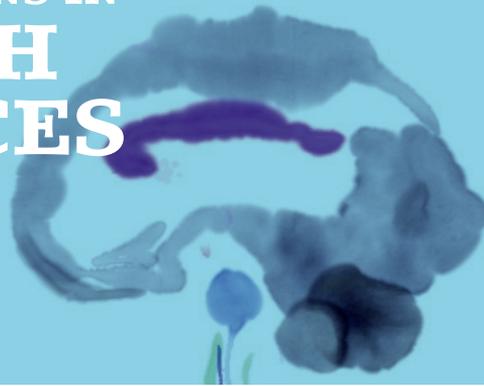
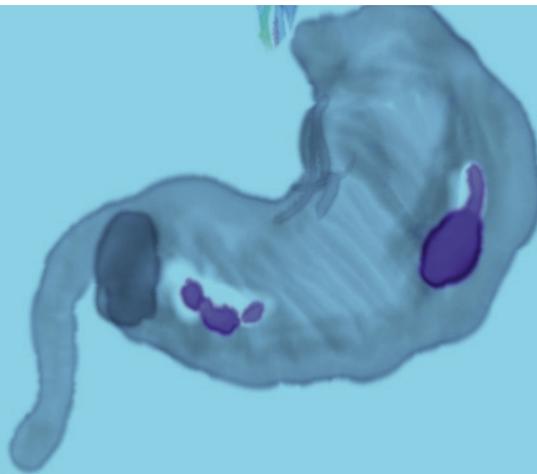


DISSERTATIONS IN  
**HEALTH  
SCIENCES**



MARKKU PAJALA

# *Psychological Distress in Dyspepsia*



PUBLICATIONS OF THE UNIVERSITY OF EASTERN FINLAND  
*Dissertations in Health Sciences*



UNIVERSITY OF  
EASTERN FINLAND

MARKKU PAJALA

*Psychological distress in dyspepsia*

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## ABSTRACT

Dyspepsia affects a quarter of the population annually. Most of them have a functional gastrointestinal disorder (FGID), eg. functional dyspepsia (FD) or irritable bowel syndrome (IBS). There is a great deal of evidence on the association between psychological factors, eg. anxiety and depression, and FGIDs. It is uncertain if 1) psychological factors cause dyspepsia, 2) dyspepsia causes psychological distress, 3) this distress leads to increased health care seeking, or 4) there is indeed bidirectional interaction between gut and brain.

In 400 dyspeptic study patients 195 had an organic dyspepsia (OD) usually gastro-oesophageal reflux or peptic ulcer disease. The remainder, 205 patients had functional dyspepsia (FD). All patients filled out questionnaires regarding abdominal symptoms, mental distress and suspicion of serious illness on admission and at the one-year follow-up. The FD cohort also gave a medical history and their visits for gastrointestinal reasons in health centers, hospitals and private clinics were evaluated.

The age- and sex-adjusted risk of having mental distress in dyspeptic patients was almost four-fold higher than in the general population, but there was no difference between dyspepsia groups. Mental distress and suspicion of serious illness were present in almost 40 and 20% of the patients, respectively. The non-relation between mental distress and abdominal symptoms in FD was confirmed in a one-year follow-up study. The correlation between changes in abdominal symptoms and psychological factors was significant only in patients with organic dyspepsia, which would support the idea that somatic symptoms cause mental distress and fear of serious illness. During the seven year follow-up, the majority of the patients re-visited their general practitioner (GP) and were prescribed antisecretory medication. Lower and upper gastrointestinal (GI) endoscopies and radiological re-investigation were both performed in a quarter of the patients. Mental distress and suspicion of serious illness did not increase the risk of health care needs. A single lower gastrointestinal symptom i.e. bowel-symptom, increased the likelihood of an additional outpatient visit or endoscopy by 19%. The non-correlation between changes in gastrointestinal symptoms and mental distress in patients with FD with a similar alleviation in mental distress questions the proposed specific link between gut and brain.

It seems, that mental distress and suspicion of serious illness is merely a nonspecific reaction to abdominal symptoms. Our findings do not support the idea of brain-gut axis in FD.

National Library of Medical Classification: WI 145, WI 147, WM 172.4, WM 172.5

Medical Subject Headings: Dyspepsia/psychology; Gastrointestinal Diseases/psychology; Stress, Psychological/psychology; Mental Disorders/complications; Health Resources/utilization



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## TIIVISTELMÄ

Neljännes väestöstä kärsii ylävatsaoireista vuosittain. Suurimmalla osalla on toiminnallinen dyspepsia tai ärtyvä suoli. Tutkimuksissa on osoitettu yhteys toiminnallisten vatsavaivojen ja mm. ahdistuneisuuden ja masentuneisuuden välille. Epäselvää on 1) aiheuttavatko psykologiset tekijät ylävatsavaivoja, 2) aiheuttavatko ylävatsavaivat henkistä kuormittuneisuutta, 3) lisääkö henkinen kuormittuneisuus terveyspalveluiden käyttöä, tai 4) ovatko vatsaoireet ja keskushermosto kaksisuuntaisella vaikutusmekanismilla yhteydessä toisiinsa?

400 peräkkäisellä ylävatsavaivaisella terveystieteiskeskuspotilaalla elimellinen syy voitiin todeta 195 potilaalla, tavallisimmin refluksi- tai ulkustauti. Lopuilla oli toiminnallinen dyspepsia. Potilaat täyttivät vatsaoirekyselyn ja henkistä kuormittuneisuutta selvittävät kaavakkeet aloitushetkellä ja vuoden kontrollissa. Toiminnallista ylävatsavaivaa sairastavien 176 potilaan muistinvaraisen terveyspalveluiden käytön lisäksi sairaskertomukset 7 vuoden seuranta-ajalta terveystieteiskeskoksissa, sairaaloissa ja yksityisvastaanotoilla käytiin systemaattisesti läpi ja kerättiin tiedot koskien ruoansulatuskanavan vaivoja.

Ikä- ja sukupuolivakioitu henkisen kuormittuneisuuden riski oli ylävatsavaivaisilla potilailla lähes nelinkertainen väestöön verrattuna. Henkisessä kuormittuneisuudessa (40 %:lla) tai vakavan sairauden epäilyssä (lähes 20 %:lla) ei ollut eroa elimellistä ja toiminnallista ylävatsavaivaa sairastavien ryhmien välillä. Vuoden seuranta tutkimuksessa korrelaatio oireiden helpottamisen ja psykologisten tekijöiden välillä voitiin todeta vain elimellistä ylävatsavaivaa sairastavilla potilailla, eli ylävatsaoireet aiheuttaisivat henkistä kuormittuneisuutta ja vakavan sairauden epäilyä. Seurannassa suurin osa toiminnallista ylävatsavaivaa sairastavista potilaista kävi lääkäriillään uudelleen vatsavaivojen takia. Tavallisimmin määrättiin haponeritystä vähentävää lääkitystä. Täyhystyksiä ja radiologisia jatkotutkimuksia tehtiin neljäsosalle potilaista. Henkisellä kuormittuneisuudella ei ollut vaikutusta terveyspalveluiden käyttöön. Jo yksi alemman ruoansulatuskanavan oire lisäsi riskiä joutua uudelleen vastaanotolle tai täyhystykseen 19 %. Korrelaation puuttuminen vatsaoireiden ja henkisen kuormittuneisuuden välillä toiminnallista ylävatsavaivaa sairastavilla potilailla, vaikka henkisessä kuormittuneisuudessa nähtiin yhtä suuri helpottuminen, kyseenalaistaa erityisen yhteyden vatsavaivojen ja keskushermoston välillä.

Vaikuttaakin siltä, että henkinen kuormittuneisuus ja vakavan sairauden pelko ovat seuraus ylävatsaoireista. Löydöksemme eivät tue käsitystä keskushermoston ja vatsaoireiden erityisestä yhteydestä toiminnallisessa dyspepsiassa.

Luokitus: WI 145, WI 147, WM 172.4, WM 172.5

Yleinen suomalainen asiasanasto: dyspepsia, toiminnallisuus, ruoansulatuselinten taudit, psykologiset tekijät, psyykkinen kuormittavuus, terveyspalvelut



Ollaanko jo perillä, joko saa rentoutua?



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This dissertation is based on the following original publications:

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# Abbreviations

ACC	Anterior cingulate cortex
ACTH	Adrenocorticotrophic hormone
AI	Anterior insulate
BDQ	Bowel Disease Questionnaire
CBT	Cognitive behavior therapy
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CNS	Central Nervous System
CRH	Corticotrophin Releasing Hormone
CSQ	Coping Strategies Questionnaire
DSM	Diagnosis and Statistics of Mental Disorders
DU	Duodenal Ulcer
EEG	Electroencephalography
EKG	Electrogastrography
FD	Functional Dyspepsia
FGID	Functional Gastrointestinal Disorder
fMRI	functional Magnetic Resonance Imaging
GE	Gastroenterology
GHQ	General Health Questionnaire
GI	Gastrointestinal
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
H2	Histamine-2 receptor antagonist
HRQoL	Health Related Quality of Life
HT	Hypnotherapy
IBS	Irritable Bowel Syndrome

## XVII

ICD	International Classification of Diseases
ITT	Intention to Treat
MMPI	Minnesota Multiphasic Personality Inventory
NNT	Number Needed to Treat
OD	Organic Dyspepsia
OR	Odds Ratio
PET	Positron Emission Tomography
PI	Psychodynamic interpersonal psychotherapy
PP	Per Protocol
QoL	Quality of Life
RR	Risk Ratio
RCT	Randomized Controlled Trial
SCID	Structured Clinical Interview
SCL	Symptom Check List
SF-36	Short Form -36 Health Survey
SNRI	Selective Noradrenaline Reuptake Inhibitor
SSRI	Selective Serotonine Reuptake Inhibitor
TCA	Tricyclic Antidepressant
U.S.	United States (of America)



# 1 Introduction

## 1.1 SCHEMATIC ILLUSTRATION OF MENTAL DISTRESS RELATION TO FUNCTIONAL GASTROINTESTINAL DISORDERS

The 12-item General Health Questionnaire (GHQ-12) is a measure of current mental health. It focuses on two major areas – the inability to carry out normal functions and the appearance of new and distressing experiences. Questions covered include: depression, anxiety, social interaction and self-confidence. It is widely validated internationally and in the Finnish population with respect to psychiatric disorders. Mental/psychological distress is a wider concept of mental ill-being and may also reflect social, economic, occupational and health problems. <sup>1-4</sup>

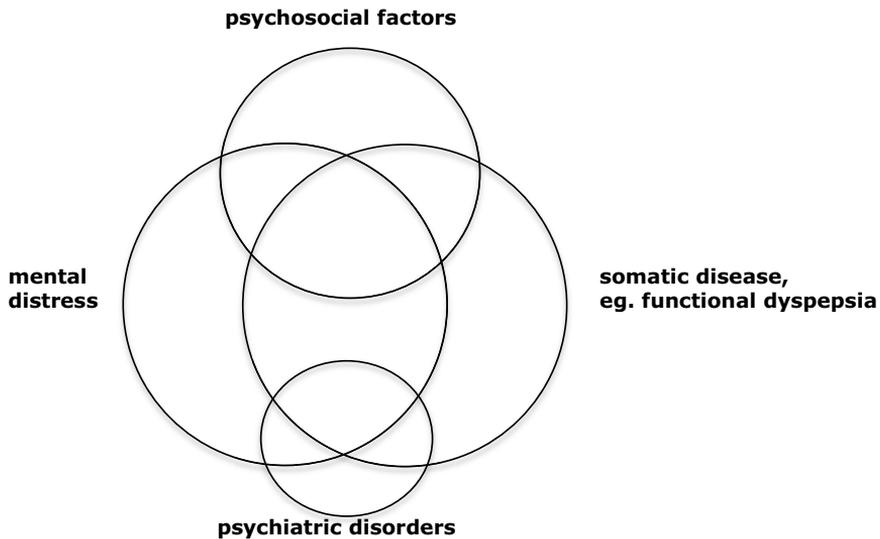


Figure 1. Co-existence of psychopathology and somatic disease.

The Rome criteria is a symptom-based classification of 28 chronic (onset at least 6 mo. ago, > 3 mo. in duration) functional gastrointestinal disorders (FGIDs) into six main domains: oesophageal, gastroduodenal, bowel, functional abdominal pain syndrome, biliary and anorectal. They are disorders of the digestive system in which symptoms cannot be explained by the presence of structural or tissue abnormality. FGIDs include irritable bowel syndrome and functional dyspepsia. <sup>5</sup>

## 1.2 INTRODUCTION TO PSYCHOLOGICAL FACTORS IN FUNCTIONAL GASTROINTESTINAL DISORDERS

Dyspepsia, bad digestion, is a vague term of one of the commonest complaints in any doctors' clinic. <sup>6</sup> An even larger portion of affected people never seek medical attention for it. <sup>7</sup> In national surveys up to 25-40% of the population suffer of upper abdominal pain or discomfort or heartburn annually. <sup>8</sup> The number of patients is pretty stable since alleviation and new onset of symptoms is constant. <sup>9</sup> The burden of functional dyspepsia (FD) on individual patients and health care is huge. In the U.S. alone, the repetitive general practitioner (GP) -consultations, costly examinations, medication and work absenteeism has been estimated to cost 18 billion dollars in 2009. <sup>10</sup>

The cause of dyspepsia is still somewhat obscure or multifactorial. <sup>11</sup> In the majority of the patients there is no identifiable cause for the symptoms e.g. gastro-oesophageal reflux disease, peptic ulcer disease, use of non-steroidal anti-inflammatory drugs. Also a malignancy, celiac disease, chronic pancreatitis or gallstone disease is encountered very seldomly. Rarely a medication such as teophylline, infiltrative disease e.g. eosinophilic disease, intestinal angina or a metabolic disturbance is a cause of dyspepsia. Lactose intolerance is very common, but has symptoms very different from dyspepsia. <sup>12-13</sup> Irritable bowel syndrome (IBS) often coexists and concomitant bowel and reflux symptoms are again accepted in the latest Rome III criteria of functional dyspepsia. If no abovementioned organic cause is found one is regarded to suffer from functional gastrointestinal disorder (FGID), such as FD or concomitant IBS. <sup>5</sup>

Several possible mechanisms have been proposed to cause these functional diseases. *Helicobacter Pylori* infection is nowadays regarded irrelevant. In some patients there is gastrointestinal hypersensitivity to normal acid secretion or balloon distension, <sup>14</sup> which may be the result of low-grade inflammation in the gut. <sup>15</sup> Motility disorders e.g. delayed gastric emptying of solids may exist in non-painful dyspeptic symptoms. In the small bowel bacterial overgrowth disturbed microbiota or handling of gases may explain bloating symptoms in IBS. <sup>16</sup> All the above-mentioned and psychological factors as adverse life events, anxiety and depression may lead to increased stress, sympathetic drive, immune activation and changes in activity in the central nervous system and eventually processing of painful or unpleasant symptoms. <sup>14-17</sup>

Some investigators have gone even further to explain FGIDs with a biological, psychological and social model. <sup>18</sup> Support for more crucial role of the central nervous system is backed by the studies in which motility disturbances in IBS disappear during sleep. <sup>19</sup> Anticipated and actual noxious distension of rectum by balloon produces differences in activation, measured with positron emission tomography (PET), of the mid-cingulate cortex and also differences in down-regulatory areas between IBS patients and healthy controls. <sup>20</sup> There is also solid evidence on familial aggregation of IBS. Genetic studies on a link between a serotonin receptor polymorphism and fibromyalgia and IBS are controversial. Again emphasizing the role of the brain, childhood learning seems to be stronger than heredity since having a mother or father with IBS is a stronger predictor of future IBS than a twin with IBS, although monozygotic twins are at higher risk than dizygotic twins. Reversing this by cognitive

behavior therapy (CBT) by the parents to reduce positive responses to recurrent abdominal pain has been shown to be beneficial.<sup>21-22</sup>

Extreme early life experiences such as sexual or physical abuse is confusingly common. A prevalence of a history of up to 30-56% of sexual, physical or emotional abuse has been reported from referral centers among patients with IBS, which is similar to non-gastrointestinal (GI) painful conditions e.g. pelvic pain, fibromyalgia and headaches. At the population level reporting is lower: any form of abuse in 22% and 13% sexual and/or physical abuse.<sup>23</sup> A French multicenter study in 196 patients confirmed 66 cases of sexual abuse, comprising 32% of IBS and 14% of organic GI-patients, respectively. Their patients also reported in detail the form of abuse. There were 8 verbal aggressions, 4 exhibitions, 11 sexual harassments, 22 sexual touches and 17 rapes. More severe forms of abuse have been linked to symptom severity, disability and poorer overall health status. Several possible mechanisms have been proposed in this extreme setting. Patients with FGID may have a concurrent psychiatric disorder or suffer from moderate psychological distress. They become self-observers and adopt maladaptive coping styles. Their adult relationships are impaired and there are changes in autonomic nervous system function, including hyperarousal.<sup>24</sup>

Life stress seems to have a strong impact on FGIDs. It is reported more often by IBS patients than abdominal pain patients and healthy controls.<sup>25</sup> It has been shown to exacerbate symptoms of heartburn. This can be a result of true increase in acid exposure or increased hypersensitivity, or it can be caused by impaired gastric emptying.<sup>26</sup> The proximity of strong stressors as domestic violence has been shown to predict onset of an FGID. Of patients exposed to a strong stressor, 70% developed IBS or FD, and in the majority this occurred simultaneously or soon after the incident.<sup>27</sup> Social chronic stressors as marital or financial threat has also predicted symptoms of gastroenterology clinic patients with FGID and was especially typical in IBS/FD. No patient improved with exposure to a stressor and all the patients that improved by 50% did so in absence of such a stressor.<sup>28</sup> This may be a neuroendocrine pathway mediated alteration in GI-function, since there are reports of changes in catecholamines and cortisol.<sup>29-30</sup>

Similar to stress, personality traits and mood disorders have been linked to onset of symptoms, symptom experience, health-related quality of life (HRQoL) and health care seeking in FGIDs.<sup>22,31</sup> It has been stated that as many as 42-61% of FGID patients have a psychiatric disorder, compared to 20-25% in healthy controls and patients with organic disease. Most studies have been done in IBS patients. The disorders most often found include anxiety disorders (panic and anxiety), mood disorders (depression and dysthymic disorder) and somatoform disorder (hypochondrias and somatization). Psychological factors may have a direct influence on gut physiology, immunology and endocrinology with alterations in neurotransmitters, which are not site specific. They are especially important in coping with dyspeptic symptoms, e.g. symptom experience and health care seeking.<sup>32</sup> The link between psychological factors and FGIDs in general may be central modulation since physical pain and psychological pain of rejection are processed in the same region of the brain, the cingulate cortex.<sup>33</sup>

The association between psychological factors and bodily symptoms is not however limited to abdominal symptoms. Patients with other medically unexplained symptoms e.g. chronic fatigue syndrome, fibromyalgia present with an increased rate of anxiety

and depression similar to IBS and FD.<sup>34</sup> Even in chest pain patients with and without coronary heart disease and in patients with rheumatoid arthritis and non-inflammatory joint pain disease psychological disorders are equally present.<sup>35-36</sup>

Four possible mechanisms have been presented: 1) psychological factors indeed cause gastrointestinal symptoms, 2) gastrointestinal symptoms cause reactive psychological distress, 3) bodily and psychological symptoms are different expressions in reaction to common distress, or 4) psychological factors alter sickness behavior and lead to health care seeking in patients with a FGID.<sup>34,37</sup> Quite recently two studies of a longitudinal nature have addressed these mechanisms. In a population-based sample it was found that in general practitioners records in 61% of the patients the psychological disorder preceded FGID, the converse was true in only 34%, and they occurred simultaneously in only a small minority.<sup>38</sup> Similar, psychophysiological findings have been reported in IBS.<sup>39</sup> A population-based prospective 12-year study from Australia confirmed that baseline anxiety and to a lesser degree depression indeed predisposed to developing IBS or FD, but even in this study it worked both ways – FGID diagnosed at baseline also tended to lead to anxiety or depression. To conclude it was stated that brain and gut interact bi-directionally.<sup>40</sup>

Instead of trying to find an answer to etiology a unifying biopsychosocial model has been introduced as a hypothesis by Drossman in 1996. It accepts that both gut and brain are operative and combines the influence of stress, emotions, psychiatric distress and coping styles to symptom experience, daily function and health outcome (Figure 2).<sup>32</sup> What remains elusive in this very practical model include 1) to what extent psychological factors are present in dyspeptic patients, 2) are they especially overrepresented in functional diseases 3) what is the possible causal relation of these factors and gastrointestinal symptoms in the long-term, and 4) if present, would they cause excessive health care utilization.

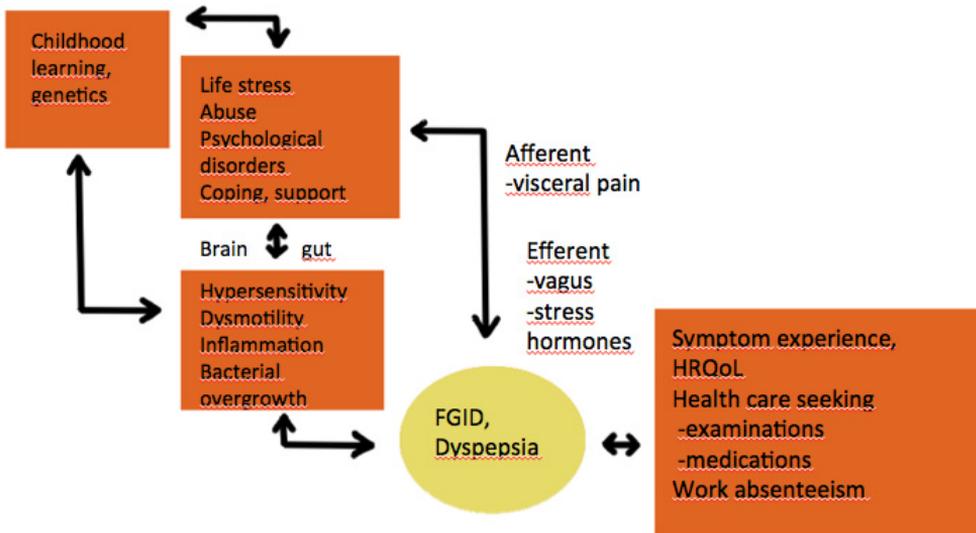


Figure 2. Biopsychosocial model. FGID, functional gastrointestinal disorders; HRQoL, health related quality of life. Adopted from Drossman et al. 1998.

## 2 Review of the Literature

### 2.1 DEFINITION OF DYSPEPSIA

#### 2.1.1 Colin-Jones and Talley`s definition

Colin-Jones introduced 1989 their broad definition of dyspepsia as a spectrum of symptoms such as pain, discomfort heartburn, abdominal distension, early satiety, post-prandial fullness, nausea, retching and vomiting thought to originate from upper gastrointestinal tract. The symptoms should be unrelated to colonic function as IBS should be used in these circumstances.<sup>41</sup> The definition of non-ulcer dyspepsia, essential dyspepsia has evolved in three decades from a vague term to a much more precise concept of FD. The purpose of this has been mainly in advancing studies in the field of dyspepsia since studies on epidemiology, underlying pathology and eventual clinical drug development have faced the problem of patient heterogeneity. Talley et al. 1991 introduced a working party definition as persistent or recurrent abdominal pain or abdominal discomfort centered in the upper abdomen.<sup>42</sup> Patients could also be subclassified as having ulcer-like, motility-like or unspecified dyspepsia. Patients in which no structural explanation for dyspepsia could be found should now termed as having functional dyspepsia. Patients with predominant reflux symptoms and no esophagitis were termed as having symptomatic gastro-esophageal reflux. Patients with IBS-symptoms simultaneously were to be classified as IBS.

#### 2.1.2 Rome criteria I-III

The Rome criteria for FGIDs, including functional gastroduodenal disorders such as FD, and five other major domains, were first introduced in 1994<sup>43</sup> with revisions in 1999 and 2006. FD defined as persistent or recurrent symptoms (pain or discomfort) in the upper abdomen, in the absence of organic disease and no association with bowel habit. In the first revision (Rome II), changes were made mostly regarding the duration of symptoms, at least 12 weeks of the past 12 months.<sup>44</sup> Rome co-operatives' most recent definition of FD from 2006 is comprised of the epigastric pain syndrome (pain or burning in epigastrium) or postprandial distress syndrome (early satiation or postprandial fullness). The evolving definition has been, however, been forced to give in to the real world, because the co-existence of reflux disease and lower gastrointestinal symptoms, i.e. IBS, are now accepted in the criteria. The time frame is also less stringent, a minimum duration of 3 months and originating 6 months prior.<sup>5</sup> Some researchers even challenge the whole separation of FGIDs into smaller entities altogether as artificial, but consider them as different manifestations of same condition.<sup>45</sup> There is indeed considerable overlap (>80%) and instability over time in more than 50% of patients with FD and IBS.<sup>46</sup>

## 2.2 ETIOLOGY OF DYSPEPSIA

In numerous studies using gastroscopy, ultrasound or laboratory testing and additional studies, a specific organic reason for dyspepsia has been detected in about half of the patients. The largest portion of patients have FD, i.e., the reason for symptoms remains unknown.<sup>47</sup>

### 2.2.1 Organic dyspepsia

Reflux disease is the cause in 27-43%, and peptic ulcer disease in 5-13%. Lactose intolerance is common (9%) in symptomatic patients. Infrequently the etiology is celiac disease, gall stone disease, malignancy, giardiasis or chronic pancreatitis (a prevalence of 1-2% percent each)<sup>47-48</sup>

### 2.2.2 Functional dyspepsia

The classification of uninvestigated dyspepsia into organic and functional mainly requires the exclusion of the above-mentioned organic causes. Reliable exclusion of organic causes with questionnaires alone remains questionable, since symptom patterns have not performed well in studies.<sup>49-50</sup> Specific functional alterations in gastroduodenal emptying, gastric accommodation, hypersensitivity to gastric distention, altered duodenal sensitivity to lipids or acids, unsuppressed postprandial gastric contractility, and autonomic nervous system-central changes can be found in these patients. However, specific tools such as scintigraphy, breath tests, ultrasonography, magnetic resonance imaging (MRI), single-photon emission tomography, EGG, barostat and satiety testing are needed to detect these changes and are mainly for investigational use only.<sup>51</sup>

## 2.3 PSYCHOLOGICAL FACTORS IN DYSPEPSIA

It has been stated that up to 42-61% of FGID patients have a psychiatric disorder.<sup>32</sup> Most studies have been done in IBS patients. IBS is by far most studied of FGIDs. Evidence of the association between psychological factors and FD is less abundant.

When evaluating individual patients, simple questions have been proposed to screen for anxiety and depression, such as “have you been worrying, lost interest or is it difficult to sleep”? For scientific work there are several validated tools that can be used: 1) structured clinical psychiatric interview techniques provide formal Diagnosis and Statistics of Mental Disorders- (DSM) and International Classification of Diseases (ICD) based diagnoses, 2) generic psychologic state self-rating scales for recent assessment of psychological well-being, e.g. the Symptom Checklist-90 (SCL-90) and General Health Questionnaire (GHQ), 3) syndrome-specific instruments for anxiety, such as the Spielberger State Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI) and Hospital Anxiety and Depression (HAD) Scale, and 4) personality questionnaires, coping strategy questionnaires and health-related quality of life instruments, e.g. the RAND Short Form-36 Health Survey. The majority of the studies have been conducted using questionnaires instead of using structured interviews or clinical judgement.<sup>32</sup>

### 2.3.1 Psychiatric disorders

Psychiatric diagnoses according to the DSM–III, such as anxiety and depression of various types, can be assigned to more half of chronic pain patients.<sup>52</sup> ICD diagnoses of psychiatric diseases are found in a similar fashion in patients with fibromyalgia (80%) and FD (83%) in comparison to controls (33%). Panic disorder is closely linked to fibromyalgia, whereas mood disorders are more common in FD.<sup>53</sup> In a classic study of this association investigators blinded to psychiatric evaluation discovered that esophageal motility disorder of the nonspecific type was saturated with psychiatric illnesses, 83% compared to 33% in the specific type and 31% in controls.<sup>54</sup> Lifetime diagnoses of psychiatric diseases were linked strongly to dyspepsia of unknown cause in comparison to gastroenterology clinic patients with organic dyspepsia (87 vs. 25%), particularly anxiety disturbances (67%).<sup>55</sup> In studies using psychiatric interviews patients with dyspepsia have high levels of anxiety and depression and personality traits with neurotic and anxious tendencies in comparison to healthy controls. They experience stressing difficulties in almost all (98%) of the patients and cope badly with less support.<sup>56</sup>

In a Norwegian study FD patients were significantly more affected by psychological diagnoses in a semi-structured psychiatric interview and psychometric testing than healthy controls and patients with duodenal ulcer. Diagnoses included state-trait anxiety, depression and general psychopathology.<sup>57</sup> Contrary to this, in psychometric testing in an earlier study clinic patients with FD were more neurotic, anxious and depressed than community controls, but did not differ from patients with DU.<sup>58</sup> Neither was there any difference in a study comparing DSM-III diagnoses of

consecutive primary care IBS patients and patients with organic dyspepsia. However in psychometric testing neuroticism and introversion scores were higher in patients with IBS, and they perceived life more negatively.<sup>59</sup> Vice versa, people with depression on population level and in patients presenting primarily with depressive, panic and anxiety disorders have also increased prevalences of IBS and FD, suggesting of shared pathophysiology.<sup>60-63</sup>

### 2.3.2 Mental distress

Mental distress, also termed psychological distress, is a psychologically troubling condition. It is characterized by loss of interest, sadness and hopelessness. Mental distress is a wider range of mental suffering than mental illness, although the terms are sometimes used interchangeably. Mental distress refers to recent onset of mental disorders, mostly anxiety and depression detectable with screening instruments as SCL-90 or GHQ. In comparison to healthy controls there are a few studies of reasonable size showing elevated level of mental distress in clinic patients with FD and in people with FD/IBS.<sup>64-65</sup> Depending on the cut-off -value the prevalence of mental distress in the background population ranges around 18.4-20.5% in women and 11.2-12.9% in men, as in a large population-based study of 68,000 inhabitants in Sweden.<sup>66</sup> In an Australian community cohort study patients with a FGID 4, 8 and 12 months reported mental distress was 38.5-44.1% compared to 14.0-22.4% in those without.<sup>67</sup> If both IBS and FD are present mental distress increases.<sup>68</sup> Mental distress, however, is not specific for dyspepsia and FGIDs. In a Dutch primary care study 45% of the 360 dyspeptics had mental distress in GHQ-12, but it is in line with other consulting patients, e.g. patients with sinusitis.<sup>69</sup> To emphasize the GHQ's non-specificity, it is even commoner in hypertensive patients (9.9%) than in the general population (4.9%) across borders of the former Soviet Union.<sup>70</sup> In two Finnish national health surveys in adults under 75 years mental distress has been present in 10-20% (Figure 3).<sup>71</sup>

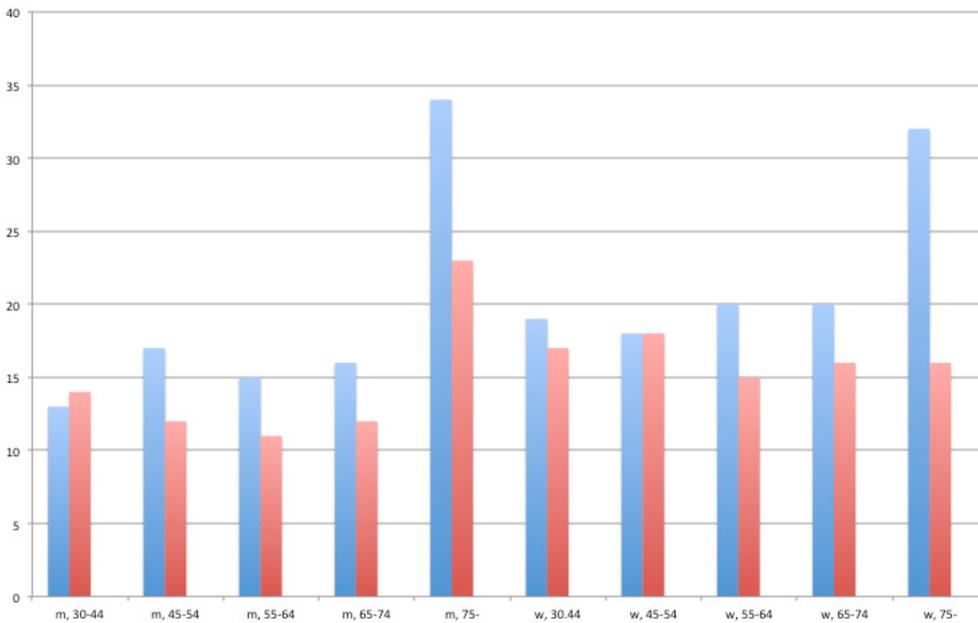


Figure 3. Percentages of men and women with mental distress (GHQ-12 >3) in the Finnish population, in 2000 (blue) and 2011 (red).<sup>71</sup>

### 2.3.3 Personality traits and disorders

FGIDs, such as FD and IBS, have higher scores of anxiety and neuroticism in comparison to healthy controls or non-patients with gastrointestinal complaints. There is not however a personality trait unique to these disorders.<sup>32</sup> Numerous studies in tertiary care have shown that in comparison to healthy controls FD has a higher frequency of anxiety, neuroticism<sup>56-58</sup>, dysfunctional attitudes<sup>57</sup> and dysfunctional coping styles.<sup>56</sup> On the population level in psychometric testing, somatization, neuroticism and hypochondriasis have been linked to patients with FD.<sup>72</sup> In comparison to organic counterparts such as peptic ulcer, the results are mixed. In some tertiary center studies FD patients have shown a higher tendency especially towards anxiety<sup>57</sup>, whereas in others the tendency is the same in FD and ulcer disease.<sup>58,73</sup> Talley even stated in 1990 after evaluating FD, IBS, DU patients and healthy controls with Minnesota Multiphasic Personality Inventory (MMPI) that psychopathology may not be the major explanation for FGIDs. Personality scales were very similar in patients with FD, IBS and DU.<sup>74</sup>

### 2.3.4 Depressive disorders

Depressive disorders include major depressive disorder and dysthymic disorder.

According to a large meta-analysis scores in psychological measurements of depression and anxiety tend to be higher in patients with FGID and in other medically

unexplained symptoms as chronic fatigue syndrome, fibromyalgia and IBS and FD in general than in healthy controls.<sup>34</sup> In some earlier tertiary center studies FD patients had higher levels of depression than DU-patients in interview and psychometric testing<sup>57</sup>, but not all studies agree.<sup>58</sup>

There is now some evidence that depression is not linked to FD in the same way as anxiety is. In a large (n=1001) population based Swedish study depression according to Hospital Anxiety Depression Scale (HADS) was not associated with FD using the latest Rome III criteria.<sup>75</sup> Another large (n=839) cross-sectional study from Malaysia comparing FD and OD patients did not find any association between FD and depression again using the HADS.<sup>76</sup> In a 12-year prospective study depression predisposed to FD.<sup>40</sup> This study has been criticized, however, because the number of patients 45/1002 developing FD is small and the OR was modest (1.09, 95% CI 1.00-1.20).<sup>77</sup> Furthermore in their original sample from 2002, which studied FGID health care seeking, anxiety, not depression, was one of the independent predictors of FGID for previous 12 months.<sup>78</sup>

### 2.3.5 Anxiety disorders

Anxiety disorders refer to panic disorder, agoraphobia, social phobia and generalized anxiety disorder.

In a Norwegian tertiary center study with 100 FD patients 65 identified anxiety and concern about seriousness of the symptoms as the main problem, as opposed to 26 reporting dyspeptic symptoms as the main problem.<sup>79</sup> State-trait anxiety was higher in FD patients than in healthy controls and DU patients.<sup>57</sup> This again was in contrast to results of the earlier Australian study.<sup>58</sup> The greater significance of anxiety over depression in FD was shown in the two above-mentioned large studies. In the Malaysian study moderate to severe anxiety was more prevalent in FD than OD (28.5 vs. 23.1%, p=0.05), but there was no difference in depression.<sup>76</sup> In the Swedish, population-based study major anxiety was associated with FD and especially with postprandial distress (OR 2.56, 95% CI 1.06-6.19).<sup>75</sup>

In a unique study of its kind, the bi-directionality between psychological factors and gastrointestinal symptoms was confirmed in the 12-year follow-up study of the Australian group. Out of 1002 subjects 217 developed new-onset FGID, and anxiety was predictive of this.<sup>40</sup> This is in concordance with their original retrospective results anxiety's importance in health care seeking with FGID over previous 12 months 12 years back from the same population.<sup>78</sup> For IBS and FD separately, the results were mixed, as anxiety and depression were predictive of IBS, whereas depression was predictive of FD. By far less confusingly, those with FGID at baseline developed significantly higher levels of anxiety and depression at the end of the study. However the authors conclude that in IBS and FD the brain-gut pathway is dominant, because separately baseline IBS or FD did not predict significant anxiety or depression, i.e. psychological distress causes somatic symptoms.<sup>40</sup>

### 2.3.6 Somatoformic disorders

Somatization refers to presence of physical symptoms that are not fully explained by a general medical condition. Somatoformic disorders include somatization disorder, conversion disorder, pain disorder and hypochondrias.

In earlier work among patients with chronic symptoms in a GE clinic, patients with FD diagnosed up to 7 years previously have had higher measurements of somatization in SCL-90 than healthy controls.<sup>80</sup> More recently there have been at least 2 separate studies in which Rome III criteria postprandial distress, not epigastric pain syndrome, has been strongly linked to psychopathological factors, especially to somatization in personality inventories ( $p=0.034 - 0.048$ ). Quite understandably it is directly linked to gastric sensitivity measured by gastric discomfort threshold, because it relies not only on subjective reporting, but also on objective gastric emptying as measured by breath test in 201 patients with FD.<sup>81-82</sup> Even this finding was in contrast to a study by the Australian group. In a population-based study with earlier Rome I criteria somatization was a risk factor for IBS, but not dyspepsia.<sup>83</sup>

### 2.3.7 Stress, coping styles and social support

At the population level patients with FD experience more stressful life events. There may also be lack of social support helping to cope.<sup>72</sup> There is also evidence of dysfunctional, confrontative coping with stressors, which they feel to be highly threatening<sup>56</sup> and uncontrollable,<sup>84</sup> especially in those patients who seek care.<sup>85</sup> Social stressors strongly predict symptomatology in FGID and is prominent especially in IBS and FD. In presence of even one stressor, e.g. marital, lawsuit, family member ill or financial threat, no patient improved in an Australian study of outpatients in a GE clinic.<sup>86</sup>

### 2.3.8 Abuse history

The literature on abuse history is virtually nonexistent in FD compared to IBS. Koloski found adulthood sexual, physical, verbal or emotional abuse to be more common in community IBS/FD subjects (40%) than healthy controls (25%).<sup>87</sup> Expression of bodily symptoms after abuse history is not specific since unexplained chest pain without heart disease or reflux is also independently linked to verbal/emotional or physical abuse (OR 5.66, 95% CI 1.01-31.80,  $p=0.049$ ). In both IBS/FD and unexplained chest pain the association was no longer significant when controlled for psychosocial factors as depression, which may function as a mediator of symptoms.<sup>87-88</sup> Despite this fact a high prevalence of abuse in tertiary care barostat studies have been reported. In one study, 84/198 (42.4%) reported overall history of abuse, 30% sexual and 20.3% physical abuse. Particularly sexual abuse influenced the gastric distension threshold.<sup>89</sup>

### 2.3.9 Health-related quality of life

Health-related quality of life (HRQoL), as measured by SF-36, is impaired in patients with FD, compared to patients with OD<sup>76</sup>, or patients with chronic liver disease and healthy controls.<sup>90</sup> Whether it can be attributed to concomitant anxiety or depression is controversial.<sup>76,90</sup> Van Oudenhove examined this more closely by separating physical and mental HRQoL. Their conclusion was that somatization and chronic fatigue mediated physical HRQoL ( $p < 0.0001$ ) and psychosocial factors such as anxiety and depression mental HRQoL, ( $p < 0.0001$ ) in 259 tertiary care FD patients undergoing barostat studies.<sup>91</sup> Interestingly in a 10-year study by Ford et al. poor QoL at baseline predicted new-onset dyspepsia during the study.<sup>92</sup>

### 2.3.10 Health care seeking and fear of serious illness

Severity of symptoms was suggested in a review article to be a driver of health care seeking in FD, but explains this only partially. The role of psychosocial factors was “left to be tested”.<sup>93</sup> The role of fear of serious illness as a driver of health care utilization was studied among Australian primary care 614 dyspeptic patients. Health care use during the previous 12 months was reported in 80%, and frequent use (>6) in 26%. Fear of serious illness was not an independent predictor of health care utilization. It was, however, increased more than twofold (OR 2.17) by frequent dyspeptic symptoms and symptom-related anxiety (OR 2.08-4.66).<sup>94</sup> In their earlier work on dyspeptic patients at the population level, greater pain severity (OR 2.49, 95% CI 2.12-2.91,  $p < 0.01$ ), concomitant IBS (OR 2.0, 95% CI 1.06-3.78) and male gender (negatively, OR 0.58, 95% CI, 0.37-0.91) were related to health care seeking.<sup>95</sup> Conventional and alternative health care seeking were both driven by other than psychological factors.<sup>96</sup> Rather confusingly, the same investigators came to the conclusion that baseline psychological distress measured by the GHQ-12 was, however, linked to having persistent GI symptoms and frequently seeking care in a 12 month study among community patients with FGID. No explanation was offered.<sup>67</sup> In case-control studies in patients with FD those who seek health care are different in perceptual and behavioral characteristics from healthy controls and those FD patients who do not. They are more likely to monitor themselves, confront stressful events in a problem-based manner and have higher scores in anxiety and depression.<sup>85</sup> There is also likely to be less social support<sup>85</sup>.<sup>72</sup> In two early studies among volunteers and female IBS non-consulters the level of psychological distress was not different from healthy controls, but was increased in those who consulted, and at least in these selected cohorts a driver of health care seeking.<sup>97-98</sup>

### 2.3.11 Treatment of psychological factors in functional gastrointestinal disorders

A Cochrane review from 2007 identified 61 randomized controlled trials (RCTs) on chronic pain. Tricyclic antidepressants (TCAs) are effective in chronic pain, with a number needed to treat (NNT) of 3.6 (95% CI 3.0 to 4.5), but there is limited evidence for selective serotonin reuptake inhibitors (SSRIs).<sup>99</sup> In a recent 2009 review article 12 studies comparing TCAs and SSRIs in IBS, treatment was effective over placebo RR 0.66 (95% CI 0.57 to 0.78; NNT 4). Psychological interventions are effective too (RR 0.67, 95% CI, 0.57 to 0.79, NNT 4), but the quality of the studies is worse.<sup>100</sup> In FD the evidence is less abundant than in IBS or chronic pain. A meta-analysis from 2005 identified 4 small RCTs with a TCA, SSRI or a combination of an anxiolytic and a TCA. The pooled RR was promising (0.55; 95% CI 0.36-0.85), but the funnel plot showed asymmetry, indicative of publication bias.<sup>101</sup> In everyday practice they are used to treat these patients since there often is co-existing anxiety and depression. What remains unclear is if the effect of the medication is on modulation of pain centrally or peripherally or on the psychological disorder.

#### 2.3.11.1 Psychopharmacological treatment in functional dyspepsia

Healthy volunteer trials have shown no effect on motility or adaptation to meal by TCAs or SSRIs.<sup>102-103</sup> In two very small trials with 7 and 27 FD patients amitriptyline has shown efficacy over placebo unrelated to motility or sleep, but may increase tolerance towards visceral sensations.<sup>104-105</sup> The largest FD patient RCT included 107 Chinese patients not responding to 8 weeks of esomeprazole and 4 weeks of domperidone therapy who were randomized to 12 weeks of imipramine or placebo. The global symptom assessment of patient-reported dyspepsia was evaluated after treatment. Treatment failure, defined as inadequate relief of dyspepsia, was significantly lower in patients on imipramine (23 vs. 46%,  $P=0.02$ ).<sup>106</sup> In a placebo controlled 8 week SSRI study with 193 FD patients followed in a tertiary clinic, there was no difference in the primary outcome, intention-to-treat (ITT) or per-protocol (PP) on global dyspepsia symptoms. Neither was there any difference in HRQoL or HADS. Unfortunately, 22% of patients dropped out, 23/24 and 11/19 occurring early at 4 weeks on sertraline 50 mg/day and placebo respectively. The only difference between groups at 8 weeks in the PP analysis was in the dyspepsia index in favor of sertraline over placebo ( $21 \pm 6.9$  vs  $23 \pm 7.2$ ,  $P = 0.02$ , respectively).<sup>107</sup> In the one study with venlafaxine, a selective serotonin and selective noradrenaline reuptake inhibitor (SNRI), the percentage of patients free of symptoms at 16 weeks were similar to placebo, 42 and 41%, respectively. Neither was there any difference in ITT on number of symptoms or symptom severity, HADS or HRQoL. Again only 45/80 (venlafaxine) and 58/80 (placebo) completed the study in the venlafaxine arm due to side-effects and recurrent or persistent symptoms in the placebo arm.<sup>108</sup> An even larger ( $n=400$ ) placebo controlled trial with TCA, amitriptyline and SSRI escitalopram is supposed to be available in 2014.<sup>109</sup>

### 2.3.11.2 Non-pharmacological treatment in functional dyspepsia

A Cochrane review from 2005 identified four trials on psychological treatment - relaxation therapy, hypnotherapy, cognitive therapy and psychodynamic interpersonal psychotherapy. A substantial reduction in dyspepsia was suggested and lasting up to 12 months. However, owing to many limitations, including low recruitment, high drop-out rate and statistical methods no meta-analysis could be done.<sup>110</sup>

Calvert et al. compared, gut directed hypnotherapy (HT) or supportive treatment consisting of 12 30-min. sessions to medical therapy (ranitidine 150 mg b.i.d.). At weeks 16 and 56 evaluated by the blinded assessor there was clear improvement over the two other groups in favor of HT group in dyspepsia symptoms, quality of life (QOL) and anxiety scores in HADS. Furthermore, in the HT group there was a clear reduction in medication use and consultation rate.<sup>111</sup> Hamilton et al. used psychodynamic interpersonal psychotherapy (PI) consisting of a 3-h session and 6 50-min sessions to treat patients with FD, and compared this to supportive therapy. PI concentrated alliance between therapist and patient and explores, reveals and modifies interpersonal difficulties. Supportive therapy concentrated on feelings and distress about the symptoms and connection of diet and symptoms of dyspepsia. The patients' own and gastroenterologist's (blinded) assessment of dyspepsia at 12 months was improved only after post-hoc exclusion of reflux patients.<sup>112</sup> A Norwegian study randomly assigned 50 FD patients to 10 50-min cognitive psychotherapy sessions and 50 patients to a control group and evaluated them at 4 and 12 months. Psychotherapy improved dyspeptic symptoms: days of epigastric pain ( $p = 0.050$ ), nausea ( $p = 0.024$ ), heartburn ( $p = 0.021$ ), diarrhoea ( $p = 0.002$ ) and constipation ( $p = 0.047$ ).<sup>113</sup> Bates et al. included 103 FD patients and assigned them to group therapy with emphasis on relaxation techniques in 8 90-min sessions or a control group. Pain intensity and number of episodes were statistically significantly reduced, but the drop-out rate was high, 40-59%.<sup>114</sup>

## 2.4 GASTRIC SENSORIMOTOR DYSFUNCTION, STRESS AND PSYCHOLOGICAL FACTORS

One possible link between psychological factors and FD is the autonomic nervous system. Previous studies have shown that stress-induced changes in antral motility are different in patients with FD from healthy volunteers. Consequently they also showed that this low vagal tone-mediated antral hypomotility on ultrasound was related to personality factors and might function as a mediator between symptoms in FD and e.g. neuroticism to a lesser degree depression .<sup>115-116</sup>

In a study among FD patients using a different modality, electrogastrography (EGG), correlations between personality traits and gastric motility<sup>117</sup> and between depression and gastric dysrhythmias were not reproduced.<sup>118</sup> Loeven group showed several interesting things in their large (n=438) tertiary center material. Rome II FD-patients are heterogeneous in symptom patterns, and can be further divided in 4 groups, which evidently led to development of Rome III. Psychopathology is associated with hypersensitivity to gastric distention, but not in all subgroups.<sup>119</sup> Consequently van Oudenhove et al. found that state anxiety correlated negatively with gastric barostat sensitivity in FD patients, and their accommodation to meal was impaired.<sup>120</sup> They also demonstrated that sexual abuse history ( $p < .001$ ), physical abuse history ( $p = .004$ ) and somatization ( $p < .001$ ) were independently associated with the gastric discomfort threshold.<sup>121</sup> Even gut-directed hypnosis has been introduced and shown to be more efficacious than cisapride on motility.<sup>122</sup>

Another possible interface between the brain and gut is the stress hormone system. In tertiary center FD patients basal prolactin was lower than in healthy controls and high degree of reflux correlated with a blunted increase in prolactin in response to stress interview.<sup>123</sup> In some IBS patients cortisol responses to adrenocorticotrophic hormone (ACTH)<sup>124</sup> and stress testing<sup>125</sup> are blunted in comparison to healthy controls, probably due to chronic stress-induced changes in the hypothalamic-pituitary-adrenal axis. A compromised negative feedback system may drive changes in corticotrophin releasing hormone (CRH) secretion, and due to its behavioral effects, result in symptoms of stress, anxiety and depression.<sup>126</sup> Specific effects have also been reported as low cortisol have been linked to high pain perception and high cortisol to depressed mood in FD/IBS.<sup>127</sup> Then again in an IBS-study excluding patients with depression, ACTH and cortisol response to CRH has been elevated, probably due to increased levels of pro-inflammatory cytokines, e.g. IL-6.<sup>128</sup>

## 2.5 BIOPSYCHOSOCIAL MODEL OF ILLNESS AND NEUROBIOLOGICAL BASIS OF BRAIN-GUT SIGNALING

The biopsychosocial model was introduced to gastroenterology by Drossman in 1998 in Psychosomatic Medicine in a presidential address in an “essay of personal experience and review of related literature”.<sup>129</sup> A case was made with three different GI diseases, reflux disease, FGID and Crohns`disease, on how a plain biomedical model would not be able to explain the variation in symptoms between patients. The model hypothesizes how psychosocial factors such as stress, emotions, psychiatric distress and coping styles combine with symptom experience and gastrointestinal abnormalities to influence daily function and outcome of FGID illness. Modern imaging modalities are now giving some promise of explaining why. In healthy individuals food digestion and GI sensory information and autonomic regulation remain largely unperceived, with exclusion of hunger and pain. They are however subconsciously processed in the central nervous system (CNS) in areas that also process emotional regulation.<sup>130</sup> Inappropriate perception or impairment in the descending modulatory system, which might be related to anxiety, leads to physiological stimuli sensed as painful or discomforting. Among patients with FD, somatosensory central activation in response to intragastric pressure occur at lower levels than in healthy controls. In addition there is impaired activation of the descending pain modulatory system that correlate with increased levels of anxiety, probably explaining hypersensitivity in FD.<sup>131</sup> Functional brain imagining modalities have produced consistent evidence on how the brain integrates homeostatic signals from the gastrointestinal tract with emotions and cognitive circuits e.g. at the level of insula and dorsal anterior cingulate cortex (dACC). The same area, anterior cingulate, has been abnormally activated in depressed young patients in a systematic review of brain imaging.<sup>132</sup> Outcome of this dysfunctioning brain-gut signaling might manifest as FD.<sup>133-134</sup>

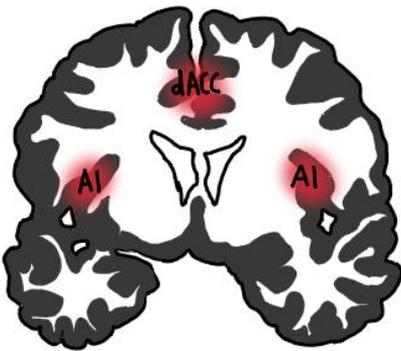


Figure 4. Overlapping areas of physical, emotional and social pain. AI, Anterior Insula (AI); dACC, dorsal anterior cingulate cortex. Adopted from Mayer et al. 2006.<sup>133</sup>

## 2.6 EVALUATION OF PSYCHOLOGICAL FACTORS

In the majority of studies questionnaires have been used to obtain information on psychological factors.<sup>32</sup> Questionnaires are validated against common criteria for diagnosis, e.g. the Structured Clinical Interview (SCID) for DSM-based diagnoses or the Composite International Diagnostic Interview (CIDI) for ICD-based diagnoses.<sup>135</sup> The two diagnostic criteria are complementary. The ICD contains the codes and the DSM up-to-date criteria. Since 1952, the American Psychiatric Association (APA) has published an authoritative guide containing descriptions, symptoms and other criteria called the Diagnostic and Statistical Manual of Mental Disorders (DSM), which is now in its 5<sup>th</sup> edition.<sup>136</sup> Psychological distress in the dyspeptic patient population can be evaluated with self-report questionnaires such as the General Health Questionnaire (GHQ) and Symptom Check List (SCL-90). Those above a certain predetermined numerical value are considered to be psychologically distressed. The manuals give cut-off points, but the scores are best compared with validated scores in national population samples.<sup>137-138</sup> An overview of psychological evaluation tools is presented in table 1.

**Table 1.** An overview of psychological measurement tools used in studies evaluating psychological factors in FGIDs, categories, tools, what is measured and their pros (+) and cons (-).

Category	Tool	Measurement	+/-
Psychiatric Interview	SCID, CIDI	Psychiatric Disorder, ICD	Golden standard (diagnostic criteria)/time consuming, inter-observer variability
Mental health scale	GHQ-12	Mental/Psychological distress	Fast, self-report, validated (Finland)/vague
Mental health scale	SCL-90	Psychological distress, psychopathology: anxiety, depression, somatization, sleep disturbances	Self-report, validated (Finland), severity estimate /moderately time consuming
Depression inventory	BDI	depression	Self-report, validated (Finland)
Anxiety Inventory	STAI	State-trait anxiety	Self-report/no validation (Finland)
Hospital anxiety and depression scale	HADS	Anxiety and depression among somatic patients	Self-report, international validation

<b>Personality Inventory</b>	<b>MMPI</b>	<b>Personality and psychopathology testing instrument</b>	<b>Widely used and standardized, self-report, computerized/in english</b>
<b>Health related quality of life</b>	<b>SF-36</b>	<b>Vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health, scale 0 to 100</b>	<b>Self-report, validated (Finland)</b>

### 2.6.1 General Health Questionnaire

The General Health Questionnaire is a self-report questionnaire that was developed in the early 1970s with the aim of devising an instrument to detect cases of recent mental disorders, mostly anxiety and depression. It is not a suitable instrument to detect long-term personality disorders, but it does identify psychotic disorders rather well. Originally it had 60 questions. The questionnaire screens every item with regard to how the respondent has experienced the recent few weeks. Each question can be given a value according to frequency or severity from 0-3. The values are then added together to give total distress score.

### 2.6.2 The 12-item General Health Questionnaire, GHQ-12

The shorter version was developed with the aim of devising a lighter instrument for screening purposes. In comparison to longer versions it has been found to perform in similar manner for this purpose. The optimal cut-off point varies among populations.<sup>137</sup> In Finland a cut-off point 3/4 has been suggested for screening purposes. Those with a score 4 or more are classified as having mental distress.<sup>135</sup> It covers 12 items with following questions.

Have you recently

1. Been able to concentrate
2. Lost sleep over worry
3. Playing a useful part in things
4. Capable of making decisions
5. Felt constantly under strain

6. Felt couldn't overcome difficulties
7. Been able to enjoy normal activities
8. Been able to face up to difficulties
9. Felt unhappy and depressed
10. Lost confidence in yourself
11. Been thinking of yourself as worthless
12. Been feeling reasonable happy, all things considered

For screening purposes, a response to a certain question, e.g. 3. Playing a useful part in things, answers are given a dichotomous value as follows: more than usual 0, the same as usual 0, less than usual 1, much less than usual 1. The values of the 12 questions are added together to give a score between 0 and 12.<sup>137</sup>

### **2.6.3 General Health Questionnaire-36**

It is also a widely used and validated instrument. It gives a score from 0 to 36. A cut-off point 8/9 has been suggested for screening mental disorders in Finland. A longer version performs similar to the shorter one for screening purposes, but has the advantage of giving an estimate of the severity of the mental distress subject is experiencing.<sup>135</sup>

### **2.6.4 Symptom Check List-90**

The Symptom Check List (SCL 90) is also a self-reporting 90-item questionnaire. It is a well validated tool available in several versions, and validated in Finland. It measures dimensions of psychological distress and psychopathology, including anxiety, agoraphobia, depression, somatization, obsessive-compulsive disorder, interpersonal sensitivity, hostility, paranoia and sleeping disturbances, on a 5-point Likert scale.<sup>135,</sup>

<sup>138</sup>

### **2.6.5 Beck Depression Inventory**

The Beck Depression Inventory (BDI) is a widely used 21-question self-screening instrument for depression. It covers areas of hopelessness, irritability, cognition, guilt, loss of sleep and interest in sex, fatigue and weight loss. It focuses on the role of cognitions in depression. Each question has at least 4 possible answers to give a scale. A cut-off point 14/15 has been validated as a screening tool for depression in Finland.<sup>139</sup>

### 2.6.6 State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI) has 40 questions on a 4-point Likert scale measuring both state (anxiety about an event) and trait anxiety (anxiety as personal characteristics).<sup>140</sup>

### 2.6.7 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) was created with the aim screening people with physical health problems. It contains seven Likert-scale questions regarding anxiety and depression giving a sum of 0-21. A cut-off point 7/8 has been suggested optimal for screening purposes, with sensitivity and specificity of 80-90%.<sup>141-142</sup>

### 2.6.8 Minnesota Multiphasic Personality Inventory

The Minnesota Multiphasic Personality Inventory is the most widely used standardized personality and psychopathology testing instrument for adults. It was originally developed in the 1940s atheoretically by selecting items endorsed by patients with known pathologies. The latest version now has 338 questions and can be received in a computerized version. It measures items such as concern with bodily symptoms, depressive symptoms, anxiety, stereotyping, suspiciousness, social alienation and introversion, hypomania, psychopathic tendencies and hysteria.<sup>143</sup>

### 2.6.9 RAND-36 and Short Form (SF)-36

The Health Related Quality of Life (HRQoL) can be measured with RAND-36 or the Short Form (36) Health Survey. They cover areas such as vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health. The weighted scale answers give a total ranging from 0 (maximum disability) to 100 (no disability).<sup>143-144</sup>

### 2.6.10 Other questionnaires

There exist specific questionnaires for illness behavior, attitude and cognition.<sup>145</sup> Social support is best determined by interview.<sup>32</sup> Maladaptive coping with pain and catastrophizing can be detected by the Coping Strategies Questionnaire (CSQ).<sup>146</sup>

## *2 Aims of the study*

The aim of this study was to determine

- 1 to what extent psychological factors are present in dyspeptic patients
- 3 if they are overrepresented in functional diseases
- 4 the directionality of the association between psychological factors and gastrointestinal symptoms
- 5 if psychological factors are associated with excessive health care utilization

## *4 Materials and methods*

### **4.1 DEFINITION OF TERMS**

#### **4.1.1 Dyspepsia**

Colin-Jones' definition of dyspepsia was introduced 1988, and it was used in this study. It is a broad definition of dyspepsia experienced as pain, discomfort, heartburn, abdominal distension, early satiety, post-prandial fullness, nausea, retching and vomiting thought to originate from the upper gastrointestinal tract. <sup>41</sup>

#### **4.1.2 Functional dyspepsia**

The term FD was introduced in 1991 for persistent or recurrent pain or discomfort in the upper abdomen in the absence of organic disease and no association with bowel habit. Patients with predominant reflux symptoms and negative gastroscopy should not be included. <sup>42</sup> The definition of FD has evolved during this study from enrollment to conclusion of the study several times (Rome I-III). <sup>43-44, 5</sup>

#### **4.1.3 Mental distress and suspicion of serious illness**

Mental distress, also termed psychological distress, is considered to be a psychologically troubling condition. It is characterized by loss of interest, sadness and hopelessness. Mental distress represents a wider range of mental suffering than mental illness, although sometimes used interchangeably. It refers to recent cases of mental disorders, mostly anxiety and depression detectable with screening instruments as GHQ. <sup>135, 137, 148</sup> Subjective suspicion of serious illness was measured with simple yes- or no-answer to question: "Do you suspect a serious underlying illness".

## 4.2 DESIGN OF THE STUDY

The patients in the study construct of 411 consecutive, unselected dyspeptic patients from Kuopio and surrounding health centers referred by the GPs. All patients presented with dyspepsia according to definition of Colin-Jones et al.<sup>41</sup> Patients with acute abdomen, those with gastroscopy performed within three months, and those under 15 years of age were excluded. All GPs were instructed to keep patients off anti-secretory medication from referral to diagnostic examinations regardless of symptom severity. Study flow is presented in figure 4.

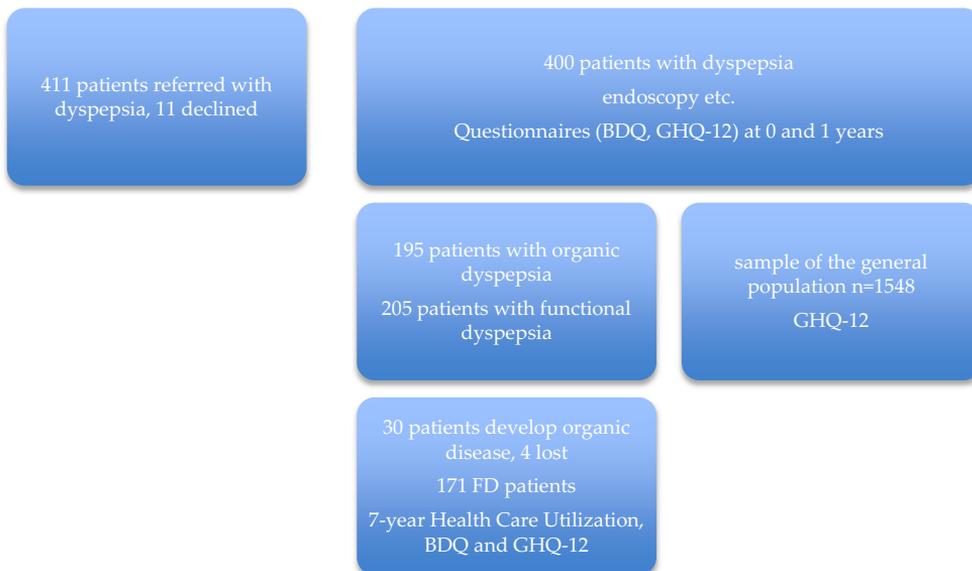


Figure 5. Study flow. BDQ, Bowel Disease Questionnaire; GHQ, General Health Questionnaire.

#### **4.2.1 Health centers and study center**

Seventeen GPs from a background population of 24,600 in Northern Savo, Eastern Finland in four health centers referred patients to the study. In all, 200 patients were recruited from rural health centers and 200 from the urban health center in Kuopio.

#### **4.2.2 Diagnostic studies**

Gastroscopy with biopsies, upper abdominal ultrasound, laboratory samples including blood count, serum concentrations of alanine aminotransferase, alkaline phosphatase, amylase and C-reactive protein, and a lactose absorption test were performed with no exceptions for all patients within one week after referral.

#### **4.2.3 Organic or functional dyspepsia**

Four hundred and eleven consecutive, unselected patients with dyspepsia were referred to the study between January 1993 and January 1994. Eleven patients refused to participate, so the final sample included 400 patients with dyspepsia. There were 151 men and 249 women filling the definition of dyspepsia according to Colin-Jones and co-workers.<sup>41</sup> The mean age of men was 58.6, SD 15.5, range 15-86 years. The mean age of women was 53.8, SD 14.8, range 19-84 years. After diagnostic examinations and a follow-up of one year organic dyspepsia was confirmed in 195 patients. There were 205 patients with FD. Of those, 37 fulfilled Manning criteria for concomitant IBS.<sup>47</sup>

#### **4.2.4 Sample of the general population**

A stratified sample general population of 1906 individuals was drawn from the Central Population Registry to represent 18-74 year old Finnish permanent citizens. All study subjects were either telephone (93%) or face to face interviewed in May 1993. The response rate (81%) and completeness of data was good. Final sample included 783 women 765 men. All interviews included the GHQ-12.

#### 4.2.5 Data Collection, Questionnaires

All patients completed self-administered questionnaires, including the modified Bowel Disease Questionnaire (BDQ), GHQ-12 and the question on suspicion of serious illness prior to diagnostic examinations and at the one-year follow-up. Of the FD cohort, 171 patients completed the same questionnaires at the 6-7 year follow-up.

##### 4.2.5.1 The Bowel Disease Questionnaire (BDQ)

The modified BDQ is a validated instrument comprehensively covering abdominal symptoms. Additional questions enabling classification of patients according to Rome II criteria were added to the questionnaire.<sup>42, 149</sup>

##### 4.2.5.2 Total dyspepsia score

The Total Dyspepsia Score has been used in several Finnish dyspepsia studies. It is derived from the BDQ upper abdominal symptom questions covering weighed symptoms of pain (1-4), nighttime pain (1-2), hunger pain (1-2), nausea (1-6) and bloating (1-2) giving a score from 0-16. In the follow-up those with a reduction of 50% from baseline are considered responders. We used the same criteria for defining meaningful response in dyspeptic symptoms.<sup>146</sup>

##### 4.2.5.3 Mental distress, GHQ-12

The questionnaires included the 12-item General Health Questionnaire. In Finland a cut-off point 3/4 has been suggested for screening purposes.<sup>135</sup> Those with a score 4 or more are referred to as those with mental distress.

##### 4.2.5.4 Suspicion of serious illness

Subjective suspicion of serious illness was measured with a yes- or no-answer to question "Do you suspect a serious underlying illness?"

### 4.3 FOLLOW-UP

One month after the examinations the patients visited their GPs for the results of the studies. Diagnoses were confirmed at the one-year visit. During the 6-7 year 30 patients developed an organic disease and 4 patients were lost to follow-up. 171 FD patients were included in the study of health care utilization. Of those 66% agreed to a voluntary gastroscopy. The follow-up appointments were held September to November 2000. In addition to BDQ and GHQ-12 patients completed self-report questionnaire of medical history for the past 7 years. To confirm subjective recollection their medical records in health centers, private clinics, regional hospitals and Kuopio University Hospital were reviewed in a structured manner to obtain information on hospitalizations, outpatient visits, medications, upper and lower endoscopies and other abdominal investigations.

### 4.4 STATISTICS

Data analyses comparing groups of organic and functional dyspepsia were conducted using first SPSS for Windows version 12.0.1, in the follow-up study SPSS version 13.0 and in the health care utilization study SPSS version 17.0.

Differences between groups were evaluated using chi-squared test, Students t-test and Mann-Whitney U-test. Differences at baseline and at the one-year follow-up were further evaluated using paired samples t-test and McNemar test. The risk of having mental distress was calculated with forced age- and sex-adjusted logistic regression model. Comparisons were made between patients with organic or functional dyspepsia and the sample of general population.

Cronbach's alpha for the GHQ-12 was 0.80 in the dyspeptics and 0.83 in the sample of general population. The figures indicate good internal consistency of data. Correlations between changes in mental distress, suspicion of serious illness and dyspeptic symptoms were assessed by calculating Spearman's Rho. Comparisons were made between patients with FD and OD regarding mental distress, suspicion of serious illness and GI-symptoms. A reduction in the total dyspepsia score by more than 50% was regarded as a response.

In the health care utilization study the Mann-Whitney U-test was used to compare means. Crude and adjusted multivariate logistic regression modeling was performed to assess the associations between upper and gastric symptoms, mental distress, suspicion of serious illness and health care utilization during the follow-up. Models were adjusted for age, sex, frequent drinking and daily smoking. P-values <0.05 were considered statistically significant.

#### **4.5 ETHICS COMMITTEE APPROVAL**

Approval for this study was given by Kuopio University Hospital Ethics Committee.

## 5 Results

### **5.1 MENTAL DISTRESS IN PATIENTS WITH FUNCTIONAL OR ORGANIC DYSPEPSIA: A COMPARATIVE STUDY WITH A SAMPLE OF THE GENERAL POPULATION (STUDY I)**

Mental distress was more common in patients with dyspepsia than in the sample of the general population (36.5% vs. 15%,  $p < 0.001$ ). Among patients with organic and FD the risk of having mental distress was similar, 36.4 and 38% respectively. Neither was there any difference in the mean GHQ-12 score (3.6 in both groups). Women were slightly overrepresented in patients with OD and FD (68.8% and 55.4%, respectively). There was no difference in GHQ-12 score or in the prevalence of mental distress between men and women with OD or FD. In the sample of the general population GHQ-12 was significantly higher in women. Age- and sex-adjusted risk of having mental distress was nearly four-fold increased among patients with dyspepsia in comparison to general population sample. (Study I, Table 2) Those with FD did not have an increased risk of mental distress compared to patients with OD (sex- and age-adjusted OR 1.04, 95% CI 0.69-1.58).

### **5.2 THE CHANGES IN GASTROINTESTINAL SYMPTOMS, MENTAL DISTRESS AND SUSPICION OF SERIOUS ILLNESS IN PATIENTS WITH FUNCTIONAL OR ORGANIC IN ONE-YEAR FOLLOW-UP (STUDY II)**

Three hundred and ninety three (98.3%) patients completed the one-year study. At baseline there was no difference between patients with FD and OD in the total dyspepsia score (mean 7.4/16 vs. 7.6/16), in the prevalence of mental distress (38.0 vs. 36.4%) or in suspicion of serious illness (13.7 vs. 19.5%), respectively. There was however clear differences in individual reported moderate to severe gastrointestinal symptoms especially at the one-year follow-up. Figure 6.

At the 1-year follow-up the total dyspepsia score fell in both groups, but more significantly in patients with organic dyspepsia (4.1/16) than FD (5.3/16). There were also more responders, i.e. patients with a 50% reduction in the total dyspepsia score, among patients with organic dyspepsia (59.2 vs. 40.8%,  $p = 0.01$ ) than in patients with FD. Mental distress fell significantly in both groups (FD 22.4%, OD 22.1%). Similar fall was noted in suspicion of serious illness (FD 9.8%, OD 9.2%).

Finally, it was assessed whether changes in mental distress and suspicion of serious illness were related to changes in gastrointestinal symptoms. Of the dyspeptic patients who were no longer mentally distressed 53.4% experienced a significant, >50% reduction in the total dyspepsia score compared to 20.5% of those with continued mental distress ( $p < 0.001$ ). Quite similarly 56.5% of those no longer suspecting a serious

illness responded compared to 23.7% of those who still suspected serious illness ( $p=0.002$ ). The significance of psychological factors on dyspeptic symptoms is presented separately for OD and FD in Figures 6 and 7. Changes in the GHQ-12 score ( $r=0.342$ ,  $p<0.01$ ) and in the suspicion of serious illness ( $r=0.171$ ,  $p<0.05$ ) correlated positively with the changes in the total dyspepsia score. However, when studied separately these correlations were significant only for organic dyspepsia.

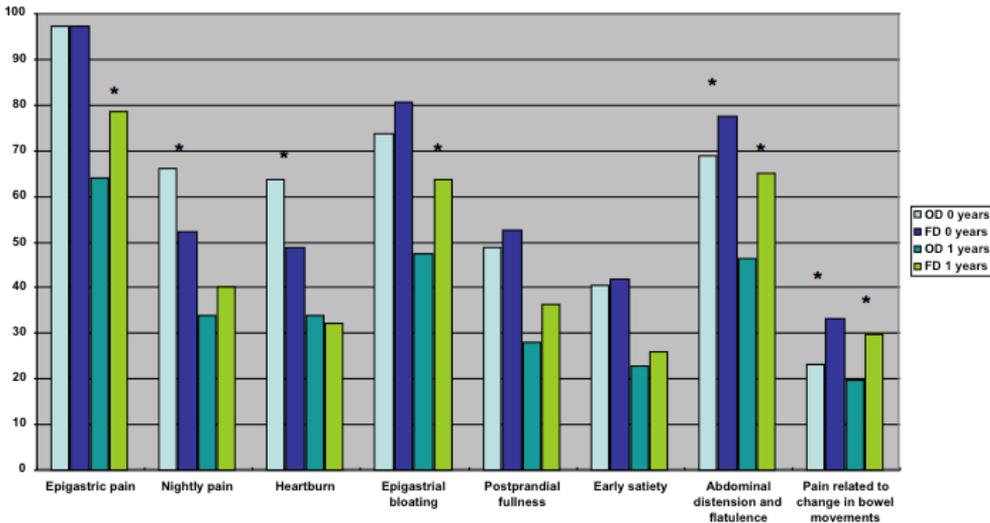


Figure 6. Self-reported moderate to severe gastrointestinal symptoms at baseline and at the one-year follow-up. Statistically significant differences in symptoms between groups are marked with an asterisk \*. OD, organic dyspepsia; FD, functional Dyspepsia.

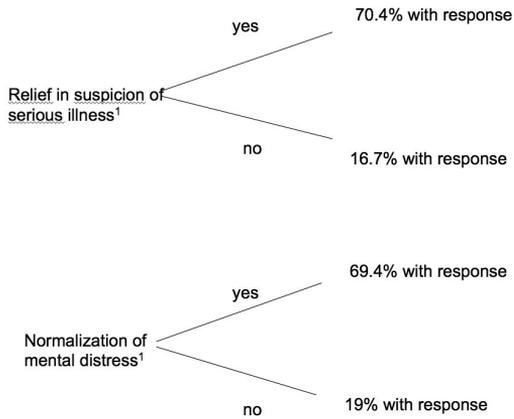


Figure 7. Statistically significant response in dyspeptic symptoms in organic dyspepsia in relation to psychological factors.  $P < 0.05$ .

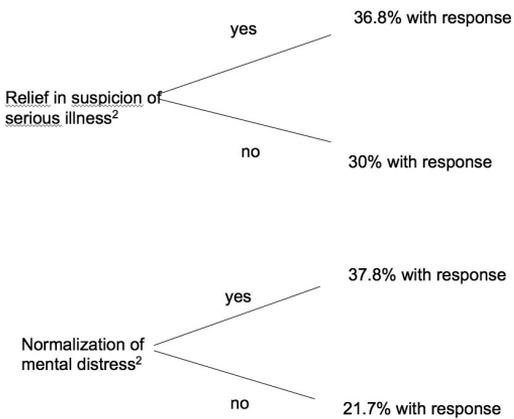


Figure 8. Statistically insignificant response in dyspeptic symptoms in functional dyspepsia in relation to psychological factors.  $P = \text{N.S.}$

### 5.3 ASSOCIATION BETWEEN MENTAL DISTRESS, GASTROINTESTINAL SYMPTOMS AND HEALTH CARE UTILIZATION IN FUNCTIONAL DYSPEPSIA: A PROSPECTIVE 7-YEAR FOLLOW-UP STUDY (STUDY III)

Of the original 205 patients with FD 4 patients were lost to follow-up and 30 developed organic diseases. A flow diagram summarizing patient selection, numbers excluded and why, and numbers followed-up and when are presented in Figure 5. The final follow-up sample thus included 119 (69.6%) women and 52 (30.4%) men. Mean follow-up time was 88 months (range 80-94 months). At the baseline the mean age of enrolled patients was 56.7 years (SD 15.8, range 15-85 years). Eighteen study subjects died during the study. The deaths were not from gastrointestinal causes. Excluding one suicide, those who died during the follow-up were aged 60-85 years at the study entry. Suspicion of serious illness was more common among those who died during the study period.

More than half (55%) of the patients were *H.Pylori* -positive, and only a small portion were prescribed eradication treatment. Non-treatment of the infection did not lead to excess outpatient visits, use of medication, repeated investigations or hospitalizations.

Repeated consultations, medications and examinations during the study period are presented in table 2. The majority of the patients re-visited their GP for abdominal complaints during the seven-year follow-up, with a mean 1.8 (SD 2.4, range 0-15) appointments. Half of the patients were prescribed or self-medicated. Drugs most often used were anti-acidic H<sub>2</sub>-antagonists (n=28; 17.0%) and proton pump inhibitors (PPIs) (n=18, 10.5%). Few patients were reinvestigated with endoscopy, mean 0.7 (0-5, SD 1.1). Those patients who were hospitalized due to gastrointestinal complaints, or revisited their GP, had initially more bowel symptoms. The total dyspepsia score did not affect use of measured health services. One additional bowel symptom increased the probability of repeated endoscopy and repeated outpatient visit by 19% (p=0.056 and 0.064, respectively). Inpatient period was increased by 51% a single bowel symptom (p=0.006).

Table 2. Health care utilization during the 7-year follow-up, number of patients and their proportions.

Consultation or investigation	Patients (n=171)	proportions
Revisit	102	59.6%
Medication	90	52.6%
Endoscopy	64	37.4%
Radiological examination	54	31.6%

<b>Oesophageal pH-monitoring</b>	<b>3</b>	<b>1.8%</b>
<b>Manometry</b>	<b>1</b>	<b>0.6%</b>
<b>Hospitalization</b>	<b>15</b>	<b>8.8%</b>

According to the final fully adjusted logistic regression models, the number of bowel symptoms at baseline was independently associated with an increased risk of hospitalization and repeated endoscopy during the follow-up. A corresponding association with an increased risk of a new outpatient visit was nearly statistically significant. Men had an increased risk of being hospitalized during the study period for gastrointestinal causes. Higher age was associated with the number of outpatient visits. Neither presence of mental distress nor suspicion of serious illness was predictive of GP seeking, excess endoscopies or an increased risk of being hospitalized. (Study III, Table IV)

## 6 Discussion

The main findings of this study were, that among consecutive, unselected primary care patients with dyspepsia mental distress was significantly more common than in the sample of the general population (36.5% vs. 15.0%,  $p < 0.001$ ). In addition, at presentation almost 20% suspected a serious underlying illness. However, there was not any difference between patients with organic or functional dyspepsia. In the follow-up of one-year one could witness several changes in the course of abdominal complaints. There were statistically more individuals with a 50% or greater reduction in the total dyspepsia score among patients with OD. For several individual moderate to severe upper and lower gastrointestinal symptoms FD patients remained or became statistically significantly more symptomatic than patients with OD. We found a correlation between change in gastrointestinal symptoms of dyspepsia and psychological factors in organic dyspepsia patients, e.g. in those with reflux disease, ulcer disease, or other organic diseases. In patients with FD there was no correlation. Consistent with this, in the seven-year follow-up study psychological factors baseline mental distress or suspicion of serious illness had no effect on health care utilization in patients with FD. Instead, just one bowel symptom increased the probability of re-visit or endoscopy by 19% and an outpatient visit by 51%.

### 6.1 DISCUSSION STUDY I

Our cross-sectional data on the presence of mental distress among dyspepsia in about 40% of patients is similar to reported data at the population level in Australia and primary care patients in Netherlands.<sup>67,69</sup> A four-fold higher sex- and age-adjusted prevalence than the sample of the general population is strong evidence of the association between dyspeptic symptoms and mental distress. However, it was not any different between OD or FD. The findings are in concordance with earlier GE clinic comparisons of duodenal ulcer- and FD-patients.<sup>58,74</sup> It is also in line with studies among patients with chest pain with or without coronary disease and rheumatoid or noninflammatory musculoskeletal joint pain.<sup>35-36</sup> Mental distress is not specific to functional disorders, but rather a non-specific CNS response to bodily symptoms.

### 6.2 DISCUSSION STUDY II

The finding that psychological factors are more persistent in FD was confirmed in the one-year follow-up study. Mental distress and suspicion of serious illness decreased in both groups of dyspepsia. With the exception of change in suspicion of serious illness in

FD these changes were statistically significant. However the total dyspepsia score fell more in OD. This without doubt is due to the fact that organic causes can be effectively treated in comparison to FD. There was a significant correlation between changes in GI symptoms and the change in mental distress and suspicion of serious illness in dyspepsia. This is best described by proportions of dyspepsia responders with relation to mental distress (yes 53.4%, no 20.5%) and suspicion of serious illness (yes 56.5%, no 23.7%). The fact that this correlation was not present in patients with FD speaks against a causal relation between psychological factors and FGID, especially since in OD and FD there was no significant difference in mental distress and suspicion of serious illness in the follow-up. Something else is responsible for the persistence of abdominal symptoms in FD. There are very few studies investigating the course and relation of psychological factors in confirmed FGID. Sloth and Jörgensen found that psychic vulnerability predicted IBS symptoms in outpatients followed for 5-7 years.<sup>151</sup> Presence of a chronic stressor seems to be pivotal in the course of IBS/FD over 16 months: no patient improved in presence of just one stressor, and all of those who improved did so in absence of such a stressor.<sup>28</sup> Similar to us, Koloski et al. did not find any correlation,, between changes in GI symptoms and changes in mental distress in their community FGID sample.<sup>67</sup> The same Australian group recently successfully completed a 12-year follow-up study with the aim of providing evidence for the gut-brain or brain-gut pathway, but ORs were very modest (1.04 -1.11) and the OR for the disappearance rate (113/1002), which was about half of the incidence (217/1002), was not reported.<sup>40</sup>

### 6.3 DISCUSSION STUDY III

In the health care seeking study it was surprising how little most of the 171 primary care FD-patients consulted in 6-7 years after thorough investigations. 40-50% did not seek a doctor for GI complaints or medication, and 60-70% did not undergo a radiological investigation or endoscopy. Less than 10% were hospitalized, and only a fraction needed additional oesophageal studies. Our findings on the reasons for health care seeking are in contradiction with most studies. The majority of these are on initial health care seeking. In our results, contrary to earlier results, fear of serious illness<sup>152</sup>, mental distress<sup>67</sup> and frequent and severe symptoms<sup>78</sup> did not increase these health care seeking. The main finding that bowel symptoms are the key driver in health care seeking for dyspepsia is quite logical. In our 1-year follow-up study lower GI symptoms were long-lasting in comparison to dyspeptic symptoms. It is also in line with an earlier Australian retrospective work on dyspeptics at the population level. Concomitant IBS increased health care seeking two-fold.<sup>95</sup>

## 6.4 STRENGTHS AND LIMITATIONS OF THE STUDY

In contrast to most previous studies we investigated consecutive primary care patients, not chronic clinic patients. We are less likely to face the problem of a highly selected and biased patient population, in which bias towards having more difficult psychological problems is enriched. All patients were thoroughly investigated; we did not rely on questionnaires to confirm the diagnoses between organic or functional diseases. All diagnoses were confirmed only after a follow-up of one year. Psychological evaluation allows us to determine the significance of mental distress and suspicion of serious illness at the onset of dyspeptic symptoms. We are aware of the fact that the GHQ-12 is not suitable for evaluating personality factors, but it does well in identifying patients with mental disorders, and it has been evaluated for this purpose in Finland.<sup>135</sup> Measurements at only two time points are too little to draw definite conclusions on the association between psychological factors and GI-symptoms. Since we studied consecutive patients with dyspepsia only the change in dyspeptic symptoms could be addressed. The correlation was evident, but only in the wrong patient group, in patients with organic diseases not regarded to be psychogenic in origin. The fact that patients with IBS were included can be criticized, but offers interesting knowledge on health care seeking (Study III). Concomitant IBS was found in 37/205 patients, but overlapping and symptom exchange between FGIDs is an acknowledged fact.<sup>46</sup> Rome III criteria again accepts concomitant IBS and even patients with reflux symptoms, and we feel that even this latest criteria of FD is fulfilled in our patients.<sup>5</sup>

## 6.5 CLINICAL IMPLICATIONS

Since we studied primary care patients the results are directly applicable to practice. In 40% of the patients with dyspepsia there is significant mental distress, which is most likely affecting the symptom experience. It is a major determinant of subjective impaired health. This can be addressed with appropriate means. Alleviation of psychological distress, however, is not likely to change the course of dyspepsia. After a year majority of the patients with FD still experience moderate to severe epigastric pain. Concomitant bowel symptoms will also persist, and they will be mainly responsible for future health care use in FD patients.

## 6.6 IMPLICATIONS FOR FURTHER STUDIES

Although it is clear that there is undoubtedly a strong association between psychological factors and dyspepsia, the existence of a specific brain-gut link and consequently causal association in FD must be questioned. The greater significance of anxiety over depression found in two different cross-sectional settings, on the population level and in the GE clinic, must be confirmed in longitudinal studies. It is also possible, as suggested by Swedish research, that the importance of anxiety as a causal factor applies only to the postprandial distress criteria of Rome III. The most recent dyspepsia criteria may produce more homogenous cohorts of patients in which psychological factors are a prominent feature. A TCA or SSRI placebo-controlled trial hardly will provide the answer. The molecules have been tested with none to moderate effect previously, and baseline anxiety predicted poor response to venlafaxine. Even with a positive result it will be impossible to say if the effect is on gut or brain. Hopefully brain imaging and gastric sensorimotor measurements will provide a better understanding of the cause of FD and produce specific, effective interventional means for FD or anxiety/depression. Only then can controlled intervention studies confirm or disprove the brain-gut axis hypothesis.

## 7 *Conclusions*

### I

Unselected, thoroughly investigated primary care dyspeptic patients have a four-fold higher prevalence of mental distress than a sample of the general population.

### II

In patients with organic and functional dyspepsia the prevalence of mental distress on presentation with dyspepsia is the similar (36.4 and 38%, respectively).

### III

There is a correlation between changes in psychological factors and upper GI-symptoms in dyspepsia, but only in patients with organic dyspepsia. This questions the hypothesis proposing a specific brain-gut axis in FD.

### IV

Psychological factors, mental distress and suspicion of serious illness are not significant drivers of health care seeking. Bowel symptoms increase health care use.

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**MARKKU PAJALA**  
*Psychological Distress in  
Dyspepsia*

There is allegedly a strong association between psychological factors and functional abdominal symptoms. Mental distress in dyspeptic patients is almost four-fold higher than in the general population, but it is similar in patients with organic and functional diseases implying a nonspecific reaction to abdominal symptoms. The non-correlation between psychological factors and functional dyspepsia symptoms was confirmed in follow-up. Health care seeking is also not driven by these factors, but rather by bowel symptoms.



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