure the impact of IBS. Our results would have been strengthened by more comprehensive measurement of the most frequent comorbid disorders associated with IBS, severity of IBS and disease specific quality of life. With regard to the severity of IBS, a recent review suggests that it should be considered a multidimensional concept, not fully explained by intensity of gastrointestinal symptoms.¹⁰⁴ The multiple components to be considered are health related quality of life, psychosocial factors, consultation behaviour and burden of illness. Interestingly, we provide evidence that the comorbidity of IBS is associated with all these features. We suggest that the comorbidity of IBS, which by definition is a co-existing phenomenon, should be assessed in addition to the multidimensional components of IBS severity and adjusted for in attempts to measure the impact of IBS.

Implications for aetiology and treatment

The strong association between IBS and somatic comorbid disorders could help us with some of the greatest challenges in interpreting research on the nature and treatment of IBS. First, it would help explain why all of the specific and measurable characteristics of IBS patients, whether autonomous dysfunction, motility disturbance, or visceral hypersensitivity are absent in a substantial proportion of patients. Second, it would explain to some degree why most efforts to treat IBS, whether pharmacologic or psychological, benefit only about one half of the patients receiving the intervention.⁴¹

With regard to gastrointestinal comorbidity, the substantial overlap between IBS, functional dyspepsia and GERD challenges the current paradigm that functional GI disorders represent multiple discreet entities.^{105;106} The most likely explanation for this overlap is shared pathophysiological mechanisms such as visceral hypersensitivity and motility abnormalities.⁴¹

With regard to somatic and psychiatric comorbidity in IBS, the aetiological implications are not straightforward. Hitherto, the aetiology of IBS has most often been conceptualised in a biopsychosocial model which suggests that (1) many factors or influences contribute to symptom development, (2) no one of these factors are necessary to the development of the disorder, and (3) these factors interact in different combinations. Interestingly, this multidimensional model includes psychiatric comorbidity as a psychological factor but excludes somatic comorbidity. This issue is addressed in the systematic review of comorbidity in IBS and several proposed hypotheses are discussed (diagnostic ambiguity, neuroendocrine-immune, somatisation and the biopsychosocial model).⁴¹ Based on available evidence, the authors put forward a “dual aetiology hypothesis”, recently renamed “the heterogeneity hypothesis”: The IBS diagnosis is applied to a

heterogeneous group of patients, some of whom have a predominantly psychological aetiology, whereas others have a predominantly biological aetiology. The presence of multiple somatic comorbid disorders is a marker for psychological influences on aetiology. This somatisation trait could be the result of genetic factors, early life events, model learning or sensitisation mechanisms at different levels of the ENS and CNS. Accordingly, those with IBS without somatic comorbidity are more likely to have a predominantly biological aetiology. End organ (e.g. gut) dysfunction caused by altered neurotransmission, infection, inflammation or visceral hypersensitivity could play a major role for IBS symptoms in these patients.

To our knowledge we were the first to test “the heterogeneity hypothesis” in patients with IBS (paper III). As described above, subgroups of patients with low, intermediate and high levels of somatic comorbidity clearly differed with regard to psychological problems, adverse life events, quality of life and use of health care. Moreover, a significant correlation was found between the number and intensity of comorbid somatic symptoms and psychological distress. Our findings lend support to the hypothesis, and suggest that subgroups of patients with different characteristics and needs of treatment can be identified by assessment of somatic comorbid symptoms.

However, there are some important limitations with this hypothesis. First, somatic comorbid symptoms represent a continuum which makes it difficult to separate patients with low and high levels of comorbidity in clinical practice. Accordingly, most patients reported intermediate levels of comorbidity, and displayed characteristics in between those with low and high comorbidity. Second, in a heterogeneous and multifactorial brain-gut disorder such as IBS, the hypothesis is likely to be an oversimplification. Indeed, the term “dual aetiology” could easily be misinterpreted by biomedically oriented physicians and endanger the recommended holistic approach in IBS. Physicians need to evaluate each patient individually both with regard to biological and psychosocial factors to provide a general treatment approach. As pointed out by the authors, it is not the intention to label patients with either a psychological or biological aetiology, rather to point out a predominance of aetiological factors in subgroups of patients.⁴¹ The term “heterogeneity hypothesis” is therefore more appropriate and is now used by Whitehead and his research group (personal communication 2005).

It is reasonable that patients with excessive somatic comorbidity will need different treatment than patients without such comorbidity. Moreover, the suffering subset with IBS and excessive somatic comorbidity in our general practice study seems to be in particular need of treatment, given their poor quality of life, working disability and increased use of health resources. In these patients, psychological interventions such as gut specific hypnotherapy,

cognitive behavioural therapy or tricyclic antidepressants could be effective treatment options. The long lasting effects on symptoms of IBS, comorbidity and quality of life by hypnotherapy are promising in this context.⁶⁷ Less promising is the fact that gut directed hypnotherapy remains unavailable in Norway 20 years after it was proven effective in patients with IBS.⁶⁶ Tricyclic antidepressants are probably more widely used by patients with IBS, but adverse effects could hamper their use in these patients.⁵⁹

In those with IBS and low somatic comorbidity (e.g. at level with the general population), targeted treatment towards specific symptoms of IBS could prove efficacious. How many of these patients who will want or need specific treatment can be questioned, given their apparently normal quality of life and limited use of health resources. This observation is of particular relevance in times when a range of new drugs targeted towards biological factors in IBS are in the pipeline.

We conclude that the comorbidity of IBS has implications for aetiology and treatment and that the “heterogeneity hypothesis” is one possible way to conceptualise this striking feature: It might be more productive to look for subgroups of patients who fit a particular pathophysiological mechanism or who respond to a specific treatment, rather than assuming that one aetiology and one treatment must characterise all patients.⁴¹ The hypothesis needs to be supported by research, with for instance randomised controlled trials of specific interventions in the proposed subsets of patients.

Assessment of comorbidity: Useful in clinical practice?

We were impressed by the fact that patients with IBS in general practice reported 20 of 22 symptoms more frequent than controls (paper III). However, GPs are not particularly impressed when I tell them about the aches, pains and psychological problems which characterise their patients with IBS: “Tell us something we don’t know!” is the classical reply. Nevertheless, it could be questioned whether physicians are able to capture the panorama of health complaints in clinical encounters with these patients. In this context, structured assessment of comorbidity could prove useful in particular for GPs responsible for general care of their patients, regardless of what organ system the symptoms are attached to. Such assessment could also be relevant for gastroenterologists who encounter patients with IBS and even higher levels of somatic and psychiatric comorbidity.⁴¹ To my experience, some of the most suffering patients with IBS attending our gastroenterology outpatient clinic have a lot more to worry about than their irritable bowel.¹⁰⁷ Identification of excessive somatic comorbidity in these patients could prevent vicious circles with repeated diagnostic evaluations by a diversity of specialists and facilitate

identification of the above mentioned subgroups with different needs of treatment. It has also been suggested that comorbid symptoms can serve as additional symptoms to cumulatively support the diagnosis of IBS.¹⁰⁸ Although GPs probably use these features in their diagnostic evaluation of patients with IBS, comorbid symptoms or disorders are not yet included in diagnostic criteria for IBS.²

Structured assessment of comorbidity could be performed by questionnaires such as the SHC inventory or questionnaires specifically developed to assess comorbid somatic symptoms and disorders in IBS. The usefulness of such assessment in clinical practice remains to be determined.

Methodological considerations

Sources of random and systematic error

In clinical and epidemiological research, random error can be handled by statistical methods. On the contrary, systematic errors such as selection bias, information bias and confounding can best be controlled for by proper study design and balanced interpretation of results.

With regard to random error, calculation of sample size will reduce the possibility of type I and II error. A limitation of our studies is our rough estimates of sample size. In the general practice study, we aimed to screen 4000 consecutive patients to identify a representative sample with abdominal complaints and IBS. This calculation was mainly based on an assumed prevalence of IBS (Rome II) at 5%. 3092 patients were screened of which 460 consulted for abdominal complaints (paper I), 553 were diagnosed by their GP and the Rome II criteria (paper II) and 208 had IBS according to Rome II criteria (paper III). The risk for type II error is probably largest in the comparison of characteristics between patients diagnosed with FGID and organic disease, as discussed in paper I. Random error is probably less likely in paper II-IV. The statistical methods used should control for other types of random error.

Selection bias

In cross sectional studies, sampling of representative study populations is crucial. The external validity of our findings depends primarily on whether adults both in general practice and in the general population of Oppland county (who constituted the population frame) systematically differ from the population of Norway at whole (target population), and whether those who participated in our studies (study population) systematically differ from those not included.

In the general practice study, we lost patients at each step of the study (see flow charts paper I-III and page x). We can not determine whether non-responders systematically differ from responders. Yet, it is reassuring that 92% of consecutive consulting patients answered the first

questionnaire and 88% of patients with abdominal complaints (for which they had consulted or wished to consult) satisfactorily completed the electronic questionnaire. Likewise, 85% of eligible patients were included in the first study (paper I), 88% of eligible patients were included in the second study (paper II) and 75% of eligible patients with Rome II IBS were included in the third study (paper III). In the third study, the majority of patients excluded at the first visit had organic disease to explain their symptoms of IBS. Patients lost to follow up did not differ with regard to the assessed characteristics at baseline. The possibility of selection bias should therefore not seriously threaten the validity of our findings.

In the population based survey of IBS, the fact that only 42% of invited subjects were included opens up for selection bias. As discussed in paper IV, responders differed with regard to age and gender. Since prevalence estimates are more vulnerable for selection bias than measures of association, we provided gender and age adjusted estimates for the prevalence of IBS. A study of non-responders in the Oslo Health study, which had many similarities with our study with regard to design, measurement and response rate (46%), no evidence of major systematic errors was found.¹⁰⁹ Still, we can not exclude that our study population differs from the population frame. This threatens the external validity of our findings as does the fact that inhabitants in Oppland might differ from the population of Norway in features associated with IBS. For instance, according to national data (www.ssb.no), the average age is higher in Oppland. Since IBS is most prevalent in young adults, the overall prevalence of IBS could be higher in Norway than what we observed in Oppland county.

Information bias

Measurement of gastrointestinal symptoms and other characteristics with questionnaires completed by patients could introduce information error. Although we used formally validated questionnaires to a large extent, this was not the case with the Rome II criteria for IBS. Our use of the electronic questionnaire (see paper I and II) made it necessary to perform a modified translation, based on the original criteria and the Rome II modular questionnaire.⁵ Although the Rome II modular questionnaire has been developed for clinical investigations, it has not been formally validated and we found it of limited value, supported by a recent survey.³ Moreover, we used a three month time frame for assessment of symptoms to reduce recall bias, as recommended by the Rome II committee. The Rome II criteria demand symptoms present for more than three months within the last year to qualify for a diagnosis of IBS. We might therefore have underestimated the prevalence of IBS in the population based survey. Concurrently, prevalence estimates might have been falsely inflated in this survey since some subjects with

Rome II IBS have organic diseases to explain their symptoms. These issues are discussed in paper IV.

We assessed mood disorder with the SCL-10, which performs almost as well as the full version (SCL-25, correlation coefficient 0.97).⁷⁴ However, the literature suggests that only 50-60% of the “cases” identified by these instruments qualify for one or more mental disorders in clinical interviews.¹¹⁰ Adverse life events were reported by patients in the general practice study. Although perhaps indicators of chronic life stress which are important features in IBS, we placed little emphasis on these measures since structured interviews of life event stress have been shown to be more reliable in this context.^{31;111;112}

With regard to the comorbidity of IBS, most studies to date have focused on the presence of disorders such as fibromyalgia and chronic fatigue syndrome in selected patient groups.⁴¹ We primarily assessed comorbid symptoms in our studies, which could be less troublesome with regard to information error than measurement of diagnosed comorbid disorders. Symptoms of fibromyalgia and chronic fatigue syndrome sometimes overlap and different criteria have been used which make comparisons difficult.⁴¹ Accordingly, the self reported prevalence of fibromyalgia in our population based survey should be interpreted with caution. Nevertheless, our results would have been strengthened by the use of validated questionnaires for specific comorbid symptoms and disorders in IBS.

Confounding

A simple definition of confounding would be the confusion, or mixing, of effects: this definition implies that the effect of exposure is mixed together with the effect of another variable, leading to bias. In this thesis, we place much emphasis on the confounding effect of comorbidity in IBS. Nevertheless, our studies of subjects with IBS and their characteristics are vulnerable for confounding effects of other unmeasured factors with possible effects on the reported associations. Moreover, cross-sectional studies can at best demonstrate associations. Further causal relations must be left to studies with proper designs (e.g. observational analytic designs). In paper III and IV the possibility of confounding is discussed.

WHAT HAVE WE LEARNED AND WHERE DO WE GO?

I have now spent five years increasing my knowledge about IBS. A major lesson for me is how much we do not understand about this disorder. Nevertheless, we have learned that:

1. IBS afflicts 8% of adults in a Norwegian general population (according to the Rome II criteria) with a female predominance and an age dependent decrease in prevalence. In such a highly prevalent chronic disorder which leads to consultations with physicians for the majority in the long run, optimal diagnosis and treatment should be of high priority.
2. Abdominal complaints represent a significant workload in general practice, with 15% of patients attending their GP reporting abdominal complaints for which they wish to consult. FGID are diagnosed in half of these patients and IBS is the most common diagnosis made by GPs. In our study, a correct distinction between FGID and organic diseases based on characteristics of patients proved difficult. Since patients with FGID require different investigations and treatment than patients with organic diseases, this distinction is of importance and could be facilitated by identification of the typical symptoms of FGID.
3. GPs are unfamiliar with symptom-based diagnostic criteria for IBS and the agreement in the diagnosis of IBS between GPs and Rome II criteria was unexpectedly poor. Since most patients with IBS are managed by GPs, the external validity of studies using these criteria is questionable. The Rome II criteria, by many considered too strict for clinical practice, identified nearly twice as many patients with IBS than did the GPs. This implies that GPs lack the detailed knowledge of the typical symptoms of IBS needed to provide a confident diagnosis. The validity and applicability of the Rome II criteria in clinical practice remains unanswered.
4. Somatic and psychiatric comorbidity are striking features of IBS with clinical implications. The odds for reporting a variety of bodily and psychological symptoms and disorders were two to seven times higher in subjects with IBS than in subjects without IBS. Importantly, we demonstrate that such comorbidity is a feature of IBS and not only of its consulters. Furthermore, our findings challenge the general assumption that IBS is a disorder which leads to reduced quality of life, working disability and increased use of health care resources. In this context, the comorbidity of IBS is a major confounder which should be taken into account in future attempts to measure the severity and impact of IBS. The comorbidity of IBS also has implications for aetiology and treatment: Structured assessment of somatic comorbidity can identify subgroups of patients with predominantly psychological and biological aetiologies in need of targeted treatments.

So, where do we go? For those of us engaged in patients with IBS, these are exciting times with research at blossom. In particular, research on basic pathophysiological mechanisms in the gastrointestinal tract receives great attention. Some experts believe IBS will turn out to represent a series of poorly understood organic diseases.¹³ Others caution against this “organification” of IBS and find it unlikely that an altered gene or set of specific biological aetiologies will explain a complex brain gut disorder such as IBS.¹⁵ Our findings suggest some roads to travel to increase our understanding of IBS and to provide better diagnosis and treatment for patients with symptoms of IBS.

Toward a better understanding of IBS?

The observed comorbidity of IBS and its implications suggests that researchers and physicians sometimes need to look beyond the gastrointestinal tract. Moreover, our findings highlight the need for further clinical and epidemiological research performed in representative samples of subjects with IBS. It could be wise to pay attention to William Grant Thompson, a major contributor to current understanding about IBS, who recently wrote: *One group of internists claim that functional disorders such as IBS are “artefacts of specialisation”. They hypothesise that such healthcare seeking patients have somatisation disorders and if they see a gastroenterologist they will leave with a diagnosis of IBS or dyspepsia, while a rheumatologist will diagnose fibromyalgia, and a neurologist non-specific headache. Many will disagree with this concept, but it should force us to think beyond our specialty. It is even tempting to speculate that the majority of those individuals with IBS symptoms who shun seeking health care do not consider it a medical problem at all. In 1984, Thomas Almy asked: Is the IBS a quantitative or merely qualitative departure from the psychophysiological reactions of human beings?” Will the IBS prove to be a disease or a series of diseases for which a structural or biochemical defect will be discovered, or are IBS symptoms, like tears, a person’s psychophysiological reaction to the environment?*¹³

These observations underline the necessity of maintaining a holistic perspective on IBS in research and in clinical encounters. By constantly looking at IBS from different viewpoints and by combining basic, clinical and epidemiological research, the future could hold considerable promise for our understanding of IBS.¹⁴

Can we improve current diagnosis and treatment of patients with IBS?

In clinical encounters with patients who present with symptoms of IBS, it is our duty as physicians to provide diagnosis and treatment based on available evidence. Although we need

to understand more about IBS, this should not keep us from implementing current knowledge about IBS in clinical practice. A positive symptom based approach is widely recommended as the preferred way of diagnosing IBS, but requires that physicians have sufficient knowledge about the typical symptoms of IBS. Sufficient knowledge would also facilitate reassurance and education which, together with a confident diagnosis, constitute cornerstones in the recommended graded general treatment approach. Since this approach is considered to be what most patients need, the efficacy of this multidimensional intervention should be explored. Evidently, some patients with IBS need specific treatment. I frequently encounter referred patients who present with severe IBS for which I have little to offer. Many of these patients have excessive comorbidity which further complicates treatment. We need to provide these patients with proven effective treatment such as gut focused hypnotherapy. Such psychological intervention and emerging drug therapies targeted at end organ dysfunction in the gut could prove even more effective if we can identify patients with predominantly different aetiologies. Our findings therefore call for research on therapy targeted at different levels of the brain gut axis, tailored to the needs of the individual patient with IBS.

REFERENCES

1. Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG *et al.* U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig.Dis.Sci.* 1993;38: 1569-80.
2. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. *Gut* 2000;46: 78-82.
3. Thompson WG, Irvine EJ, Pare P, Ferrazzi S, Rance L. Functional gastrointestinal disorders in Canada: first population-based survey using Rome II criteria with suggestions for improving the questionnaire. *Dig.Dis.Sci.* 2002;47: 225-35.
4. Harvey RF, Salih SY, Read AE. Organic and functional disorders in 2000 gastroenterology outpatients. *Lancet* 1983;1: 632-34.
5. Drossman, D. A., Corazziari, E., and Talley, N. J. The functional gastrointestinal disorders: Diagnosis, Pathophysiology, and Treatment: A Multinational Consensus. 2nd edition. 2000. McLean(VA):Degnon;2000.
6. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999;45 Suppl 2:II43-II47.
7. El Serag HB, Pilgrim P, Schoenfeld P. Systemic review: Natural history of irritable bowel syndrome. *Aliment.Pharmacol.Ther.* 2004;19: 861-70.
8. Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: long-term prognosis and the physician-patient interaction. *Ann.Intern.Med.* 1995;122: 107-12.
9. Kay L, Jorgensen T, Jensen KH. The epidemiology of irritable bowel syndrome in a random population: prevalence, incidence, natural history and risk factors. *J.Intern.Med.* 1994;236: 23-30.
10. Cumming W. Electro-galvanism in a peculiar affliction of the mucous membrane of the bowels. London Medical Gazette. 1849.
11. Chaudhary NA, Truelove SC. The irritable colon syndrome. A study of the clinical features, predisposing causes, and prognosis in 130 cases. *Q.J.Med.* 1962;31: 307-22.
12. Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. *Aliment.Pharmacol.Ther.* 2003;17: 643-50.
13. Talley NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? *Lancet* 2002;360: 555-64.
14. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *Br.Med.J.* 1978;2: 653-54.
15. Drossman DA. The "organification" of functional GI disorders: implications for research. *Gastroenterology* 2003;124: 6-7.
16. Mayer EA, Raybould HE. Role of visceral afferent mechanisms in functional bowel disorders. *Gastroenterology* 1990;99: 1688-704.
17. Mayer EA, Collins SM. Evolving pathophysiologic models of functional gastrointestinal disorders. *Gastroenterology* 2002;122: 2032-48.

18. Engel GL. The need for a new medical model: a challenge for biomedicine. *Science* 1977;196: 129-36.
19. Drossman DA. Presidential address: Gastrointestinal illness and the biopsychosocial model. *Psychosom.Med.* 1998;60: 258-67.
20. Wilhelmsen I. Brain-gut axis as an example of the bio-psycho-social model. *Gut* 2000;47 Suppl 4:iv5-iv7.
21. Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. *Gastroenterology* 1995;109: 40-52.
22. Bouin M, Plourde V, Boivin M, Riberdy M, Lupien F, Laganier M *et al.* Rectal distention testing in patients with irritable bowel syndrome: sensitivity, specificity, and predictive values of pain sensory thresholds. *Gastroenterology* 2002; 122:1771-7.
23. Prior A, Maxton DG, Whorwell PJ. Anorectal manometry in irritable bowel syndrome: differences between diarrhoea and constipation predominant subjects. *Gut* 1990;31: 458-62.
24. Whitehead WE, Palsson OS. Is rectal pain sensitivity a biological marker for irritable bowel syndrome: psychological influences on pain perception. *Gastroenterology* 1998;115: 1263-71.
25. Silverman DH, Munakata JA, Ennes H, Mandelkern MA, Hoh CK, Mayer EA. Regional cerebral activity in normal and pathological perception of visceral pain. *Gastroenterology* 1997;112: 64-72.
26. Mertz H, Morgan V, Tanner G, Pickens D, Price R, Shyr Y *et al.* Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology* 2000;118: 842-8.
27. Gwee KA. Postinfectious Irritable Bowel Syndrome. *Curr.Treat.Options.Gastroenterol.* 2001;4: 287-91.
28. Gwee KA, Leong YL, Graham C, McKendrick MW, Collins SM, Walters SJ *et al.* The role of psychological and biological factors in postinfective gut dysfunction. *Gut* 1999;44:400-6.
29. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002;123: 2108-31.
30. Koloski NA, Talley NJ, Boyce PM. Predictors of health care seeking for irritable bowel syndrome and nonulcer dyspepsia: a critical review of the literature on symptom and psychosocial factors. *Am.J.Gastroenterol.* 2001;96:1340-49.
31. Wilhelmsen I. The role of psychosocial factors in gastrointestinal disorders. *Gut* 2000;47 Suppl 4:iv73-iv75.
32. Whitehead WE, Bosmajian L, Zonderman AB, Costa PT, Jr., Schuster MM. Symptoms of psychologic distress associated with irritable bowel syndrome. Comparison of community and medical clinic samples. *Gastroenterology* 1988;95: 709-14.
33. Drossman DA, McKee DC, Sandler RS, Mitchell CM, Cramer EM, Lowman BC *et al.* Psychosocial factors in the irritable bowel syndrome. A multivariate study of patients and nonpatients with irritable bowel syndrome. *Gastroenterology* 1988;95: 701-08.
34. Talley NJ, Boyce PM, Jones M. Predictors of health care seeking for irritable bowel syndrome: a population based study. *Gut* 1997;41: 394-98.
35. Osterberg E, Blomquist L, Krakau I, Weinryb RM, Asberg M, Hultcrantz R. A population study on irritable bowel syndrome and mental health. *Scand.J.Gastroenterol.* 2000;35: 264-8.

36. Thompson WG. Irritable bowel syndrome: prevalence, prognosis and consequences. *CMAJ*. 1986;134: 111-13.
37. Mearin F, Badia X, Balboa A, Baro E, Caldwell E, Cucala M *et al*. Irritable bowel syndrome prevalence varies enormously depending on the employed diagnostic criteria: comparison of Rome II versus previous criteria in a general population. *Scand.J.Gastroenterol*. 2001;36: 1155-61.
38. Johnsen R, Jacobsen BK, Forde OH. Associations between symptoms of irritable colon and psychological and social conditions and lifestyle. *Br.Med.J.(Clin.Res.Ed)* 1986;292:1633-35.
39. Jones J, Boorman J, Cann P, Forbes A, Gomborone J, Heaton K *et al*. British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. *Gut* 2000;47 Suppl 2:ii1-19.
40. Agreus L. Rome? Manning? Who cares? *Am.J.Gastroenterol*. 2000;95: 2679-81.
41. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology* 2002;122: 1140-56.
42. El Serag HB, Olden K, Bjorkman D. Health-related quality of life among persons with irritable bowel syndrome: a systematic review. *Aliment.Pharmacol.Ther*. 2002;16: 1171-85.
43. Wells NE, Hahn BA, Whorwell PJ. Clinical economics review: irritable bowel syndrome. *Aliment.Pharmacol.Ther*. 1997;11: 1019-30.
44. Talley NJ, Gabriel SE, Harmsen WS, Zinsmeister AR, Evans RW. Medical costs in community subjects with irritable bowel syndrome. *Gastroenterology* 1995;109: 1736-41.
45. Sandler RS, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C *et al*. The burden of selected digestive diseases in the United States. *Gastroenterology* 2002;122: 1500-11.
46. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? *Lancet* 1999;354: 936-9.
47. Monsbakken KW, Vandvik PO, Farup PG. The value of a general therapeutic approach in subjects with irritable bowel syndrome. *Aliment.Pharmacol.Ther*. 2005;21: 21-7.
48. Gulbrandsen P, Hjortdahl P, Fugelli P. General practitioners' knowledge of their patients' psychosocial problems: multipractice questionnaire survey. *BMJ* 1997;314:1014-18.
49. Robinson A, Lee V, Kennedy A, Middleton L, Rogers A, Thompson DG *et al*. A randomised controlled trial of self-help interventions in patients with a primary care diagnosis of IBS. *Gut* 2005.
50. Saito YA, Prather CM, Van Dyke CT, Fett S, Zinsmeister AR, Locke GR, III. Effects of multidisciplinary education on outcomes in patients with irritable bowel syndrome. *Clin.Gastroenterol.Hepatol*. 2004;2: 576-84.
51. Lea R, Whorwell PJ. The role of food intolerance in irritable bowel syndrome. *Gastroenterol.Clin.North Am*. 2005;34: 247-55.
52. Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut* 2004;53:1459-64.
53. Dapoigny M, Stockbrugger RW, Azpiroz F, Collins S, Coremans G, Muller-Lissner S *et al*. Role of alimentation in irritable bowel syndrome. *Digestion* 2003;67: 225-33.

54. Schneider A, Enck P, Streitberger K, Weiland C, Bagheri S, Witte S *et al.* Acupuncture treatment in irritable bowel syndrome. *Gut* 2005.
55. Spanier JA, Howden CW, Jones MP. A systematic review of alternative therapies in the irritable bowel syndrome. *Arch.Intern.Med.* 2003;163: 265-74.
56. Mertz HR. Irritable bowel syndrome. *N.Engl.J.Med.* 2003;349: 2136-46.
57. Talley NJ. Evaluation of drug treatment in irritable bowel syndrome. *Br.J.Clin.Pharmacol.* 2003;56: 362-9.
58. Lesbros-Pantoflickova D, Michetti P, Fried M, Beglinger C, Blum AL. Meta-analysis: the treatment of irritable bowel syndrome. *Aliment.Pharmacol.Ther.* 2004;20: 1253-69.
59. Jackson JL, O'Malley PG, Tomkins G, Balden E, Santoro J, Kroenke K. Treatment of functional gastrointestinal disorders with antidepressant medications: a meta-analysis. *Am.J.Med.* 2000;108: 65-72.
60. Muller-Lissner S, Holtmann G, Rueegg P, Weidinger G, Loffler H. Tegaserod is effective in the initial and retreatment of irritable bowel syndrome with constipation. *Aliment.Pharmacol.Ther.* 2005;21: 11-20.
61. Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. *Lancet* 2000;355: 1035-40.
62. Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). *Dig.Dis.Sci.* 1984;29: 239-47.
63. Bijkerk CJ, Muris JW, Knottnerus JA, Hoes AW, de Wit NJ. Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome. *Aliment.Pharmacol.Ther.* 2004;19: 245-51.
64. Talley NJ, Owen BK, Boyce P, Paterson K. Psychological treatments for irritable bowel syndrome: a critique of controlled treatment trials. *Am.J.Gastroenterol.* 1996;91: 277-83.
65. Drossman DA, Toner BB, Whitehead WE, Diamant NE, Dalton CB, Duncan S *et al.* Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. *Gastroenterology* 2003;125: 19-31.
66. Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable-bowel syndrome. *Lancet* 1984;2:1232-4.
67. Gonsalkorale WM, Miller V, Afzal A, Whorwell PJ. Long term benefits of hypnotherapy for irritable bowel syndrome. *Gut* 2003;52: 1623-29.
68. Simren M, Brazier J, Coremans G, Dapoigny M, Muller-Lissner SA, Pace F *et al.* Quality of life and illness costs in irritable bowel syndrome. *Digestion* 2004;69: 254-61.
69. Lea R, Houghton LA, Calvert EL, Larder S, Gonsalkorale WM, Whelan V *et al.* Gut-focused hypnotherapy normalizes disordered rectal sensitivity in patients with irritable bowel syndrome. *Aliment.Pharmacol.Ther.* 2003;17: 635-42.
70. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997;277: 968-71.
71. Kennedy T, Jones R, Darnley S, Seed P, Wessely S, Chalder T. Cognitive behaviour therapy in addition to antispasmodic treatment for irritable bowel syndrome in primary care: randomised controlled trial. *BMJ* 2005;331: 435.

72. Eriksen HR, Ihlebaek C, Ursin H. A scoring system for subjective health complaints (SHC). *Scand.J.Public Health* 1999;27: 63-72.
73. Ihlebaek C, Eriksen HR, Ursin H. Prevalence of subjective health complaints (SHC) in Norway. *Scand.J.Public Health* 2002;30: 20-29.
74. Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord.J.Psychiatry* 2003;57:113-18.
75. Speckens AE, Spinhoven P, Sloekers PP, Bolk JH, van Hemert AM. A validation study of the Whitely Index, the Illness Attitude Scales, and the Somatosensory Amplification Scale in general medical and general practice patients. *J.Psychosom.Res.* 1996;40: 95-104.
76. Grayson DA. Latent trait analysis of the Eysenck Personality Questionnaire. *J.Psychiatr.Res.* 1986;20: 217-35.
77. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE *et al.* Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J.Clin.Epidemiol.* 1998;51:1171-78.
78. Thomas P. The research needs of primary care. *BMJ* 2000;321: 2-3.
79. Koop A, Mosges R. The use of handheld computers in clinical trials. *Control Clin.Trials* 2002;23: 469-80.
80. Talley NJ, Zinsmeister AR, Melton LJ, III. Irritable bowel syndrome in a community: symptom subgroups, risk factors, and health care utilization. *Am.J.Epidemiol.* 1995;142: 76-83.
81. Chang L, Heitkemper MM. Gender differences in irritable bowel syndrome. *Gastroenterology* 2002;123: 1686-701.
82. Hillila MT, Farkkila MA. Prevalence of irritable bowel syndrome according to different diagnostic criteria in a non-selected adult population. *Aliment.Pharmacol.Ther.* 2004;20: 339-45.
83. Boyce PM, Koloski NA, Talley NJ. Irritable bowel syndrome according to varying diagnostic criteria: are the new Rome II criteria unnecessarily restrictive for research and practice? *Am.J.Gastroenterol.* 2000;95: 3176-83.
84. Talley NJ, Zinsmeister AR, Van Dyke C, Melton LJ, III. Epidemiology of colonic symptoms and the irritable bowel syndrome. *Gastroenterology* 1991;101: 927-34.
85. Kristensen P, Sandbakken P, Johannessen T, Loge I, Hafstad PE, Petersen H *et al.* [Gastrointestinal diseases in general practice. A general practice register]. *Tidsskr.Nor Laegeforen.* 1985;105:728-31.
86. Fullerton S. Functional digestive disorders (FDD) in the year 2000--economic impact. *Eur.J.Surg.Suppl* 1998;62-64.
87. Olden KW. Diagnosis of irritable bowel syndrome. *Gastroenterology* 2002;122: 1701-14.
88. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome: the view from general practice. *Eur.J.Gastroenterol.Hepatol.* 1997;9:689-92.
89. Longstreth GF, Burchette RJ. Family practitioners' attitudes and knowledge about irritable bowel syndrome: effect of a trial of physician education. *Fam.Pract.* 2003;20: 670-74.
90. Gladman LM, Gorard DA. General practitioner and hospital specialist attitudes to functional gastrointestinal disorders. *Aliment.Pharmacol.Ther.* 2003;17:651-54.

91. Bijkerk CJ, de Wit NJ, Stalman WA, Knottnerus JA, Hoes AW, Muris JW. Irritable bowel syndrome in primary care: the patients' and doctors' views on symptoms, etiology and management. *Can.J Gastroenterol* 2003;17:363-68.
92. Rosendal M, Olesen F, Fink P. Management of medically unexplained symptoms. *BMJ* 2005;330:4-5.
93. Agreus L, Talley NJ, Svardsudd K, Tibblin G, Jones MP. Identifying dyspepsia and irritable bowel syndrome: the value of pain or discomfort, and bowel habit descriptors. *Scand.J.Gastroenterol.* 2000;35:142-51.
94. Simren M, Abrahamsson H, Svedlund J, Bjornsson ES. Quality of life in patients with irritable bowel syndrome seen in referral centers versus primary care: the impact of gender and predominant bowel pattern. *Scand.J.Gastroenterol.* 2001;36: 545-52.
95. Lee OY, Mayer EA, Schmulson M, Chang L, Naliboff B. Gender-related differences in IBS symptoms. *Am.J.Gastroenterol.* 2001;96: 2184-93.
96. Corney RH, Stanton R. Physical symptom severity, psychological and social dysfunction in a series of outpatients with irritable bowel syndrome. *J.Psychosom.Res.* 1990;34: 483-91.
97. Whorwell PJ, McCallum M, Creed FH, Roberts CT. Non-colonic features of irritable bowel syndrome. *Gut* 1986;27: 37-40.
98. Donker GA, Foets M, Spreeuwenberg P. Patients with irritable bowel syndrome: health status and use of health care services. *Br.J.Gen.Pract.* 1999;49: 787-92.
99. Brage S. [Utilization of national insurance in connection with functional somatic disorders]. *Tidsskr.Nor Laegeforen.* 2002;122:1397-401.
100. Brage S, Laerum E. [Spinal disorders in Norway--an epidemiological report]. *Tidsskr.Nor Laegeforen.* 1999;119: 1619-23.
101. Levy RL, Von Korff M, Whitehead WE, Stang P, Saunders K, Jhingran P *et al.* Costs of care for irritable bowel syndrome patients in a health maintenance organization. *Am.J.Gastroenterol.* 2001;96: 3122-9.
102. Spiegel BM, Gralnek IM, Bolus R, Chang L, Dulai GS, Mayer EA *et al.* Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. *Arch.Intern.Med.* 2004;164: 1773-80.
103. Chang L. Review article: epidemiology and quality of life in functional gastrointestinal disorders. *Aliment.Pharmacol.Ther.* 2004;20 Suppl 7: 31-39.
104. Lembo A, Ameen VZ, Drossman DA. Irritable bowel syndrome: toward an understanding of severity. *Clin.Gastroenterol Hepatol.* 2005;3: 717-25.
105. Cremonini F, Talley NJ. Review article: the overlap between functional dyspepsia and irritable bowel syndrome -- a tale of one or two disorders? *Aliment.Pharmacol.Ther.* 2004;20 Suppl 7:40-49.
106. Locke GR, III, Zinsmeister AR, Fett SL, Melton LJ, III, Talley NJ. Overlap of gastrointestinal symptom complexes in a US community. *Neurogastroenterol.Motil.* 2005;17: 29-34.
107. Guthrie EA, Creed FH, Whorwell PJ, Tomenson B. Outpatients with irritable bowel syndrome: a comparison of first time and chronic attenders. *Gut* 1992;33: 361-63.
108. Maxton DG, Morris J, Whorwell PJ. More accurate diagnosis of irritable bowel syndrome by the use of 'non-colonic' symptomatology. *Gut* 1991;32: 784-86.

109. Søgaaard AJ, Selmer R, Bjertnes E TD. The impact of self-selection in a large, population-based survey. *Int J for Equity in Health* 2004;3.
110. Sandanger I, Moum T, Ingebrigtsen G, Dalgard OS, Sorensen T, Bruusgaard D. Concordance between symptom screening and diagnostic procedure: the Hopkins Symptom Checklist-25 and the Composite International Diagnostic Interview I. *Soc.Psychiatry Psychiatr.Epidemiol.* 1998;33: 345-54.
111. Creed F, Craig T, Farmer R. Functional abdominal pain, psychiatric illness, and life events. *Gut* 1988;29: 235-42.
112. Whitehead WE, Crowell MD, Robinson JC, Heller BR, Schuster MM. Effects of stressful life events on bowel symptoms: subjects with irritable bowel syndrome compared with subjects without bowel dysfunction. *Gut* 1992;33: 825-30.
113. Thompson WG. A world view of IBS. In Camilleri M, Spiller RC, eds. *Irritable Bowel Syndrome. Diagnosis and Treatment*, Elsevier Science Limited, 2002.
114. Drossman DA. What does the future hold for irritable bowel syndrome and the functional gastrointestinal disorders? *J.Clin.Gastroenterol* 2005;39:S251-S256.

APPENDIX

A comment on some commonly used terms and definitions

IBS; Disease, disorder or illness?

I use the term functional gastrointestinal disorder (FGID) in this thesis, as recommended by the Rome committee. However, IBS meets dictionary definitions of disorder, disease and illness in English language which probably explains why these terms are used interchangeably in the literature. The word disorder is usually applied when function is altered without morphological change, often implying unknown or psychological causes, leaving disease for entities with an organic cause. Accordingly, the term functional disorder applies to IBS since no organic cause has been identified. Illness is a broader concept that differs from physicians' biomedical concept and embodies a sick person's experience, so regardless of whether the term disease or disorder is used, illness applies from the patient's perspective.

In our studies, we translated FGID to "funksjonelle mageplager". In Norwegian language, there is a major difference in labelling IBS plage (disorder), lidelse (illness) or sykdom (disease) at least in clinical encounters with patients. To my experience, researchers and physicians in Norway do not use the disease term in IBS.

Aetiology, pathogenesis, causes and mechanisms

I use the term aetiology to describe a variety of factors which together contribute to the development (pathogenesis) of IBS. However, the aetiology of IBS is poorly understood and a range of causes and mechanisms have been associated with the pathogenesis in IBS (see general introduction). More than one factor is necessary to develop IBS, as conceptualised in the biopsychosocial model and in line with modern epidemiological concepts where causes of disease have both genetic and environmental determinants.

Comorbidity of IBS, subjective health complaints, somatisation or medically unexplained physical symptoms (MUPS)?

I use the term comorbidity to describe co-occurring somatic (=bodily) and psychiatric symptoms and disorders/ diseases in subjects with IBS. This term contrasts with the frequently used terms "extraintestinal/ non-gastrointestinal symptoms of IBS" because it does not imply that these symptoms are aetiologically linked to IBS.

We assessed comorbid symptoms in patients with IBS with the Subjective health complaints (SHC) inventory (see paper III). The term subjective health complaints describes common health problems reported by subjects without making aetiological inferences or linking

symptoms to specific diagnoses. The same thinking applies for MUPS, although this term is reserved for physical (=somatic) symptoms where no medical explanation can be found.


What about somatisation? This term describes a phenomenon with multiple somatic symptoms without a plausible explanation by pathological findings. Whereas some infer that these symptoms result from psychological distress, others define somatisation as medically unexplained physical symptoms (MUPS) without making aetiological inferences. I use the term somatisation as a possible explanation of excessive somatic comorbidity in a subset of patients with IBS. In this context, somatic symptoms have been proposed to be markers for psychological influences on aetiology (see general discussion).

Consultation behaviour in IBS: Subjects with IBS, Consulters/ non-consulters or patients/ non-patients?

Not all with IBS consult physicians, and those who do might end up seeing their GP or different kinds of specialists in secondary and tertiary health care (see general introduction). In research, this feature is frequently labelled consultation behaviour or healthcare seeking behaviour.

Different terms are used to separate subjects with IBS who do not consult (non-consulters, non-patients) from those who do consult (consulters, patients). In the population based survey, I divide subjects with IBS in IBS consulters and IBS non-consulters. In the general practice study, I use the term patients with IBS (all had consulted or wished to consult their GP for abdominal complaints).





Screening questionnaire in the waiting room

	Kartlegging av mageplager i almen praksis
Draft	
Fylles ut av legesekretær	
Utfylt dato <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Pasientnummer <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
PASIENTFORESPØRSEL	
Vi vil lære mer om mageplager i almen praksis og vil i den anledning stille deg noen spørsmål. Med mageplager mener vi alle typer plager som du oppfatter har med magen og fordøyelsen å gjøre (for eksempel magesmerter og mage - ubehag, luftplager, kvalme, sure oppstøt, hals - og brystbrann, diaré, forstoppelse, mat du ikke tåler, smerter og ubehag når du spiser eller har avføring).	
Spørsmål: Sett kryss i boksen utenfor det svar - alternativ du synes passer.	
1. Vil du være så vennlig å svare på dette enkle spørreskjemaet om mageplager?	<input type="checkbox"/> Ja <input type="checkbox"/> Nei
Hvis nei, vennligst lever skjemaet til legesekretæren.	
2. Kjønn <input type="checkbox"/> Mann	
<input type="checkbox"/> Kvinne	
3. Alder <input type="text"/> <input type="text"/> år	
4. Har du hatt mageplager som nevnt i innledningen de siste 3 måneder?	<input type="checkbox"/> Ja <input type="checkbox"/> Nei
Hvis nei, vennligst lever skjemaet til legesekretæren.	
5. Har mageplagene vært slik at du har tatt det opp med legen eller ønsker å ta det opp med legen?	<input type="checkbox"/> Ja <input type="checkbox"/> Nei
6. Har du tenkt å ta opp mageplagene med legen i dag?	<input type="checkbox"/> Ja <input type="checkbox"/> Nei
Vennligst lever dette skjemaet til legesekretæren etter utfylling. Hvis du svarte ja på spørsmål 5 eller 6, ønsker vi å kartlegge dine mageplager nærmere. Informasjon om dette får du av legesekretæren.	
Med vennlig hilsen	
Dr. Per Olav vandvik, prosjektleder Medisinsk avdeling, Oppland Sentralsykehus avd. Gjøvik 2819 GJØVIK. Telefon 61137000	Legekantorets navn (stempel)
<i>Kun for legesekretær: Hvis pasienten har svart Ja på spørsmål 3 eller 4.</i>	
Har pasienten gitt skriftlig samtykke for å fylle ut palm top?	<input type="checkbox"/> Ja <input type="checkbox"/> Nei
Hvis ja, hadde pasienten problemer med å fylle ut palm top? <i>(Hvis pasienten hadde problemer med å fylle ut palm top, vennligst spesifiser i fritekst på baksiden)</i>	<input type="checkbox"/> Ja <input type="checkbox"/> Nei
<small>Skjema utarbeidet ved Enhet for anvendt klinisk forskning / Kontor for klinisk kreftforskning Tlf.: 73 86 72 71/73 86 84 44</small>	

Rome II questionnaire for IBS translated to Norwegian

The questions were similar in the general practice study and in the population based survey of IBS. The layout was different in the general practice study, due to the electronic questionnaire.

1	
MAGESMERTER/UBEHAG SISTE TRE MÅNEDER	
1.1	Har du vært plaget av smerter eller ubehag i magen i løpet av de siste 3 måneder?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
	Hvis Nei, hopp til spørsmål 2
1.2	Har du kjent disse plagene minst 1 dag i uken i 3 uker eller mer i løpet av de siste 3 måneder?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
1.3	Blir smertene/ubehaget i magen bedre etter at du har hatt avføring?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
1.4	Begynner plagene i forbindelse med at du får enten hyppigere eller sjeldnere avføring?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
1.5	Begynner plagene i forbindelse med at du får enten løsere eller fastere avføring?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
2	
OM FORDØYELSE- OG TARM-FUNKSJONER	
2.1	Hender det at du har mindre enn 3 avføringer pr uke?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
2.1.1	Hvis Ja, De siste 3 måneder, har dette hendt oftere enn hver 4.uke?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
2.2	Hender det at du har hard eller knollet avføring?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
2.2.1	Hvis Ja, De siste 3 måneder, har du hatt hard eller knollet avføring oftere enn hver 4. gang du er på toalettet?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
2.3.	Hender det at du har mer enn 3 avføringer pr. dag?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
2.4.	Hender det at du har løs (grøtaktig) eller vandig avføring?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
2.4.1	Hvis ja: De siste 3 måneder: har avføringen vært løs/grøtaktig eller vandig mer enn 3 av 4 ganger (75%) du er på toalettet?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
2.5	Hender det at du har følelsen av ikke å få ut all avføringen når du er på toalettet?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
2.6	Hender det at du må presse eller trykke for å få avføring?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
2.7	Hender det at du må på toalettet med en gang fordi du har problemer med å vente med (holde tilbake) avføringen?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
2.8	Hender det at du ser slim i avføringen?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
2.9	Hender det at du føler deg stinn eller oppblåst (luft) i magen?
	Ja <input type="checkbox"/> Nei <input type="checkbox"/>

  Kartlegging av mageplager i almennt praksis Helseplager siste 30 dogn				
<i>Fylles ut av legesekretær</i> Utfylt dato <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		Pasientnummer <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		
På denne siden nevnes noen vanlige helseplager. Vi vil be deg om å vurdere hvert enkelt problem/symptom, og oppgi i hvilken grad du har vært plaget av dette i løpet av de siste tretti dogn.				
Sett kryss i den ruten som passer best for hvor plaget du har vært de siste 30 dogn.				
	Ikke plaget	Litt plaget	En del plaget	Alvorlig plaget
1. Forkjølelse, influensa	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Hoste, bronkitt	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Astma	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Hodepine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. .Nakkesmerter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Smerter øverst i ryggen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Smerter i korsryggen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Smerter i armer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Smerter i skuldre	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Migrene	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Hjertebank, ekstraslag	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Brystmerter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Pustevansker	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Smerter i føttene ved anstrengelser	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Sure oppstøt, "halsbrann"	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Sug eller svie i magen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Magekatarr, magesår	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Mageknipe	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. "Luftplager"	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. Løs avføring, diarè	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. Forstoppelse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Eksem	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. Allergi	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24. Hetetokter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. Sovnproblemer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. Tretthet	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. Svimmelhet	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
28. Angst	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29. Nedtrykt, depresjon	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
 Skjema utarbeidet ved Enhet for anvendt klinisk forskning / Kontor for klinisk kreftforskning Tlf.: 73 86 72 71 73 86 84 44				

Papers I-IV

Paper I

Abdominal complaints in general practice

Diagnoses and characteristics of patients

Per Olav Vandvik¹, Pål Kristensen², Lars Aabakken³ and Per G. Farup^{1,4}

¹Department of Medicine, Innlandet Hospital Health Authority, Gjøvik, ²Ranheim Medical Centre, Trondheim, ³Department of Medicine, Rikshospitalet University Hospital, Oslo, ⁴Unit for Applied Clinical Research, NTNU, Trondheim, Norway.

Scand J Prim Health Care 2004;22:157–162. ISSN 0281-3432

Objective – The study evaluates the prevalence and diagnoses of abdominal complaints in general practice, and compares characteristics and symptoms of patients with functional gastrointestinal disorders (FGIDs) and organic diseases.

Design – A cross-sectional study.

Setting – Nine centres with 26 participating general practitioners (GPs) in Norway.

Subjects – 3097 out of 3369 consecutive adult patients answered a questionnaire regarding abdominal complaints within the last 3 months. Those who consulted for the complaints were eligible for this study.

Main outcome measures – The GPs' diagnoses and patients' characteristics were reported in questionnaires.

Results – 460 out of 1499 patients with abdominal complaints consulted for these complaints; 392 were included in this study. The

GPs diagnosed a FGID in 167 (42.6%) patients, organic disease in 145 (37.0%), and made no diagnosis in 80 (20.4%). Stress-related symptoms were a statistically significant predictor of a FGID (OR 1.95) and weight loss predicted in addition organic disease (OR 2.7) in 128 patients with a verified diagnosis.

Conclusion – Abdominal complaints are a common problem in general practice. The distinction between FGID, which accounted for half of the diagnoses, and organic disease was difficult. The only significant predictor for FGID was stress-related symptoms.

Key words: diagnoses, functional gastrointestinal disorders, gastrointestinal diseases, general practice.

Per Olav Vandvik, Department of Medicine, Innlandet Hospital Health Authority, Kyrre Greppsgt. 11, NO-2819 Gjøvik, Norway.
E-mail: per.vandvik@start.no

Most patients with abdominal complaints are diagnosed and treated in general practice, where such problems account for 7–10% of the consultations (1,2). At least half of these consultations are for functional gastrointestinal disorders (FGIDs), such as irritable bowel syndrome (IBS) and functional dyspepsia (1,2). Since the FGIDs and the organic diseases are in large part handled differently, the GP must consider at an early stage which of them is most likely. This distinction is important for selection of further investigations or referral to secondary care, and for correct treatment. There is little knowledge on how to make this distinction based on symptoms alone (3,4). It is likely that GPs, who often are unfamiliar with the use of strict diagnostic criteria for FGIDs, use other characteristics than merely the abdominal symptoms to separate FGIDs and organic disease (1,3). Increased knowledge about characteristics in patients with FGIDs and organic diseases could help the GPs to a correct diagnosis.

This study investigates the prevalence of abdominal complaints in general practice and the spectrum of diagnoses made by GPs, and compares characteristics of patients diagnosed with FGIDs with those diagnosed with organic diseases.

MATERIAL AND METHODS

The study was carried out in the county of Oppland, which comprises 110 000 inhabitants served by 99 GPs and one hospital. In Norway, patients must seek medical care through their locally assigned GP. In all 26 GPs, working in 9 (out of 12 invited) general practices of varying sizes, participated in the study. Two practices were located in a town with 18 000 inhabitants, 7 were located in the countryside. The study period was from February to April 2001, during

Most patients with abdominal complaints are managed by their GP. A correct distinction between functional disorders and organic diseases is necessary.

- Consultations for abdominal complaints constituted a significant workload for GPs.
- Functional disorders were diagnosed as frequently as organic diseases.
- Patients with functional disorders and organic diseases displayed apparently similar characteristics, which made this distinction a challenge for the GP.

10 days of practice for each participating GP. Members of the practice staff were responsible for administration of questionnaires. GP characteristics such as age, sex, professional experience, and knowledge of diagnostic criteria for FGID were recorded.

Consecutive patients aged 18 years or older consulting their GPs were asked to complete a brief questionnaire in the waiting room. This questionnaire assessed sex, age, presence of abdominal complaints within the past 3 months, and consultations for the complaints. Patients with abdominal complaints who wished to consult the GP the same day for these complaints (main or additional problem) were eligible for the study.

Patients who had given informed consent completed an additional questionnaire developed by the authors, regarding certain symptoms and characteristics. This questionnaire was administered on a palm-top computer. Patients were assisted by practice staff in completing the questionnaire, if necessary. The severity of abdominal pain/discomfort was measured as mild (no interference with daily activities), moderate (some interference, but not disruption of daily activities) and severe (with disruption of daily activities) and frequency of abdominal pain/discomfort as number of days per week with abdominal pain/discomfort. Two questions assessed the patients' own opinion of stress and psychological factors as relevant to the abdominal complaints ("stress-related symptoms") and whether patients feared that the abdominal complaints could be due to cancer/other serious disease ("fear of cancer").

General practitioners' diagnosis

The GPs' diagnosis for the abdominal complaints was based on all available information about the patient, in accordance with daily practice. If the abdominal complaints had been sufficiently evaluated (known from earlier or evaluated during the current consultation) the GP reported the diagnosis on the palm-top computer. The GP had to choose one of three main categories (functional disorder, organic gastrointestinal disease, other disease) and thereafter one option within the chosen category. Since some of these diagnoses might have been provisional and therefore unreliable, the GPs were also asked whether the diagnosis was considered to be verified (meaning that, for the FGID, they had no evidence of organic disease, and for the organic diseases that tests had confirmed organic disease). The GPs also reported the number of previous visits for abdominal complaints during the last two years (0/1–5/>5).

Statistics

Differences in characteristics between groups were evaluated with chi-squared, MannWhitney U, and Student's t-tests and 95% confidence intervals (CI) were calculated if possible. A stepwise forward logistic regression analysis was performed to predict characteristics of patients with FGID and organic diseases. All variables with a p-value <0.20 in univariate analyses were entered in the model. The statistical analyses were carried out using SPSS for Windows v. 10.0, and StatXact v. 5.

Ethics

The study was performed according to the Declaration of Helsinki, and approved by the Regional Committee for Medical Research Ethics at the University of Oslo, and the Data Inspectorate, Oslo, Norway.

RESULTS

General practitioners and patients

Of the 26 participating GPs (20 M and 6 F, median age 45 years [range 26–68]), 15 were specialists in general practice and the median number of years in general practice was 10 (range 0–20). Three of 26 GPs knew of diagnostic criteria for FGID, but none applied such criteria regularly. Fig. 1 shows the flow chart of patients in the study. Of 460 patients with abdominal complaints for which they wanted to consult, 392 patients (147 M and 245 F) with mean age 52 years (SD 17.2, range 18–90) were further characterized in the electronic questionnaire. Duration of complaints for more than 1 year was reported by 290 patients (74%), and 273 (70%) had consulted their GP for abdominal complaints earlier. In 114 patients (30%) the abdominal pain/discomfort was mild, in 215 patients (56%) moderate, and 53 patients (14%) reported severe abdominal pain/discomfort. One hundred and fifty patients (38%) feared that the abdominal complaints could be due to cancer or other serious disease. There were no significant differences between men and women regarding these characteristics (data not shown).

GPs' diagnoses for the abdominal complaints

The GP reported a diagnosis in 312 patients; 128 had a diagnosis that was considered by the GP as verified. The proportion of verified diagnoses was significantly lower in patients with no previous visits for abdominal complaints during the last 2 years than in patients with 1 to 5 visits and in patients with more than 5 visits (25%/47%/52%, $p=0.001$). Table I shows the diagnoses in all patients and in those with a verified diagnosis. No diagnosis of malignant disease was made by the GPs in this study.

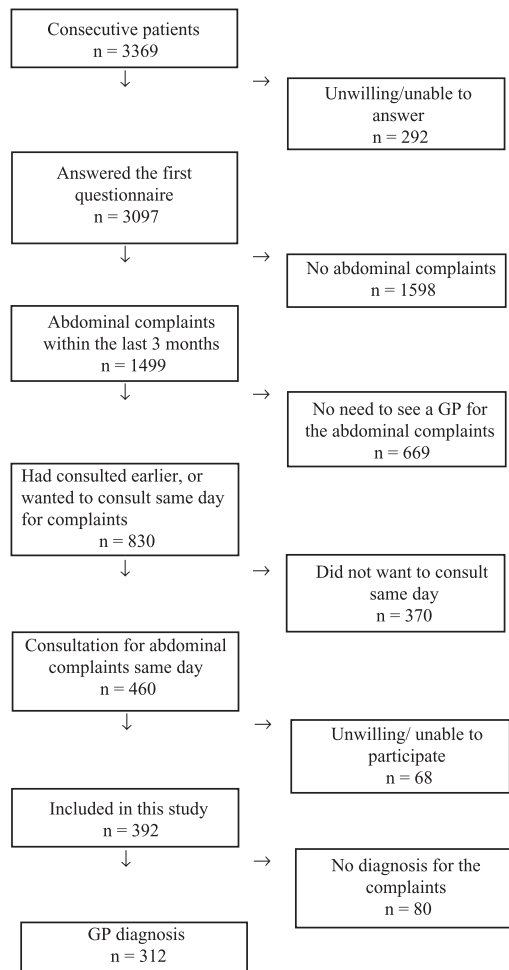


Fig. 1. Flow chart of patients in the study.

Comparison of patients with FGID and organic diseases

Table II shows the characteristics of patients (all patients and the subset with verified diagnoses) with FGID and organic diseases (both gastrointestinal and other diseases) and a comparison between the groups with univariate analyses. By logistic regression, "stress-related symptoms" predicted a diagnosis of FGID in all patients (OR 1.95, 95% CI: 1.24–3.1), and "stress-related symptoms" (OR 2.7, 95% CI: 1.25–5.6) and "no weight loss last year" (OR 2.7, 95% CI: 1.1–6.7) predicted FGID in patients with a verified diagnosis.

DISCUSSION

Main findings

In this general practice population, 14% wished to consult for abdominal complaints during the current

Table I. General practitioners' diagnoses in all patients, and in patients with a verified diagnosis. Results are given as numbers and whole percentages.

Diagnosis	All patients	Patients with a verified diagnosis
No diagnosis	80 (20%)	0 (0%)
Functional gastrointestinal disorders	167 (43%)	50 (39%)
Functional reflux	12 (3%)	5 (4%)
Functional dyspepsia	20 (5%)	7 (5%)
IBS	52 (13%)	22 (17%)
Functional diarrhoea	14 (4%)	3 (2%)
Functional constipation	24 (6%)	7 (5%)
Functional bloating	17 (4%)	1 (1%)
Functional abdominal pain	20 (5%)	4 (3%)
Functional other	8 (2%)	1 (1%)
Benign organic gastrointestinal diseases	109 (28%)	61 (48%)
GERD/oesophagitis	41 (10%)	23 (18%)
Peptic ulcer disease	6 (2%)	5 (4%)
Infectious gastroenteritis	6 (2%)	1 (1%)
Small bowel disease	3 (1%)	2 (2%)
Food allergy/intolerance	2 (1%)	1 (1%)
Liver/biliary/pancreatic disease	9 (2%)	5 (4%)
Inflammatory bowel disease	5 (1%)	3 (2%)
Diverticulosis/diverticulitis	18 (5%)	12 (9%)
Ano-rectal disease	6 (2%)	4 (3%)
Adherences	7 (2%)	4 (3%)
Other gastrointestinal disease	6 (2%)	1 (1%)
Other diseases	36 (9%)	17 (13%)
Drug adverse event	17 (4%)	7 (5%)
Kidney/urinary disease	7 (2%)	4 (3%)
Gynaecologic disease	4 (1%)	3 (2%)
Psychiatric disease (in need of treatment)	8 (2%)	3 (2%)
Malignancies	0 (0%)	0 (0%)
Total	392 (100%)	128 (100%)

consultation. This suggests a somewhat higher frequency of consultations than reported earlier (1,2). Although a common reason for consultation, the complaints seldom disrupted daily activities and a minority had consulted their GP more than 5 times during the last 2 years. Importantly, nearly half of the patients in this study feared that the abdominal complaints could be due to cancer or other serious disease. Such fear should be recognized by the GP, as it may have been the incentive to consult and has negative impact on the course of the abdominal complaints (1,4).

The GPs' diagnoses for the abdominal complaints represent a wide range of non-malignant disorders and diseases. Our study adds to the evidence that the FGIDs constitute a considerable workload for GPs, with IBS being the most frequent functional disorder (1,2).

Table II. Characteristics of patients with functional gastrointestinal disorders (FGID) and organic diseases, with differences between the groups. All values are expressed as percentages, if not otherwise indicated.

Characteristics	All patients with GP diagnosis			Patients with verified GP diagnosis		
	FGID n = 167	Organic n = 145	Statistics*	FGID n = 50	Organic n = 78	Statistics*
Females	65	62	3 (-7; 14)	73.5	73.1	0.4 (-16; 16)
Age in years (mean/SD)	52.6 (16.4)	53.2 (18)	0.8 (-4.7; 3)	54.1 (15.6)	53.1 (18.6)	0.75 (-5.3; 7.4)
Symptom duration >1 year	76	72	4 (-6; 13)	88	82	6 (-8; 17)
Symptom severity (mild/moderate/severe)	29/55/15	24/62/14	p=0.51	20/67/12	26/62/12	p=0.54
Symptom frequency (0-3/4-5/>5 days/week)	57/15/28	56/15/30	p=0.35	59/16/25	55/15/30	p=0.2
Stress-related symptoms	60	43	17 (5; 27)	64	42	22 (5; 39)
Fear of cancer/serious disease	42	37	5 (-6; 16)	36	35	1 (-18; 16)
Visits for complaints last 2 yrs (0/1-5/>5)	26/66/8	25/64/11	p=0.51	12/78/10	18/69/13	p=0.73
Alarm symptoms						
Weight loss last year	25	32	7 (-3; 17)	18	35	17 (1; 31)
Nocturnal symptoms	60	50	10 (-1; 21)	58	51	7 (-11; 24)
Observed blood in stools	16	18	2 (-6; 11)	18	17	1 (-11; 17)
Colon cancer in first-degree relatives	10	12	2 (-5; 9)	12	9	3 (-8; 17)
Milk-related symptoms	28	30	2 (-9; 12)	30	35	5 (-12; 21)

*Statistics are given as differences between groups with 95% confidence intervals, or with p-values.

We found, like others, that the GPs do not know or use strict symptom-based criteria to diagnose the FGID (1,3). How then do GPs distinguish between the FGIDs and organic diseases in daily practice? Our findings suggest that GPs often trust their clinical judgement without the need for verification by extensive tests or referrals, as only half of the diagnoses were considered verified even in the most frequent consulters. It is also likely that the GPs use other factors than merely abdominal symptoms to make a diagnosis for the complaints. In a general practice study from the UK, patients with IBS were more often women, feared cancer more often, attributed their complaints to stress, and consulted their GP more often compared with patients with organic disease (1). In our study, there were no significant differences between patients with FGID and organic diseases for these and other characteristics, except for "stress-related symptoms", which predicted FGID, and "weight loss last year", which predicted organic disease in those with a verified diagnosis. A recently published study shows that GPs often believe that symptoms in the FGID are related to psychological factors (3). It is also shown that denial of a role of stress in explaining abdominal symptoms predicts referral to specialists (1,5). We suggest that the GPs might use stress-related symptoms in distinguishing between functional disorders and organic disease. Whether stress-related symptoms play a greater role in the FGID than in organic diseases remains unclear.

Symptoms that may predict organic disease (alarm symptoms) are considered to be important in the diagnostic evaluation of patients with abdominal complaints. Guidelines for FGID define weight loss, blood in the stools, and nocturnal symptoms as alarm symptoms, which should lead to further investigations (6-8). However, the predictive values of alarm symptoms in patients with dyspepsia in primary care are questionable, and the decision on whether and how to investigate is complex (9,10). In our study, the only alarm symptom that predicted organic disease was "weight loss last year". This predictor was found only in those with a verified diagnosis. On the other hand, we fail to confirm that "observed blood in the stools" predicts organic disease. Two studies have shown that rectal bleeding is associated with cancer in general practice (11,12). However, one study of subjects with IBS found blood in the stools to be frequent and not associated with organic disease (13). Nocturnal symptoms were present in half of the patients, and more often in patients with FGID than in patients with organic disease (p=0.07). One study has found nocturnal awakening to be associated with organic dyspepsia (14). Milk intolerance, defined as worsening of abdominal complaints by intake of milk products, was reported by one-third of the patients, suggesting lactose malabsorption (LM). However, the clinical value of detecting LM seems unclear (15-17).

Strengths and limitations

A particular strength of the study is the high participation rate among the patients (see Fig. 1)

and the design of the study, which allowed the GPs to perform their practice as usual. This should minimize the risk for selection bias and ensure that the GPs' diagnoses are representative of "real life" diagnoses. However, some limitations need to be considered. The observed proportion of patients who wished to consult for abdominal complaints may be an overestimate, as some of the patients might have been reminded about minor complaints that they wished to discuss with the GP in addition to the planned agenda for the consultation.

Another limitation of our study is the lack of a gold standard for the diagnosis of FGID and organic disease. It may be questioned whether the GPs' diagnoses identify patients with "true" functional disorders and organic diseases. It is also possible that organic diseases such as diverticulosis coexist with FGIDs such as IBS in some patients. Although it is likely that the FGIDs could have been better classified with the use of strict criteria, we have no reason to believe that the distinction between FGIDs and organic diseases is incorrect.

Since the sample size is limited and the confidence intervals are wide, clinically significant differences might have been missed (type II error). However, there was no trend towards any clinical significant differences apart from the reported predictors. Our selection of patient characteristics was limited, and did not include a thorough characterization of abdominal symptoms. Guidelines suggest that identification of the typical abdominal symptoms within the various FGID syndromes is the key to a correct and confident diagnosis (6–8,18). We do not know to what extent GPs use such characteristics in their daily practice, although we have shown that few use strict criteria.

The lack of predictive value for alarm symptoms (blood in stools, nocturnal symptoms, milk intolerance) in this study, except weight loss, should be interpreted with caution. For example, not all organic diseases are associated with blood in the stools, nocturnal symptoms, or hereditary factors. It is also possible that our simple questionnaire is likely to be less accurate than the detailed assessment of alarm symptoms by an experienced doctor. Interestingly, a recent review on the diagnosis of IBS suggests that alarm symptoms are suitable for use in questionnaires (19).

Conclusion and implications for future research

Abdominal complaints represent a significant workload and a diagnostic challenge in general practice. The similar characteristics in patients with FGIDs and organic diseases make this distinction difficult. Whether the typical symptoms defined by the criteria for FGID are more helpful in distinguishing patients

with FGIDs from those with organic diseases should be evaluated.

ACKNOWLEDGEMENTS

The authors express their gratitude to the participating GPs and practice staff. The study was funded by an unrestricted grant from Glaxo Smith Kline, Norway and from a research fund at Innlandet Hospital Health Authority.

REFERENCES

1. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. *Gut* 2000;46:78–82.
2. Kristensen P, Sandbakken P, Johannessen T, Løge I, Hafstad PE, Petersen H, et al. Gastrointestinal disorders in general practice. *Tidskr Nor Lægeforen* 1985;11:728–31.
3. Gladman LM, Gorard DA. General practitioner and hospital specialist attitudes to functional gastrointestinal disorders. *Aliment Pharmacol Ther* 2003;17:651–4.
4. Bleijenberg G, Fennis JF. Anamnestic and psychological features in diagnosis and prognosis of functional abdominal complaints: a prospective study. *Gut* 1989;30:1076–81.
5. Van der Horst HE, van Dulmen AM, Schellevis FG, van Eijk JT, Fennis JF, Bleijenberg G. Do patients with irritable bowel syndrome in primary care really differ from outpatients with irritable bowel syndrome? *Gut* 1997;41:669–74.
6. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999;45 (Suppl 2):II43–7.
7. Dent J, Jones R, Kahrilas P, Talley NJ. Management of gastro-oesophageal reflux disease in general practice. *BMJ* 2001;322:344–7.
8. Jones J, Boorman J, Cann P, Forbes A, Gomborone J, Heaton K, et al. British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. *Gut* 2000;47(Suppl 2):ii1–19.
9. Meineche-Schmidt V, Jørgensen T. "Alarm symptoms" in patients with dyspepsia: A three year prospective study from general practice. *Scand J Gastroenterol* 2002;37:999–1007.
10. Meineche-Schmidt V, Jørgensen T. "Alarm symptoms" in dyspepsia. How does the general practitioner investigate? *Scand J Prim Health Care* 2003;21:224–9.
11. Wauters H, Van Casteren V, Buntinx F. Rectal bleeding and colorectal cancer in general practice: diagnostic study. *BMJ* 2000;321:998–9.
12. Helfand M, Marton KI, Zimmer-Gembeck MJ, Sox HC, Jr. History of visible rectal bleeding in a primary care population. Initial assessment and 10-year follow-up. *JAMA* 1997;277:44–8.
13. Talley NJ, Phillips SF, Melton LJ, Mulvihill C, Wiltgen C, Zinsmeister AR. Diagnostic value of the Manning criteria in irritable bowel syndrome. *Gut* 1990;31:77–81.
14. Stanghellini V, Anti M, Porro GB, Corinaldesi R, Gasbarini G, Giacosa A, et al. Risk indicators of organic diseases in uninvestigated dyspepsia: a one-week survey in 246 Italian endoscopy units. *Eur J Gastroenterol Hepatol* 1999;11:1129–34.
15. Tolliver BA, Jackson MS, Jackson KL, Barnett ED, Chastang JF, DiPalma JA. Does lactose maldigestion really

- play a role in the irritable bowel? *J Clin Gastroenterol* 1996;23:15–7.
16. Parker TJ, Woolner JT, Prevost AT, Tuffnell Q, Shorthouse M, Hunter JO. Irritable bowel syndrome: is the search for lactose intolerance justified? *Eur J Gastroenterol Hepatol* 2001;13:219–25.
 17. Suarez FL, Savaiano DA, Levitt MD. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N Engl J Med* 1995;333:1–4.
 18. Talley NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? *Lancet* 2002;360:555–64.
 19. Olden KW. Diagnosis of irritable bowel syndrome. *Gastroenterology* 2002;122:1701–14.

Paper II

Diagnosing Irritable Bowel Syndrome: Poor Agreement Between General Practitioners and the Rome II Criteria

P. O. Vandvik, L. Aabakken & P. G. Farup

Dept. of Medicine, Innlandet Hospital Health Authority, Gjøvik, Norway; Unit for Applied Clinical Research, Norwegian University of Science and Technology, Trondheim, Norway; Dept. of Medicine, Rikshospitalet University Hospital, Oslo, Norway

Vandvik PO, Aabakken L, Farup PG. Diagnosing irritable bowel syndrome: poor agreement between general practitioners and the Rome II criteria. *Scand J Gastroenterol* 2004;39:448–453.

Background: The new guidelines for diagnosing irritable bowel syndrome (IBS) in clinical practice recommend the use of the Rome II criteria. In this study the agreement between general practitioners (GPs) and the Rome II criteria for diagnosing of IBS and functional bowel disorders (FBD) is examined. **Methods:** Consecutive patients in general practice were asked to report on abdominal complaints, for which they had consulted or wanted to consult a GP. Patients with such complaints completed a questionnaire based on the Rome II criteria for FBD. After consultations, the GPs reported their diagnoses on the abdominal complaints. **Results:** Of 3097 screened patients, 553 patients were diagnosed by their GP and had complete data in the questionnaire. Of these patients, 107 had IBS according to the GPs and 209 had IBS according to the Rome II criteria (agreement 58%, kappa 0.01 (CI: -0.06; 0.09)). Agreement on IBS and FBD in patients without organic disease, without reflux or dyspepsia and in patients with a verified diagnosis was 45%–58%, with kappa values from -0.02 to 0.13. IBS and FBD cases were diagnosed by the Rome II criteria more often than by the GPs in all these groups of patients ($P < 0.001$). In patients with diagnostic discrepancies concerning IBS, 'stress-related symptoms' was predictive of a diagnosis of IBS made by the GPs only (OR 2.17 (CI: 1.1; 4.2)). **Conclusions:** This study shows poor agreement in the diagnosis of IBS between GPs and the Rome II criteria. Therefore, current knowledge about IBS based on strict criteria is not necessarily transferable to patients with IBS in general practice.

Key words: Diagnosis; general practice; irritable bowel syndrome; Rome II criteria

Per Olav Vandvik, M.D., Dept. of Medicine, Innlandet Hospital Health Authority, Gjøvik, Kyrre Greppsgt. 11, NO-2819 Gjøvik, Norway (fax. +47 61157439, e-mail. per.vandvik @start.no)

As long as there are no diagnostic tests available, diagnosing irritable bowel syndrome (IBS) will be a challenge for general practitioners (GPs). New guidelines recommend a positive diagnosis, based on the presence of typical symptoms, absence of alarm symptoms and absence of structural and metabolic abnormalities to explain the symptoms (1–3). By employing symptom-based criteria, such as the Rome II criteria (3), this diagnostic strategy could be facilitated. These criteria are used in clinical studies, and are also recommended for use in clinical practice (4–6). Nevertheless, the criteria are largely unknown and are poorly validated in general practice, where most patients are treated (6–8). If data from research and clinical practice are to be compared, diagnoses in research and practice must be comparable or, ideally, identical (6).

The primary aim of this study was to assess the agreement between the GPs' diagnosis of IBS and the diagnosis of IBS according to the Rome II criteria. Furthermore, agreement was assessed for the diagnosis of functional bowel disorders (FBD), which is a generic term for IBS, functional diarrhoea, functional constipation and functional abdominal bloating, to

investigate whether a broader definition of bowel disorders altered the agreement. Possible explanatory factors in cases of diagnostic discrepancy for IBS were also explored.

Materials and Methods

General practitioners and patients

The study was carried out in the county of Oppland, which comprises 110,000 inhabitants served by 99 GPs and one hospital. In Norway, patients must seek medical care through their locally assigned GP. The study period was from February to April 2001, during 10 days of practice for each participating GP. Different practices were selected to obtain a variety of GPs, practice types and patient profiles. Members of the practice staff were responsible for conducting the study, and were released from other duties and trained to ensure satisfactory protocol adherence in a busy clinical setting.

Consecutive patients aged 18 years or older consulting their GPs were asked to report on abdominal complaints, using a brief paper questionnaire administered in the waiting-room. Patients with abdominal complaints within the past three

months for which they either had consulted or wished to consult the GP were eligible for this study. This selection was chosen to identify patients who were likely to have had a diagnosis for the abdominal complaints made by the GP. These patients were asked for informed consent to participate in the study.

Patient questionnaires and Rome II diagnosis

Before the consultation, the patients included in the study answered a detailed questionnaire concerning gastrointestinal symptoms within the past three months. Questions were based on the Rome II criteria (Modular Questionnaire) for FBD. The process of translating the questions into Norwegian included several revisions by experienced specialists and one general practitioner. Patients were also characterized regarding duration (more than one year), severity (mild/moderate/severe) and frequency (number of days per week) of abdominal pain/discomfort. Two questions assessed the relation between abdominal complaints and stress/psychological factors ('stress-related symptoms') and patients' fear of cancer or other serious disease. The questionnaire was administered on a handheld computer (Palm m100[®]), programmed (Pendragon Forms[®]) to classify diagnoses according to the Rome II criteria for FBD. The questions were presented one by one on the screen, requiring an answer before the next question was presented. Patients entered their answers by touching the corresponding buttons on the screen, assisted by practice staff, if necessary.

General practitioners' diagnoses

After the consultation, the GPs answered questions presented in the electronic questionnaire, blinded to the

patients' answers. If the abdominal complaints had been sufficiently evaluated, the GPs reported the diagnosis by choosing one option from a list of clinically relevant diagnoses within three predefined categories (functional gastrointestinal disorder, organic gastrointestinal disease, or other disease) (Fig. 1).

In order to evaluate the reliability of the diagnoses, the GPs were asked whether their diagnoses were considered to be verified or not. The GPs were instructed to interpret 'verified' meaning that for the functional gastrointestinal disorders, they had no evidence of organic disease, and for the organic diseases, that tests had confirmed organic disease. In addition, the GPs reported whether the patient was known from earlier consultations, whether a new visit for abdominal complaints was scheduled, and the number of visits for abdominal complaints during the past two years (0/1–5/>5).

The GPs were instructed to manage their patients according to ordinary clinical practice, with no special attention to the study, and they received no formal information about IBS. GPs' age, sex, professional experience and knowledge of diagnostic criteria were recorded.

Analysis of patient groups

Assessment of agreement was performed in five groups of patients (Fig. 2). The analysis was primarily carried out in all patients with complete data in the questionnaire and with a diagnosis of the abdominal complaints made by their GP (Group A). To evaluate the reliability of the results in group A, the same analyses were done in the following selections of patients: Group B (patients in group A without verified organic disease, as Rome II criteria demand absence of organic disease), group C (patients in group A without a GP's

Functional GI disorder	Organic GI disease	Other diseases
Functional reflux	Infect. gastroenteritis	Renal--Urinary
Functional dyspepsia	GERD/Oesophagitis	Gynaecology
IBS	Ulcer disease	Other malignancy
Functional diarrhoea	Small bowel disease	Drug adverse event
Functional constipation	Food intolerance	Psychiatric disease
Functional bloating	Liver disease	
Functional abdominal pain	Biliary disease	
Functional GI--other	Pancreatic disease	
	IBD	
	Diverticulosis/-itis	
	Ano-rectal disease	
	Adherences	
	GI--malignancy	
	Other GI disease	



Fig. 1. General practitioners' (GPs') diagnostic options in the electronic questionnaire. The GPs first selected one of the three main groups, and were then presented with several options within the selected group, of which only one could be chosen. The picture shows the handheld computer. GI = gastrointestinal; IBS = irritable bowel syndrome; IBD = inflammatory bowel disease; GERD = gastroesophageal reflux disease.

diagnosis of heartburn or dyspepsia, as heartburn and dyspepsia often occur together with IBS and the GPs were only allowed to choose one diagnosis), group D (patients who consulted the GP for abdominal complaints the same day) and group E (patients in group D with a verified diagnosis).

In order to examine possible explanatory factors in cases of diagnostic discrepancy, two groups of patients within group A were compared: patients with IBS according to the GP but not according to the Rome II criteria ('GP IBS only') and patients

with IBS according to the Rome II criteria but not according to the GP ('Rome II IBS only').

Statistics

Agreement was assessed using kappa statistics. Differences between- and within groups were evaluated with the chi-squared test, the Mann-Whitney U test and the MacNemar tests. Multivariate analysis was done using stepwise logistic regression to identify the characteristics of patients with

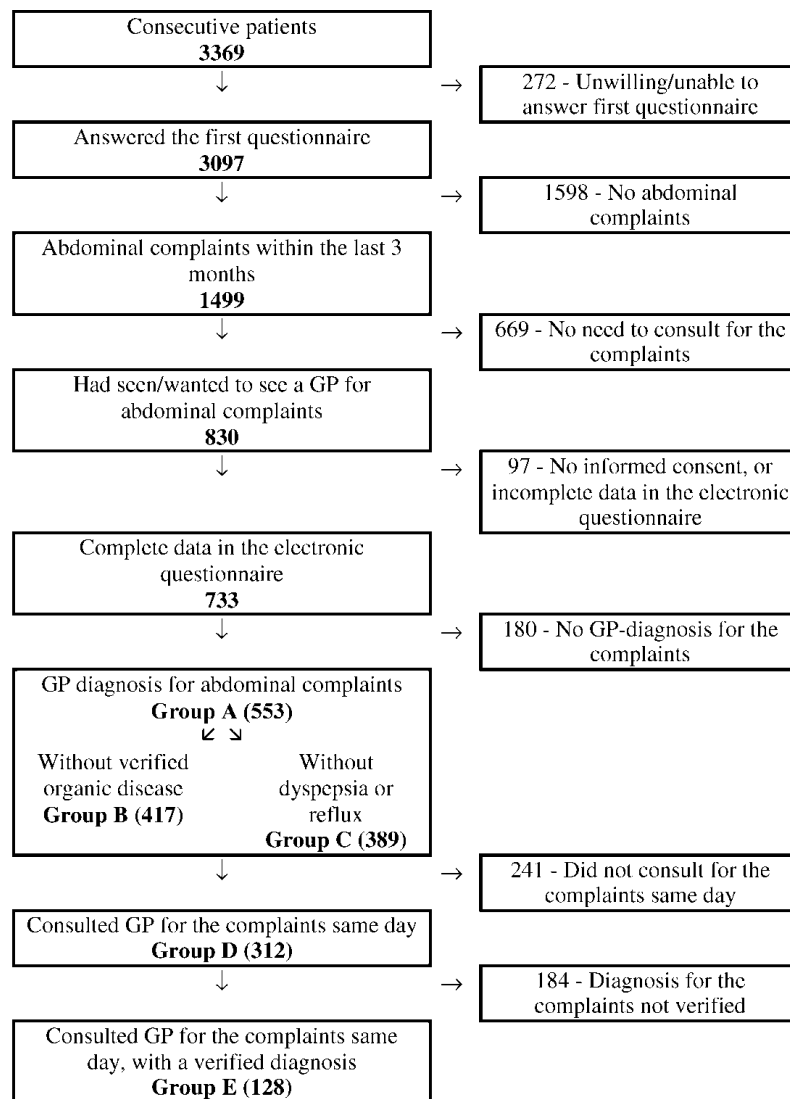


Fig. 2. Flow chart of patients in the study, with the groups of patients selected for agreement analysis shown in boxes (groups A–E).

Table I. Characteristics of all patients with complete data in the questionnaire and a diagnosis made by the general practitioner (GP) (group A), and in patients with 'Rome II IBS only' and 'GP IBS only', with a comparison between the last two groups. The results are given as percentages, if not otherwise indicated

Patient characteristics	All patients (Group A)	'Rome II IBS only'	'GP IBS only'	Statistics
No. of patients	553	167	65	
Mean age (years)	51.6	52.2	46.8	$P = 0.03$
Females	65	65	77	n.s. ($P = 0.07$)
Duration of abdominal complaints >1 year	79	80	83	n.s. ($P = 0.20$)
Abdominal pain/discomfort severity (mild/moderate/severe)	31/56/12	30/54/16	26/68/6	ns ($P = 0.67$)
Abdominal pain/discomfort frequency (0–3/4–5/>5 days)	64/15/21	58/15/27	66/14/15	$P = 0.03$
Stress-related symptoms	54	56	74	$P = 0.014$
Fear of cancer/serious disease	32	35	34	ns ($P = 0.92$)
Verified diagnosis	50	47	52	ns ($P = 0.53$)
Patient known by GP	94	95	95	ns ($P = 0.81$)
New consultation for abdominal complaints scheduled	29	33	19	$P = 0.03$
Visits for abdominal complaints last 2 years (0/1–5/>5)	25/66/8	25/61/14	20/70/9	ns ($P = 0.90$)

diagnostic discrepancies concerning IBS. P -values of less than 0.05 were regarded as statistically significant and 95% confidence intervals (CI) were calculated. Statistical analyses were carried out using SPSS for Windows® v. 10 and StatXact® v. 5.

Ethics

The study was conducted according to the Declaration of Helsinki, and approved by the Regional Committee for Medical Research Ethics in Oslo, and the Data Inspectorate, Oslo, Norway.

Results

General practitioners

Out of 12 invited general practices, 9 participated in this study, each with 2 to 5 GPs. Owing to insufficient capacity, three practices and five GPs did not participate. Three centres were located in a town with 18,000 inhabitants, and six were located in the countryside.

Twenty-six GPs (20 M and 6 F) median age 45 years (range 26–68) participated in the study. The GPs reported a median number of 16 years in general practice (range 0–38) and a median of 10 years in the current practice (range 0–20) and 15 were specialists in general practice. Twenty-three GPs had never heard of diagnostic criteria for IBS. Three GPs had

heard of, but did not use, such criteria. None reported a special interest in gastroenterology.

Patients

Of 3369 consecutive patients, 3097 (92%) answered the first questionnaire in the waiting-room. The flow of patients screened for abdominal complaints and the number of patients included in the groups analysed for agreement are itemized in Fig. 2. Characteristics of the 553 patients in group A are presented in Table I.

Agreement between general practitioners and the Rome II criteria

Tables II and III show the number of patients with diagnoses of IBS and FBD in group A, and the agreement between the GPs and the Rome II criteria. Agreement for IBS and FBD in groups B–E ranged from 45% to 58%, with kappa values from -0.02 to 0.13 . These kappa values did not differ significantly from zero (data not shown), except for the diagnosis of FBD in group B (kappa 0.12 (95% CI: 0.003 ; 0.13)). In all groups, IBS was diagnosed significantly more often ($P < 0.001$) by the Rome II criteria than by the GPs (data shown only for group A in Table II).

In group A, 167 patients had 'Rome II IBS only'. In these patients, the GPs diagnosed other functional disorders, organic gastrointestinal diseases and other diseases in 78 (46.7%), 68 (40.7%) and 21 (12.6%) patients, respectively.

Table II. Number of patients with a diagnosis of IBS, according to the Rome II criteria and according to the general practitioners, in group A. The agreement for IBS was 58% (kappa 0.01 (95% CI: -0.06 ; 0.09))

		General practitioner IBS		
		Yes	No	Total
Rome II IBS	Yes	42	167	209
	No	65	279	344
	Total	107	446	553

IBS = irritable bowel syndrome.

Table III. Number of patients with a diagnosis of FBD, according to the Rome II criteria and according to the general practitioners, in group A. The agreement was 49% (kappa 0.05 (95% CI: 0.003 ; 0.13))

		General practitioner FBD		
		Yes	No	Total
Rome II FBD	Yes	136	225	361
	No	56	136	192
	Total	192	361	553

FBD = functional bowel disorder.

Explanatory factors in patients with diagnostic discrepancies

Differences between groups of patients within group A with diagnostic discrepancies concerning IBS ('GP IBS only' and 'Rome II IBS only') are listed in Table I. By logistic regression analysis, 'stress-related symptoms' (OR 2.17 (95% CI: 1.12; 4.2)) and low frequency of symptoms (OR 1.32 (95% CI: 1.01; 1.72)) were the only significant predictors of a diagnosis of IBS only, according to the GPs.

Discussion*Principal findings*

To our knowledge, this is the first study in which diagnosis of IBS according to GPs and to the Rome II criteria is compared. The main finding is the poor agreement between the GPs' diagnosis of IBS and the diagnosis of IBS according to the Rome II criteria, with kappa values reflecting agreement by chance. This finding implies that GPs do not identify the same group of patients as the criteria do. As most current knowledge about IBS, such as proven efficacy of novel therapies, is based upon patients fulfilling such criteria, this knowledge cannot necessarily be transferred to general practice where most patients are diagnosed and treated. The fact that agreement remained poor for the wider diagnosis of FBD in this study supports our finding of poor agreement for IBS but was unexpected. In a British study, the GPs diagnosed IBS in 58% of patients who merited it (according to the Rome criteria and a consensus expert opinion), but a further 22% were given a functional label, so 80% were correctly called functional (9). We therefore expected agreement to increase for a broader definition of IBS, as the British investigators suggested that specific diagnostic labels were of little importance to the GPs.

Another noteworthy finding is that the Rome II criteria diagnosed IBS approximately twice as often as the GPs. This is in conflict with a recent report suggesting that these criteria are too restrictive for clinical practice (10). It is likely that more patients with IBS will be identified if GPs increase their knowledge about the typical symptoms of IBS.

The poor agreement observed in this study raises the question of how GPs diagnose IBS. In our study, few GPs had heard of diagnostic criteria and none applied such regularly, which is in harmony with earlier findings (7, 8). The fact that 'stress-related symptoms' were reported more often in patients with 'GP IBS only' than in patients with 'Rome II IBS only', suggests that GPs use other characteristics than merely abdominal symptoms in the diagnostic evaluation. This is in accordance with results from a study of British general practice (9). In the same study it was found that a major predictor of specialist referral was that the patient denied the role of stress in their symptoms. We postulate that GPs will more readily conclude with a functional diagnosis in patients reporting stress-related symptoms, since the patients will more readily accept the diagnosis. Patients with 'Rome II IBS only' reported more frequent abdominal pain/discomfort

than patients with 'GP IBS only'. This is probably due to the definition of IBS in the Rome II criteria, which requires that symptoms are present, at least every fourth week.

Strengths and weaknesses

Owing to the high response rate (92%), the patients in this study should be representative of the real population in general practice. The study design, which allowed GPs to practice 'business as usual', was carefully chosen to ensure that the GPs' diagnoses reflected diagnoses given to patients in this clinical setting. The reliability of the GPs' diagnoses is further supported by the fact that nearly all patients included in the agreement analysis were already known by their locally assigned GP. This should also minimize the risk of missing known organic disease.

However, some methodological limitations should be considered. First, symptom questions were translated from the published Rome II criteria (Modular Questionnaire) and applied in electronic questionnaires. The translated Norwegian version of the questionnaire was not formally validated, and no such versions are available in Norway. The Rome II questionnaires are developed for clinical investigation and clinical practice, but a recent publication states that 'Rome criteria and questionnaires remain works in progress' (11). Regarding the use of electronic questionnaires, handheld computers are well accepted by patients, with good data quality and reliability, in various clinical settings (12). We therefore believe our electronic questionnaires provided good data on bowel symptoms and correct classification of Rome II diagnoses. Second, the Rome II criteria require absence of structural or metabolic abnormalities to explain the symptoms. The computerized Rome II criteria did not include a clinical judgement, which possibly could have influenced diagnosis. Still, agreement did not improve to reach satisfactory values when patients with verified organic disease (group B) were excluded from the analysis. Third, the GP was only allowed to choose one diagnosis for the complaints. Surely patients may have multiple abdominal symptoms at the same time; for instance both heartburn- and IBS symptoms, and they probably present the currently most bothersome symptoms to the GP. Agreement did not, however, improve when we excluded patients with a GP diagnosis of dyspepsia or heartburn (group C) from the analysis. Fourth, if the GP suggested a diagnosis for the complaints based only on earlier knowledge of the patient, he or she may have chosen a diagnostic option representing symptoms not reported by the patient at the time of consultation, due to the fluctuating course of functional gastrointestinal disorders. The fact that agreement remained unchanged in patients consulting the GP for abdominal complaints the same day (group D), does not indicate that this has confounded our results.

Implications for clinical practice and future research

Our findings have important clinical implications as they question the use of diagnostic criteria for IBS in general

practice. In both epidemiological and clinical research, diagnostic criteria are clearly necessary to ensure homogeneity in study populations. In clinical practice, a positive symptom-based diagnosis of IBS may increase both the patients' and the GPs' confidence in the diagnosis, reduce anxiety about cancer and reduce the need for costly and potentially harmful tests (4, 9). However, whether diagnostic criteria are a necessary tool to make such a positive diagnosis in general practice, and which diagnostic criteria perform best, remains unanswered. One study of the Rome criteria has shown high predictive values for IBS, in the absence of red flags (13). This finding is, however, based on selected patients. It has been suggested that the Rome II criteria may be unnecessarily complicated for clinical practice. A Swedish group has shown that simpler criteria show satisfactory agreement with the Rome criteria (14). Saito et al. have demonstrated good agreement between all commonly used definitions of IBS (Manning, Rome I and Rome II) but it remains unclear which study definition is the 'best for clinical use' (15). If the criteria are applied in time-consuming questionnaires, it is also possible that attention may be drawn away from the clinical encounter and they may represent an obstacle for successful doctor-patient interaction. Another issue of interest is whether characteristics that occur frequently in patients with IBS, such as psychosocial problems and non-gastrointestinal symptoms, should be implemented in future diagnostic criteria for IBS. Such characteristics could, for instance, be added in the additional criteria cumulatively to support the diagnosis of IBS. More research is needed to clarify this issue. We conclude that IBS remains a diagnostic challenge for the GP, and that the role of the Rome II criteria is unclear in this clinical setting. Given the potential benefits of a positive, symptom-based diagnostic strategy, future research should address the applicability and validity of diagnostic criteria for IBS in general practice.

Acknowledgements

The study was funded by an unrestricted grant from GlaxoSmithKline(GSK), and from a research fund at Innlandet Hospital Health Authority. We thank the participating practice staff and the following GPs: Dag Lunder, Ivar Skeie, Gro Leonardsen (Åslundmarka, Gjøvik); Sidsel L. Berge, Thomas Schopf (Gran); Per Erik Bø, Anders Sollien (Bøverbru); Stefan Løfsløtten, Marlene Andersen, Vebjørn

Noddeland (Torpa); Øyvind Bekkhus, Geirr Karlsson (Odnes); Bent Monsbakken, Karin Monsbakken, Hedinn Sigurdsson, Lene Dæhlen Selnes, Niels Jahren (Sørbyen, Gjøvik); Karin Frydenberg, Erling Egenæss, Arjan Nieland (Skreia); Tore Mellbye, Morten Breiby (Gjøvik); Knut B. Kielland, Jens A. Mørch, Alamdar Khourawi, Trond Fladsrud (Hov)

References

1. Jones J, Boorman J, Cann P, Forbes A, Gomborone J, Heaton K, et al. British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. *Gut* 2000;47 Suppl 2:ii1-19.
2. Talley NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? *Lancet* 2002;360:555-64.
3. Drossman DA. The functional gastrointestinal disorders and the Rome II process. *Gut* 1999;45 Suppl 2:II1-II5.
4. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999;45 Suppl 2:II43-II7.
5. Olden KW. Diagnosis of irritable bowel syndrome. *Gastroenterology* 2002;122:1701-14.
6. Agreus L. Rome? Manning? Who cares? *Am J Gastroenterol* 2000;95:2679-81.
7. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome: the view from general practice. *Eur J Gastroenterol Hepatol* 1997;9:689-92.
8. Gladman LM, Gorard DA. General practitioner and hospital specialist attitudes to functional gastrointestinal disorders. *Aliment Pharmacol Ther* 2003;17:651-4.
9. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. *Gut* 2000;46:78-82.
10. Boyce PM, Koloski NA, Talley NJ. Irritable bowel syndrome according to varying diagnostic criteria: Are the new Rome II criteria unnecessarily restrictive for research and practice? *Am J Gastroenterol* 2000;95:3176-83.
11. Thompson WG, Irvine EJ, Pare P, Ferrazzi S, Rance L. Functional gastrointestinal disorders in Canada: first population-based survey using Rome II criteria with suggestions for improving the questionnaire. *Dig Dis Sci* 2002;47:225-35.
12. Koop A, Mosges R. The use of handheld computers in clinical trials. *Control Clin Trials* 2002;23:469-80.
13. Vanner SJ, Depew WT, Paterson WG, DaCosta LR, Groll AG, Simon JB, et al. Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. *Am J Gastroenterol* 1999;94:2912-7.
14. Agreus L, Talley NJ, Svardsudd K, Jones MP. Identifying dyspepsia and irritable bowel syndrome: the value of pain or discomfort, and bowel habit descriptors. *Scand J Gastroenterol* 2000;35:142-51.
15. Saito YA, Locke GR, Talley NJ, Zinsmeister AR, Fett SL, Melton LJ III. A comparison of the Rome and Manning criteria for case identification in epidemiological investigations of irritable bowel syndrome. *Am J Gastroenterol* 2000;95:2816-24.

Received 14 October 2003

Accepted 17 December 2003

Paper III

Comorbidity of irritable bowel syndrome in general practice: a striking feature with clinical implications

P. O. VANDVIK*·§, I. WILHELMSSEN†, C. IHLEBÆK‡ & P. G. FARUP*·§

*Department of Medicine, Innlandet Hospital Health Authority, Gjøvik; †Institute of Medicine, Haralds plass Deaconal Hospital, Bergen; ‡Department of Biological and Medical Psychology, University of Bergen, Bergen; §Unit for Applied Clinical Research, NTNU, Trondheim, Norway

Accepted for publication 24 August 2004

SUMMARY

Background: Somatic comorbid symptoms might identify irritable bowel syndrome patients with different aetiologies and needs of treatment.

Aims: To measure comorbid symptoms in patients with irritable bowel syndrome in general practice, and to explore characteristics of patients with low, intermediate and high somatic comorbidity.

Methods: Prospective study of 208 of 278 consecutive patients with irritable bowel syndrome (Rome II) in nine general practices. Questionnaires assessed 22 comorbid symptoms (subjective health complaint inventory), psychosocial factors including psychological distress (Symptom Check list-10) and quality of life (Short form-12). Subjective health complaint data from 1240 adults (controls) constituted a reference material. Patients with low, intermediate and high somatic

comorbidity were identified by a somatic comorbidity score (17 subjective health complaint items). Health care seeking was assessed after 6–9 months.

Results: Patients with irritable bowel syndrome (67% females, mean age 50, s.d. 16) reported 20 of 22 comorbid symptoms significantly more frequent than controls (odds ratios = 2–7, $P < 0.001$). The somatic comorbidity score correlated with psychological distress ($R = 0.46$, $P < 0.001$). Patients with high somatic comorbidity reported higher levels of mood disorder, health anxiety, neuroticism, adverse life events and reduced quality of life and increased health care seeking when compared to those with low and intermediate somatic comorbidity (P -values < 0.05).

Conclusions: Our findings support the hypothesis that structured assessment of comorbid somatic symptoms might identify subgroups with different aetiology and needs of treatment.

INTRODUCTION

Most patients with irritable bowel syndrome (IBS) are cared for by their general practitioner (GP), but most knowledge about this prevalent and poorly understood disorder of the brain-gut axis remains to be based on a small subset of referred patients.¹ An intriguing feature

of IBS is the frequent comorbidity with other disorders and symptoms, which questions whether IBS represents a specific diagnostic entity or a part of a functional somatic syndrome.^{2–4} A recent systematic review of the comorbidity of IBS concludes that IBS most likely is a distinct disorder.⁵ The authors propose a dual-aetiology hypothesis to explain the comorbidity of IBS. The excessive somatic symptoms are markers for somatization and identify a subgroup of patients with a predominantly psychological IBS aetiology, whereas patients with no comorbid conditions and few general

Correspondence to: Dr P. O. Vandvik, Department of Medicine, Innlandet Hospital Health Authority, Gjøvik, Kyrre Greppsgt. 11, 2819 Gjøvik, Norway.
E-mail: per.vandvik@start.no

physical complaints are more likely to have a predominantly biological IBS aetiology. If this hypothesis is supported by research, it would help to explain why both biological markers in the gut, such as visceral hypersensitivity or motility disturbances, are absent in one half of patients evaluated, and why most efforts to treat IBS, whether pharmacological or psychological, benefit only a subset of patients. The clinical implication of the hypothesis is that these two groups need to be identified, because they are likely to respond to different treatment strategies. We are not aware of any studies, which have tested this hypothesis in a general practice setting.

Our study was undertaken to explore characteristics, and in particular to measure comorbid symptoms, in patients with IBS in general practice. Secondly, we aimed to answer the following research question: Do patients with low, intermediate and high levels of somatic comorbidity (SC) constitute subgroups with different characteristics, natural course of symptoms and health care seeking (HCS) behaviour?

MATERIAL AND METHODS

Study design and material

This observational, prospective multicentre study was designed to identify and follow-up a representative sample of patients with IBS in Norwegian general practice. The study was carried out during 2001 in nine practices of different sizes in the county of Oppland, during 10 days of practice for each participating GP. Twenty-six GPs (20 males and six females) median age 45 years (range: 26–68) participated in the study. The GPs were instructed to manage their patients according to ordinary clinical practice. In Norway, patients must seek health care through their locally assigned GP. Members of the practice staff performed the practical work related to the study.

Consecutive adults aged 18 years or older consulting their GPs, were asked to report on abdominal complaints, using a brief paper questionnaire administered in the waiting room. Those with abdominal complaints within the past 3 months, for which they either had consulted or wished to consult the GP, were diagnosed according to the Rome II criteria for functional gastrointestinal disorders (FGID). This sampling procedure was chosen to identify patients with IBS (Rome II), as opposed to non-patients with IBS (those without a need

to consult their GP). Patients with IBS were invited to participate in the present study, if the GP had no knowledge of organic disease to explain their abdominal complaints. See Figure 1 for flow chart of patients. A thorough characterization of patients with IBS, with emphasis on comorbid symptoms, was accomplished by self-administered questionnaires completed at the first visit. After 6–9 months, included patients were followed up with an interview.

Questionnaires at the first visit

Sociodemographic variables, such as 12 different adverse life events within the past 6 months and present employment status were reported in a separate questionnaire.

Gastrointestinal (GI) symptoms within the past 3 months were assessed in an electronic touch-screen questionnaire. Questions were based on the Rome II criteria for IBS, functional dyspepsia and functional heartburn (modified Rome II modular questionnaire), translated to Norwegian by the authors.⁶ The duration (number of years), severity (mild, moderate and severe) and frequency (average number of days per week with symptoms) of abdominal pain/discomfort was recorded and an intensity score was calculated by multiplying the severity with the frequency (range: 0–12). Patients were asked whether stress and psychological worsened the abdominal complaints ('stress-related symptoms') and whether they feared that the abdominal complaints could be due to cancer/other serious disease ('fear of cancer').

Coexisting somatic and psychological symptoms and quality of life (QoL) were measured by standardized and validated questionnaires. Twenty-two somatic and psychological symptoms were assessed by the subjective health complaint (SHC) inventory, which consists of 29 common health complaints experienced the last 30 days.⁷ Seven items of GI symptoms were excluded. The intensity of each symptom in the SHC is graded on a 4-point scale (not at all/little/some/severe). Psychological distress was measured by a 10-item version of the Hopkins Symptom Check list (SCL-10) with the intensity of each symptom graded from 'not at all' to 'extremely'. The average item score is often used as a measure of psychological distress, with a cut off point of 1.85 recommended as a valid predictor of mood disorder (anxiety/depression).⁸ Health anxiety was measured with the Whitely index which consists

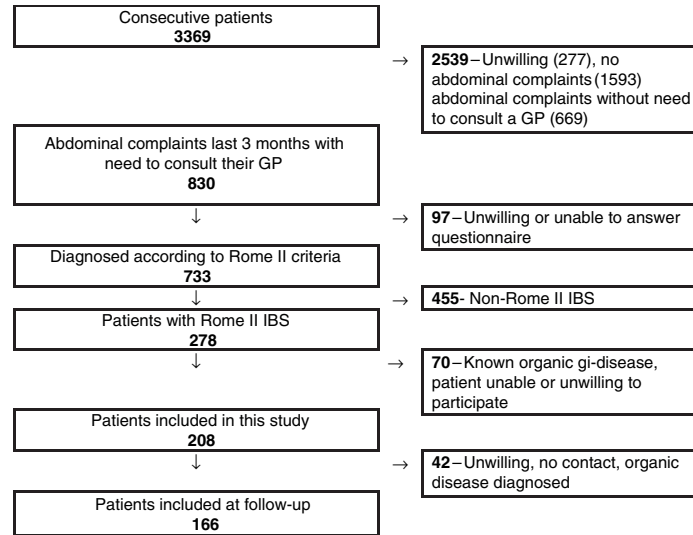


Figure 1. Flow chart of the patients in the study. GP, General Practitioner; IBS, irritable bowel syndrome.

of 14 questions, with the intensity of each symptom graded from 'not at all' to 'a great deal'.⁹ The personality trait neuroticism was measured by the Eysenck Personality Questionnaire (EPQ-10).¹⁰ Health-related quality of life (HRQoL) was measured by Short form-12 (SF-12), with summary physical (PCS) and mental (MCS) component scores.¹¹

Follow-up interview and measures of outcome

The patients were invited after 6–9 months to an interview with a member of the practice staff. GI symptoms were again reported in the electronic questionnaire. The natural course of IBS was measured as the presence or absence of abdominal pain/discomfort and the abdominal pain/discomfort intensity score within the last 3 months of the follow-up period.

Health care seeking, both related to IBS and for all causes, was measured as the number of visits to the GP (by examination of the computerized records) and alternative health care providers (by patients recall) during the last 6 months of the follow-up period.

Data analysis

Reference material for comorbid symptoms. The 22 non-GI symptoms assessed in patients with IBS by the SHC were compared with reference values from a Norwegian normal population, consisting of 1240 adults (53%

females, mean age 41 years) included in a cross-sectional survey in Norway during 1996.¹²

Comparison of patients with different levels of somatic comorbidity. The dual-aetiology hypothesis predicts that the absolute prevalence of comorbid symptoms are greater in IBS than in a normal population because of amplification processes, that the SC is correlated to psychological distress, that patients with predominantly biological or psychological aetiology can be reliably identified by counting comorbid symptoms and that a group of patients will display intermediate SC.

A SC score was created by adding the scores of 17-items in the SHC. Seven items of GI symptoms and 5-items associated with psychological distress (sleep problems, tiredness, dizziness, anxiety and depression) were excluded. We hypothesized that dividing patients with IBS into three groups with low, intermediate and high levels of SC would increase the chance of identifying those with a predominantly biological and psychological aetiology, in each end of the comorbidity spectrum. The reference population mean score was used to distinguish between low and intermediate comorbidity, the reference population mean \pm 2 s.d. to distinguish between intermediate and high comorbidity. These three groups of patients were compared for the assessed characteristics at the first visit, and for HCS and the natural course of IBS in the follow-up period.

Statistics. Comparisons between groups were analysed with chi-squared, Mann–Whitney *U*-, Student's *t*-tests and one-way ANOVA. A paired sample *t*-test was applied to analyse change of abdominal pain/discomfort intensity in the follow-up period. The association between SC (17-items in the SHC) and psychological distress (SCL-10) was assessed by correlation analysis (Pearson *r*). Chi-squared tests were performed to determine whether the observed differences in the SHC-items between patients with IBS and the reference population were effects of female gender. All statistical analyses were carried out with SPSS for Windows 11.0.

Ethics

The study was performed according to the Declaration of Helsinki, and approved by the Regional committee for Medical Research Ethics at the University of Oslo, and the Data Inspectorate, Oslo, Norway.

RESULTS

Characteristics of patients with IBS

Table 1 gives the characteristics of the 208 included patients. The 70 patients with IBS not included

Table 1. Characteristics of patients with IBS, reported at the first visit

Variable	Patients with IBS (<i>n</i> = 208)
Age (mean/s.d.)	50.3 (16)
Female gender (%)	67
Rome II heartburn (%)	40
Rome II dyspepsia (%)	10
Duration complaints (> 1 year, %)	79
Duration in years (median)	10 (range: 1–55)
APD-severity (mild/moderate/severe, %)	32/55/13
APD-frequency (0–3/4–5/> 5, %)	65/15/20
APD-intensity score (mean/s.d.)	4.4 (3.1)
IBS visits past 2 years (0/1–5/> 5, %)	39/52/7
Stress-related symptoms (yes/no, %)	56
Fear of cancer/serious disease (yes/no, %)	34
Mood disorder (SCL-10 score > 1.85, %)	38
Health anxiety (Whitely) (mean/s.d.)	25.9 (8.5)
Neuroticism (EPQ-10) (mean/s.d.)	4.1 (3)
Two or more of adverse life events (%)	31
Disability pension (%)	17
Quality of life-mental (mean/s.d.)	44.8 (11.7)
Quality of life-physical (mean/s.d.)	38.8 (11.6)

APD, abdominal pain/discomfort; IBS, irritable bowel syndrome; SCL, Symptom Check list; EPQ, Eysenck Personality Questionnaire.

(Figure 1) did not differ significantly from patients included in the study with regard to gender, age or GI symptom characteristics (data not shown). In the 208 patients with IBS, 117 (56%) consulted for abdominal complaints during the current consultation and 154 (74%) had consulted for such complaints earlier. No significant gender differences were found for the assessed characteristics, with the exception of age [53.8 years (s.d. 15.4) in males and 48.6 years (s.d. 16) in females, $P = 0.03$].

Table 2 shows that there were significant differences between patients with IBS and the reference population for all comorbid symptoms, except eczema and colds, flu. In the gender-adjusted analysis of comorbidity in patients with IBS and in the reference population, all the observed differences in the individual symptoms remained statistically highly significant ($P < 0.001$, data not shown).

Natural course of symptoms and use of health resources

After 6–9 months, 172 of 208 patients (83%) completed the follow-up interview, of whom six were excluded because they had been diagnosed with organic GI disease by the GP during the follow-up period. The 36 patients lost to follow-up did not differ significantly from patients included at follow-up for any of the baseline characteristics (data not shown). In the 166 patients, 145 patients (87%) reported abdominal pain/discomfort within the last 3 months. The intensity of abdominal pain/discomfort was significantly lower at follow-up (mean 3.6, s.d. 3.1) than at the first visit (mean 4.4, s.d. 3.2) ($P < 0.001$). Thirty-two patients (20%) had consulted their GP, and 11 patients (7%) had consulted alternative health care providers, for abdominal complaints. The overall numbers of visits to GPs was 3.7 (s.d. 2.9, range: 0–14) and to alternative health care providers 1.9 (s.d.: 0.6, range: 1–9), respectively.

Application of the dual aetiology hypothesis: patients with low, intermediate and high comorbidity

As predicted in the dual aetiology hypothesis, the SC score was significantly higher in patients with IBS (mean 13.0, s.d. 8.1) than in the reference population (mean 5.8, s.d. 5.1) ($P < 0.001$), showed a significant correlation with psychological distress ($R = 0.46$, $r^2 = 0.22$, $P < 0.001$) and displayed normal distributions in both groups.

Table 2. Percentage of any comorbid symptoms (score 1 or more) and of substantial comorbid symptoms (score 2 or more) in patients with IBS and in a Norwegian reference population (normals)

Variable	Patients with IBS (<i>n</i> = 208)		Normals (<i>n</i> = 1240)		Statistics (OR with 95% CI) IBS vs. normals	
	Any	Substantial	Any	Substantial	Any	Substantial
Headache	76	40	51	20	3.1 (2.2–4.3)	2.7 (2.0–3.8)
Neck pain	73	49	38	19	4.5 (3.2–6.3)	4.2 (3.1–5.7)
Upper back pain	50	32	18	10	4.5 (3.3–6.1)	4.2 (3.0–6.0)
Low back pain	71	43	40	19	3.7 (2.7–5.1)	3.2 (2.4–4.4)
Arm pain	60	34	23	12	4.8 (3.5–6.6)	3.8 (2.7–5.3)
Shoulder pain	69	43	38	20	3.6 (2.6–5.0)	3 (2.2–4.2)
Migraine	17	9	8	5	2.6 (1.7–3.9)	2 (1.2–3.5)
Leg pain	48	22	22	10	3.3 (2.4–4.6)	2.5 (1.7–3.8)
Palpitation	40	19	13	5	4.3 (3.1–6.0)	4.6 (2.9–7.2)
Hot flushes	39	20	9	3	6.9 (4.8–9.8)	8.3 (5.1–13.6)
Sleep problems	63	33	28	11	4.4 (3.2–6.0)	4 (2.8–5.7)
Tiredness	81	45	51	22	4.2 (2.9–6.1)	2.9 (2.1–3.9)
Dizziness	60	22	17	5	7.1 (5.1–9.7)	5.2 (3.4–7.9)
Anxiety	40	19	10	3	6 (4.2–8.5)	6.5 (4.0–10.6)
Depression	55	22	25	9	3.8 (2.8–5.1)	3 (2.1–4.5)
Asthma	20	12	5	3	4.9 (3.1–7.6)	5.3 (3.0–9.4)
Breathing difficulties	39	15	8	3	7 (5.0–10.2)	5.5 (3.2–9.2)
Eczema	18	7	14	5	1.4 (0.9–2.1)	1.4 (0.8–2.5)
Allergies	28	19	12	5	2.9 (2.0–4.2)	4.5 (2.9–7.1)
Chest pain	38	12	13	4	4.2 (3.0–6.0)	3.4 (2.0–5.9)
Colds, flu	45	24	49	23	0.8 (0.6–1.1)	1.02 (0.7–1.5)
Cough	37	19	23	8	1.9 (1.4–2.7)	2.5 (1.7–3.9)

IBS, irritable bowel syndrome; OR, odds ratio; CI, confidence interval.

All differences (both for any and substantial complaints) are statistically significant ($P < 0.001$) with the exception of eczema and colds, flu.

Table 3 gives the characteristics differences between patients with low (score ≤ 6), intermediate (score 7–16) and high SC (score >16).

At follow-up, patients with high SC reported higher intensity of abdominal pain/discomfort than patients with intermediate or low comorbidity, with mean scores of 4.4, 3.3 and 2.8 respectively ($P = 0.02$). Patients with high comorbidity had also visited their GP more frequently than those with intermediate or low comorbidity, with mean number of visits 4.4, 3.6 and 3.1, respectively ($P = 0.03$). No significant differences between these groups of patients were found for GP visits related to IBS or for visits to alternative health care providers.

DISCUSSION

This study clearly demonstrates that somatic comorbid symptoms are common features in patients with IBS in general practice. Although common in the population at whole, the odds for reporting 20 of 22 somatic and

psychological symptoms were two to seven times higher in patients with IBS, with similar results for complaints of substantial intensity. Likewise, other GI symptoms such as heartburn or dyspepsia were also reported by a substantial proportion of patients with IBS. These findings harmonize well with two other studies from general practice,^{13, 14} and suggest that comorbid symptoms are as frequent in patients with IBS in general practice as they are in referred patients.⁵ The estimated 38% prevalence of mood disorder is considerably higher than the prevalence of 11% in a Norwegian population and implies that levels of mood disorder in patients with IBS in general practice lie somewhere in between that observed in individuals with IBS who do not consult and in referred patients with IBS.^{8, 15} The observed levels of health anxiety and neuroticism are also likely to be higher than in a population without IBS, although we have no control group in our study to confirm these differences.¹⁶

Symptoms of IBS were in most patients, regardless of gender, of mild-to-moderate intensity, long-standing

Variable	Low comorbidity	Intermediate comorbidity	High comorbidity	P-values*
Number	42	100	61	
Age (mean/s.d.)	51 (16.6)	49 (17.0)	51 (13.7)	0.81
Female gender (%)	57	69	72	0.27
Duration IBS (>1 year, %)	62	84	84	0.01
Rome II heartburn (%)	29	37	53	0.01
Rome II dyspepsia (%)	20	7	8	0.07
APD-intensity score (mean/s.d.)	4 (3.6)	4.2 (2.6)	5 (3.4)	0.23
Stress-related symptoms (%)	33	61	66	0.007
Fear of cancer (%)	33	35	34	0.99
Health anxiety (Whitely, mean/s.d.)	22.5 (6.0)	24 (7.3)	31.6 (9.2)	< 0.001
Mood disorder (SCL-10, %)	13	32	63	< 0.001
Neuroticism (EPQ-10, mean/s.d.)	2.5 (2.3)	3.9 (2.9)	5.7 (2.8)	< 0.001
Two or more adverse life events (%)	11	33	51	< 0.001
Disability pension (%)	10	10	34	< 0.001
Quality of life-mental (mean/s.d.)	48.8 (11.6)	46.1 (11.3)	40.1 (11.0)	< 0.001
Quality of life-physical (mean/s.d.)	47.1 (10)	40.7 (10.8)	30.4 (8.4)	< 0.001

IBS, irritable bowel syndrome; APD, abdominal pain/discomfort; SCL, Symptom Check list; EPQ, Eysenck Personality Questionnaire.

* One way ANOVA or chi-squared tests.

and remarkably stable, with only a small proportion of patients frequently seeking health care for abdominal complaints. These data add to the evidence that IBS is less of a problem for patients handled in general practice than in those referred to specialists, although symptoms are likely to persist in the majority of patients.^{14, 17, 18}

Implications of the observed comorbidity and application of the dual-aetiology hypothesis

It may be questioned whether the excessive comorbidity observed in this study is in accordance with current understanding of IBS and of importance for the clinical handling of patients. Both somatic and psychiatric comorbidity are well known clinical features of patients with IBS which are associated with increased use of health resources and a poor outcome.^{17, 19–21} GPs recognize patients with IBS to be polysymptomatic and it has been suggested that non-colonic symptoms could result in a more accurate diagnosis of IBS.^{17, 22} However, although guidelines for IBS recommend a general therapeutic approach,

they place little emphasis on comorbid somatic symptoms.^{15, 23} We postulate that approaching only symptoms of IBS, whether it be by a well performed consultation or by novel drug therapies, will not ameliorate overall suffering or use of health resources in all patients with IBS.²⁴

The clinically significant differences in characteristics between patients with low and high SC suggest that subgroups of patients with different aetiologies and treatment needs do exist, and that they are possible to identify. However, the observed continuum of comorbid symptoms demonstrates clouds of patients with considerable overlapping, more than distinct subgroups with different aetiologies. Accordingly, with our defined cut off levels, most patients reported intermediate levels of SC. We agree that the hypothesis is an oversimplification, and that the aetiology in many patients is likely to be explained by interaction of psychological and physiological factors.⁵

With these limitations in mind, patients with IBS and excessive somatic symptoms (high comorbidity) represent a subset of patients with high levels of psychological distress, neuroticism and adverse life events as well

Table 3. Characteristics of patients with IBS and low, intermediate and high somatic comorbidity

as reduced QoL and ability to work and increased use of health resources. These patients have a SC score above 16, which equals reporting severe intensity of five to six different somatic symptoms (such as headache and low back pain). We postulate that the comorbid somatic symptoms and the psychological symptoms together contribute to the reduced QoL and increased use of health resources. These patients are likely to have a sensitive mind in a sensitive body with bodily symptoms associated with psychological distress. This somatization trait may be acquired either by birth, by sensitization, by learned illness behaviour or by underlying psychiatric disorders such as anxiety and depression.^{25, 26} Unfortunately, our cross-sectional study does not allow determination of the nature or the direction of the relationship between psychological symptoms and somatic symptoms. Drawing such causal inferences might be difficult under any circumstance, since these relations can be regarded as circular processes with complex interactions in the brain-gut axis, more than linear relationships.²⁶ We suggest that it is more important for doctors to identify the comorbid symptoms and help patients solve their current problems than to establish 'what came first'. Furthermore, we postulate that mind-based therapies such as hypnotherapy, cognitive behaviour therapy (CBT) or tricyclic antidepressants, could prove particularly efficacious in this subset of patients. The long-term effects of hypnotherapy in IBS with regard to psychological distress, QoL and use of health resources, as well as reduction of SC in one study, lends promise to this approach.^{27, 28} A current problem with hypnotherapy and CBT is their limited availability, and that few GPs would consider referral to such treatment.^{29, 30} Our findings suggest, in contrast to what has been reported in referred patients,³¹ that such intervention will be welcomed by patients with IBS and excessive comorbidity, since the majority related their abdominal complaints to stress and psychological factors.

Patients with IBS and few or no other bodily symptoms (low comorbidity) were characterized by apparently normal psychological profiles, HRQoL, adverse life events and ability to work. These individuals might be more genuine IBS patients whose symptoms mainly result from physiological disturbances in the gut, such as visceral hypersensitivity, dysmotility or inflammation.³² Whether these patients will respond satisfactorily to emerging drug therapies towards these disturbances, are exciting possibilities which remain to

be studied. However, it is unclear how many of these patients will need or want drug treatment for IBS given their apparently normal HRQoL.

A finding of note is that the intensity of abdominal pain/discomfort did not differ significantly between the groups, revealing the limitations of focusing purely on GI symptoms in the clinical evaluation of patients with IBS. We had expected fewer and less severe GI symptoms in the low comorbidity group, based on earlier reports and our findings of lighter overall symptom load and better QoL.³³ These patients might have increased awareness towards abdominal symptoms, while the less specialized group with high comorbidity might be somewhat distracted from their abdominal symptoms by all the other symptoms and problems they have.

Strengths and limitations

Strengths of our study, which should limit selection bias, are that 92% of all attending patients were screened for abdominal complaints, that the majority of consecutive patients with IBS were included and that those not included displayed apparently similar characteristics to included patients. The use of validated questionnaires for assessment of comorbid somatic and psychological symptoms and QoL should make these data reliable. The use of the SHC inventory allowed a comparison of a wide range of symptoms between patients with IBS and a large sample from a normal population. The prospective design should make data on the natural course of symptoms and HCS reliable.

However, methodological limitations are present. First, these patients have IBS according to the Rome II criteria, but not necessarily according to their GP, who seldom use such criteria.³⁴ This lack of diagnostic agreement questions the applicability of our findings to patients diagnosed with IBS by their GP. Secondly, the excessive comorbidity reported by patients with IBS in this study could potentially be features of the broader medical population from which the patients were selected. Thirdly, in addition to the above-mentioned limitations with the dual aetiology hypothesis, we cannot confirm that merely counting comorbid somatic symptoms will identify patients with different aetiologies in IBS. The observed correlation between SC and psychological distress emerged only when we included the intensity of each comorbid symptom as an additional dimension. Palsson *et al.* reported a correlation at

level with ours, by counting 26 frequent comorbid symptoms in IBS, assessed in the Recent Physical Symptoms Questionnaire (RPSQ).³⁵ The SHC is probably less powerful than the RPSQ to measure SC in IBS, which might explain why counting symptoms proved unsuccessful in our study. On the contrary, comorbid symptom intensity might be an additional dimension to be included in the search for patients with predominantly psychological aetiology in IBS.

CONCLUSIONS

Apart from being intriguing and strikingly frequent, comorbid somatic symptoms might identify subgroups of patients with IBS with different characteristics and needs, as proposed in the dual aetiology hypothesis. Structured assessment of SC, as part of a graded and multicomponent approach, could provide caring doctors with a necessary overview of their patients' main problems and reasons for suffering. Future research should establish the aetiological and clinical implications of assessing comorbid symptoms and identifying the proposed subgroups of patients, both with regard to diagnosis and hopefully more effective treatment for this large and heterogeneous group of patients.

ACKNOWLEDGEMENTS

Authors express our gratitude to the participating patients, GPs and practice staff. The study was funded by an unrestricted grant from Glaxo Smith Kline, Norway and Novartis, Norway and from a research fund at Innlandet Hospital Health Authority.

REFERENCES

- 1 Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome: the view from general practice. *Eur J Gastroenterol Hepatol* 1997; 9: 689–92.
- 2 Whorwell PJ, McCallum M, Creed FH, Roberts CT. Non-colonic features of irritable bowel syndrome. *Gut* 1986; 27: 37–40.
- 3 Azpiroz F, Dapoigny M, Pace F, *et al.* Nongastrointestinal disorders in the irritable bowel syndrome. *Digestion* 2000; 62: 66–72.
- 4 Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? *Lancet* 1999; 354: 936–9.
- 5 Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology* 2002; 122: 1140–56.
- 6 Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999; 45 (Suppl. 2): II43–7.
- 7 Eriksen HR, Ihlebaek C, Ursin H. A scoring system for subjective health complaints (SHC). *Scand J Public Health* 1999; 27: 63–72.
- 8 Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord J Psychiatry* 2003; 57: 113–8.
- 9 Speckens AE, Spinhoven P, Sloekers PP, Bolk JH, van Hemert AM. A validation study of the Whitely Index, the Illness Attitude Scales, and the Somatosensory Amplification Scale in general medical and general practice patients. *J Psychosom Res* 1996; 40: 95–104.
- 10 Grayson DA. Latent trait analysis of the Eysenck Personality Questionnaire. *J Psychiatr Res* 1986; 20: 217–35.
- 11 Gandek B, Ware JE, Aaronson NK, *et al.* Cross-validation of item selection and scoring for the SF-12 health survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol* 1998; 51: 1171–8.
- 12 Ihlebaek C, Eriksen HR, Ursin H. Prevalence of subjective health complaints (SHC) in Norway. *Scand J Public Health* 2002; 30: 20–9.
- 13 Donker GA, Foets M, Spreeuwenberg P. Patients with irritable bowel syndrome: health status and use of health care services. *Br J Gen Pract* 1999; 49: 787–92.
- 14 Bijkerk CJ, de Wit NJ, Stalman WA, Knottnerus JA, Hoes AW, Muris JW. Irritable bowel syndrome in primary care: the patients' and doctors' views on symptoms, etiology and management. *Can J Gastroenterol* 2003; 17: 363–8.
- 15 Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002; 123: 2108–31.
- 16 Wilhelmssen I, Berstad A. Reduced relapse rate in duodenal ulcer disease leads to normalization of psychological distress: twelve year follow up. *Scand J Gastroenterol* 2004; 39: 717–21.
- 17 Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. *Gut* 2000; 46: 78–82.
- 18 El Serag HB, Pilgrim P, Schoenfeld P. Systemic review: Natural history of irritable bowel syndrome. *Aliment Pharmacol Ther* 2004; 19: 861–70.
- 19 Levy RL, Von Korff M, Whitehead WE, *et al.* Costs of care for irritable bowel syndrome patients in a health maintenance organization. *Am J Gastroenterol* 2001; 96: 3122–9.
- 20 Khan AA, Khan A, Harezlak J, Tu W, Kroenke K. Somatic symptoms in primary care: etiology and outcome. *Psychosomatics* 2003; 44: 471–8.
- 21 Koloski NA, Talley NJ, Boyce PM. Does psychological distress modulate functional gastrointestinal symptoms and health care seeking? A prospective, community cohort study. *Am J Gastroenterol* 2003; 98: 789–97.
- 22 Maxton DG, Morris J, Whorwell PJ. More accurate diagnosis of irritable bowel syndrome by the use of 'non-colonic' symptomatology. *Gut* 1991; 32: 784–6.

- 23 Jones J, Boorman J, Cann P, *et al.* British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. *Gut* 2000; 47 (Suppl. 2): ii1–19.
- 24 Ilnyckyj A, Graff LA, Blanchard JF, Bernstein CN. Therapeutic value of a gastroenterology consultation in irritable bowel syndrome. *Aliment Pharmacol Ther* 2003; 17: 871–80.
- 25 Levy RL, Whitehead WE, Von Korff MR, Feld AD. Intergenerational transmission of gastrointestinal illness behavior. *Am J Gastroenterol* 2000; 95: 451–6.
- 26 Wilhelmsen I. Brain-gut axis as an example of the bio-psycho-social model. *Gut* 2000; 47 (Suppl. 4): iv5–7.
- 27 Gonsalkorale WM, Miller V, Afzal A, Whorwell PJ. Long term benefits of hypnotherapy for irritable bowel syndrome. *Gut* 2003; 52: 1623–9.
- 28 Palsson OS, Turner MJ, Johnson DA, Burnelt CK, Whitehead WE. Hypnosis treatment for severe irritable bowel syndrome: investigation of mechanism and effects on symptoms. *Dig Dis Sci* 2002; 47: 2605–14.
- 29 Palsson OS, Whitehead WE. The growing case for hypnosis as adjunctive therapy for functional gastrointestinal disorders. *Gastroenterology* 2002; 123: 2132–5.
- 30 Raine R, Carter S, Sensky T, Black N. General practitioners' perceptions of chronic fatigue syndrome and beliefs about its management, compared with irritable bowel syndrome: qualitative study. *BMJ* 2004; 328: 1354–7.
- 31 van der Horst HE, van Dulmen AM, Schellevis FG, van Eijk JT, Fennis JF, Bleijenberg G. Do patients with irritable bowel syndrome in primary care really differ from outpatients with irritable bowel syndrome? *Gut* 1997; 41: 669–74.
- 32 Talley NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? *Lancet* 2002; 360: 555–64.
- 33 Longstreth GF, Wolde-Tsadik G. Irritable bowel-type symptoms in HMO examinees. Prevalence, demographics, and clinical correlates. *Dig Dis Sci* 1993; 38: 1581–9.
- 34 Vandvik PO, Aabakken L, Farup PG. Diagnosing irritable bowel syndrome: poor agreement between general practitioners and the Rome II criteria. *Scand J Gastroenterol* 2004; 39: 448–53.
- 35 Palsson O, Levy RL, Feld AD, Von Korff M, Turner MJ, Whitehead WE. Comorbidity and psychological distress in irritable bowel syndrome (IBS). *Gastroenterology* 2002; 124 (Suppl. 1): A-388.

Paper IV

ORIGINAL ARTICLE

Prevalence, comorbidity and impact of irritable bowel syndrome in Norway

PER OLAV VANDVIK^{1,2}, STIAN LYDERSEN² & PER G. FARUP^{1,2}¹Department of Medicine, Innlandet Hospital Health Authority, Gjøvik, Norway, and ²Unit for Applied Clinical Research, NTNU, Trondheim, Norway**Abstract**

Objective. To study the prevalence of irritable bowel syndrome (IBS) and its comorbidity in a Norwegian adult population. **Material and methods.** In 2001, 11,078 inhabitants (aged 30–75 years) in Oppland County were invited to take part in a public health survey. A total of 4622 subjects (42%) completed the questionnaires on symptoms of IBS (Rome II criteria), comorbidity, health-care visits and medications. The impact of comorbidity on global health, working disability and use of health-care resources in subjects with IBS was explored by stepwise logistic regression. **Results.** The population prevalence of IBS was 388/4622 (8.4% (95% CI: 7.6–9.4%)) with a female predominance and an age-dependent decrease. The proportion who had consulted for IBS ranged from 51% among 30-year-olds to 79% in 75-year-olds ($p=0.05$). IBS was associated with musculoskeletal complaints (OR=2.4–3.4 for six different items), fibromyalgia (OR=3.6 [2.7–4.8]), mood disorder (OR=3.3 (2.6–4.3)), reduced global health (OR=2.6 (2.1–3.2)), working disability (OR=1.6 (1.2–2.1)), more frequent health-care visits and use of medications (OR 1.7–2.3). When controlling for comorbidity, reduced global health (OR=1.5 (1.1–2.0)) and use of alternative health care (OR=1.7 (1.3–2.4)) remained associated with IBS. Severity of abdominal pain/discomfort was a predictor of having to seek a consultation for IBS (OR=1.3 (1.2–1.5)). **Conclusions.** Symptoms of IBS were reported by 8% of Norwegian adults and had resulted in consultations with physicians for the majority in the long run. Subjects with IBS in the community were characterized by frequent somatic and psychiatric comorbidity. Their observed reduced health, working disability and increased use of health resources were largely explained by comorbid symptoms and disorders.

Key Words: *Epidemiology, fibromyalgia, functional bowel disease, health resources, health survey, mood disorder, Rome II criteria*

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder that is associated with impaired quality of life and increased use of health resources [1–3]. However, these associations are possibly confounded by unmeasured somatic and psychiatric disorders, which frequently co-occur with IBS [4,5]. Most studies have assessed comorbid disorders in those who consult physicians for IBS. It is therefore unclear whether comorbidity is a feature of IBS or of its consulters. Moreover, the comorbidity of IBS has possible implications for aetiology, diagnosis and treatment [4,6]. No studies have formally addressed the prevalence of IBS in Norway. Since IBS has no pathophysiological marker, its definition and diagnosis depend entirely on clinical

features. The Rome II criteria are recommended for epidemiological surveys of IBS [7,8].

The aim of this study was to measure the prevalence of IBS in a Norwegian adult population and to investigate the possible differences in characteristics between 1) subjects with IBS and subjects without IBS and 2) IBS consulters and IBS non-consulters, with emphasis on somatic and psychiatric comorbidity.

Material and methods*Study design and sample*

This cross-sectional population-based survey was conducted as part of the OPPHED (Oppland and Hedmark) health study in 2001, performed by the

Correspondence: Per Olav Vandvik, MD, Department of Medicine, Innlandet Hospital Health Authority, Gjøvik, Kyrre Greppsgt.11, NO-2819 Gjøvik, Norway. Tel: +47?????????. Fax: +47 6115 7439. E-mail: per.vandvik@start.no

(Received 2 May 2005; accepted 21 October 2005)

ISSN 0036-5521 print/ISSN 1502-7708 online © 2006 Taylor & Francis
DOI: 10.1080/00365520500442542

National Health Screening Service (NHSS), now the Norwegian Institute of Public Health. All men and women in the selected age groups (born in 1970, 1960, 1955, 1940 and 1925) in the county of Oppland (a mostly rural county with 183,000 inhabitants, of whom 53,000 live in two cities) were invited by mail to participate. Of 11,078 invited subjects, 4622 (42%) participated in this study and completed the questionnaires, including an additional questionnaire regarding abdominal complaints. The NHSS questionnaires were completed in a bus located nearby the participants' place of living. The additional questionnaire was completed at home and posted by mail to the NHSS. Non-responders received two reminders. Responders were more likely to be women than non-responders (56% versus 51%, $p < 0.001$), more frequently born in 1940 (23% versus 17%) and less frequently born in 1970 (15% versus 22%) ($p < 0.001$). No other characteristics were available for non-responders.

AQ1*Measurement*

OPPHED questionnaire. The questionnaire designed by the NHSS has been used in several similar health surveys in different regions of Norway and is available at www.fhi.no/tema/helseundersokelse/oslo/index.html. Questions were asked about socio-demographic variables, including civil status, years of education, working status, current global health status (rated: poor, not very good, good, very good) somatic and psychological comorbidity and use of health resources. Somatic comorbidity was assessed by six items on musculoskeletal complaints (MSCs) within the past four weeks (neck/shoulder, arms/hands, upper back, lower back, hip/legs/feet and other locations) with the intensity of each complaint rated as none, some, severe. A MSC score was calculated by summarizing the scores of each item (range 0–12). Current or earlier presence of fibromyalgia/chronic pain syndrome was also reported. Symptoms of anxiety/depression were measured with the Hopkins' Symptom Check List-10 (SCL-10) which consists of 10 questions with response categories on a four-point ordinal scale ranging from "not at all" to "extremely". The average item score is often used as a measure of psychological distress, with a cut-off point of ≥ 1.85 recommended as a valid predictor of mood disorder [9]. The presence of earlier or current mental problems, for which the subject had applied for help, was noted.

Use of health resources was measured as the number of health-care visits (0/1-3/ 4 or more) within the last year to general practitioners (GPs), psychiatrists/psychologists, other specialists and alternative health-care providers, and the use of

medications (analgesics over the counter and anti-depressants) during the past month (none/less than weekly/weekly but not daily/daily).

Abdominal complaints questionnaire. The questionnaire included 26 items regarding specific bowel symptoms based on the Rome II modular questionnaire which was translated into Norwegian by the authors [7]. A 3-month time frame was used and only the main criteria were used to diagnose IBS, as recommended by the Rome II committee. The additional supportive symptoms allowed a subdivision into diarrhoea-predominant IBS (D-IBS: two or more diarrhoea symptoms and a maximum of one symptom of constipation) constipation-predominant IBS (C-IBS = two or more constipation symptoms and a maximum of one symptom of diarrhoea) and alternating IBS (A-IBS = all subjects with IBS not qualifying for D-IBS or C-IBS). Abdominal pain discomfort severity (mild/moderate/severe) and frequency (average number of days per week: 0/1/2–3/4–5/>5) were recorded and multiplied to an intensity score (range 0–12). The duration of abdominal complaints (more or less than one year) and earlier consultations with a physician for abdominal complaints (lifelong, rated yes/no) were reported. One question assessed whether subjects considered that stress/psychological factors worsened the abdominal complaints (stress-related symptoms).

Data analysis

The data were collected and entered into a data file by the NHSS. Data were analysed by SPSS. Prevalence estimates were calculated for the study population and the target population (adults in Oppland above 20 years of age). Corresponding age- and gender-adjusted prevalence estimates were computed by direct adjustment for age and gender (5 age groups, 2 gender groups: total 10 groups) using the direct adjustment method. These analyses were done in order to adjust for the different response rates between the groups. A logistic regression model was used to fit to the data, using birth year and gender as predictors. Possible non-linearity in birth year, as well as interaction, was checked and found to be non-significant. The prevalence of IBS in the target population was estimated by applying the fitted logistic regression model to the total age and gender-specific population of Oppland per January 2001, available at Statistics Norway (www.ssb.no).

Comparisons between different groups of subjects were done by univariate and multivariate analyses. The groups compared were subjects with IBS versus

subjects without IBS, IBS consulters versus IBS non-consulters, IBS non-consulters versus subjects without IBS and men with IBS versus women with IBS. Univariate analyses were performed with Pearson's chi-square test, Student's *t*-test or the Wilcoxon-Mann-Whitney test. Multivariate analyses were performed in stepwise logistic regression models. The confounding effects of comorbidity were examined by separate multivariate analyses with global health, working disability, use of health care and medications as dependent variables. IBS, comorbid symptoms (MSC score, fibromyalgia, mood disorder, earlier or current mental problems), age and gender were independent variables in the separate analyses. In addition, stepwise logistic regression models were used to identify predictors of having consulted for IBS (IBS consulters versus IBS non-consulters) and to control for confounding effects of consultation behaviour on characteristics associated with IBS (IBS non-consulters versus subjects without IBS). In these models, variables with *p*-values <0.20 in the univariate analysis were entered.

Statistics are reported as estimates with odds ratios (ORs) and 95% confidence intervals (CIs) for ordinal variables, and as *p*-values for continuous variables, with the level of statistical significance specified at 0.05.

Ethics

The survey was performed in accordance with the Declaration of Helsinki, and approved by the Regional Committee of Research Ethics and the Data Inspectorate, Oslo.

Results

Prevalence of IBS

Of the 4622 subjects included in the study, 388 reported IBS according to the Rome II criteria, yielding an overall unadjusted prevalence of IBS for all the five birth-year cohorts of 8.4% (95% CI: 7.6–9.2%). Figure 1 shows the observed age and gender-specific prevalence of IBS, and prevalence estimates derived from the fitted logistic regression model. The prevalence of IBS in the target population was estimated to 8.1% for all, 6.3% for men and 9.8% for women. Fifty-four subjects (14%) reported IBS symptoms of less than one year's duration.

Characteristics of subjects with IBS

The characteristics of subjects with IBS, compared with those of 4234 subjects without IBS are presented in Table I. In the 388 subjects with IBS, the

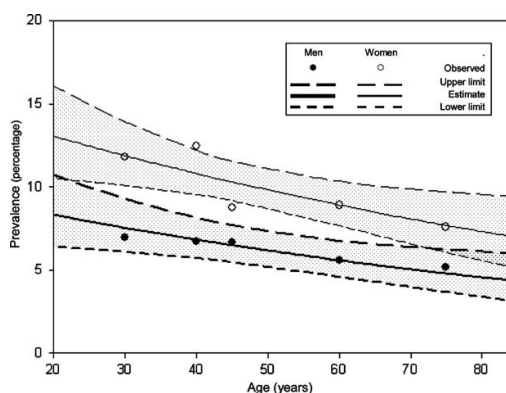


Figure 1. Observed prevalence of irritable bowel syndrome (IBS), and estimated mean prevalence with 95% confidence interval from the fitted logistic regression model.

intensity of abdominal pain/discomfort was mild in 49%, moderate in 47% and severe in 4%, while 9% reported the presence of abdominal pain/discomfort for more than five days per week. The most common additional symptoms were abdominal bloating (96%), straining (80%), incomplete evacuation (76%) and urgency (61%). D-IBS was reported by 23%, C-IBS by 24% and A-IBS by 53%.

In the 388 subjects with IBS, statistically significant gender differences were observed. In men and women, mean intensity levels of abdominal pain/discomfort were 3.6 and 3.0, respectively ($p=0.01$), mean intensity levels of musculoskeletal complaints were 3.4 and 4.0, respectively ($p=0.05$) and mean psychological distress levels were 1.4 and 1.5, respectively ($p=0.03$). We found that 37% of men and 16% of women had D-IBS, and 13% of men and 29% of women had C-IBS ($p<0.001$). Women reported fibromyalgia more frequently than men (26% versus 9%, $p<0.001$).

The univariate analysis showed that IBS was significantly associated with reduced global health, working disability, use of health care and medications (Table I). When controlling for comorbidity, age and gender in the multivariate analysis, IBS remained statistically significantly associated with reduced global health (OR=1.5 (1.1–2.0)) and visits to alternative health care (OR=1.7 (1.3–2.4)), but not with working disability, visits to GPs, visits to psychiatrists or other specialists, or use of analgesics or antidepressants. Fibromyalgia (OR=2.5) and mental problems (OR=1.9) were more strongly associated with reduced global health than IBS in the multivariate analysis. Accordingly, the association between IBS and reduced global health was reduced in the multivariate analysis (OR=1.5) when compared with the univariate analysis (OR=2.6, Table I). Use of alternative

4 P. O. Vandvik et al.

Table I. Characteristics of subjects with and without IBS (non-IBS). Results are given as whole percentages or mean values with standard deviations.

Variable	IBS <i>n</i> = 388	Non-IBS <i>n</i> = 4234	Statistics OR (95% CI) or <i>p</i> -values
Female gender	68	55	1.7 (1.4–2.1)
Marital status – separated	4	2	2.2 (1.3–3.9)
Years of education (mean/SD)	12 (3.5)	12 (3.5)	<i>p</i> = 0.49
Disability pension	19	13	1.6 (1.2–2.1)
Global health poor or not very good	44	23	2.6 (2.1–3.2)
Comorbidity			
Pain in shoulder	76	53	2.7 (2.1–3.5)
Pain arms/hands	59	36	2.6 (2.1–3.3)
Pain upper back	48	23	3.2 (2.5–4.0)
Pain lower back	68	45	2.6 (2.1–3.4)
Pain hips/legs/feet	65	43	2.4 (1.9–3.0)
Pain other locations	22	8	3.4 (2.5–4.7)
Musc. skel. pain intensity score (mean/SD)	3.8 (2.8)	2.4 (2.3)	<i>p</i> < 0.001
Fibromyalgia/chronic pain syndrome	20	7	3.6 (2.7–4.8)
Earlier or present mental problems	27	12	2.6 (2.0–3.4)
Mood disorder (SCL-10)	25	9	3.3 (2.6–4.3)
Health-care visits last year			
>4 GP visits	36	22	2.0 (1.6–2.5)
Psychologist/psychiatrist	8	3	2.7 (1.7–4.1)
Other specialist	39	28	1.7 (1.3–2.1)
Alternative health care	21	10	2.3 (1.7–3.1)
Use of drugs in the past month (>weekly)			
Analgesics over the counter	22	11	2.3 (1.8–3.1)
Antidepressants	10	5	2.3 (1.6–3.3)

Abbreviations: IBD = irritable bowel syndrome; SCL = symptom check list; GP = general practitioner.

health care was most strongly associated with IBS in the multivariate analysis, with mental problems (OR = 1.4) and MSC score (OR = 1.2) as other significant predictors.

Characteristics of IBS consulters and IBS non-consulters

In all, 235 subjects with IBS (61%) had sought consultations for abdominal complaints (IBS consulters). The proportion that had consulted increased with age, from 51% among 30-year-olds to 79% in 75-year-olds (*p* = 0.05, chi-square for trend). Sixty-eight (44%) of the 153 IBS non-consulters wished to consult a physician for their abdominal complaints, leaving 82 (21%) of 388 subjects with IBS who had never consulted nor wished to consult for IBS. The results of a comparison between IBS consulters and IBS non-consulters are reported in Table II. In the multivariate analysis of predictors of having consulted for IBS (IBS consulters), the intensity of abdominal pain/discomfort (OR = 1.3 (1.2–1.5)) remained significant.

We also made a comparison of IBS non-consulters versus subjects without IBS for all variables shown in Table I. This analysis was performed to determine whether the observed characteristics in subjects with IBS could be confounded by consultation behaviour.

In the univariate analysis, the following variables remained associated with IBS (all *p*-values < 0.001): Female gender (OR = 1.8), reduced global health (OR = 1.7), somatic comorbidity (OR 1.9–2.6 for six items of MSC and OR = 2.2 for fibromyalgia), psychiatric comorbidity (OR = 1.9 for mental problems and OR = 3.2 for mood disorder) visits to psychiatrists (OR = 3.2) and use of analgesics (OR = 2.2). In the multivariate analysis, female gender, reduced global health, somatic and psychiatric comorbidity and visits to psychiatrists remained associated with IBS (all *p*-values < 0.001).

Discussion

Main findings

Our study clearly demonstrates that comorbid symptoms and disorders are common features in adults with IBS in the general population of Norway. This finding is important because studies have mainly assessed comorbidity in those who seek health care for IBS [4,10]. In concert with these studies, the odds for reporting a variety of MSCs, fibromyalgia, mental problems or current mood disorders were two to three times higher in subjects with IBS than in subjects without IBS. Importantly, somatic and psychiatric comorbidity remained asso-

Table II. Characteristics of IBS consulters and IBS non-consulters. Results are given as whole percentages or mean values with standard deviations (SD).

Variable	IBS consulters <i>n</i> = 235	IBS non-consulters <i>n</i> = 152	Statistics OR (95% CI) or <i>p</i> -values
Female gender	66	69	1.1 (0.7–1.8)
Disability pension (75-year-olds excluded)	22	15	1.6 (0.9–2.9)
Global health poor or not very good	51	34	2.0 (1.3–3.1)
Gastrointestinal symptoms			
Abd. pain/discomfort score (mean/SD)	3.7 (2.7)	2.5 (1.6)	<i>p</i> < 0.001
Stress-related symptoms	63	73	0.6 (0.4–1.0)
Comorbidity			
Musc. skel. Pain intensity score (mean/SD)	4.1 (2.8)	3.4 (2.5)	<i>p</i> = 0.02
Fibromyalgia/chronic pain syndrome	25	14	2.0 (1.1–3.5)
Earlier or present mental problems	31	22	1.6 (1.0–2.6)
Mood disorder (SCL-10 > 1.85)	25	25	1.0 (0.6–1.6)
Health-care visits last year			
> 4 GP visits	42	27	2.0 (1.3–3.1)
Psychologist/psychiatrist	7	10	0.7 (0.3–1.6)
Other specialist	46	29	2.1 (1.3–3.3)
Alternative health care	27	13	2.5 (1.4–4.6)
Use of drugs in the past month (>weekly)			
Analgesics (over the counter)	23	21	1.1 (0.7–1.8)
Antidepressants	12	7	1.7 (0.8–3.5)

Abbreviations: IBD = irritable bowel syndrome; SCL = symptom check list; GP = general practitioner.

ciated with IBS after controlling for consultation behaviour (IBS non-consulters versus subjects without IBS). With regard to psychiatric comorbidity, the increased prevalence of mood disorders (25%) in both IBS consulters and non-consulters contrasts with the prevailing opinion that non-consulters with IBS display psychological profiles similar to those in the general population [11,12]. Our findings are supported by two other studies [1,13] and demonstrate the interplay between psychology and biology also in those who do not consult for their IBS symptoms.

The hypothesis that comorbid symptoms confounded the observed reduced global health status, working disability and increased health-care seeking and use of analgesics was largely confirmed. In our previous study of IBS in general practice, patients with excessive somatic comorbidity reported frequent psychiatric problems (mood disorder in 63%), markedly reduced quality of life and increased use of health resources, when compared with those with few or no comorbid symptoms [10]. Taken together, our findings suggest that comorbid symptoms and disorders need to be considered when measuring the impact of IBS on people's lives and costs for the community. Furthermore, the comorbidity of IBS might indicate predominantly different aetiologies and have possible implications for the diagnosis and treatment of IBS [4,6]. Subsets of patients with IBS and excessive somatic comorbidity might have a predominantly psychological aetiology

and benefit from psychological interventions, such as hypnotherapy or tricyclic antidepressants [14]. Those without comorbidity might have a predominantly biological aetiology and could respond well to novel drug therapies for IBS. Our findings are perhaps of particular relevance these days when drugs targeted towards specific symptoms of IBS are being marketed.

With regard to the prevalence of IBS, 8% reported IBS according to the Rome II criteria with a female predominance and an age-dependent decrease, in line with other surveys of Rome II IBS in Europe (prevalence 9.6%), Canada (prevalence 12.1%) and Australia (prevalence 6.9%) [1,8,15]. In Sweden, 7% of men and 13% of women had IBS, but it is unclear which criteria were used [11]. In Spain, a 2.9% prevalence of Rome II IBS has been reported [16]. Although the Rome II criteria represent the strictest criteria, they show satisfactory agreement with the earlier Rome criteria [8,17]. It remains to be determined whether the observed differences in Rome II prevalence estimates reflect geographical variations as suggested by the European study, or rather reflect methodological differences such as selection procedures, cultural interpretations or differences in translation and wording [1]. Importantly, the role of diagnostic criteria in clinical practice is unclear since they have not been formally validated in relevant clinical settings.

Some other characteristics of IBS should be noted. Few subjects (7%) reported severe abdominal pain/

discomfort and 86% reported having symptoms of IBS for more than one year, in line with what is reported by patients with IBS in general practice [10]. Current knowledge about IBS, including the efficacy of treatment, is mostly based on studies of small subsets of referred patients [18]. We confirm that the severity of symptoms is a major predictor of health-care seeking in IBS [19]. A pertinent question, given the apparent mildness of IBS and the impact of comorbidity observed in our studies, is whether the majority of adults with IBS in the community and in general practice will need specific treatment for symptoms of IBS. The male predominance of D-IBS and female predominance of C-IBS was unexpected. More than half the subjects with IBS had consulted a physician for their abdominal complaints, with an age-dependent increase of up to 79% in the 75-year-olds. One possible explanation for the observed high proportion of IBS consulters, similar to that reported from Australia but higher than in other Western countries, is the public health-care system in Norway with its high accessibility and low costs for the patient [1,20].

Strengths and limitations

The strengths of our survey are the population-based design, the substantial number of subjects with IBS identified and the use of well-defined criteria for IBS. The main limitation of our survey is the modest response rate (42%). This might introduce selection bias and reduce the external validity of our findings, particularly with regard to prevalence estimates which are more sensitive for selection bias than measures of association. However, self-selection according to socio-demographic variables had little impact on prevalence estimates and measures of association in a study of non-responders in the Oslo Health Study. This NHSS survey had an identical design to our study and was conducted in 2001 with a 46% response rate [21]. Another limitation is that we have no information regarding diagnoses of abdominal complaints. In the US householder survey, 3% of subjects with IBS according to the Rome criteria reported the presence of organic disease, which suggests a slight overestimate of prevalence in our study [22]. Furthermore, our translation of the Rome II criteria was not formally validated, which might have introduced information bias because of differences in wording. The Rome II questionnaires developed for research purposes have not been formally validated and were impossible to apply in our survey. Assessment of IBS symptoms within the recommended three-month time frame probably reduces recall bias. However, some might have had symptoms of IBS for more than three

months during the past year, but not within the past three months. Since these patients would qualify for a diagnosis of IBS according to the Rome II criteria, we might have underestimated the true prevalence of IBS. With regard to characteristics of subjects with IBS, measurement of other commonly occurring comorbid disorders, worry about cancer/serious disease (as a predictor of consultations for IBS), quality of life and use of health resources specifically related to IBS would have strengthened our results. Finally, confounding is an inherent problem with descriptive studies that cannot fully be controlled by entering comorbidity, age and gender in a logistic regression model. Although other unmeasured factors might contribute, it seems plausible that comorbid symptoms and disorders play a main part in explaining the observed reduced global health and increased use of health resources.

Conclusion and implications for future research

In a highly prevalent chronic disorder reported by 8% of adults in the community which leads to consultations with physicians for the majority in the long run, optimal diagnosis and treatment should be of high priority. We provide further evidence to show that psychiatric and somatic comorbidities are common features in IBS and not just features of its consulters. Moreover, the comorbidity explained a substantial part of the reduced global health and increased use of health resources associated with IBS. The comorbidity of IBS might also have implications for aetiology, diagnosis and treatment. The role of diagnostic criteria in clinical practice needs to be determined since our knowledge of IBS largely depends on studies employing these criteria.

Acknowledgements

We thank the NHSS for inviting us to participate in this survey, and for pleasant collaboration, and Innlandet Hospital Health Authority for providing us with grants. We also thank Stephen Lock of Aldeburgh, UK, for invaluable comments on the manuscript. Competing interests: none declared.

References

- [1] Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. *Aliment Pharmacol Ther* 2003;17:643–50.
- [2] El Serag HB, Olden K, Bjorkman D. Health-related quality of life among persons with irritable bowel syndrome: a systematic review. *Aliment Pharmacol Ther* 2002;16: 1171–85.

- [3] Badia X, Mearin F, Balboa A, Baro E, Caldwell E, Cucala M, et al. Burden of illness in irritable bowel syndrome comparing Rome I and Rome II criteria. *Pharmacoeconomics* 2002;20:749–58.
- [4] Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology* 2002;122:1140–56.
- [5] Levy RL, Von Korff M, Whitehead WE, Stang P, Saunders K, Jhingran P, et al. Costs of care for irritable bowel syndrome patients in a health maintenance organization. *Am J Gastroenterol* 2001;96:3122–9.
- [6] Maxton DG, Morris J, Whorwell PJ. More accurate diagnosis of irritable bowel syndrome by the use of “non-colonic” symptomatology. *Gut* 1991;32:784–6.
- [7] Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999;45 Suppl 2: II43–7.
- [8] Boyce PM, Koloski NA, Talley NJ. Irritable bowel syndrome according to varying diagnostic criteria: are the new Rome II criteria unnecessarily restrictive for research and practice? *Am J Gastroenterol* 2000;95:3176–83.
- [9] Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord J Psychiatry* 2003;57:113–8.
- [10] Vandvik PO, Wilhelmson I, Ihlebaek C, Farup PG. Comorbidity of irritable bowel syndrome in general practice: a striking feature with clinical implications. *Aliment Pharmacol Ther* 2004;20:1195–203.
- [11] Whitehead WE, Bosmajian L, Zonderman AB, Costa PT, Jr, Schuster MM. Symptoms of psychologic distress associated with irritable bowel syndrome. Comparison of community and medical clinic samples. *Gastroenterology* 1988;95:709–14.
- [12] Drossman DA, McKee DC, Sandler RS, Mitchell CM, Cramer EM, Lowman BC, et al. Psychosocial factors in the irritable bowel syndrome. A multivariate study of patients and nonpatients with irritable bowel syndrome. *Gastroenterology* 1988;95:701–8.
- [13] Osterberg E, Blomquist L, Krakau I, Weinryb RM, Asberg M, Hultcrantz R. A population study on irritable bowel syndrome and mental health. *Scand J Gastroenterol* 2000;35:264–8.
- [14] Palsson OS, Whitehead WE. The growing case for hypnosis as adjunctive therapy for functional gastrointestinal disorders. *Gastroenterology* 2002;123:2132–5.
- [15] Thompson WG, Irvine EJ, Pare P, Ferrazzi S, Rance L. Functional gastrointestinal disorders in Canada: first population-based survey using Rome II criteria with suggestions for improving the questionnaire. *Dig Dis Sci* 2002;47:225–35.
- [16] Mearin F, Badia X, Balboa A, Baro E, Caldwell E, Cucala M, et al. Irritable bowel syndrome prevalence varies enormously depending on the employed diagnostic criteria: comparison of Rome II versus previous criteria in a general population. *Scand J Gastroenterol* 2001;36:1155–61.
- [17] Saito YA, Locke GR, Talley NJ, Zinsmeister AR, Fett SL, Melton LJ, III. A comparison of the Rome and Manning criteria for case identification in epidemiological investigations of irritable bowel syndrome. *Am J Gastroenterol* 2000;95:2816–24.
- [18] Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome: the view from general practice. *Eur J Gastroenterol Hepatol* 1997;9:689–92.
- [19] Koloski NA, Talley NJ, Huskic SS, Boyce PM. Predictors of conventional and alternative health care seeking for irritable bowel syndrome and functional dyspepsia. *Aliment Pharmacol Ther* 2003;17:841–51.
- [20] Talley NJ, Boyce PM, Jones M. Predictors of health care seeking for irritable bowel syndrome: a population based study. *Gut* 1997;41:394–8.
- [21] Sogaard AJ, Selmer R, Bjertness E, Thelle D. The Oslo Health Study: the impact of self-selection in a large, population-based survey. *Int J Equity Health* 2004;3:3. Available from: <http://www.equityhealthj.com/content/3/1/3>.
- [22] Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, et al. U.S. household survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci* 1993;38:1569–80.

Dissertations at the Faculty of Medicine, NTNU

1977

1. Knut Joachim Berg: EFFECT OF ACETYLSALICYLIC ACID ON RENAL FUNCTION
2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED *IN VITRO*

1978

3. Karel Bjørn Cyvin: CONGENITAL DISLOCATION OF THE HIP JOINT.
4. Alf O. Brubakk: METHODS FOR STUDYING FLOW DYNAMICS IN THE LEFT VENTRICLE AND THE AORTA IN MAN.

1979

5. Geirmund Unsgaard: CYTOSTATIC AND IMMUNOREGULATORY ABILITIES OF HUMAN BLOOD MONOCYTES CULTURED *IN VITRO*

1980

6. Størker Jørstad: URAEMIC TOXINS
7. Arne Olav Jenssen: SOME RHEOLOGICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MUCOID SPUTUM FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

1981

8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS *IN VITRO*

1983

9. Tore Syversen: EFFECTS OF METHYLMERCURY ON RAT BRAIN PROTEIN.
10. Torbjørn Iversen: SQUAMOUS CELL CARCINOMA OF THE VULVA.

1984

11. Tor-Erik Widerøe: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.
12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REACTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AND STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
15. Inngard Lereim: TRAFFIC ACCIDENTS AND THEIR CONSEQUENCES.
16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.

17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OF DRUGS.

1985

18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
19. Terje Espevik: THE CYTOSKELETON OF HUMAN MONOCYTES.
20. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.
21. Ole-Jan Iversen: RETROVIRUS-LIKE PARTICLES IN THE PATHOGENESIS OF PSORIASIS.
22. Lasse Eriksen: EVALUATION AND TREATMENT OF ALCOHOL DEPENDENT BEHAVIOUR.
23. Per I. Lundmo: ANDROGEN METABOLISM IN THE PROSTATE.

1986

24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
25. Odd Arnold Kildahl-Andersen: PRODUCTION AND CHARACTERIZATION OF MONOCYTE-DERIVED CYTOTOXIN AND ITS ROLE IN MONOCYTE-MEDIATED CYTOTOXICITY.
26. Ola Dale: VOLATILE ANAESTHETICS.

1987

27. Per Martin Kleveland: STUDIES ON GASTRIN.
28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
29. Vilhjalmur R. Finsen: HIP FRACTURES

1988

30. Rigmor Austgulen: TUMOR NECROSIS FACTOR: A MONOCYTE-DERIVED REGULATOR OF CELLULAR GROWTH.
31. Tom-Harald Edna: HEAD INJURIES ADMITTED TO HOSPITAL.
32. Joseph D. Borsi: NEW ASPECTS OF THE CLINICAL PHARMACOKINETICS OF METHOTREXATE.
33. Olav F. M. Sellevold: GLUCOCORTICOIDS IN MYOCARDIAL PROTECTION.

34. Terje Skjærpe: NONINVASIVE QUANTITATION OF GLOBAL PARAMETERS ON LEFT VENTRICULAR FUNCTION: THE SYSTOLIC PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT.
35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.
1989
43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF- α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.
1990
52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofslisli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.
1991
65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, P50 P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.

70. Arnulf Hestnes: STUDIES ON DOWN'S SYNDROME.
 71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
 72. Bjørn Hagen: THIO-TEPA.
 73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAPHY AND ULTRASONOGRAPHY.
- 1992
74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
 75. Stig Arild Slørdahl: AORTIC REGURGITATION.
 76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
 77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
 78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
 79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
 80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
 81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.
- 1993
82. Gunnar Bovim: CERVICOGENIC HEADACHE.
 83. Jarl Arne Kahn: ASSISTED PROCREATION.
 84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
 85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
 86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
 87. Piotr Kruszcwski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
 88. Mette Haase Moen: ENDOMETRIOSIS.
 89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
 90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
 91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.
- 1994
92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
 93. Sverre Helge Torp: *erbB* ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
 94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
 95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
 96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
 97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
 98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
 99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
 100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
 101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
 102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
 103. Unni Syversen: CHROMOGRANIN A. Physiological and Clinical Role.
- 1995
104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
 105. Terje Egan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
 106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
 107. Finn Egil Skjeldstad: INDUCED ABORTION: Timetrends and Determinants.
 108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
 109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.
- 1996
110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.

111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamm: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.
- 1997
124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUATION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gräwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.
- 1998
132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR TNF AND LPS: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.
- 1999
141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.

142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noëmi Becser Andersen: THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morphological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilities.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACHS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunön: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES
- 2000
158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.

174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.
- 2001
178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENCES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR HISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RECEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTURAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingsaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCIUM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIGUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES
- 2002
201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS

203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
 204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
 205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
 206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING β -CELLS
 207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
 208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONMENTAL FACTORS. EXPERIMENTAL AND CLINICAL STUDIES OF PAIN WITH FOCUS ON FIBROMYALGIA
 209. Pål Klepstad: MORPHINE FOR CANCER PAIN
 210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
 211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
 212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
 213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
 214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
 215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS
- 2003
216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
 217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
 218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
 219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
 220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
 221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
 222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
 223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARIAN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
 224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
 225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
 226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
 227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
 228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
 229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
 230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING

231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAGE HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAGE STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE
- 2004
235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAGE HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETIC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE
- 2005
248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAGE HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaasheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS

260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtøft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE
- 2006
269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULTICENTRE RANDOMISED STUDIES
278. Hilde Pley: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION

*There once was a fellow from Sparta
A really magnificent farter
On the strength of one bean,
He farted "God save the Queen"
And Beethoven`s "Moonlight Sonata."*

- Anonymous -