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**FUNCTIONAL
GASTROINTESTINAL DISORDERS**
-
**CO-MORBIDITY AND NON-
SOMATIC ASPECTS**

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The rebellions of the belly are the worst.

Fr. Bacon, Essays 15 (1625)

Av alla upprorsmakare är magen den värsta.

To my Mother, Kerstin, Karin, Anders, Cecilia and Erik.

ABSTRACT

Aims of the thesis: The first aim, study I, of this thesis was to compare co-morbidity of the reported symptoms and its relation to healthcare seeking behaviour among non-patients who had persistent functional gastro-intestinal disorders (FGID) or who were strictly GI symptom-free (SSF). The second aim, study II, was to compare FGID sufferers' primary health care consumption, as registered in their medical records. The third aim, study III, was to investigate the occurrence of a history of abuse, and the possible association with consultation rate, and the fourth aim, study IV, was to investigate the possible influence of a negative parental rearing experienced during childhood.

Methods: The Abdominal symptom questionnaire (ASQ) was mailed to a random sample of 1537 adults aged 20-87 years from the municipality of Östhammar, Sweden (n= 21,545 in 1995). From the obtained response and by integrating results from previous studies performed in 1988 and 1989, 244 subjects with FGID (e.g. FD and/or IBS) and 219 SSF subjects were invited to their local health centers for completing the ASQ again in addition to a set of other questionnaires. From the results in the ASQ, 141 subjects with persistent FGID and 97 SSF subjects formed the study groups of the studies I,III and IV. A subgroup living in the eastern part of Östhammar constituted the study groups in study II. The used questionnaires were; Complaint score questionnaire (CSQA), Psychological General Well-Being (PGWB), Hospital Anxiety and Depression Scale (HADS), Sexual, physical and emotional abuse (ABQ), Coping strategies questionnaire (CSQ), Social support (ISSI), and the Multidimensional Health locus of control scale (MHLC).

Results: In study I: Non-patients with FGID have a higher risk of psychological illness (OR 8.4, CI95: 4.0-17.5) than somatic illness (OR 2.8, CI95: 1.3-5.7) or ache and fatigue symptoms (OR 4.3, CI95:2.1-8.7). Patients with FGID have more severe GI symptoms than healthy controls. In study II: of the FGID patients, 97% had a non-GI diagnosis, compared to 100% of SSF (ns). The mean number of consultations, prescriptions, diagnoses as well as anxiety level and depression were all statistically significantly higher ($p < 0.05$) in FGID compared to SSF, whereas the number of referrals and sick leave were not. Besides a GI diagnosis, there was no significant difference ($p > 0.05$) in the spectrum of morbidity in terms of ICD-9 subgroup classification, except an increased proportion of older SSF subjects with circulatory disorders and hypertension. In study III: Women with FGID had a higher risk of having a history of some kind of abuse, as compared with the SSF controls (45% vs.16%), in contrast to men (29% vs. 24% n.s.). Women with a history of abuse and FGID had reduced HRQoL as compared with women without abuse history. In study IV: Neuroticism and a parental rejective rearing style were identified as risk factors for FGID. FGID consulters reported an increased parental rejection and reduced health-related quality of life. Moreover, consulters had a higher exposure to abuse in childhood, a lower availability of social attachment and less adequacy of social interaction than non-consulters.

Conclusions: FGID is related to an increased demand on primary health care due to an increased overall co-morbidity. Women with longstanding FGID often have a history of physical, emotional or sexual abuse which is associated with a poor HRQoL and increased health care seeking. Negative parental upbringing represents an aggravating factor in FGID. The treatment of FGID should involve assessment of psychological distress.

Key words: Epidemiology, gastrointestinal diseases, irritable bowel syndrome, dyspepsia, quality of life, child abuse, battered women, social support, anxiety, depression

LIST OF PUBLICATIONS

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TABLE OF CONTENTS

1.	Introduction	1
1.1.	Functional dyspepsia (FD) and irritable bowel syndrome (IBS)	1
1.2.	Historical remarks	1
1.3.	Definitions	3
1.4.	Pre-Rome definitions	3
1.4.1.	Manning criteria for IBS	3
1.4.2.	Kruis scoring system for IBS	4
1.4.3.	Colin-Jones criteria for FD	4
1.5	The Rome criteria for functional gastrointestinal disorder	5
1.5.1	Rome I criteria for FD and IBS	5
1.5.1.1	FD	5
1.5.1.2	IBS	5
1.5.2	Rome II criteria for FD and IBS	5
1.5.2.1	FD	5
1.5.2.2	IBS	6
1.5.3	Rome III criteria for FD and IBS	6
1.5.3.1	FD	6
1.5.3.2	IBS	7
1.6	Biopsychosocial considerations in FGID	8
1.6.1	The central nervous system (CNS)	8
1.6.2	The enteric nervous system (ENS)	9
1.6.3	Genetic factors	10
1.6.3.1	Genotype	10
1.6.3.2	Gender	10
1.6.3.3	Familial	10
1.6.3.4	Ethnicity	11
1.6.4	Psychosocial factors	11
1.6.4.1	Personality, anxiety, depression and coping	11
1.6.4.2	Social support	12
1.6.4.3	Stressful life events	12
1.6.4.4	Co-morbidity	12
1.6.4.5	Abuse	12
1.6.5	Physiology	13
1.6.5.1	Motility	13
1.6.5.2	Sensation	13
1.6.5.3	Inflammation and post-infectious IBS	13
1.6.5.4	Bacterial flora	13
1.6.6	Outcome	14
1.6.7	Treatment	14
1.6.7.1	Functional dyspepsia	14
1.6.7.2	The irritable bowel syndrome	15

2.	Aims	16
3.	Materials and methods	17
3.1	Definitions	17
3.1.1	Definition of FD	17
3.1.2	Definition of IBS	17
3.1.3	Definition of FGID	18
3.1.4	Definition of minor symptoms	18
3.1.5	Definition of strictly GI symptom free	18
3.1.6	Concordance with functional disease	19
3.2	Subjects	19
3.2.1	Subjects in study I,III and IV	19
3.2.2	Subjects in study II	20
3.2.3	Generalizability	21
3.2.4	Questionnaires	22
3.2.4.1	Abdominal symptom questionnaire (ASQ)	22
3.2.4.2	The Complaint score questionnaire (CSQA)	23
3.2.4.3	The Abuse questionnaire (ABQ)	23
3.2.4.4	The Psychological general well-being quest. (PGWB)	23
3.2.4.5	The Hospital anxiety and depression scale (HADS)	23
3.2.4.6	The Memories of childhood questionnaire (EMBU)	23
3.2.4.7	Coping strategies questionnaire (CSQ)	24
3.2.4.8	The interview schedule for social integration (ISSI)	24
3.2.4.9	Multiple health locus of control (MHLC)	24
3.2.4.10	Eysenck personality quest. short form (EPQ-N)	24
3.2.4.11	Other questions	24
3.3	Response and recall bias	24
3.4	Blood examination	25
3.5	Statistical methods	25
3.5.1	Power analyses	27
4	Results	28
4.1	Study I	28
4.1.1	Study groups characteristics	28
4.1.2	CSCQ and FGID vs. SSF	29
4.1.3	Risk modelling	29
4.1.4	Consulters vs non-consulters	31
4.1.5	ASQ symp. severity and cons. beh. vs CSCQ factors... ..	31
4.2	Study II	33
4.2.1	Doctor face-to face and phone consultations	33
4.2.2	Co-morbidity	34

4.2.3	Referrals	35
4.2.4	Sick-leave	35
4.2.5	Anxiety and depression	35
4.2.6	Comparison with ROME II definition	36
4.3	Study III	36
4.3.1	Demographic and sexual, physical and emotional abuse	36
4.3.2	Women	38
4.3.3	Men	38
4.3.4	Anxiety and depression	38
4.3.5	Quality of life	39
4.3.6	Multivariate risk modelling	39
4.3.7	Consulters and non-consulters with FGID	41
4.4	Study IV	41
4.4.1	Associations and scores of parental rearing	41
4.4.2	Rates of well-being and abuse FGID/Consulters vs non-cons...41	
4.4.3	Assoc. and rates of neuroticism, coping, social support and health locus of control in FGID/SSF and consulters vs non-consulters	43
4.4.4	Multivariate risk modelling	43
4.5	Helicobacter pylori prevalence	46
5	General discussion	47
6	Conclusions	51
7	Acknowledgements	52
8	Populärvetenskaplig sammanfattning	54
9	References	57

LIST OF ABBREVIATIONS

ABQ	The Abuse Questionnaire
ASQ	The Abdominal Symptom Questionnaire
CI	Confidence interval
C-IBS	Constipation predominant irritable bowel syndrome
CNS	Central nervous system
CSQA	The Complaint Score Questionnaire
CSQ	The Coping Strategies Questionnaire
D-IBS	Diarrhea predominant irritable bowel syndrome
ENS	Enteric nervous system
EMBU	The Memories of childhood questionnaire
EPQ-N	The Eysenck Personality Questionnaire
FD	Functional dyspepsia
fMRI	Functional magnetic resonance imaging
GERD	Gastroesophageal reflux disease
GERS	Gastroesophageal reflux symptoms
GI	Gastrointestinal
GiCon	The Gastrointestinal Consult study
<i>H. pylori</i>	<i>Helicobacter pylori</i>
HADS	The Hospital Anxiety and Depression Scale
IBD	Inflammatory bowel disease
IBS	The Irritable bowel syndrome
ISSI	The Interview Schedule for Social Interaction
MHLC	The Multiple health locus of control questionnaire
MUPS	Medically unexplained physical symptoms
OR	Odds ratio
PET	Positron emission tomography
PGWB	The General well-being questionnaire
PUD	Peptic ulcer disease
RAP	Recurrent abdominal pain
SF-36	The 36-item Short Form health survey

1 INTRODUCTION

1.1 FUNCTIONAL DYSPEPSIA (FD) AND THE IRRITABLE BOWEL SYNDROME (IBS)

Patients commonly present in primary care with symptoms for which no physical pathology can be found, so called medically unexplained physical symptoms (MUPS) [1, 2].

Functional gastrointestinal disorder (FGID) is defined as troublesome gastrointestinal illness without known organic findings after normal investigations i.e., endoscopy, radiology, histology, pathology, infectious samples. The most common FGIDs are functional dyspepsia (FD) and the irritable bowel syndrome (IBS).

FD is defined as the presence of one or more dyspeptic symptoms that are considered to originate from the gastro-duodenal region, and IBS is defined as pain or discomfort, attributable to the middle or lower GI tract, associated with a change in bowel habits, and/or features of disordered defecation [3].

Symptoms in FGID are supposed to originate from malfunction of the gut and/or nervous misperception, and FGIDs are among the most common gastrointestinal (GI) illnesses.

Although many symptoms of functional disorders also exist in other GI diseases like inflammatory bowel disease, peptic ulcer disease, cancer and are also attributable to complications of systemic disease such as gastroparesis in diabetes, bowel disturbances in thyroid disease and lactose intolerance, the cause in the majority of cases with such symptoms remains unknown. Symptoms of FGIDs should be troublesome and chronic in their nature in order to separate them from transient gut symptoms [3-6].

IBS and FD symptoms like nausea, vomiting, pain, bloating, diarrhea, constipation, or difficult passage of food or feces often but not always have no structural signs [7]. Dyspepsia, for example, has been shown to lack an organic cause in up to 55% of primary health care patients [8].

1.2 HISTORICAL REMARKS

Descriptions of gut dysfunction have been found in the first known medical texts. Papyrus records have revealed that ancient Egyptians used a diverse range of plants to treat stomach ailments such as indigestion and constipation and also seem to have recognized that stress could contribute to illness.

They established sanitariums where people would undergo "dream therapy" and treatments with "healing waters." Plato, Aristotle, and Hippocrates in Greece proposed the principle of holism about 3,400 years ago, and later in the 12th century a Jewish physician and philosopher Maimonides reexamined this philosophy. Based on holism, the study of medical disease took into account the whole person rather than merely the diseased part [9, 10].

The French philosopher Descartes (1596-1650) made a separation of mind and body which at that time represented a concept that harmonized with societal views of separation of church and state. This dualistic concept, introduced the biologic reductionistic model of disease, where the effort was to identify a single underlying biological etiology and this had an influence on the view of illness and disease during three centuries. The concept was successful in finding new causes and treatments for various diseases. The view of the mind (i.e. the central nervous system, CNS) as playing a role in illness and disease was marginalized for almost 300 years.

The first reliable English description of IBS appeared in 1818 by Powell, who pointed out the three main symptoms; abdominal pain, “derangement of digestion,” and “flatulence” [11]. At that time physicians searched for a single etiological factor either of psychological or structural nature.

A paradigm shift in the end of 1970s moved away from the reductionistic model to a more integrated, holistic concept, the biopsychosocial model of illness and disease [12-14]. This model allowed for symptoms to be both physiologically multidetermined and modifiable by cultural and psychosocial influences. More than half of the gut disorders encountered by primary care doctors and a lower proportion encountered by gastroenterologists are supposed to be functional diseases [15]. For a long time they were described in terms of exclusion diagnoses, rather than as real entities. In 1962 a retrospective review of IBS patients [16] that was the first systematic description in this field, started a new era towards a positive diagnosis of IBS. An investigation in 1978 found 6 out of 15 symptoms to be more common in IBS than organic gut diseases and these became the “Manning criteria” [17]. Nevertheless, some physicians exhibited negative attitudes toward patients [18] and some physicians pursued excessive diagnostic studies to find something “real”, which resulted in increased health care costs and inappropriate care [19].

There has been a growth of investigative methods during the last two decades that provide evidence for the FGIDs as disorders of brain-gut interaction: motility assessment [20], testing visceral hypersensitivity with the barostat [21], positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) of the brain provide linkages of GI function with emotional and cognitive areas [22] and the discovery of mast cells in close contact to the mucosal nerve endings has been correlated to the perceived intensity of abdominal pain and discomfort in IBS patients [23]. Recently, an elevated number of eosinophils have been found in the duodenum of FD sufferers [24]. Moreover, standardized psychological instruments have been developed during the last decades to allow the assessment of emotions, stress and cognitions in order to investigate their influences on symptoms and health outcomes. New serotonin-receptor active drugs have been released to treat constipation and diarrhea [25].

1.3 DEFINITIONS

There have been attempts to classify patients in terms of observed aberrant motility in order to rationalize the nomenclature [26] but these attempts have not gained general acceptance. The current diagnostic nomenclature system, Rome III, used by specialist investigators, is exclusively based on symptoms, and although artificial, considered to be the most appropriate so far.

Before the Rome process of establishing diagnostic criteria for the FGIDs, there had been prior attempts focusing on IBS with the Manning criteria [17] and the Kruis criteria [27] and also the Colin-Jones definition of FD [28].

The Rome I definition for IBS was first published in 1989 [29], and the full publication came in 1994 [30] followed by the Rome II Criteria for FGID in 1999 [31]. The latest Rome III Criteria were published in 2006 [3]. The Rome classification excludes patients with predominant symptoms of gastroesophageal reflux (GERD) from FD and thus FGID. It is well known, however, that there is a high symptom overlap, i.e. people report symptoms on more than one functional disorder, and also that there is some symptom flux between GERD and dyspepsia or IBS [32, 33].

The positive predictive value for the diagnosis of IBS in patients referred to a gastroenterology clinic using the Rome I criteria and with alarm symptoms excluded (significant weight loss, blood in stools, age > 50 years, family history of colon cancer or inflammatory bowel disease, fevers, or anemia) was 98% during a one-year follow up [34]. Other studies following patients over many years confirmed that the application of IBS criteria with limited diagnostic tests rarely leads to a later revision in diagnosis [35].

1.4 PRE - ROME DEFINITIONS

1.4.1 Manning criteria for IBS [17]

Previous 12 months the presence of:

1. Visible abdominal distension
2. More frequent bowel movements at the onset of pain
3. Pain eased after bowel movement (often)
4. Looser stools at the onset of pain

The more of these four symptoms that are present, the more likely the diagnosis is IBS.

1.4.2 Kruis scoring system for IBS [27]

A scoring system based on patients questions and a doctor's evaluation.

Patient questions and score:

1. Complaints for more than two years (16)
2. Presence of abdominal pain, flatulence or irregularities of bowel movement (34)
3. Abdominal pain described as burning, cutting, very strong, terrible, feeling of pressure, dull, boring, not so bad (23)
4. Alternating constipation and diarrhea (14)

Doctor checklist and score:

1. Abnormal findings and/or a pathognomonic history for anything other than IBS (-47)
2. ESR >20mm/2hr (-13)
3. Leucocytosis > 10.000/ccm (-50)
4. Hemoglobin female <12 g%; male < 14g% (-98)
5. History of blood in the stool (-98)

The positive predictive value for the diagnosis of IBS in cases having a score > 44 points was 94% in a population with about 20% prevalence of IBS,

1.4.3 Colin-Jones criteria for FD [28]

Organic dyspepsia was defined as dyspepsia due to specific lesions- such as peptic ulcer, reflux esophagitis, gastric carcinoma, and cholelithiasis- which could be readily identified on routine investigation.

Non-ulcer dyspepsia was defined as upper abdominal or retro-sternal pain, discomfort, heartburn, nausea, vomiting, or other symptom considered to be referable to the proximal alimentary tract, and lasting for more than 4 weeks, unrelated to exercise, and for which no focal lesion or systemic disease can be found responsible. In contrast to

Non-ulcer dyspepsia was divided into:

1. *Gastro-esophageal Reflux-like Dyspepsia*: substernal or epigastric discomfort and heartburn; a burning upper epigastric pain; and regurgitation of acid or, occasionally, food.
2. *Dysmotility-like Dyspepsia*: this overlaps with the IBS and is associated with a feeling of flatulence, bloating and distension, meteorism, and early satiety.
3. *Ulcer-like Dyspepsia*: a small group of patients have symptoms suggestive of an ulcer – being woken by pain at night; getting pain relief from eating small meals or antacid; episodic pain; using one or two fingers to point to localized epigastric discomfort – and yet no ulcer is found.
4. *Aerophagia*: varies from an exaggeration of normal swallowing to an abnormal technique of swallowing in which the upper esophageal sphincter relaxes with the glottis closed, so that air

is sucked in by negative intrathoracic pressure. Aerophagia is most frequently postprandial and may be related to stress.

5. *Idiopathic, or Essential, Dyspepsia*: about 25% of patients with non-ulcer dyspepsia do not fit into the groups indicated above.

1.5 THE ROME CRITERIA FOR FUNCTIONAL GASTROINTESTINAL DISORDERS

1.5.1 Rome I criteria for FD and IBS [30, 36]

1.5.1.1 FD

Three months or more of:

1. Chronic or recurrent abdominal pain or discomfort centered in the upper abdomen (above the navel).
2. No clinical, biochemical, endoscopic or ultra-sonographic evidence of any known organic disease that is likely to explain the symptoms and no history of major gastric or intestinal surgery.

Patients with history of past chronic peptic ulcer disease (PUD) should not be classified as having functional dyspepsia at least until the relationship between these entities is clarified.

1.5.1.2 IBS

At least 3 months continuous or recurrent symptoms of:

1. Abdominal pain or discomfort which is
 - a. Relieved with defecation
 - b. and/or associated with a change in frequency of stool
 - c. and/or associated with a change in consistency of stooland
2. Two or more of the following, at least at 25% of occasions or days:
 - a. Altered stool frequency
 - b. Altered stool form (lumpy/hard or loose/watery)
 - c. Altered stool passage (straining, urgency, or feeling of incomplete evacuation)
 - d. Passage of mucus
 - e. Bloating or feeling of abdominal distension.

1.5.2 Rome II Criteria for FD and IBS [37]

1.5.2.1 FD

At least 12 weeks, this need not be consecutive, in the preceding 12 months of:

1. Persistent or recurrent pain or discomfort centered in the upper abdomen (above the navel); and
2. No evidence of organic disease (including at upper endoscopy) that is likely to explain the symptoms; and
3. No evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form.

In addition a subclassification has been made on predominant symptom: ulcer-like dyspepsia, dysmotility-like dyspepsia and unspecified dyspepsia.

1.5.2.2 IBS

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

1. Relieved with defecation, and/or
2. Onset associated with a change in frequency of stool, and/or
3. Onset associated with a change in form (appearance) of stool.

1.5.3 Rome III Criteria for FD and IBS [3]

1.5.3.1 FD

For the last 3 months at least 1 day/week one or more of the following:

1. Bothersome postprandial fullness
2. Early satiation
3. Epigastric pain
4. Epigastric burning

AND

Onset more than 6 months prior diagnosis and no evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.

In addition to these criteria a subclassification has been made:

- A. Postprandial distress syndrome (PDS) defined as bothersome postprandial fullness, occurring after ordinary-sized meals, at least several times per week AND/OR early satiety that prevents finishing a regular meal, at least several times per week.

- B. Epigastric pain syndrome (EPS) which must include all of the following: Pain or burning of at least moderate severity, in middle of abdomen, at least 1 day/week, pain or burning often disappears completely in the same day, chest pain occurs once a month or less often, never or rarely gets better after defecation, not fulfilling criteria for gallbladder and sphincter Oddi disorders.

1.5.3.2 IBS

For the last 3 months at least 3 days per month of recurrent abdominal pain or discomfort, associated with 2 or more of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

AND

Onset more than 6 months prior to diagnosis.

In addition to these criteria, a subclassification has been made based on dominant bowel habits; diarrhea (D-IBS) or constipation predominance (C-IBS), bloating or unspecified.

1.6 BIOPSYCHOSOCIAL CONSIDERATIONS IN FGID

1.6.1 The central nervous system (CNS)

A bio-psychosocial model is presented in Figure 1. The central efferent motor control of the upper digestive tract is situated in the brainstem; the nucleus ambiguus contains motor neurons that supply the striated muscle, and the dorsal nucleus of the vagus nerve has parasympathetic neurons that supply the smooth muscles. The vagal efferents release acetylcholine which stimulates nicotinic excitatory receptors to produce contractile responses.

Spinal pathways transmit nociceptive information to processing centers in the thalamic nuclei [38].

Moreover, downwardly directed traffic in the dorsal columns can modulate the descending control of visceral nociceptive processing [39]. Glutamate and substance P are the main neurotransmitters in the spinal processing of visceral pain. Descending spinal modulatory pathways with serotonergic, noradrenergic, and to a lesser extent dopaminergic projections can be inhibitory, facilitatory, or both, depending on the nature of the visceral stimulus. Exaggeration of descending facilitating signals from the brain and sensitization due to receptor alterations occurring within the spinal cord might explain symptoms of visceral hypersensitivity found in patients with IBS [40].

fMRI and PET brain imaging techniques have revealed that visceral sensation is primarily represented in the secondary somatosensory cortex, in paralimbic and limbic structures. Future studies with this technique might determine whether the abnormal sensitivity in FGID patients is mainly due to central or peripheral (e.g. tissue injury or inflammation) factors. There is a report that patients with IBS and IBD dream more about their bowels than do controls [41] which indicates a cognitive brain-gut interaction.

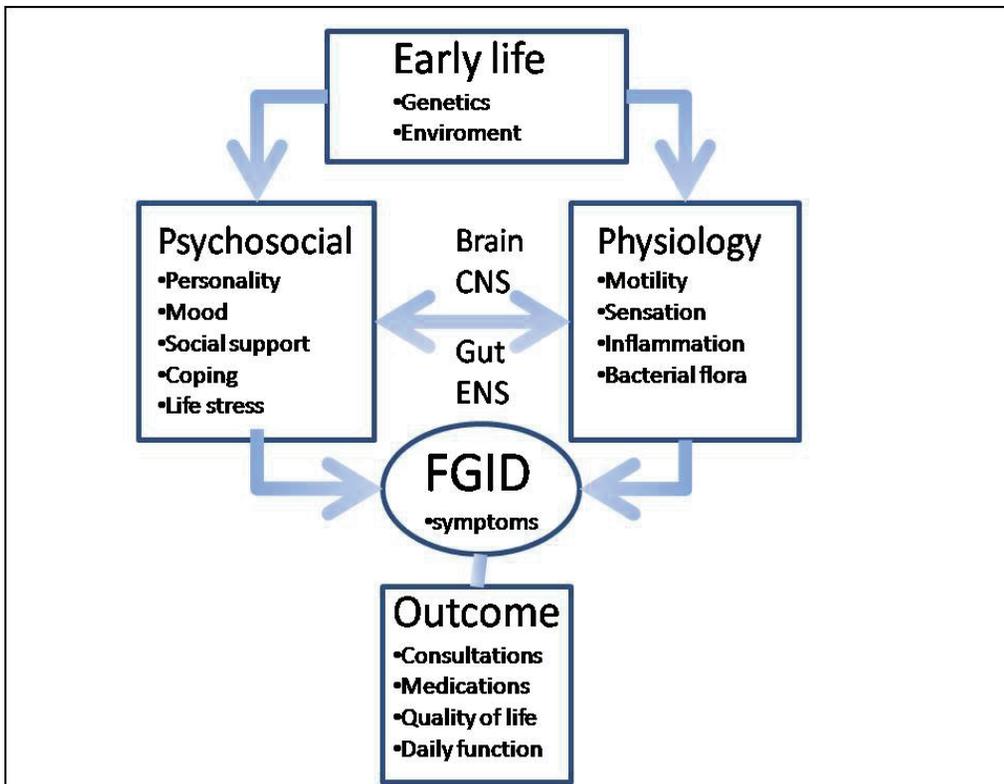


Figure 1. Biopsychosocial aspects of FGID.

1.6.2 The enteric nervous system (ENS)

The ENS is part of the autonomic nervous system which also comprises the sympathetic and parasympathetic nervous systems. ENS is essential to coordinate the behavior of the gut’s motility, blood flow and secretion. Nicotinic, purinergic and serotonergic 5-HT₃ receptors are found in ENS neurons supported by enteric glial cells (EGC), similar to the astroglia in the CNS; the ENS is often called “brain-in-the-gut”. EGC also may modify the intestinal barrier function and have a protective function against pathogens [42]. Vagal and spinal sensory neurons terminate within the musculature, mucosa, and ganglia of the ENS [43]. Vagal mechanoreceptors have low distension thresholds whereas spinal mechanoreceptors can be low-threshold, high-threshold or silent receptors. The latter receptor can become responsive to distension when the intestine is injured or inflamed, a phenomenon known as peripheral sensitization. The sensitization exaggerates the intensity of pain (i.e., hypersensitivity).

1.6.3 Genetic factors

1.6.3.1 Genotype

A genetic predisposition to develop FD has been hypothesized as findings demonstrate that the *GNβ3* CC genotype is twice as prevalent in patients with dyspepsia, especially those with dysmotility-like dyspepsia [44].

1.6.3.2 Gender

There is a genetic contribution to IBS but not dyspepsia; this may be mediated by the heritability of anxiety and depression. Most studies report no significant variation in prevalence of uninvestigated dyspepsia in women and men [45, 46] although there are exceptions. For example, in the Kalixanda study, women had a higher prevalence of dyspepsia than men [47, 48]. Women, compared to men, are more prone to delayed gastric emptying [49]. In most population based studies, IBS is more prevalent in women than men [46, 50-52]. Women with IBS report more constipation, bloating, nausea, extra-intestinal symptoms [53] and psychiatric illness [54], and men report more diarrhea [55]. The menstrual cycle seems to enhance IBS symptoms during the late luteal and early menstruation phases [56].

A meta-analysis revealed that women have a small increase in visceral pain sensitivity and less pain tolerance compared to men [57]. With barostat-assisted distensions of the rectum and sigmoid colon women with IBS had the greatest rectal sensitivity compared with men with IBS and healthy women, who had the least [58]. Brain activation measured by fMRI, in response to rectal distension revealed different patterns for women and men; women had a greater cortical activity during rectal distension than men [59]. The difference in pain response between women and men with IBS has evoked hypothetical explanations such as differences in sex hormones [60], differences in sex-related pain modulatory pathways mediated by serotonin [61] and other agents [62, 63] or differences in behavioral responses to stress in women and men: women building on an attachment process referred to as “tend-and-be-friend” while men respond with the more aggressive “fight-or-flight” response to stress [64].

1.6.3.3 Familial

A familial association has been reported for FD and IBS in adults [65]. A twin study reported that not only genetic disposition but also what children learn from their parents adds to the risk of developing FGID [66], while another study reported an association for IBS but not for FD [48]. Children of adult IBS patients make more consultations and are incurring more health care costs, than the children of non-IBS parents [67, 68]. Population-based studies report that children with recurrent abdominal pain (RAP) have frequent bodily symptoms in adulthood [69], family members with GI problems [70] and mothers with high neuroticism scores [71]. Modeling and positive reinforcement [72] are some mechanisms that can explain social learning in children with RAP.

1.6.3.4 Ethnicity

There is difficulty in interpreting results from different countries due to differences in cultures and methodology, help-seeking, sampling methods, study population and diagnostic criteria. The prevalence of IBS in Asian countries seems to be much lower than in western societies. From Singapore there has been a report of a 2.3% overall prevalence with no differences found among the Chinese, Malay and Indian ethnic subgroups [73].

According to the Rome I criteria, a prevalence of 4.1% was found for IBS among the Chinese in Hong Kong [74]. Similarly low prevalence rates were reported from Thailand [75] and among Asian Americans living in the USA [51]. A study in African American psychology students reported that race made no differences in the criteria for IBS, 16.9% for African Americans and 15.0% for Caucasians [53].

1.6.4 Psychosocial factors

1.6.4.1 Personality, anxiety, depression and coping

Personality is an expression of how an individual relates to other people and responds to environmental stimuli and changes. Personality traits are evident in early adult life and are considered to be stable throughout life.

Personality expressed as higher neuroticism and mood scores have been recorded in both IBS patients and in IBS sufferers in the general population [15, 76-78], and this may be more pronounced than in peptic ulcer disease [79]. However, when symptoms resolve, there has been a reported reduction in the neuroticism scores [80], which indicates that the measured scores do not reflect a true personality trait. In FD patients, higher scores for neuroticism have been reported in patients but not convincingly in FD population subjects [15]. Psychological distress is associated with functional dyspepsia and IBS in non-consulters compared to healthy controls [81, 82] and relates to health care seeking in some studies [81, 83] but not in another [84].

There is a strong association between symptoms of IBS and symptoms of anxiety and depression, whereas depressive patients in remission do not have more IBS symptoms than controls [85]. Anxiety correlates with rectal hypersensitivity in IBS patients [86]. Anxiety and depression are significant and independent predictors of postinfective IBS [87, 88] and also predict a poor outcome of treatment of IBS [89].

Coping is defined as behavior or mental activity that manages environmental and internal stressors which tax or exceed a person's resource. Coping can probably be learned or represent a part of the personality. It may be adaptive (e.g. problem-focused) or maladaptive (emotion-focused),

“catastrophizing”) in terms of health status and consequently positively or negatively affect health outcomes [90, 91]. Health beliefs, such as worries of serious disease, have been found to be an important reason for consulting in dyspepsia [92] and IBS [93].

1.6.4.2 Social support

It has been reported that both FD and IBS are associated with less social and interpersonal support, in patients [82, 91, 94].

1.6.4.3 Stressful life events

Stressful life events are associated with IBS, heartburn, RAP in children and frequent health care seeking as demonstrated in prospective studies [77, 95, 96]) and chronic life stress is a main predictor of IBS symptom intensity [97].

1.6.4.4 Co-morbidity

It is well-known that patients with FD and especially IBS report common mental and somatic symptoms [15, 98, 99]. Non-cardiac chest pain is associated with IBS [100] and Wallander et al. recently reported that dyspepsia is associated with chest pain, general pain, sleep disorders, angina, and osteoarthritis/rheumatoid arthritis [101]. Patients with dyspepsia had an increased likelihood of a diagnosis of the irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD) or peptic ulcer disease (PUD) during the following year [101]. In IBS there are several reports of both somatic and psychiatric diagnosis [102]: at least 50% of patients also report symptoms like fibromyalgia, arthralgia, pelvic pain and similar diagnoses, and up to 90% mental psychiatric disorders. Moreover, there are reports on a higher proportion of abdominal and pelvic surgery among those with IBS as compared to controls [5, 99, 103].

1.6.4.5 Abuse

Abuse can be difficult to define and is often under-recognized in clinical practice [104]. Population studies have led to conflicting results regarding whether there is an association between self-reported FGID and abuse [105, 106] and similarly inconsistent results in patients visiting for FGID [105, 107]. High prevalence rates of abuse in women have been reported from outpatient clinics [108], higher in secondary than in primary care [51, 104]. There is a high prevalence of childhood abuse reported in patients with chronic or recurrent disorders like fibromyalgia, pelvic pain and headaches [109]. Severe abuse experiences such as rape, multiple abuses and life-threatening physical abuse have an association with more severe pain, greater impairment in daily life, more anxiety and more frequent consultations in GI patients [94, 110]. An association between sexual and physical abuse and FGIDs is generally accepted, although data on men are absent [111].

1.6.5 Physiology

1.6.5.1 Motility

The human digestive tract has the role of producing propulsion along the gut, to mix the contents and expose them to the absorptive surface and also support a temporary storage, prevent retrograde progress and dispose of residues. Local inflammatory, infiltrative, immune or degenerative factors can directly affect the smooth muscle of the gut or the ENS effector system. Indirectly visceral afferent fibers can trigger dysmotility via prevertebral ganglia and induce autonomic changes integrated in the brain stem, such as changes in heart rate, alterations in colonic tone. Psychosocial stressors can also induce alterations in gastrointestinal motility. Patients with FGID sometimes have an greater GI motor response to stressful conditions than do controls [3].

1.6.5.2 Sensation

The processes of digestion involve numerous stimuli. Distension can be simulated by means of a balloon mounted over a tube, chemical stimulation can be performed by meal ingestion or infused intraluminal nutrients. 50-90 % of FD and IBS patients appear to have visceral hypersensitivity [112], but there is no convincing evidence that visceral hypersensitivity is characteristic for IBS [113]. The effect of nutrients is exaggerated in FD, resulting in hypersensitivity of both the proximal stomach and antrum [114] and the proximal duodenum [115]. In IBS patients, intraluminal continuous gas infusion is delayed and symptoms of bloating are greater than in controls [116].

1.6.5.3 Inflammation and post-infectious IBS

Gastroduodenal inflammation has been reported in non-ulcer dyspepsia patients [117]. A meta-analysis has revealed evidence for an increased incidence of IBS after a gastroenteritis [118] and inflammation in the plexus myentericus has been found in IBS patients [119]. Post infectious IBS, characterized by a low-grade inflammation with increased T lymphocytes and mast cells, is developed with a prevalence of 6-17 % after an acute episode of bacterial gastroenteritis [120]. Female gender, a more severe episode, anxiety, depression, somatization and neurosis are risk factors for development of post infectious IBS [121, 122].

1.6.5.4 Bacterial flora

H. pylori eradication may be an effective therapy for patients with *H. pylori* positive non-ulcer dyspepsia [123]. However, follow up studies one year after the eradication of *H. pylori* revealed no benefit compared to placebo [124] or compared to anti-acid therapy [125]. The fecal microbiota is altered in IBS patients [126] and an association between antibiotic use and IBS has been reported [127].

IBS patients may respond to the use of probiotic bacterial preparations [128, 129] and the eradication of small intestinal bacterial overgrowth [130].

1.6.6 Outcome

Functional dyspepsia in patients has a chronic and benign nature [131]. Despite their benign course FD and IBS are related to a poor quality of life [55, 132]. IBS patients have similar or worse quality of life scores with the 36-item Short Form health survey (SF-36), except for physical functioning, than patients with gastroesophageal reflux disease and diabetes [133]. Consultation incurs a considerable cost for society mainly due to sick-leave and medication. Dyspepsia alone is responsible for an annual cost of five thousand million Swedish crowns (€ 450 million) in Sweden 1997 [134]. The costs for IBS also seem to be considerable [135]. It is well known, that many people with gastrointestinal (GI) symptoms never consult a physician [136, 137]. Consulting is influenced by the severity and frequency of the abdominal symptoms [84, 138, 139], as well as by psychological factors [83, 140, 141] and fear of serious disease [92, 142]. Consultation with non-medical practitioners is associated with younger age and poor mental health [137]. A 10-year follow-up study in dyspepsia patients revealed that *H. pylori* infection, lower socioeconomic status, frequent or severe symptoms, and increasing age were independent predictors of consultation [143].

1.6.7 Treatment

Treatments for FD and IBS are controversial. After exclusion of organic disease, reassurance is important and is most effective in an established therapeutic patient-physician relationship. The treatment is individualized and include explanation and also sometimes alterations in diet, drug treatment aimed at predominant symptoms, and psychotherapy [144]. General dietary and life-style modifications include smoking cessation, regular sleep and exercise; also avoiding foods known to affect the function of the GI tract such as alcohol and caffeine may be beneficial. In FD acid inhibitors can provide some relief but because the studies sometimes include patients with gastro-esophageal reflux symptoms, the efficacy of the drugs is difficult to assess. Most patients with functional dyspepsia are not infected with *H. pylori* but antibiotic therapy that eradicates *H. pylori* can offer a little relief [145].

1.6.7.1 Functional dyspepsia

Studies have reported that a negative endoscopy in FD patients can improve quality of life [146]. Screening for *H. pylori* in the general population and eradicating it, results in only a slight reduction of dyspepsia symptoms and has no effect on quality of life [147]. Elimination diets are only advisable in patients with proven intolerance. Dietary modifications have not been formally evaluated in large clinical trials [148] but if patients are consistently bothered by specific foods, they should avoid them.

However, patients should be appropriately counseled so that they do not become food-phobic. Dyspeptic symptoms may be increased by dietary fat [149] and specific foods such as onions, peppers, citrus fruit, coffee, carbonated beverages, and spices [148, 150]. Avoidance of late-evening meals and eating smaller, more frequent meals has been advocated [148, 150, 151]. Methodological issues make it difficult to draw conclusions about psychological therapies such as cognitive therapy, hypnotherapy, psychodynamic psychotherapy, and applied relaxation therapy [152], although hypnotherapy has been reported to be effective [153].

At present none of the medications commonly used to treat FD is approved by the Swedish Medical Products Agency or the US Food and Drug Administration. Pharmacological treatments that may benefit FD patients are *H. pylori* eradication [154], proton pump inhibition [155], prokinetic agents such as metoclopramide [155] and antidepressants such as amitriptyline [156].

1.6.7.2 The irritable bowel syndrome

Although soluble dietary fiber is recommended its treatment of C-IBS is not clear since fiber seems to improve some IBS symptoms and exacerbate others with no effect of abdominal pain [157].

Psychosocial factors such as stress are associated with IBS and will exacerbate IBS symptoms [158] and IBS patients with coexistent psychiatric abnormalities such as anxiety, depression, abuse, somatization, and phobia may benefit from psychotherapy, hypnotherapy, cognitive behavioral therapy and biofeedback [159].

Pharmacological treatments such as antidiarrheals (e.g. loperamide), laxatives and antispasmodics are primarily targeting individual symptoms. Polyethylene glycol osmotic laxatives (eg. Movicol[®], Forlax[®]) are safe and efficient in the treatment of chronic constipation [160] and can be used in C-IBS. Probiotics may improve bloating [161]. In some patients anti-depressants, and tegaserod (which has cardiovascular side effects and is not approved in Sweden) can have an effect [162, 163]; newer serotonergic agents, anti-depressants, peripheral and autonomic neural receptor agents and gut immune modulators are under development [164].

2 AIMS

This study was planned with the purpose of clarifying how psychological, social- and personality factors and other components such as quality of life, well-being, symptom interpretation, locus of control, illness behaviour, coping strategies and childhood experiences, among adults influence the prevalence of FGID and the inclination to consult a doctor. To achieve this, subjects from the general population, unbiased by health care seeking behaviour, need to be investigated. The outcome from the study may lead to a better understanding of FGID and thus contribute to improved treatment strategies. We called this study “the gastrointestinal consult study” (GiCon).

- I. The first aim of this study was to compare the reported symptoms co-morbidity and its relation to health care seeking behaviour among non-patients with persistent FGID with those who were strictly GI symptom-free (Paper I).
- II. The second aim was to compare FGID sufferers’ primary health care consumption, as registered in their medical records, compared to those strictly GI symptom free (Paper II).
- III. The third aim was to investigate the occurrence of a history of abuse experienced in childhood or later in life, among women and men with FGID and the possible association with consultation rate, as compared with subjects free from FGID (Paper III).
- IV. The fourth aim was to investigate whether the history of negative parental rearing experienced as a child among adults in the general population with and without FGID is associated with the prevalence of FGID and self-reported GI health care seeking behavior (Paper IV).

3 MATERIAL AND METHODS

3.1 Symptom definitions

The definitions of dyspepsia and IBS used in this study were those used in the original study from 1988 [5], before the Rome criteria were published. We opted to retain the original definitions despite changes in later definitions, as it allowed comparison of the prevalence of diseases over time. Thus, our definition of dyspepsia was more restricted in terms of symptoms than the Rome II and III definition, but wider in terms of abdominal location, as not only epigastric but also mid-abdominal symptoms were included. The IBS definition used was in accordance with the Rome II and III criteria and made it possible to compare previous results from the longitudinal study. The definitions used for FGID (dyspepsia and IBS) are in good concordance with the ROME II classification since we found that only 4.8% were erroneously classified as having FGID, and there was an overall agreement of 95.2% between the combinations of FGID definitions.

3.1.1 Definition of FD

Definitions of symptoms from the ASQ

(See Fig. 2) [5].

Dyspepsia was defined as one or more of the *-marked symptoms (reflux episodes, heartburn, retrosternal pain, nausea, vomiting, early satiety, uncomfortable feeling of fullness after meals, abdominal distension), *and* one or more of the abdominal pain modalities in part 2 of figure 2 (burning sensation, aching, pain, tenderness, sinking feeling, “butterflies”, cramp, twinge, stitch, colic, gripes) with any abdominal location except the lower part, but no concomitant IBS.

3.1.2 Definition of IBS

The Irritable Bowel Syndrome (IBS) was defined as one or more of the **-marked symptoms (abdominal distension, abdominal discomfort or pain on defecation, abdominal discomfort or pain relieved by defecation, feeling of incomplete defecation, mucous stools) *and* one or more of the ***-marked symptoms (diarrhea, constipation, alternating diarrhea and constipation) *and* one or more of the abdominal pain modalities in part 2 of the figure 2 (burning sensation, aching, pain, tenderness, sinking feeling, “butterflies”, cramp, twinge, stitch, colic, gripes), at any location.

When using these definitions of dyspepsia and IBS, responders with only reflux symptoms, i.e. heartburn, and/or reflux episodes, and/or retrosternal pain but no abdominal pain or discomfort, were classified as having GERS and not dyspepsia, while those with reflux symptoms and abdominal pain or

discomfort fell into the dyspepsia group. Also, IBS, as defined above, was given priority over dyspepsia. Thus, concomitant occurrence of both led to a diagnosis of IBS.

3.1.3 Functional Gastrointestinal Disorder, FGID

FGID was defined as either dyspepsia or IBS or both.

3.1.4 Definition of minor symptoms

Minor symptoms refer to symptoms not fulfilling the criteria for dyspepsia or IBS. By definition, those with GERS were included in this group.

3.1.5 Definition of strictly GI symptom-free

“Strictly Symptom Free” (SSF) is defined as having no reported symptoms at all in the Abdominal Symptom Questionnaire in the 1995 survey, and subjects stating that they had not even been troubled previously with abdominal symptoms. Those subjects who had participated in the two former surveys in 1988 and 1989 (n=265) should also have reported no symptoms in each of those two investigations. “Prior symptomatics” (n=177) were those with no symptoms in the 1995 survey but with GI symptoms reported in the prior studies of 1988 and 1989.

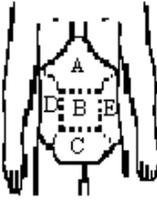
Part 1 General Symptoms		Part 2 Pain modalities	Master sketch
1.Loss of appetite	15.Feeling of incomplete defecation**	Burning sensation	 <p>The letters indicate the five eligible abdominal regions</p>
2.Loss of weight	16.Mucous stools**	Aching	
3.Dysphagia	17.Diarrhoea***	Pain	
4.Reflux episodes*	18.Constipation***	Tenderness	
5.Heartburn*	19.Alternating diarrhoea and constipation***	Sinking feeling	
6.Retrosternal pain*	20.Blood stains in stools	"Butterflies"	
7.Eructations*	21.Black stools	Cramp	
8.Nausea*	22.Borborygmus	Twinge	
9.Vomiting*	23.Flatus	Stitch	
10.Early satiety*	24.Nightly urge of defecation	Colic	
11.Uncomfortable feeling of fullness after meals*		Gripes	
12.Abdominal distension*/**			
13.Abdominal discomfort or pain on defecation**			
14.Abdominal discomfort or pain relieved by defecation**			

Figure 2. Symptoms asked for in the ASQ [5].

3.1.6 Concordance with functional disease

From data collected in this population-based epidemiological study, it was not possible to distinguish between organic and functional causes in individual cases. It is reasonable to assume, however, judging from studies of primary care patients [165-168] and previous population surveys [169, 170], that dyspepsia and bowel-related symptoms in unselected people are mainly functional. In population-based investigations, Bernersen *et al* [171] found active ulcers in only 3.9% and in the Kalixanda study only 4.1% of people with abdominal symptoms had PUD [47], and the prevalence of celiac disease was about 1% [172] and lactose intolerance probably not higher than 5% [173]. Moreover, in a prior part of this study during the 6 year follow-up in 1995, only 3% of the participants who developed organic gastrointestinal disease had it verified by endoscopy. Preliminary data from a Swedish random sample population-based colonoscopy study reported that only a small minority of subjects had macroscopic bowel findings that could explain their GI symptoms (Kjellström data on file). We therefore have reasons to believe that our data are relevant to functional disorders of the gastrointestinal tract.

3.2 SUBJECTS

3.2.1 Subjects in study I, III and IV

The municipality of Östhammar had 22,454 inhabitants (50.7% males) on average in 1995 and 96.3% were Swedish citizens. A sample was drawn from the National Swedish Population Registry 1995, involving all Swedish citizens in the Östhammar municipality born between 1909 to 1974 and thus 20 to

87 years of age, born on day 3, 12 or 24 of each month (n=1537), i.e. using the same date of birth criteria as in previous studies on the same population in 1988 and 1989 which corresponds to a random sampling. The sampling procedure and formation of the study groups is presented in Figure 3.

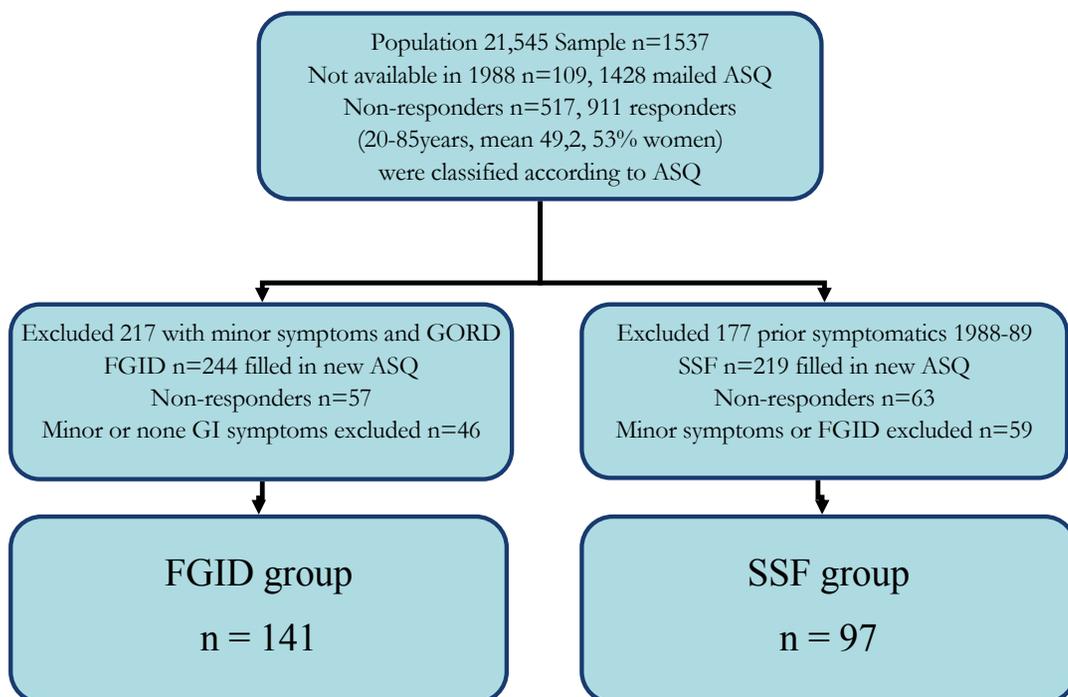


Figure 3. Sampling procedure in the gastrointestinal consult study (GiCon).

3.2.2 Subjects in study II

The Östhammar community (n= 22,454 in 1995) is served by five primary health care centers, three to the west (Gimo, Österbybruk and Alunda) and two to the east (Öregrund and Östhammar city, n=9959 in 1995); the latter two serve almost half of the population. The two eastern health centers were the only centers included in the second study, as they were in a more remote area serving the inhabitants with 24 hr primary care, including emergency care. Moreover, their medical records were computerized, making data collection more reliable. Of the 141 FGID and 97 SSF living in Östhammar, 71 FGID and 48 SSF lived in the east part of the community.

3.2.3 Generalizability

The population in Östhammar has been stable over time and the distribution by age, sex, family size, income, occupational category was largely similar to the national average in 1988 [174]. The number of inhabitants were 21,338 in 1988, 21,545 in 1995 and 21,421 in 2007 and the proportion of foreign citizens remained the same at 4% [175]. The samples from 1988, 1995 and 1996 were analyzed for mean age, sex ratio and educational level in the corresponding FGID and SSF groups in order to investigate the effect of drop-outs during the sampling procedure see Table 1 [174]. There were no significant differences in any of these aspects. The east part did not differ from the west population in terms of age (mean age: east 49 y, west 48 y, $p=0.86$) or gender (males: east 39%, west 39%, $p=1$). However, the mean educational level was higher (east 3.1, west 2.7, $p=0.01$), although the median (=3) was the same. The results suggest that there was no sampling bias.

Table 1. Comparison between previous population studies in Östhammar, Sweden
Age, sex and educational level at different stages of the sampling process. From the first population sample in 1988 to the present study 1996. ns = p>0.05.

Group (G)	Sample	Year	n	Age years mean (SD)	Sex % males	Education median level (range)
1	First population sample	1988	1156	48.9 (16.0)	50.4	3 (1-4)*
2	Eligible sample	1995	1428	49.9 (17.2)	49.9	3 (1-4)**
3	Population sample	1995	911	49.2 (16.46)	47.0	3 (1-4)
4	Sample group FGID	1995	244	45.5 (15.3)	36.1	3 (2-4)
5	Sample Group SSF	1995	219	51.7 (17.6)	51.6	3 (1-4)
6	Study Group FGID	1996	141	45.7 (14.3)	34.0	3 (2-4)
7	Study Group SSF	1996	97	52.4 (15.3)	48.0	3 (1-4)
G2 vs G3				ns	ns	
G1 vs G3				ns	ns	ns
G4 vs G6				ns	ns	ns
G5 vs G7				ns	ns	ns

*responders=1156 **responders n=1384

3.2.4 Questionnaires

Questionnaire characteristics presented to the community in 1996.

3.2.4.1 The Abdominal Symptom Questionnaire (ASQ)

The Abdominal Symptom Questionnaire has been validated previously and found to be reliable and reproducible [5, 174, 176]. In the questionnaire, subjects were asked if they had been troubled (Yes/No) by any of the 29 listed general gastrointestinal symptoms over the previous three months. They were also asked if they had been troubled by any of 11 listed descriptors of abdominal pain and to describe the symptom location (upper, centre or lower abdominal, right and left flank, respectively), as shown in Figure 2. A similar ASQ was used for the postal survey and the surgery visit, with the extension of the latter extended to include a symptom severity Likert scale graded from zero to seven, for each symptom

asked for. In the analysis, the data were pooled into a three-graded scale (1, 2-4, 5-7).

3.2.4.2 *The Complaint Score Questionnaire (CSQA)*

The Complaint Score Questionnaire contains 30 questions, indicating the presence or absence of 30 different symptoms [177]. The questions are dichotomous and can be categorized into six domains: abdominal/urinary, ache/fatigue, muscular-skeletal, nutritional, cardio-vascular and depressive.

3.2.4.3 *The Abuse Questionnaire (ABQ)*

In the Abuse Questionnaire, the questions about sexual abuse were those initially developed for the National Population Survey of Canada [178] from survey questionnaires that fulfill reliability criteria [179]. The questions were translated into Swedish and back-translated into English for validation. Questions were written separately for childhood ≤ 13 years and adulthood (>13), including six categories of abuse: sexual, physical and emotional, each for child or adult [104].

3.2.4.4 *The Psychological General Well-Being (PGWB)*

The Psychological General Well-Being index is a health-related quality of life (HRQoL) instrument including 22 items divided into 6 domains: anxiety, depressed mood, positive well-being, self-control, general health, and vitality. Items are scored on a 6-grade Likert scale, with higher scores indicating better HRQoL. The total score with a high responsiveness and validity for dyspepsia [180] was used in this study. HRQoL scores varying between 102 and 105 have been observed in a normal healthy population [181]. The total score was dichotomized at the median with a cut-off point 107/108, at the upper 95% CI for functional dyspepsia. Consequently, a good HRQoL was considered to be a total score of 108 or more, which was reached by 117 subjects (score 108-132; mean 117.5 SD=6.3), while a poor HRQoL was reached by 120 subjects (score 49-107; mean 90.8 SD=12.6).

3.2.4.5 *The Hospital Anxiety and Depression Scale (HADS)*

The Hospital Anxiety and Depression Scale is a validated, reliable instrument with subscales for measuring anxiety and depression [182-184]. The questionnaire has seven items, graded 0-3, with possible ranges of 0-21 for each subscale (total minimum score of 0, total maximum score of 42). A score of 7 or less on each subscale (out of a maximum of 21), denotes a non-case, 8 to 10 a doubtful case, and 11 or more a definite case of anxiety or depression. The cut-off point 10/11 was set for identifying sufferers in this study.

3.2.4.6 *The Memories of childhood questionnaire (EMBU)*

The Memories of childhood questionnaire, (EMBU is a Swedish acronym for 'my memories concerning upbringing'), was developed for the assessment of perceived parental rearing behavior [185]. Questions about the father and mother have to be answered separately for the father and mother on a 4-point Likert

scale. All of the items are behavior-oriented in their formulation, without attributional evaluation. In a transcultural study, the items formed three domains ('rejection', 'emotional warmth' and 'overprotection'), and their generalizability across nations was demonstrated [186]. Test-retest comparisons revealed no significant differences in any of the factor scores [187].

3.2.4.7 *The Coping Strategies Questionnaire (CSQ)*

Coping Strategies Questionnaire with six subscales includes 50 items that relate to coping with painful conditions. The subscale "catastrophizing" shows the most reliable relationships with the negative sequelae of chronic pain such as disability and psychological distress [188, 189].

3.2.4.8 *The Interview Schedule for Social Interaction (ISSI)*

Interview Schedule for Social Interaction [190, 191] measuring availability and adequacy of social integration, is an instrument with a proven validity in different patient groups, [192]. It has four subscales: availability of social integration (AVSI), adequacy of social integration (ADSI), availability of attachment (AVAT), and adequacy of attachment (ADAT).

3.2.4.9 *The Multidimensional Health Locus of Control questionnaire (MHLC)*

Multidimensional Health Locus of Control [193] measuring internal, external and powerful others health locus of control.

3.2.4.10 *The Eysenck Personality Questionnaire (EPQ-N)*

The Eysenck Personality Questionnaire [194] short form is measuring neuroticism as a general tendency to overreactivity. The typical high EPQ-N scorer is an anxious, worrying individual, moody, frequently depressed and is prone to suffer from various psychosomatic disorders.

3.2.4.11 *Other questions*

The participants were asked to state their coffee, alcohol and tobacco consumption, and whether if they had ever had peptic ulcer disease or had ever consulted a doctor for GI complaints. Also, the past three months of general pain and all GI medication were indicated. Educational background was registered at five levels (elementary, comprehensive, secondary, upper secondary, university) and medical knowledge was evaluated by means of a self-explained questionnaire. The answers were scored with a sum of 0-15.

3.3 RESPONSE AND RECALL BIAS

Response bias is limited by letting the subjects complete the questionnaire in a calm and confident environment, anonymously, only assisted by a nurse when needed. We compared response rates for the

different questionnaires and also compared the correlation for answers of similar questions. Response rate was lowest 80.7% for the ISSI and totaling to 99.6% for the PGWB questionnaires. The abuse questionnaire, which was completed last, had a response rate of 97.7%. The response rates indicate that there was no “exhaustion effect”. Comparing the answers about a feeling of depression, question 3 in PGWB and question 6 in HADS had a correlation coefficient $r=0,49$ $p<0.0001$. The results indicate a consistent response across questionnaires. Recall bias is possible with retrospective data, e.g. FGID sufferers over-reporting symptoms compared to GI symptom free. Hardt published 2004 a review of the evidence for validity of retrospective reports in adulthood of major adverse experiences in childhood and found a substantial rate of false negative reports, but false positive reports were probably rare [195]. Similarly, memories of parental behaviour seem to be stable over time [186]. Thus, we assume that recall bias cannot be a major compromising factor of the results.

3.4 BLOOD EXAMINATION

Analysis of IgG antibodies to *H. pylori*, was performed using Pyloriset EIA-G, (Orion Diagnostica, Finland).

3.5 STATISTICAL METHODS

Pearson Chi-2 test, Student’s t-test, Fisher’s exact test and the Wilcoxon rank-sum test were used for testing comparison in univariate analyses. Ninety five per cent confidence intervals (CI) were computed with parametric methods: a p-value of 0.05 or less was considered statistically significant and all reported p-values were two-sided. The statistical package Stata 8 was used for analyses in study I and II and Stata 9 in study III and IV [196, 197].

In study I multivariate analyses were performed using a logistic regression model [198]with FGID/SSF as dependent variable and also an ordered logistic regression with dyspeptic severity as the dependent variable. Age and BMI were linear to outcome and were thus handled as continuous variables. To test the symptoms in the questionnaire CSQA, we built an age and sex adjusted logistic regression model for each symptom and accepted a P value less than $0.05/(\text{number of symptoms}) = 0.05/30 \approx 0.0016$ as significant which is an approximation of the Bonferroni adjustment [199]. The Bonferroni adjustment is acceptable when searching for significant associations without pre-established hypotheses [200]. The explanatory variables were evaluated by a logistic regression in a sex- and age adjusted model with the inclusion of clinically known determinants, a strategy suitable for small data sets [201]. The association between each potential determinant obtained from the questionnaires and the presence of FGID was quantified by using odds ratios and 95% confidence intervals. All exposure variables with $P<0.25$ were then entered together in a multivariate logistic regression model to evaluate which was independently associated with the presence of FGID. A factor analysis [202] was performed using all 30 complaints

and the factors were chosen that had eigenvalues greater than 1.3. Four factors were obtained by a principal component analysis with varimax rotation. The 30 variables were dichotomized with the higher 1/3 given the value 1 and the rest the value 0. A logistic regression was performed with the four factors age- and sex adjusted, and factors with $p > 0.05$ were excluded. To test whether the model fitted the data, a Pearson goodness-of-fit test with p values greater than 0.05 was performed. When the number of covariates approximated the number of observations, the Hosmer-Lemeshow test was performed to determine whether the model fitted the data. For the ordinal logistic model, comparison with a multinomial model made an approximate fit test. No interactions were found between the variables in the main model.

In study II a multiple logistic regression was performed with age, sex, education, depression and anxiety as independent variables and health care factors (doctor consultations, phone calls, prescriptions, referrals, sick-leave episodes and number of different diagnosis) as dependent variables: all variables dichotomized.

In study III a Spearman rank correlation test was performed for the variables anxiety, depression and quality of life. A multiple logistic regression analysis was performed with FGID/SSF and Consulters/non-consulters as outcome variables, each of the abuse variables as exposure variables and the possible confounding factors: age (-40/40- years), sex (female/male), education level, anxiety (1-HADS subscale >10 , 0-HADS subscale <11), depression (1-HADS subscale >10 , 0-HADS subscale <11) and health related quality of life (HRQoL) score 1 - >108 , 0- ≤ 108) as explanatory variables. In order to adjust for the influence of explanatory variables the variables were included one by one using a multiple logistic regression technique and if the variable affected the odds ratios of the outcome variables less than $\pm 10\%$ and with $p > 0.10$, the variable was eliminated from the model. The Hosmer-Lemeshow goodness-of-fit test was performed for each model, and model improvements were tested with the likelihood-ratio test. Tests for interactions were completed between the abuse variables and age, sex and HRQoL. No significant interactions were found.

In study IV a Spearman rank correlation analysis was computed with each of the six parental rearing exposure variables against the explanatory variables in order to find possible confounders (data not shown). The p -values were adjusted by the Bonferroni procedure. All six exposure variables were tested by multiple logistic regression analysis for each of the two outcome variables, FGID/SSF and Consulters/Non-consulters in the crude models. Subsequently, the six exposure variables were tested for each of the two outcome variables by adding one explanatory variable at a time, with the logistic regression method. Explanatory variables were eliminated from the analysis, except for age and sex, if the corresponding p -value was greater than 0.10 and the variables did not influence the odds ratio of

exposure variable more than $\pm 10\%$, because they were not considered to affect the exposure variable sufficiently. Finally, each of the outcome variables was introduced with exposure variables and all significant explanatory variables, and then insignificant variables were eliminated one at a time by using the multiple logistic regression technique. A power analysis was computed for a 90% power at the $P < 0.05$ levels to detect a 20% absolute difference in the exposure variables (20).

3.5.1 Power analyses

Study I, III and IV: One hundred and twenty three subjects were required (in each the FGID and SSF groups) in order to have a 90% power at the $P < 0.05$ level to detect a 20% absolute difference in exposure variables. This assumed a 24% prevalence of FGID in the population, equal numbers of subjects in the FGID and SSF groups, 15 and 20% absolute difference in the exposure variables within the two steps of the study, 75% response rate on the ASQ, and 25% exclusion from each group in the last step.

Study II: In order to have 90% power at the $P < 0.05$ level to detect a 100% absolute difference in mean consultation rate, 72 subjects in the FGID and 36 subjects in the SSF groups were needed. This assumed an annual consultation rate of two for the FGID and one for the SSF group, a $SD=3$ in both groups and twice as many subjects in the FGID group as in the SSF group.

4 RESULTS

4.1 STUDY I

4.1.1 Study Group Characteristics

As shown in Table 2, there were more females among those with FGID. However, there were no intergroup differences in education, medical knowledge, BMI, intake of coffee, alcohol and smoking. The age difference was irrelevant, as those with SSF had been largely excluded due to prior study results. Disease-related variables were significantly different between the study groups. These variables were introduced to further modelling, as shown below. The variables ‘intake of GI medicine’ and ‘previous PUD’ were not included due to sparse data.

Table 2. Comparison between explanatory variables for subjects with FGID and SSF adjusted for sex and age. Ordinal variables are presented as median (range), dichotomous variables as proportion %, and continuous variables as mean (SD).

4.2 VARIABLE	FGID n=141	SSF n=97	P
AGE	45.7 (14)	52.4 (15)	not relevant
SEX (female %)	66	53	0.026 ***
BMI	26.3 (4.7)	26.2 (4.2)	Ns *
Education	3 (2-4)	3 (1-4)	Ns **
Medical knowledge	10 (4-15)	11 (5-15)	Ns **
GI sympt severity	4 (3-5)	0 (0-0)	<0.0005 **
GI Consultation (ever)	72%	8%	<0.0005 ***
Pain medicine (3 month)	77%	34%	<0.0005 ***
GI MEDICINE (3 MON)	32%	1%	<0.0005 ***
Previous PUD (ever)	12%	1%	0.006 ***
Coffee	2 (2-3)	2 (2-3)	Ns **
Alcohol	4 (3-4)	3 (2-4)	Ns **
Smoking	1 (1-2)	1 (1-2)	Ns **

*=Student’s t-test **= Mann-Whitney test ***= Pearson Chi-2 test

4.1.2 CSQA and FGID vs. SSF

The results from the 30 CSQA complaints for the FGID and SSF study groups are presented in Figure 4. Those with persistent FGID scored statistically higher on all variables except difficulties in passing urine, excessive weight, coughing and impaired hearing.

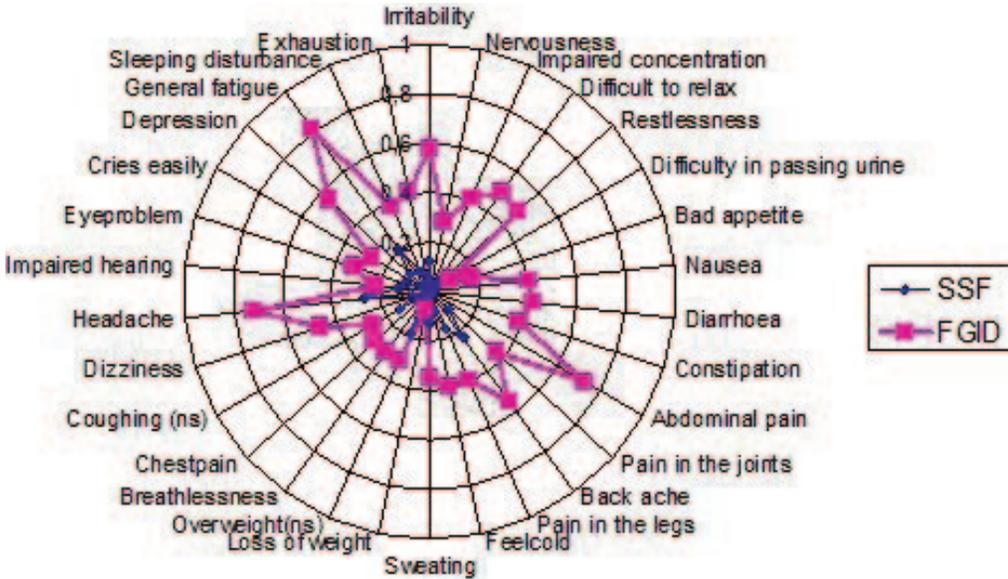


Figure 4. Proportion of complaints in the CSQA for the FGID and SSF study groups

4.1.3 Risk Modelling

Risks of reported CSQA complaints for FGID vs. SSF, expressed as age and sex adjusted OR, are presented in Table 3. GI complaints (abdominal pain, nausea, diarrhea and constipation) were excluded as we aimed to analyze the co-morbidity with GI symptoms. The OR was significant for all except four complaints. After adjusting for alcohol and pain and GI drug intake (Table 3), 20 complaints remained significant. A factor analysis was performed including the 26 non-GI complaints. After a varimax rotation of the four factors with eigenvalues > 1.3, we found four factors representing psychological illness, somatic illness, ache/fatigue and one “miscellaneous” (Table 3). Each factor was then introduced in a logistic regression model adjusted for sex and age (Table 3), and the “miscellaneous” factor was shown to be non-significant. In the last sequential analysis, the three factors that remained significant in the prior analysis were introduced together into a main effect model, adjusted for age and sex. The OR for these factors remained significant, as shown in Table 3.

Table 3. Odds ratios (OR, with 95% confidence intervals (95% CI)) of FGID/SSF (n=238) for complaints elicited by the CSQA. Logistic regression is presented in different models. A factor analysis extracted four factors: A= psychological illness factor, B=somatic illness factor, C=miscellaneous factor, D=ache/fatigue factor. These were used in the modelling in the right two columns.

1) Reference group (OR=1) is those coded 0 in each factor

Symptom	I OR (95% CI) by Models adjusted for sex and age	II OR (95% CI) by Models adjusted for sex, age, alcohol, pain tablets, GI- tablets	III FAC- TOR	IV OR (95% CI) by Models adjusted for sex and age	V OR (95% CI) by a main effect model adjusted for sex and age
SSF (all variables)	1 (Reference)	1 (Reference)			
FGID					
Cries easily	6.7 (2.3-19.9)	9.8 (2.0- 47)	A		
Sleeping disturbance	6.2 (2.7-14.0)	3.2 (1.3-8)	A		
General fatigue	14.5 (7.4-28.7)	12.6 (5.3-30)	A, D		
Irritability	8.8 (4.1-17.8)	5.6 (2.3 - 13.7)	A, D		
Nervousness	18.4 (4.2-80.3)	14.3 (2.8 -72)	A	8.0 (4.1-15.8) ¹⁾	8.4 (4.0-17.5) ¹⁾
Impaired concentration	19.0 (5.7-63.8)	15.3 (4.0 – 58)	A	Psychological illness	Psychological illness
Difficulty to relax	15.7 (6.0-41.5)	10.9 (3.7- 32)	A		
Restlessness	40.0 (9.4-170)	32.2 (6.7-154)	A		
Depression	8.6 (4.1-18)	4.7 (2.0 -11)	A		
Exhaustion	12.7 (4.4-37)	9.1 (2.7-30)	A		
Chest pain	40.0 (5.3-300)		B		
Pain in the joints	6.2 (2.8-13.6)	7.5 (2.6- 21)	B		
Pain in the legs	4.4 (2.2-8.9)	3.8 (1.6- 9.3)	B		
Overweight	2.0 (1.0-4.0)	1.4 (0.6- 3.6)	B	3.7 (2.0-7.1) ¹⁾	2.8 (1.3-5.7) ¹⁾
Breathlessness	8.9 (3.2-25)	12.1 (3.3-45)	B	Somatic illness	Somatic illness
Dizziness	10.1 (4.2-24)	11.4 (3.8- 34)	B		
Impaired hearing	3.0 (1.3-6.8)	3.1 (1.0- 9.5)	B		
Eye problem	4.2 (1.9-9.1)	3.4 (1.3- 9.0)	B		
Loss of weight	-	-	C		
Bad appetite	-	-	C		
Feeling cold	7.3 (3.1-17)	7.0 (2.6-19)	C	1.7 (0.9-3.0) ¹⁾	
Difficulty in passing urine	9.6 (2.0-47)	9.1 (1.4- 59)	C	Miscellaneous	
Back ache	4.4 (2.4-8.2)	2.0 (0.9-4.3)	D	2.9 (1.6-5.2) ¹⁾	4.3 (2.1-8.7) ¹⁾
Headache	6.3 (3.4-12)	4.1 (1.9 -9.1)	D	Ache/fatigue	Ache/fatigue
Sweating	3.6 (1.7 -7.4)	3.3 (1.3 - 8.5)			
Coughing	2.0 (0.98-4.2)	1.7 (0.6-4.4)			

4.1.4 Consulters versus non consulters

Consulters and non-consulters among those with persistent FGID were compared regarding their complaints, as reported in the CSQA. The proportion (0-1.0) per complaint is shown in Figure 5. There were no statistically significant differences between the consulters and non-consulters for any of the complaints (adjusted for age and sex, $p > 0.0016$).

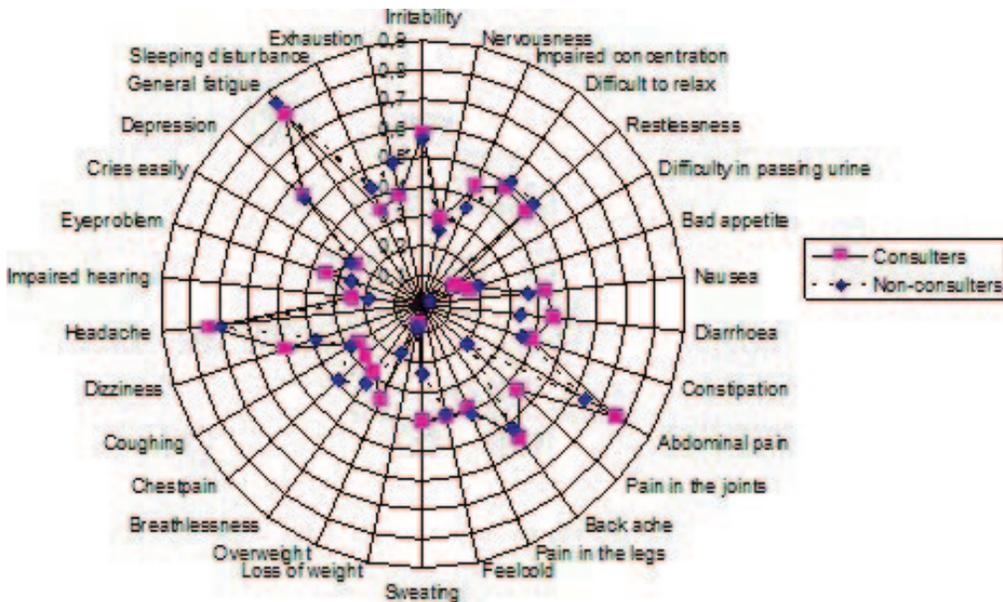


Figure 5. Proportion of complaints in the CSQA for the consulters and non-consulters among FGID

4.1.5 ASQ Symptom Severity and Consulting Behaviour vs CSQA Factors

From the ASQ, the mean grades of GI symptom severity for affirmative symptoms were analyzed against the three final CSQA factors from Table 3 (psychological illness, somatic illness, ache/fatigue) and for age, sex and consulting behaviour, as shown in Table 4. The analysis showed an obviously higher risk of increased GI symptom severity for consulters (OR 12.3) and for psychological illness (OR 4.5), while somatic illness and ache/fatigue had a low risk, with the 95% CI close to 1.0. From the ASQ, consulting behaviour was analyzed for the CSQA factors psychological illness, abdominal illness, age and sex. The analysis showed a greater chance of being a consulter for abdominal illness (OR 2.0) and psychological illness (OR 2.2).

A factor analysis and subsequent logistic regression revealed that subjects with FGID had a higher risk of psychological illness [OR 8.4, 95% CI 4.0-17.5] than somatic illness [OR 2.8, 95% CI 1.3-5.7] or ache and fatigue symptoms [OR 4.3, 95% CI 2.1-8.7]. Subjects with psychological illness had a higher risk of severe GI symptoms than controls; moreover they have a greater chance of being consulters. Patients with FGID had more severe GI symptoms than non-patients.

Table 4. Odds ratios (OR, with 95% confidence intervals (95% CI)) of graded (0,1,2) GI symptom severity in the ASQ for consulting, psychological illness, somatic illness and ache/fatigue factors, age and sex, for both FGID and SSF (n=232). Ordinal logistic regression.

Variable	OR (95% CI)
Psychological illness	1
low	
high	4.5(2.4-8.4)
Somatic illness low	1
high	2.0(1.1-3.8)
Ache/fatigue low	1
high	2.1(1.1-4.2)
Consulters no	1
yes	12.3(6.3-23.9)
Age (continuous)	0.96 (0.94-0.99)
Sex female	1
male	0.9 (0.5-1.7)

4.2 STUDY II

4.2.1 Doctor face-to-face and phone consultations

For any disorder there were 300 consultations for the FGID entered in the medical records and 110 consultations for the SSF groups. The health care actions are summarised in Table 5.

Table 5. Healthcare actions per person for FGID and SSF 1996-1997 and reported mood disorder. Odds ratios for FGID compared to SSF (SSF=1) adjusted for age, sex, education, anxiety and depression: health care actions are dependent variables, all introduced into a multivariate analysis with the logistic regression method.

	Doc consult n=410	Phone calls n=103	Prescription n=552	Referrals n=34	Sick- leave episodes n=56	Sick- leave days n=1204	Diagnoses n=247	Anxiety	Depression
	Mean 95% CI	Mean 95% CI	Mean 95% CI	Mean 95% CI	Mean 95% CI	Mean 95% CI	Mean 95% CI	Mean(median) 95% CI	Mean(median) 95% CI
FGID n=71	4.2 3.2-5.3	1.1 0.8- 1.5	6.0 4.3-7.8	0.3 0.2-0.5	0.6 0.1-1.1	13.2 0-31	2.5 2.0-3.0	6.2 (6) 5.2-6.3	3.9 (3) 2.9-4.0
SSF n=48	2.3 1.5-3.1	0.5 0.2- 0.8	3.7 1.8-5.6	0.2 0.1-0.4	0.3 0-0.7	5.5 0-14	1.5 1.0-2.0	3.2 (3) 2.9-3.5	1.5 (1) 1.3-2.1
P (Mann- Whitney)	0.004	0.004	0.02	0.4	0.2	0.5	0.002	<0.0001	0.0001
OR	3.5	3.4	2.4	1.6	1.6	0.71	2.9	11.5	5.2
FGID (SSF=1)	0.007 (1.4- 8.6)	0.008 (1.4- 8.3)	0.036 (1.1-5.5)	0.30 (0.6-4.2)	0.69 (0.4-5.7)	0.70 (0.1- 4.1)	0.022 (1.2-7.3)	0.025 (1.4-96)	0.038 (1.1-25)
P (95%CI)									

Those with FGID consulted a doctor more often, made more phone calls, received more diagnoses and obtained more prescriptions than the SSF group. The distribution of consultations and phone calls is presented in Table 6, and prescriptions and diagnoses in Table 7.

Table 6. Number of consultations and phone calls for subjects with FGID and SSF 1996-1997.

Number of doctor consultations and phone calls	FGID consult. n=300	%	SSF consult. n=110	%	FGID calls n=81	%	SSF calls n=22	%
11-20	8	11	1	2	-	-	-	-
7-10	5	7,0	4	8	-	-	-	-
3-6	24	34	10	21	15	21	4	8
1-2	23	32	15	31	20	28	7	15
0	11	16	18	38	36	51	36	75
Total	71	100	48	100	71	100	48*	100

* one missing

Table 7. Number of different diagnoses and number of prescriptions recorded at consultations for patients in Öregrund-Östhammar 1996-1997.

Number of diagnoses per subject	FGID n=176	%	SSF n=71	%	Number of prescriptions per subject	FGID n=385	%	SSF n=167	%
6-8	6	8	1	2	13-33	12	17	5	10
3-5	22	31	10	21	5-12	16	22	6	13
1-2	31	44	19	40	1-4	26	37	16	33
0	12	17	18	37	0	17	24	21	44
Total	71	100	48	100	Total	71	100	48	100

4.2.2 Co-morbidity

The FGID patients had a non-GI diagnosis code recorded in a majority, 97%, of the consultations, compared to a non-GI diagnosis code in all consultations among SSF patients. Two SSF patients within the SSF had an additional GI diagnosis set: one with gastroesophageal reflux and one with meteorism. Co-morbidity was presented as the number of different ICD-9 diagnostic groups in each consultation, for 410 consultations (FGID: n=300; SSF: n=110). There was no statistical significance in the distribution of set diagnoses for the 14 diagnostic groups determined by univariate comparison between the FGID and SSF groups, except for the GI, circulatory and hypertension diagnostic groups. In the latter two diagnostic groups, FGID patients had a lower mean age than SSF (circulation, 58y (FGID) and 66y

(SSF), $p=0.049$: hypertension, 63y (FGID) and 75y (SSF), $p=0.004$). The morbidity is illustrated in Figure 6.

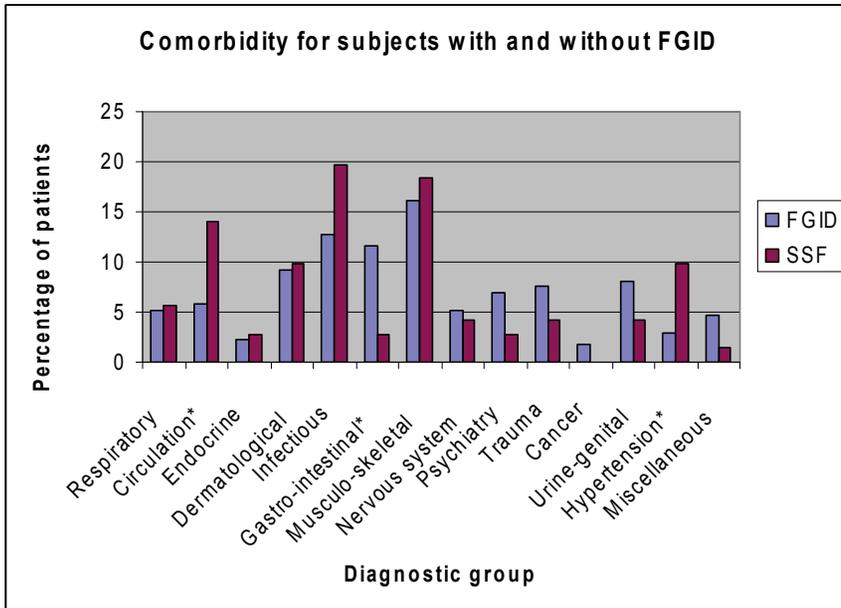


Figure 6. Morbidity for subjects with FGID and SSF as presented in their medical records.

4.2.3 Referrals

There were 34 referrals recorded for the FGID and SSF groups, and nobody was referred more than twice. In the FGID group, 27% were referred to a specialist, compared to 21% in the SSF group (ns).

4.2.4 Sick-leave

There were no differences in either the number of sick-leave episodes or the number of sick leave days for those with FGID and SSF, as highlighted in Table 2. The reason for sick-leave for GI disorders was 9% for the FGID (out of 956 days) and 0% for SSF (out of 329 days) and thus the corresponding figures for non-GI disorders were 91% for the FGID and 100% for SSF, respectively.

4.2.5 Anxiety and depression

FGID had increased levels of anxiety ($p<0.0001$) and depression ($p=0.0001$) and a significant age- and sex-adjusted higher risk for anxiety OR=11.5 (95% CI 1.4-96; $p=0.025$) and for depression OR=5.2 (95% CI 1.1-25; 0.038). See Table 5.

4.2.6 Comparison with the ROME II definition

The definition of dyspepsia was more restricted in terms of combinations of symptoms than the Rome II definition, but wider in terms of abdominal location, as not only epigastric but also mid-abdominal and flank symptoms were included. The IBS definition requires, aside from compulsory "abdominal pain and discomfort" a combination of bowel habit disturbances (diarrhoea and/or constipation) and a symptom mainly labelled as "supportive" in the Rome II definition of IBS).

Adopting the Rome II definitions for FGID (dyspepsia and IBS) as closely as possible, 4.8% of the 911 subjects in the population sample (18) were erroneously classified as having FGID instead of "minor symptoms", with an overall agreement of 95.2% between the combinations of FGID definitions.

4.3 STUDY III

4.3.1 Demographic and sexual, physical and emotional abuse

The distribution of age, sex, education, GI consultation, anxiety, depression, HRQoL, and sexual, physical and emotional abuse for persons with FGID and SSF is presented in Table 8. Forty-one percent of those with FGID had experienced some kind of abuse, as compared with twenty percent ($p < 0.01$) among SSF controls. Impaired anxiety and HRQoL were significantly more common among subjects exposed to prior abuse, while depression was not.

Table 8. Distribution of age, sex, education, previous GI consultation and abuse for women and men with functional gastrointestinal disorder (FGID) and strictly GI symptom free (SSF) and previous consulters / non-consulters for FGID.

	FGID(n=141) n (%)	SSF (n=97) n (%)	Statistic p	Consulters GI (n=99) n (%)	Non consulters GI (n=39) n (%)	Statistic p
Mean age years (SD) ²	45.7 (14.3)	52.4 (15.4)	0.0007	46.7 (13.4)	41.4 (14.2)	0.041
Female ¹	93 (66.0)	51 (52.6)	0.038	66 (66.7)	26 (66.7)	0.1
Completed high school ¹	66 (47.1)	28 (29.5)	0.007	43 (43.4)	23 (60.0)	0.100
Consulted for GI ever ¹	99 (71.7)	8 (8.3)	<0.001	not relevant	not relevant	
Psychological	96.8	114.6	<0.0001	96.8	96.6	0.963
General Well-Being ²						
Anxiety ¹	13 (10.0)	0 (0.0)	0.002	5 (7.5)	8 (13.1)	0.507
Depression ¹	5 (4.8)	1 (1.7)	0.319	3 (5.4)	2 (4.3)	0.942
<i>Childhood abuse</i>						
Childhood sexual abuse ¹	19 (13.9)	3 (3.1)	0.006	16 (16.5)	3 (7.9)	0.196
Childhood physical abuse ¹	15 (11.0)	3 (3.2)	0.029	14 (14.4)	1 (2.6)	0.050
Childhood emotional abuse ¹	37 (27.4)	15 (16.1)	0.046	32 (33.7)	5 (13.2)	0.017
Any childhood abuse ¹	43 (31.4)	18 (18.8)	0.031	37 (38.1)	6 (15.8)	0.012
<i>Adulthood abuse</i>						
Adult sexual abuse ¹	17 (12.4)	2 (2.1)	0.005	14 (14.4)	3 (7.9)	0.303
Adult physical abuse ¹	3 (2.2)	1 (1.1)	0.513	3 (3.1)	0 (0.0)	0.273
Adult emotional abuse ¹	32 (23.7)	5 (5.4)	<0.001	24 (25.3)	8 (21.1)	0.608
Any adulthood abuse ¹	40 (29.2)	8 (8.3)	<0.001	30 (30.9)	10 (26.3)	0.598
Any childhood, not adulthood, abuse ¹	16 (14.6)	11 (12.4)	0.654	15 (20.0)	1 (3.0)	0.022
Any adulthood, not childhood, abuse ¹	13 (11.8)	1 (1.1)	0.003	8 (10.7)	5 (15.2)	0.509
<i>Any abuse (child or adult)</i>						
Sexual abuse ¹	30 (21.9)	4 (4.2)	<0.001	25 (25.8)	5 (13.2)	0.113
Physical abuse ¹	17 (12.4)	3 (3.2)	0.014	16 (16.5)	1 (2.6)	0.029
Emotional abuse ¹	48 (35.6)	15 (16.1)	0.001	39 (41.1)	9 (23.7)	0.060
Any abuse ¹	56 (40.9)	19 (19.8)	0.001	45 (46.4)	11 (29.0)	0.064

¹=Pearson CHI²-test ²=Student's t-test

4.3.2 Women

There were 144 women, 93 with FGID and 51 SSF in the study. Almost half of the women, 42 out of 93 (45%) with FGID had a history of abuse, in contrast to the 8 out of 51 (16%, $p < 0.01$) SSF controls. Women with FGID had a higher prevalence than SSF women for sexual, physical and emotional abuse in childhood and for sexual and emotional abuse in adulthood, as presented in table 9.

Table 9. The number of people, and the proportion of individuals (%) with a history of sexual, physical and emotional abuse in women and men with a functional gastrointestinal disorder (FGID) and strictly GI symptom free (SSF). The total number of FGID/SSF for both childhood and adulthood abuse in women was 93/51 and 48/46 in men.

	Childhood abuse				Adulthood abuse			
	number FGID n(%) / SSF n(%)				number FGID n(%) / SSF n(%)			
	p				p			
	Sexual	Physical	Emotional	Any	Sexual	Physical	Emotional	Any
Women	18(19) / 3(6)	11(12) / 1(2)	26(28) / 5(10)	32(34) / 7(14)	14(15) / 2(4)	2(2) / 0(0)	24(26) / 2(4)	31(33) / 4(8)
	0.027	0.048	0.021	0.006	0.044	0.403	0.001	<0.001
Men	1(1) / 0(0)	4(8) / 2(4)	11(23) / 10(22)	11(23) / 11(24)	3(6) / 0(0)	1(2) / 1(2)	8(17) / 3(7)	9(19) / 4(9)
	1.00	0.876	0.937	1.00	0.331	1.00	0.343	0.382

P value computed with Fisher's exact two-sided test.

Out of the 50 women with a history of abuse, 24 (48%, FGID n=21, SSF n=3, $p < 0.01$) had experienced sexual, physical or emotional abuse both in childhood and as adults. In the FGID group, 42 (46%) women reported abuse in childhood and/or adulthood, as compared with 8 (16%, $p < 0.01$) in the SSF group. Moreover, in the FGID group, 32 (35%) women had a history of childhood abuse as compared with 7 (14%, $p < 0.01$) in the SSF group.

4.3.3 Men

In contrast to the women, the men had no significant difference for a history of abuse; 14 out of 48 (29%) men with FGID versus 11 out of 46 (24%, $p = 0.69$) SSF men. Similarly, no statistically significant difference was found for a history of sexual, physical or emotional abuse in the subgroups childhood and adulthood for men, see Table 9.

4.3.4 Anxiety and depression

Women and men with FGID significantly more often reported anxiety ($p < 0.01$), consultations for GI problems ($p = 0.02$), childhood abuse ($p < 0.01$) and adulthood abuse ($p < 0.01$) than SSF women and men. In contrast, depression had no significant univariate association with FGID, GI consulting, childhood abuse or adulthood abuse. FGID (OR=2.1 95% CI: 1.1-4.0) and anxiety (OR=10.7 95% CI: 2.3-51) were

the only remaining independent predictors for abuse when adjusted for age, sex, education and depression when tested with the multiple logistic regression technique.

4.3.5 Quality of life

Subjects with FGID had a significant reduction in HRQoL, as measured by the PGWB, with a mean value of 97 (95% CI: 94-99), as compared with SSF controls, who scored 115 (95% CI: 112-116). There was no significant difference in HRQoL between women and men either for the FGID subjects (women 96; 95% CI: 92-99; men 99; 95% CI: 95-102) or for the SSF group (women 114; 95% CI: 110-117; men 115; 95% CI: 112-119). Women with a history of some kind of abuse and FGID had significantly reduced HRQoL, with a mean value of 91 (95% CI: 85-97) as compared with a mean value of 100 (95% CI: 96-104) for women without abuse history. Similarly, men with a history of some kind of abuse and FGID had significantly reduced quality of life, with a mean value of 90 (95% CI: 82-99) as compared with a mean value of 102 (95% CI: 98-105) for men without abuse history.

The HRQoL for FGID consulters and non-consulters was the same; both groups had a mean value of 97 with 95% CI 93-100 and 92-102, respectively. However, FGID consulters with a history of abuse had significantly lower HRQoL, with a mean value of 92 (95% CI: 86-97), than FGID consulters without a history of abuse with a mean value of 100 (95% CI: 97-104, $p < 0.05$). There was a significant negative correlation between HRQoL and anxiety $r = -0.61$ ($p < 0.01$) and between HRQoL and depression $r = -0.54$ ($p < 0.01$).

4.3.6 Multivariate risk modelling

Persons with FGID had higher odds ratio 2.2 (95% CI: 1.1 – 4.4), of a history of some kind of abuse, (in childhood or adulthood, sexual, physical or emotional), as compared with the SSF controls adjusted for age, sex, and HRQoL (main model, adding the variable anxiety or education did not improve the model). Some kind of abuse in adulthood had odds ratio 2.8 (95% CI: 1.1-7.1) with the same strategy. Emotional abuse in adulthood had the highest (and only significant) odds ratio 3.1 (95% CI: 1.0-9.4), while sexual abuse did not reach significance. In childhood, physical abuse seems to have the highest odds ratio 2.9 (95% CI: 0.7-12) for future FGID, although significance was not reached in this study (data not shown).

With the main model, women had significantly high odds ratios for FGID: from some kind of abuse 3.13 (95% CI: 1.21-8.10), emotional abuse 3.66 (95% CI: 1.22-11.0), physical abuse 5.07 (95% CI: 0.55-47.1) and sexual abuse 3.03 (95% CI: 0.89-10.3) the latter two types of abuse did not reach significance, as presented in Table 10. There were significantly high odds ratios in women with the crude model for FGID from all types of abuse in childhood and adulthood, except adult physical abuse (probably owing

to the small number of observations). Similarly, with the main model, there were high odds ratios in women, but they did not reach significance, see Table 10.

In contrast, men did not have the same elevation of odds ratio for FGID from any type of abuse as compared to women. The highest odds ratio in men for FGID was for some kind of adulthood abuse was 2.41 (95% CI: 0.55-10.5), while adult emotional abuse was 2.78 (95% CI: 0.55-14.0) but neither were significant, see Table 10.

Table 10. Odds ratio and 95% confidence interval (95% CI) for having a functional gastrointestinal disorder (FGID) (logistic regression) in different groups of abuse, women and men, in crude model and main model adjusted for age and health related quality of life (HRQoL).

Variable	Crude Model		Main Model (adjusted for age and HRQoL)	
	Women	Men	Women	Men
Childhood abuse				
No childhood sexual abuse	1		1	
Childhood sexual abuse	3.95 (1.10-14.1)	*	2.44 (0.60-10.0)	*
No childhood physical abuse	1	1	1	1
Childhood physical abuse	6.88 (0.86-54.9)	1.95 (0.34-11.2)	4.93 (0.53-46.3)	1.61 (0.21-12.3)
No childhood emotional abuse	1	1	1	1
Childhood emotional abuse	3.71 (1.32-10.4)	1.00 (0.38-2.68)	2.71 (0.87-8.4)	1.14 (0.37-3.55)
No childhood abuse	1	1	1	1
Any childhood abuse	3.41 (1.38-8.43)	0.94 (0.36-2.47)	2.50 (0.91-6.85)	1.10 (0.36-3.38)
Adulthood abuse				
No adult sexual abuse	1		1	1
Adult sexual abuse	4.45 (0.97-20.5)	*	3.20 (0.60-16.9)	1.51 (0.53-4.29)
No adult physical abuse		1		1
Adult physical abuse	*	0.93 (0.06-15.4)	*	0.84 (0.03-25.3)
No adult emotional abuse	1	1	1	1
Adult emotional abuse	8.86 (2.00-39.3)	2.74 (0.67-11.1)	3.42 (0.70-16.9)	2.78 (0.55-14.0)
No adulthood abuse	1	1	1	1
Any adulthood abuse	6.07 (2.00-18.4)	2.43 (0.69-8.57)	3.10 (0.92-10.3)	2.41 (0.55-10.5)
Any abuse (child or adult)				
No sexual abuse	1		1	1
Sexual abuse	3.57 (1.34-9.5)	*	3.03 (0.89-10.3)	1.49 (0.52-4.24)
No physical abuse	1	1	1	1
Physical abuse	7.59 (0.96-60.2)	2.5 (0.46-13.6)	5.07 (0.55-47.1)	1.84 (0.26-13.0)
No emotional abuse	1	1	1	1
Emotional abuse	5.83 (2.11-16.1)	1.26 (0.48-3.28)	3.66 (1.22-11.0)	1.31 (0.43-3.95)
No abuse	1	1	1	1
Any abuse	4.61 (1.95-10.9)	1.31 (0.52-3.32)	3.13 (1.21-8.10)	1.32 (0.45-3.90)

1 = Reference * = too few observations

4.3.7 Consulters and non-consulters with FGID

Consulters with FGID more often (46 % of them) had a history of abuse as compared with non-consulters (29%, $p=0.06$) although it did not reach significance as shown in Table 8. Some kind of abuse in childhood was more prevalent: 38% in consulters versus 16% in non-consulters ($p=0.01$) and correspondingly for childhood emotional abuse 34% and 13% ($p=0.02$) and for childhood physical abuse 14% and 3% ($p=0.05$). Moreover, there was a significantly higher prevalence of physical abuse in childhood or adulthood in consulters, 17%, versus non-consulters 3%, $p=0.03$. Female consulters with a history of some kind of abuse had odds ratio 2.47 (95% CI: 0.92-6.7) and with a history of childhood emotional abuse this was significant, 4.20 (95% CI: 1.12 -15.7.7), in contrast to male consulters, with odds ratio 1.66 (95% CI: 0.37-7.50) for some kind of abuse and 2.10 (95% CI: 0.37-12.0) for childhood emotional abuse.

4.4 STUDY IV

4.4.1 Associations with parental rearing

In the FGID/SSF group there was a significantly higher degree of reported rejection from the mother (8.0 ± 0.25 vs. SSF 6.9 ± 0.14 , $p<0.01$) and father (8.0 ± 0.25 vs. SSF 7.0 ± 0.21 , $p<0.01$). Moreover, there was reported more maternal overprotection (18.1 ± 0.39 vs. SSF 16.9 ± 0.37 , $p<0.05$) and less paternal emotional warmth (15.2 ± 0.39 vs. SSF 16.4 ± 0.45 , $p=0.05$). Among consulters an increased rejection from mother (8.1 ± 0.31 vs. non-consulters 7.0 ± 0.13 , $p<0.05$) and father (8.3 ± 0.33 vs. non-consulters 7.0 ± 0.14 , $p<0.01$) was reported.

Maternal rejection was positively correlated with FGID ($r=0.218$ $p<0.005$) as was maternal overprotection ($r=0.147$ $p<0.05$) and paternal rejection ($r=0.206$ $p<0.005$). Parental rejection was also positively correlated with all kinds of abuse (maternal rejection $r=0.334$ $p<0.0005$; paternal rejection $r=0.311$ $p<0.001$).

4.4.2 Rates of well-being and abuse in FGID and Consulters versus non-consulters

Well-being as measured by the PGWB was significantly lower ($p<0.0001$) within the FGID group than among those SSF, but equal between consulters and non-consulters as presented in Table 11 and published before [15].

Table 11. Demographic and psycho-social factors for community subjects with functional gastrointestinal disorder (FGID) and for those being strictly GI symptom free (SSF) (left part). Previous consulters for GI symptoms/disorders among those FGID, and non-consulters (right part).

	FGID (n=141) n (%)	SSF (n=97) n (%)	p-value	Consulters GI (n=99) n (%)	Non consulters GI (n=39) n (%)	p-value
Mean age years (SD) ²	45.7 (14.3)	52.4 (15.4)	<0.001	46.7 (13.4)	41.4 (14.2)	<0.05
Gender Female ¹	93 (66.0)	51 (52.6)	<0.05	66 (66.7)	26 (66.7)	0
Completed high school ¹	66 (47.1)	28 (29.5)	<0.01	43 (43.4)	23 (60.0)	ns
Consulted for GI ever ¹	99 (71.7)	8 (8.3)	<0.001	not relevant	not relevant	
Neuroticism (EPQ-N) ³	12.8 (0.20)	10.8 (0.14)	<0.0001	12.8 (0.24)	11.3 (0.16)	<0.0001
<i>EMBU Parental rearing, mother</i>						
Rejection ³	8.0 (0.25)	6.9 (0.14)	<0.005	8.1 (0.31)	7.0 (0.13)	<0.05
Emotional warmth ³	16.3 (0.39)	17.0 (0.41)	ns	16.2 (0.47)	16.9 (0.35)	ns
Overprotection ³	18.1 (0.39)	16.9 (0.37)	<0.05	18.1 (0.48)	17.3 (0.31)	ns
<i>EMBU Parental rearing, father</i>						
Rejection ³	8.0 (0.25)	7.0 (0.21)	<0.005	8.3 (0.33)	7.0 (0.14)	<0.005
Emotional warmth ³	15.2 (0.39)	16.4 (0.45)	0.05	15.0 (0.46)	16.2 (0.37)	ns
Overprotection ³	16.8 (0.36)	16.3 (0.37)	ns	16.7 (0.43)	16.5 (0.32)	ns
Psychological General Well-Being (PGWB) ²	96.8	114.6	<0.0001	96.8	96.6	ns
<i>Anxiety and depression (HADS)</i>						
Anxiety ¹	13 (10.0)	0 (0.0)	<0.01	5 (7.5)	8 (13.1)	ns
Depression ¹	5 (4.8)	1 (1.7)	ns	3 (5.4)	2 (4.3)	ns
Abuse (ABQ) (sexual, physical, emotional) ¹	56 (40.9)	19 (19.8)	<0.005	45 (46.4)	11 (29.0)	ns
Coping strategies (CSQ) Catastrophizing ³	9.0 (0.57)	7.1 (0.76)	<0.05	9.0 (0.69)	7.6 (0.62)	ns
<i>Social support (ISSI)</i>						
Availability of social integration ³	5.7 (0.16)	6.2 (0.21)	<0.05	5.8 (0.19)	6.0 (0.17)	ns
Adequacy of social attachment ³	6.2 (0.21)	7.1 (0.18)	<0.005	6.2 (0.25)	6.8 (0.17)	ns
Availability of attachment ³	2.5 (0.06)	2.6 (0.08)	ns	2.4 (0.07)	2.7 (0.07)	<0.005
Adequacy of attachment ³	7.9 (0.25)	9.4 (0.12)	<0.0001	8.0 (0.30)	8.9 (0.18)	<0.05
<i>Health locus of control of behavior (MHLC)</i>						
Internal ³	23.5 (0.36)	24.5 (0.48)	ns	23.4 (0.44)	24.4 (0.38)	ns
Powerful others ³	21.4 (0.55)	22.5 (0.83)	ns	21.8 (0.65)	21.8 (0.66)	ns
Chance ³	19.4 (0.54)	20.9 (0.74)	ns	19.4 (0.67)	20.4 (0.57)	ns

¹=Pearson CHI²-test, ²=Student's t-test, ³=Mann-Whitney rank sum test, ns=not significant

The subjects in the FGID group when compared to the SSF, more frequently reported a history of abuse of the most common types - emotional/verbal (35.6% vs. 16.1% $p<0.01$), sexual (21.9% vs. 4.2% $p<0.01$) and physical 12.4% vs. 3.2% $p=0.01$). Consulters had a history of emotional/verbal abuse in 41.1%, sexual in 25.8% and physical abuse in 16.5% compared to 23.7% ($p=0.06$) emotional, 13.2% (ns) sexual and 2.6% ($p=0.03$) physical abuse among non-consulters. The results for any kind of abuse are presented in Table 11.

4.4.3 Associations and rates of neuroticism, coping, social support and health locus of control in FGID/SSF and Consulters versus non-consulters

As shown in table 12 the FGID group reported a higher degree of neuroticism ($p<0.01$) compared to SSF and similarly for consulters ($p<0.001$) compared to non-consulters. Coping strategies differed significantly between FGID and SSF with increased catastrophizing for FGID sufferers ($p=0.03$) compared with SSF and a less efficient release of pain strategy for FGID ($p=0.01$) than for SSF. No differences in coping strategies were found between consulters/non-consulters. Social support was found reduced among FGID concerning availability of social integration ($p=0.03$), adequacy of social integration ($p<0.01$) and adequacy of attachment ($p<0.01$). Consulters had a reduced availability of attachment ($p<0.01$) and reduced adequacy of attachment ($p<0.05$) compared to non-consulters. No differences were found in health locus of control, neither between FGID and the SSF, nor between consulters and non-consulters.

4.4.4 Multivariate risk modelling

The three parental rearing behaviours were analyzed for FGID/SSF and consulters/non consulters, respectively. In a crude model there was a higher risk of reporting FGID for a rejecting maternal (OR=2.11 95%CI 1.21 -3.70) and paternal rearing (OR=2.35 95%CI 1.33 -4.16), respectively. The risk remained in main models adjusted for age, sex and neuroticism, for paternal rejective rearing style (OR=2.30 95% CI 1.21-4.38) and was almost significant for maternal rejecting rearing style (OR=1.84 95% CI 0.98-3.45). The results are presented in Table 12. The outcome variable FGID/SSF was introduced in a model with reverse elimination of the explanatory variables: father's rejecting rearing style, age, sex, neuroticism, anxiety, depression, any abuse, child abuse, adult abuse, HRQoL, availability of social interaction, availability of social integration and adequacy of attachment. In the final model (log likelihood = -107.5 $n=206$), the following three explanatory variables remained: increased neuroticism (OR=3.15 95% CI 1.54-6.43), increased paternal rejecting rearing style (OR= 2.01 95% CI 1.04-3.88) and reduced health related quality of life (OR=0.21 95% CI 0.10-0.42).

The outcome variable consulter/non-consulter among FGID, similarly modelled, ended in a model with the three remaining explanatory variables: exposure to abuse in childhood (OR=3.87 95% CI 1.27-11.8),

reduced availability of attachment (OR= 0.18 95% CI 0.06-0.57) and reduced adequacy of social interaction (OR=0.37 95% CI 0.14-0.96). Paternal and maternal rejecting rearing style, health related quality of life and the other explanatory variables did not reach statistical significance and were excluded.

Table 12. Odds ratio (OR) and 95% confidence interval (CI) with logistic regression; for parental rearing variables by parent, HRQoL, anxiety, depression, abuse, coping and social support in FGID's and the SSF groups and (to the right) GI consulters and non-consulters among FGID-sufferers. Unadjusted crude model and main models adjusted for age, sex and neuroticism.

VARIABLE	FGID (N=141) AND SSF (N=97)		CONSULTERS (N=99) AND NON-CONSULTERS (N=39)	
	Crude model OR (95% CI) n	Main model adjusted for age, sex and neuroticism OR (95% CI)	Crude model OR (95% CI) n	Main model adjusted for age, sex and neuroticism OR (95% CI) n
EMBU				
No rejection	reference	reference	reference	reference
Rejection				
Mother	2.11 (1.21–3.70) 209	1.84 (0.98–3.45) 209	0.75 (0.32–1.72) 121	0.82 (0.35–1.92) 121
Father	2.35 (1.33–4.16) 206	2.30 (1.21–4.38) 206	1.38 (0.62–3.09) 122	1.47 (0.65–3.34) 122
EMBU				
No emotional warmth	reference	reference	reference	reference
Emotional warmth				
Mother	0.98 (0.57–1.68) 219	1.36 (0.73–2.55) 219	0.76 (0.34–1.67) 127	0.70 (0.31–1.58) 127
Father	0.70 (0.40–1.21) 216	0.90 (0.48–1.68) 216	0.84 (0.38–1.85) 128	0.77 (0.34–1.74) 128
EMBU				
No overprotection	reference	reference	reference	reference
Overprotection				
Mother	1.53 (0.89–2.64) 220	1.50 (0.81–2.77) 220	0.71 (0.32–1.60) 129	0.68 (0.30–1.54) 129
Father	1.20 (0.69–2.07) 216	1.10 (0.60–2.02) 214	0.48 (0.22–1.07) 127	0.50 (0.22–1.13) 127
PGWB				
Normal HRQoL	reference	reference	reference	reference
Poor HRQoL	9.27 (5.03–17.1) 237	5.26 (2.66–10.4) 237	0.95 (0.42–2.15) 138	1.22 (0.49–3.05) 138
HADS				
No anxiety	reference	reference	reference	reference
Anxiety	14.7 (1.93–112) 217	5.83 (0.71–48.2) 217	1.70 (0.52–5.50) 128	2.15 (0.63–7.30) 128
No depression	reference	reference	reference	reference
Depression	8.87 (1.14–69.3) 162	2.65 (0.31–22.8) 162	1.1 (0.31–3.78) 103	1.17 (0.32–4.29) 103
ABQ				
No abuse	reference	reference	reference	reference
Abuse, any	2.80 (1.53–5.14) 233	1.93 (0.98–3.79) 233	2.12 (0.95–4.76) 135	2.30 (1.00–5.30) 135
CSQ				
No catastrophizing	reference	reference	reference	reference
Catastrophizing	1.61 (0.92–2.80) 216	1.14 (0.59–2.18) 216	1.15 (0.53–2.42) 133	1.15 (0.53–2.50) 133
ISSI				
Not Avail. Soc. Int.	reference	reference	reference	reference
Avail. Soc. Int.	0.48 (0.27–0.88) 192	0.62 (0.32–1.21) 192	1.66 (0.69–4.00) 117	1.46 (0.59–3.61) 117
Not Adeq. Soc. Int.	reference	reference	reference	reference
Adeq. Soc. Int.	1.96 (1.11–3.49) 207	1.17 (0.60–2.30) 207	0.76 (0.35–1.67) 125	0.88 (0.38–2.00) 125
Not Adeq. of attach.	reference	reference	reference	reference
Adeq. of attach.	0.37 (0.19–0.70) 161	0.55 (0.26–1.19) 161	0.7 (0.29–1.71) 96	0.60 (0.23–1.52) 96

4.5 HELICOBACTER PYLORI PREVALENCE

H. pylori antibodies were measured in 172 subjects, 110 FGID (mean age 46.4 years) and 62 SSF (mean age 53.4 years). The prevalence of *H.pylori* was 15.5 % in the FGID group compared to 35.5 % in the SSF group with $p=0.004$ (Fisher's exact test). For subjects older than 50 years the prevalences were 29.3 % ($n=41$, mean age=62y) and 48.6 % ($n=35$, mean age=64y; $p=0.10$ n.s.) in FGID and SSF, respectively.

5 GENERAL DISCUSSION

The first study demonstrates that among subjects with longstanding FGID, there is a remarkably high prevalence of psychological illness and also of non-GI somatic complaints. These are present regardless of whether or not the subjects have consulted their doctor about their GI problems, and are more severe in subjects with persistent FGID. Although FGID is more common in women, the consultation rates in sufferers are similar for males and females and are not age-related. Only about a quarter of the sufferers have never consulted their doctor due to gastro-intestinal problems.

The second study confirms that persistent FGID in the general population is related to increased comorbidity and increased health care consumption due to non-GI disorders. Subjects with FGID have more diagnoses, consultations and phone calls to their doctors and additional medication prescribed in primary and outpatient care than strictly GI symptom free subjects do. The increased burden to health care is thus not explained by GI problems, but by the whole spectrum of diagnoses within the ICD-9 diagnostic groups also including the hypertensive and circulatory diseases, since the difference found is probably a consequence of the older age of the SSF group. As it is not likely that FGID can be a cause of all different diseases, it seems probable that FGID is in some way related to somatic and psychological distress.

The third study makes clear that women, but not men, with longstanding FGID often have a history of abuse. Women with FGID reported past sexual, physical or emotional abuse in 45% of the cases, as compared with 16% in women without FGID, 29% in men with FGID and 25% in men without FGID. In this study emotional and sexual abuse is the most common type of threat to women's health related to FGID. This study also shows that childhood emotional abuse is a predictor for consulting with GI problems. Moreover, longstanding FGID is associated with a significantly reduced HRQoL, and a history of abuse further reduces the HRQoL in women and men. The findings reveal that a history of abuse is an important psycho-social factor linked to FGID in women. In contrast, the association in men is less clear, although men with a history of some kind of abuse and FGID had significantly reduced HRQoL as compared with men with FGID without any history of abuse. The study does not support the idea that consulters with FGID generally have a poorer HRQoL than non-consulters, but a history of abuse had a negative effect on HRQoL for consulters with FGID.

The fourth study reports that persistent FGID in the general population is related to a parental rejective rearing style, a neurotic personality, and a poor health-related quality of life. Moreover, consulting for GI problems among FGID sufferers is related to an experience of childhood abuse and inadequate social support. Poor health-related quality of life, anxiety, depression and neuroticism are increased in FGID sufferers. However, this study does not find those factors significantly related to GI consulting.

The validity of the research tools is a potential source of bias. However, for symptom reporting, only well-validated questionnaires were used. The definition of functional dyspepsia and IBS used is not exactly the same as the presently recommended Rome III criteria [203]. The definition of dyspepsia and IBS used in this study were those used in the original study from 1988 [5], before current recommendations were available. Our IBS definition was in accordance with the Rome III criteria and our definition of dyspepsia was more restrictive in terms of symptoms, but wider in terms of abdominal location. The definitions used for FGID (dyspepsia and IBS) is in good concordance with the ROME II classification since only 4.8% were erroneously classified as having FGID, with an overall agreement of 95.2% between the combinations of FGID definitions. We consider the overall prevalence of FGID in this study and the concordance on an individual level to be applicable within the current definition [203] and thus we consider our results conclusive. Both the Abdominal symptom questionnaire and the Complaint score questionnaire have been adequately validated in population samples [176, 204]. Likewise, Memories of childhood questionnaire [187, 205], the Coping strategies questionnaire [189], the Eysenck personality questionnaire short form [194], the Multidimensional health locus of control [193], Psychological General Well-Being [180, 206], the Hospital Anxiety and depression Scale Hospital Anxiety and depression Scale [182, 183, 207], the Abuse questionnaire [104, 178, 179] and the Interview schedule for social integration [191] have been validated in patient and/or population samples.

Response bias was reduced by informing the subjects that they had to allocate enough time for the visit to the health center and letting them complete the questionnaires in a calm and confident environment, anonymously, only assisted by a nurse when needed. We could not measure a negative effect of the substantial number of questionnaires presented to the subjects since the response rate to the individual questionnaires did not diminish and the answers to similar questions were the same.

Recall bias is possible with retrospective data, e.g. FGID sufferers over-reporting symptoms compared to GI symptom free. The medical records investigation we made in study 2 among the same study groups revealed that FGID sufferers had a significantly higher co-morbidity and health care utilization than GI symptom free, which is in agreement with a true difference in reporting. A review of the evidence for validity of retrospective reports in adulthood of major adverse experiences in childhood have revealed that there is a substantial rate of false negative reports, but false positive reports were probably rare [195]. Similarly, memories of parental behaviour seem to be stable over time [186]. Thus, we think that recall bias cannot be a major compromising factor of the results obtained in the study.

One strength of this study was the population-based approach, thus, avoiding sample bias due to healthcare-seeking behaviour in subjects with gastro-intestinal complaints [92] as FGID sufferers often refrain from consulting a doctor for their problems [136]. The sampling method with repeated reporting of dyspepsia or IBS twice for the FGID group (1995 and 1996), and up to four times for the SSF group

(1988, 1989, 1995 and 1996), with the same type of questionnaire (ASQ), assured defined study groups and a precise measure of the outcome variables. The electronic medical records used in study 2 and the validated HADS questionnaire secured valid measurements of the exposure variables. A possible selection bias in study 2 is the restriction to the eastern part of the municipality. This was justified by the constant use of electronic medical records in that area which assured correct notes of contacts, diagnoses, prescriptions and sick-leave. Aside from the slightly higher education level in the eastern part, there were no major differences between the area investigated and the remainder of Östhammar. As the population in the entire Östhammar region had a slightly lower educational level than the Swedish population [208], the sample from the eastern area was probably more representative of the general Swedish population. People in the eastern area made most outpatient and almost all non-specialist consultations within their own community area (data on file). Thus, consultations made outside the catchments area could not bias the results and we conclude that the restriction to the eastern part did not influence the representativeness of the study in a negative way.

Healthcare seeking behaviour is complex and its interaction with sick leave has been mainly studied in patient samples. This study was not a case control study, but rather a study of all subjects with FGID compared to those repeatedly SSF within the population sample. The original study base was formed in 1988 from the Swedish National Population register, which guarantees complete coverage of all citizens. There were no differences in age, gender or education level between the study and the sample groups or between the population samples from 1988 and 1995. Also, the proportions of those reporting symptoms explicable in terms of an organic disease have been shown to be insignificant [174]. Thus, the FGID subjects and the symptom-free subjects would seem to be representative. Subjects with FGID were on average younger than SSF as the prevalence of dyspepsia and IBS is higher in younger age groups: age was adjusted in the multivariate analysis and mean age analysis. We consider that our findings can be generalized to the whole population, as the study groups were sampled from a well-defined and thoroughly investigated population, most of whom had participated in prior studies [5, 32].

The observed aggregation of FGIDs in families [65] indicates that both genetic and environmental factors influence children developing FGIDs. More prolonged symptoms in children with recurrent abdominal pain (RAP) are associated with high levels of stress, anxiety, depression and somatization in the child's parents [209]. Studies have demonstrated that greater anxiety is associated with more parental overprotection and rejection [210] which is in agreement with the findings in this study showing that FGID is related to rejecting parental rearing. Abuse-sexual, physical and emotional- is associated with IBS and often under-reported by patients [104]. GI patients with abuse histories report more severe abdominal and psychological symptoms, more doctor visits and greater functional impairment in their daily life than GI patients without an abuse history [94, 211] which is in agreement with our results. The

finding that paternal rejecting rearing was more important than maternal is in agreement with other results where somatization was significantly associated with paternal behaviour in IBS patients [212].

Many diseases have psychosocial consequences, but they are particularly important in FGIDs because of the close connection between the central nervous system (CNS) and the enteric nervous system (ENS) through the autonomous nervous system [3] and through the hypothalamic-pituitary-adrenal axis.

Patients have a multi-causal (for example emotion, stress and own personality) explanation of their gastrointestinal troubles [213].

Previous studies in the field have reported that about half the patients referred to a gastroenterology clinic, had a history of sexual or physical abuse [104, 110]. Moreover, 71% of women who reported domestic violence to the police had FGID according to Perona M et.al 2005 [214]. In the literature, a history of childhood or adult abuse characterizes patients who present with a variety of functional symptoms apart from FGID [111]: headaches [215], pelvic pain [216], panic disorders [217]non-epileptic attack disorders [218]and back pain [219]. Psychological factors such as anxiety [76], as well as physiological factors such as enhanced visceral sensitivity, all contributed to a poor health outcome [111]. A recent study reported that psychological distress contributes more than personality to poor QoL in IBD patients [220]. Only a few studies have focused on abuse and FGID in the general population, where Koloski et al. [221] found abuse to be significantly associated with IBS and/or functional dyspepsia, but less important when psychosocial factors were controlled for, a finding confirmed by others [222, 223].

The same research team found that past sexual, physical, and emotional abuse was not a significant predictor for health care seeking, in contrast to our finding that a history of childhood emotional abuse was associated with consulting, and that anxiety and FGID were independent predictors for previous abuse. It is clear from our study that many subjects with traumatic memories and uncomfortable symptoms never seek health care, and that when they do it is important to take a thorough medical history.

Our findings indicate that a negative parental upbringing and the personality trait neuroticism are predictors for FGID and those taken together with a poor quality of life and a reduced social support are a predictor for consulting. In order to reassure the patient and improve her/his quality of life but also to avoid unnecessary and expensive investigations, the treatment for FGID should be through a holistic health care approach. Future research should address what methods, pharmacological and psychological, are the most applicable in the treatment of patients with FGID.

6 CONCLUSIONS

Study I: Psychological illness proved to be an important co-morbidity factor among subjects with FGID, and the severity of the two was linked. We cannot conclude anything about the cause of the relationship. The presence of psychological illness was also associated with a greater need for medical consultation.

Study II: FGID was related to an increased demand on primary health care due to an increased overall co-morbidity. The findings indicate that FGID is a type of intestinal reaction, related to somatic and psychological distress in a subgroup of subjects.

Study III: Women with longstanding FGID in many cases had a history of physical, emotional or sexual abuse in childhood or adulthood, which is associated with a poor HRQoL and increased health care seeking.

Study IV: The result stresses the importance of taking a thorough medical history from patients with persistent FGID addressing dysfunctional parental upbringing and abuse in childhood as associated factors when planning treatment.

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8 POPULÄRVETENSKAPLIG SAMMANFATTNING

Magbesvär har plågat människor i alla tider och finns beskrivna i de äldsta av medicinska skrifter. Redan i det forna Egypten och för 3400 år i det antika Grekland propagerade man för en helhetssyn, holism, när det gäller behandling av sjukdom. Under 1600-talet i Europa så gjorde filosofen Descartes en uppdelning av människan i kropp och själ, i dualismen. Denna filosofi introducerade den biologiska reduktionismen i synen på sjukdom vilket innebär att man ville finna en enda bakomliggande biologisk orsak. Detta synsätt var framgångsrikt inom medicinen i Europa under mer än 300 år. Ett paradigmskifte i slutet av 1970-talet medförde att man inkluderade själen och det centrala nervsystemet och därmed övergick till en mer integrerad syn på sjukdom, den så kallade biopsykosociala modellen.

Många patienter söker i primärvården för medicinskt oförklarliga symptom från magen, muskler och leder, trötthet, ångest och nedstämdhet. Dessa symptom överlappar varandra och kan ändras över tiden. Ont i magen, gasspanning, uppsvällighet i buken, illamående, diareer, förstoppning är symptom som är mycket vanliga i befolkningen och orsakar obehag för individen och kostnader för samhället i form av läkemedel, frånvaro från arbetet och utnyttjande av sjukvård. Efter noggranna medicinska undersökningar så hittar man hos ungefär hälften av patienterna ändå ingen bakomliggande orsak. Sådana magbesvär utan tydlig orsak, kallas för funktionella magbesvär (FGID). Funktionella magbesvär från övre delen av magen benämns funktionell dyspepsi (FD) och symptom från nedre delen av magen kallas för irritable bowel syndrome (IBS = engelska för irritable bowel syndrome).

Mag-tarmkanalen har ett eget nervsystem, det enteriska nervsystemet, som står i nära samband med det centrala nervsystemet dvs hjärnan och ryggmärgen genom olika nervbanor och hormoner, på engelska kallat "brain-gut axis". Människors upplevelser och känslor påverkar mag-tarmkanalen och det finns även kommunikation i motsatt riktning. Ärftlighet, personlighet, ålder, kön och yttre faktorer som stress och infektioner påverkar förekomsten av funktionella magbesvär. Det finns ett tydligt samband med ångest och depression. Ångest ökar känsligheten för smärta i tarmväggen och ångest, depression och en orolig personlighet har visat sig öka risken för att utveckla IBS efter en mag-tarminfektion, och gör även att man söker läkare mer även om symtomen inte är värre.

De flesta studier som undersökt personer med funktionella magbesvär har gjorts på patienter som söker läkare. Data från en tidigare studie på Östhammars befolkning visar att uppemot hälften av alla med magbesvär inte sökt läkare pga symptomen. Det är därför viktigt att man inkluderar personer som inte söker läkare, när man vill veta mer om funktionella magbesvär.

De fyra studier som ingår i doktorsavhandlingen har som gemensam nämnare att de undersöker personer i Östhammars befolkning, även de som inte sökt läkare, avseende olika psykosociala faktorer samverkan med funktionella magbesvär och benägenheten att söka läkare. Målsättningen är att hos personer med funktionella magbesvär undersöka förekomsten av samtidiga kroppsliga och psykiska symptom och deras påverkan på benägenheten att söka läkare, utnyttjandet av primärvård, förekomst av fysisk, psykisk och emotionell misshandel samt att undersöka inverkan av uppfostran. Som kontrollgrupp används personer ur samma befolkning som vid upprepade tillfällen uppger att de inte har några magbesvär.

Studien gjordes på de 21,545 personer som bodde i Östhammars kommun 1995. Genom befolkningsregistret togs det fram ett slumpmässigt urval på sammanlagt 1537 personer mellan 20 och 85 år gamla. De tillfrågades genom ett brev om de ville vara med i undersökningen och svarade på ett frågeformulär som innehöll frågor om olika magsymptom, tidigare utnyttjande av sjukvård och allmänna frågor om ålder, kön och utbildning. Genom de svar som lämnades så delades personerna in i grupper med funktionella magbesvär (FD och/eller IBS, tillsammans kallat FGID), mindre magsymptom och en grupp utan magsymptom. Totalt 463 försökspersoner kallades 1996 till sin närmaste vårdcentral i Östhammar, Öregrund, Gimo, Alunda, Österbybruk samt en i Uppsala och fick där fylla i en uppsättning frågeformulär som mätte olika kroppsliga och psykologiska symptom, intag av mediciner, livskvalitet, ångest och depression, personlighet, förhållningssätt till sjukdom, social uppbackning, upplevda obehagliga händelser (fysiska, psykiska och sexuella övergrepp) och uppfostran. En ny uppdelning gjordes för att få fram de som hade FD och IBS och de som var symptomfria. Kvar blev 141 personer som angett funktionella magbesvär både 1995 och 1996, samt 97 personer som var helt fria från magbesvär 1995 och 1996 samt också symptomfria vid tidigare undersökningar 1988 och 1989 om de deltagit i dessa. På så sätt fick vi fram två tydliga jämförbara grupper ur samma befolkning en grupp med och en grupp utan funktionella magbesvär.

Studie I visar att det är en viss övervikt av kvinnor med FGID men skillnaden mellan män och kvinnor försvinner när man tar hänsyn till ålder och förekomst av symptom utanför mag-tarmkanalen. Det är ingen skillnad mellan grupperna när det gäller utbildning, medicinska kunskaper, vikt, intag av kaffe, alkohol eller rökning. Svaren på 30 olika kroppsliga och psykiska symptom upplevda under de senaste 3 månaderna visar att gruppen med FGID har en klart större andel personer med olika besvär som inte kan hänföras till mag-tarmkanalen. Personer med FGID som sökt läkare för magbesvär har emellertid inte mer av övriga symptom än personer som inte sökt läkare. Studien visar också att personer med FGID har högre risk för psykiska och kroppsliga besvär samt högre risk för smärta och trötthet, jämfört med personer utan FGID.

Studie II är en genomgång av journalerna på vårdcentralerna i Östhammar och Öregrund med syftet att studera sjukvårdsutnyttjandet för grupperna med och utan FGID. Resultatet visar att personer med FGID har dubbelt så många läkarbesök, telefonsamtal och receptförskrivningar jämfört med personer utan FGID och fler antal diagnoser. Gruppen med FGID har dessutom ökade besvär med ångest och depression. Diagnoserna vid besöken är i så gott som alla tillfällen, 97%, en diagnos som inte härrör från magen. De vanligaste diagnoserna är olika infektioner och sjukdomar i muskler och skelett. Resultatet visar att personer med FGID har ett högre sjukvårdsutnyttjande än personer utan FGID, och att magsymptomen inte utgör orsaken till kontakterna.

Studie III studerar svaren från frågeformulären om livskvalitet, ångest och depression och upplevda obehagliga händelser som fysiska, psykiska och sexuella övergrepp. Studien visar att kvinnor med FGID, men inte män, ofta har upplevt övergrepp eller misshandel. Kvinnor med FGID rapporterade i 45 % av fallen att de varit utsatta för psykiska, fysiska eller sexuella övergrepp i jämförelse med 16 % för kvinnor utan FGID. Motsvarande siffror för män med FGID var 29% och för män utan FGID 25 %. Risken för att ha sökt läkare för magproblem och samtidigt ha en upplevelse av övergrepp är signifikant högre för kvinnor med FGID än för män med FGID. I 46 % av kvinnorna, finns en upplevelse av övergrepp jämfört med 29 % bland de kvinnor som inte sökt för magbesvär. Ökad ångest och sämre livskvalitet är vanligare i gruppen som varit utsatt för övergrepp. Resultaten visar att tidigare upplevelser av övergrepp är en viktig psykosocial faktor som har samband med FGID hos kvinnor. Hos män hittar man inte samma samband men män med tidigare upplevelser av övergrepp har sämre livskvalitet än män utan sådana upplevelser.

Studie IV analyserar data om upplevd uppfostran, social uppbackning och personlighet. Resultatet visar att FGID kan ha samband med en upplevelse av en sträng, avståndstagande uppfostran, en neurotisk personlighet och en dålig social uppbackning.

Sammanfattningsvis så visar denna studie på sambandet mellan funktionella magbesvär och upplevelser av olika psykiska och fysiska besvär som kommer till uttryck i en sänkt livskvalitet och ökat sjukvårdsutnyttjande. Dessutom finns ett samband hos kvinnor mellan funktionella magbesvär och tidigare upplevelser av övergrepp. Uppfostran tycks också spela roll. Vad som är orsak och verkan kan inte avgöras med denna studie men tillsammans med tidigare forskningsresultat så bidrar den med viktig ny kunskap framförallt när det gäller samband med uppfostran och övergrepp i barndomen hos de som konsulterar sjukvården för magbesvär.

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