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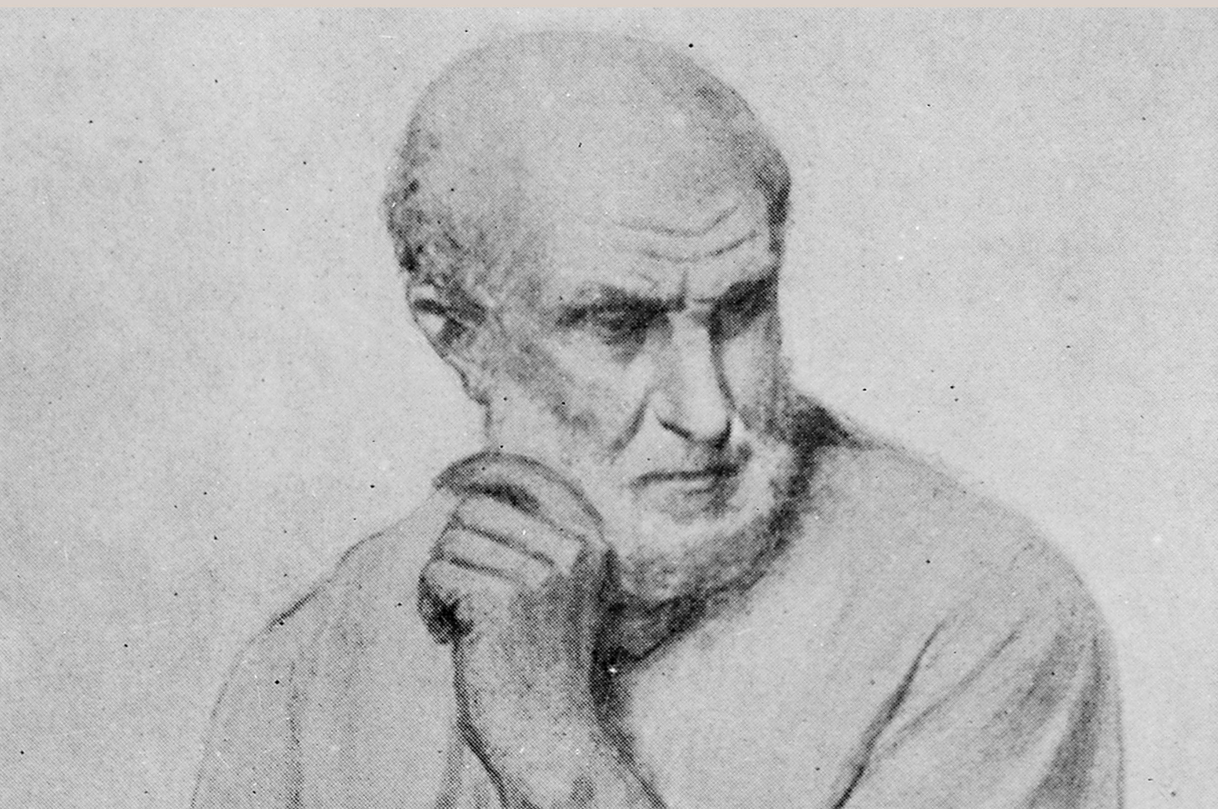
Erik Lexne

Psychiatric aspects on acute abdominal pain



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Psychiatric aspects on acute abdominal pain
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Abstract

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ISBN: 978-91-89460-13-3 (print), 978-91-89460-14-0 (pdf).

Introduction: Psychiatric comorbidity is estimated to occur in up to 40% of all patients with somatic disorders, and it can have an influence on patient morbidity and mortality. Approximately 20% of patients who seek care for abdominal pain receive the diagnosis non-specific abdominal pain, and later develop chronic abdominal pain. This condition and other abdominal conditions without organic explanation are sometimes called diseases of gut-brain interaction, and psychosocial factors (personality, psychiatric conditions, etc.) have been suggested to play an important role. Organic dyspepsia (which in this thesis is limited to peptic ulcer, gastritis and gastro-esophageal reflux disease, or GERD) has previously been reported to be associated with personality traits and psychiatric conditions. Despite these known associations, few studies have specifically investigated psychiatric comorbidity in patients with acute abdominal conditions.

The aim of this thesis is to investigate the prevalence of psychiatric comorbidity in patients with acute abdominal pain conditions in the emergency setting and to evaluate the possible long term psychiatric problems of these patients.

Methods: Consecutive patients with who came to emergency care with acute abdominal pain conditions were divided into three diagnostic groups: acid-dependent organic dyspepsia (peptic ulcer, gastritis and GERD), specific abdominal diagnoses, and non-specific abdominal pain. These groups were evaluated for personality traits, psychiatric symptoms, and self-rated health. A follow-up study explored prescription of antidepressant and anxiolytic (anti-anxiety) medications in this patients 10–15 years after the initial visit to emergency care.

Results: Among the various diagnostic groups, patients with acid-dependent organic dyspepsia had significantly more anxiety-related personality traits, less mature characters, significantly more psychiatric symptoms, and poorer self-rated health. Patients with non-specific abdominal pain also had more personality traits associated with anxiety, although to a lesser extent. Personality factors were significantly associated with poor self-rated health. The long-term follow-up showed that patients with organic dyspepsia and non-specific abdominal pain were prescribed antidepressants and anxiolytic drugs statistically more often than patients with specific abdominal diagnoses.

Conclusion: Patients with abdominal pain who seek emergency care have enhanced psychiatric comorbidity, more anxiety-related personality traits, and poorer perceived health. This trend is particularly evident in patients with a diagnosis of acid-dependent organic dyspepsia, and to a lesser degree, patients with a diagnosis of non-specific abdominal pain. These factors also predict future prescription of depression and anxiety medications. These results suggest that patients who come to emergency care with acute abdominal pain could potentially benefit from psychiatric consultation.

To my mother, who believed that I could take down the stars, and my father who taught me that to quit - that is not an option!

“One school is finished, and the time has come for another to begin”

- Richard Bach, Jonathan Livingston Seagull

LIST OF PAPERS

I. Lexne E, Brudin L, Strain JJ, Nylander PO, Marteinsdottir I. Temperament and character in patients with acute abdominal pain. *Comprehensive psychiatry*. 2018;87:128-33.

II. Lexne E, Brudin L, Marteinsdottir I, Strain JJ, Nylander PO. Psychiatric symptoms among patients with acute abdominal pain. *Scandinavian journal of gastroenterology*. 2020:1-8.

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SVENSK POPULÄRVETENSKAPLIG SAMMANFATTNING

Psykiatrisk komorbiditet, definierat som samtidig kroppslig och psykisk sjukdom, är vanlig hos patienter, oavsett om de befinner sig inom primärvård eller sjukhusvård. De flesta studier som rapporterar om sambandet är gjorda på patienter med kroniska medicinska tillstånd (t.ex. diabetes) eller akuta medicinska sjukdomar (t.ex. hjärtinfarkt). Få studier är utförda på kirurgiska patienter eller på akutmottagningar.

Mot slutet av förra seklet upptäcktes att bakterien *Helicobacter pylori* orsakade magsår, en sjukdom som dittills ansetts vara en psykosomatisk dvs att personlighetsfaktorer, sociala förhållanden eller psykiska tillstånd (t.ex. depressioner) hade betydelse för utveckling av sjukdomen. Även om denna upptäckt medfört att magsår kunnat behandlas mer effektivt, så saknar upp till 20% av patienterna med magsår en organisk förklaring. Detta har lett till fler studier om huruvida psykiska eller sociala faktorer kan spela roll i sjukdomsutvecklingen. Många studier har på 2000-talet rapporterat om att personlighetsfaktorer, sociala förhållanden eller psykiska tillstånd, faktiskt är kopplade till magsårssjukdomen. Emellertid bygger de flesta av dessa studier på enkätundersökningar, eller intervjuer, utan direkt koppling till medicinska journaler. I de fall där man studerat psykiska faktorer kopplat till gastroskopi, så har man inte gjort det vid samma tillfälle vilket exempelvis inte utesluter spontanläkning av magsår under väntetiden. Magsår, tillsammans med refluxsjukdom och gastrit, kallas för organisk dyspepsi, och utgör ungefär 50% av förklaringen till dyspepsi (högt sittande buksmärtor, illamående, tidig mättnadskänsla osv.), ett symptom som uppskattningsvis ca 25% av befolkningen lider av. De resterande 50% utgörs av funktionell dyspepsi, dvs samma symptom, men utan organisk förklaring. Denna sistnämnda grupp, funktionell dyspepsi, ingår numera i en annan grupp, DGBI (disorders of gut-brain interactions). Som namnet antyder, anser man att symptombilden bäst förklaras av samspelet mellan det centrala nervsystemet (CNS) och magtarmkanalen, som har sitt eget nervsystem, det enteriska nervsystemet (ENS). I gruppen DGBI ingår många diagnoser som nämnts, funktionell dyspepsi, men även t.ex. IBS (Irritable Bowel Syndrome). Det finns väl visat att patienter med DGBI har en överrepresentation av sociala faktorer (t.ex. stress), psykiatriska tillstånd (t.ex. ångest) samt personlighetsfaktorer (t.ex. neuroticism).

Buksmärtor är en vanlig orsak till att söka akutsjukvård där den vanligaste diagnosen är icke-specifik buksmärta dvs man hittar ingen organisk orsak till symptomen. Emellertid visar det sig att för 29% av dessa patienter kvarstår buksymptom efter 20 år och cirka 20% utvecklar det som kallas kroniska buksmärtor. Denna sistnämnda grupp passar ofta in i gruppen DGBI.

Denna avhandling sammanfattar fyra studier på patienter som sökt akutsjukvården pga akuta buksmärtor och där psykiatriska aspekter (personlighet, psykiska symptom, självupplevd hälsa samt förskrivning av psykofarmaka 10-15 år efter sjukvårdstillfället) värderas mot diagnoserna organisk dyspepsi (magsår, refluxsjukdom samt gastrit), specifika bukdiagnoser (man hittar en organisk förklaring) och icke-specifika buksmärtor (ingen organisk förklaring kan hittas).

Resultaten visar att gruppen av patienter med magsår, refluxsjukdom eller gastrit, skiljer sig åt från patienter med specifik bukdiagnos eller icke-specifik bukdiagnos, när det gäller personlighet, psykiatriska symptom och självupplevd hälsa. Bland skillnaderna märks personlighetsfaktorer kopplade till ökad ångest, pessimism, brist på energi, sämre ansvarstagande, mindre utvecklad karaktär men även ökad förmåga till känsla av samhörighet och andligt accepterande. Vidare att man har fler symptom kopplade till depression och ångest samt att den självupplevda hälsan är sämre och tendenser till alkoholproblem. Dessa fynd bekräftas av en ökad frekvens förskrivning av läkemedel mot depression och ångest 10-15 år efter akutvårdstillfället.
Även för patienter med icke-specifik buksmärta finns avvikande personlighetsfaktorer i termer av tendenser mot brist på energi och sämre ansvarstagande och tendenser till alkoholproblem. Dessa patienter har också en högre förskrivning av läkemedel mot depression och ångest.

I sammanfattning dras slutsatsen att bland patienter med akut buksmärta, i synnerhet de som har organisk dyspepsi, finns psykiatrisk komorbiditet med risk för långtidsproblematik. Detta faktum talar för att psykiatrisk kompetens, parallellt med vanlig kroppslig undersökning och behandling, bör kopplas till akut omhändertagande av patienter med akuta buksmärtor.

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ABBREVIATIONS

AD	Antidepressant drugs
ADAX	Antidepressant and anxiolytic drugs in unique combination
CO	Cooperativeness
DGBI	Diseases of Gut-Brain Interactions
DSM	Diagnostic and Statistical Manual of Mental disorders
FD	Functional dyspepsia
FFM	Five Factor Model
FFT	Five Factor Theory
FGID	Functional gastrointestinal disorders
GAD	Generalized anxiety disorder
GERD	Gastro-esophageal reflux disease
HA	Harm Avoidance
LOS	Length of stay
NaSSA	Antidepressant drug with noradrenergic and specific serotonergic action
NEO-PI	NEO Personality Inventory
NS	Novelty Seeking
NSAP	Non-specific abdominal pain
NSAID	Nonsteroidal anti-inflammatory drugs
NSTEMI	Non ST Elevation Myocardial Infarction
OD	Organic dyspepsia
P	Persistence
PD	Psycho-pharmaceutical drugs
Prime-MD	An instrument for screening and determination of psychiatric diagnoses
RD	Reward Dependence
SAD	Specific Abdominal Diagnose
SD	Self-Directedness
SNRI	Antidepressant drug with serotonin and noradrenalin reuptake inhibition
SRH	Self-rated health
SSRI	Antidepressant drug with specific serotonin reuptake inhibition
ST	Self-Transcendence
TCI	Temperament and Character Inventory

DEFINITIONS

Psychiatric comorbidity	Simultaneous presence of somatic disorder and psychiatric disorder
Extra-gastrointestinal symptoms	Symptoms outside of the gastrointestinal tract (e.g. palpitations)
Organic dyspepsia (in this thesis)	Dyspeptic symptoms that can be explained by organic findings associated with hydrochloric acid (HCl).
Specific abdominal diagnoses	Any diagnose that explain the abdominal symptoms by specific findings (e.g. gallbladder disease by ultrasound findings). This group includes patients with dyspeptic symptoms explained by a non-acid etiology (e.g. ventricular tumor).
Non-specific abdominal pain	A condition where an etiologic factor cannot be found. Usually the discharge diagnose is Abdominal pain NOS R104 in ICD-10.

INTRODUCTION

"It is more important to know what sort of person has a disease, than to know what sort of disease a person has" said Hippocrates, 'the father of medicine', 2500 years ago (1). Although most modern physicians and other health professionals would probably agree that Hippocrates statement is taking the issue too far, most of them would probably also agree that personality certainly has an impact on several levels, including presentation of symptoms and prognosis. Hippocrates proposed thorough examination of patients, including physical status, age, sex, occupation, past and present diseases and personality before making a diagnosis and prognosis (2). An offspring of Hippocrates thinking might be the development of psychosomatic medicine proposed by Franz Alexander, although he himself refers to other scientists. Among those that Alexander referred to was Sigmund Freud, who developed a systematic method to explore the human mind, based on the concept of unconscious and the division of the self into three levels (id, ego and superego).

Franz Alexander proposed that for some diseases, specific patterns of personality in emotional crisis can, together with a specific organ vulnerability ("the X factor"), acquired early in life, explain the occurrence of a disease. For example, in the case of duodenal ulcer, the specific personality pattern would be the inability to accept one's need for help and "the X factor" would be a vulnerable duodenum (3). This thinking is not too far away from the thinking of Hippocrates. Alexander thereby acknowledges that personality, or psychiatric symptoms, are not sufficient to explain a disease, but that the explanation for some diseases must have a combined somatic and a psychological explanation. This is the concept of a psychosomatic disease. Since Franz Alexander's days, science has moved on and the discovery of *Helicobacter pylori* changed the etiology of a duodenal ulcer from a psychosomatic disease to an infectious disease. However studies have shown that even though this explanation suffices for most patients, around 5-20% of duodenal ulcers lack an organic etiology (4).

In the 1960s several psychiatric clinics moved into general hospitals, thereby facilitating the collaboration between the psychiatric medical field, and the somatic medical field. At present the sub-discipline of Consultation Liaison

Psychiatry (CLP) deals with psychiatric comorbidity, i.e. the simultaneous occurrence of a psychiatric disorder and a somatic disease. Over the years, several conditions where psychiatric comorbidity has affected the morbidity and mortality of somatic diseases have been detected, for instance in acute myocardial infarction (5), diabetes mellitus (6), rheumatoid arthritis (7) and hip fracture (8). The opposite relationship, that a somatic disorder may have an impact on the development of psychiatric symptoms or even psychiatric disorders, has also been reported, e.g. asthma causing depression (9) or sepsis causing delirium (10). The work of a CLP-physician in a somatic environment is, not surprisingly, a thorough examination of patients, including physical status, psychic status, age, sex, occupation, past and present diseases and personality before making a diagnosis and prognosis.

My intention with this thesis is to expand the knowledge about psychiatric comorbidity among patients with acute abdominal pain conditions in an emergency department, because these conditions have been little investigated.

BACKGROUND

The panorama of acute abdominal pain in the emergency department

Abdominal pain is a common reason for seeking emergency care and is estimated to be 5-8% of visits to emergency care (11, 12).
Finding the cause of abdominal pain can be difficult even after taking the patients history, physical examination, laboratory testing and various investigations (e.g. x-rays)(11). What sort of investigation chosen often depends on the presentation of pain and the investigating physician's suspicion of the cause. If for example the cause is suspected to be in the upper abdomen (peptic ulcer, gastro-esophageal reflux disease, gastritis, pancreatitis, gallbladder disease or malignancies in these regions) gastroscopy, ultrasound and/or CT-abdomen might be appropriate (13). Other possible causes lead to other investigations, but even though there are several avenues for investigation, still about 25% of the patients will be admitted for further observation/investigation in the hospital (11).
After investigation, the most common diagnosis for acute abdominal pain is non-specific abdominal pain compromising 21-37% of cases in repeated observations for the last decades (12, 14).
The definition of non-specific abdominal pain is controversial, but a possible consensus might be 'short-lived abdominal pain without any obvious etiology after thorough investigation that resolves spontaneously' (11, 14). However, even though no specific cause can be identified, a small percentage of patients diagnosed with non-specific abdominal pain do receive a cancer diagnosis within a year after admission and this frequency increase with patient age (11).

Different studies report different frequencies of other abdominal diagnoses but acute appendicitis, biliary diseases, bowel obstruction, diverticulitis, gastritis, gastric/duodenal ulcer and acute pancreatitis are common (12, 14).

Abdominal diagnoses in emergency ward covered in this thesis.

Dyspepsia

Oustamanolakis & Tack (2012) review of the concept of dyspepsia, which means ‘difficult digestion’ and includes “various symptoms in the upper abdomen, such as fullness, discomfort, early satiation, bloating, heartburn, belching, nausea, vomiting, or pain” (page 1(15)). In the western world dyspepsia is considered to have a prevalence of 20-25%. Dyspepsia is divided into two main categories, organic dyspepsia (OD), where an organic cause can be identified that explains the symptoms, and functional dyspepsia (FD), where no organic cause can be found (15). The prevalence of the two differ: Oustamanolakis & Tack (2012) report 50% OD and 50% FD, while the numbers in other reports are 25% OD and 75% FD (16) and 66% FD and 44% OD (17). Dyspepsia, regardless of cause, leads to decreased quality of life (16).

Organic dyspepsia (OD) vs functional dyspepsia (FD)

OD are diagnoses in which an organic cause that can explain the dyspeptic symptoms, and these causes can include peptic ulcer (5-10% of cases), gastroesophageal reflux disease (GERD; erosive form 20%, non-erosive form 20%), gastritis and to a small percentage, diseases of pancreas or gallbladder/duct and also tumors of the ventricle (15). OD cannot be differentiated from FD, as symptoms of functional and organic dyspepsia overlap. OD requires objective findings of gastroscopy, like from x-rays or ultrasound (18, 19). In this thesis, the term OD will mean acid-dependent organic dyspepsia, as opposed to organic dyspepsia with other causes (e.g. gallbladder disease).

The bacteria *Helicobacter pylori* is one major etiologic factor for peptic ulcer, while another major factor is use of nonsteroidal anti-inflammatory drugs (NSAID) (15, 18, 20).

Gastro-esophageal reflux disease (GERD) is a diagnosis for almost 80% of cases of organic dyspepsia. It is divided into non-erosive reflux disease (NERD) and erosive reflux disease (ERD) the latter is considered more serious because it can lead to esophageal cancer. Gastro-esophageal reflux disease

occurs when gastric contents comes up into the esophagus giving rise to pain, regurgitation and heartburn. Extra-esophageal symptoms such as hoarseness and cough occur in some cases and there is an association with asthma. Infection of *Helicobacter pylori* into the gastric mucosa might either increase or decrease symptoms depending on location of the infection. The disease might have a natural course with decline of symptoms over a ten year period. However, for some patients, the symptoms cannot be cured by antiulcer mediations or by anything else (21).

Gastritis is inflammation of the ventricular mucosa and has two main forms, acute and chronic. Acute gastritis presents as sudden epigastric pain, nausea, or vomiting. However, many patients are asymptomatic or develop very discrete dyspeptic symptoms. Acute gastritis may convert into chronic gastritis if not cured. The etiologies of the condition are several, including infectious agents, autoimmune gastritis, bile reflux gastritis and so forth. It may also be associated with other diseases like Crohns disease or sarcoidosis. The diagnosis gastritis can only be concluded with gastroscopy, often with biopsy of the ventricular mucosa for histologic evaluation of exact type. The most common etiology for gastritis is *Helicobacter pylori*. Chronic gastritis is very common and might eventually result in various conditions like iron-deficiency anemia), peptic ulcer or cancer in the ventricle (22).

Functional dyspepsia is defined as dyspeptic symptoms without an organic genesis however there are studies that associate the condition with anomalies in the function of the ventricle (15). Previously functional dyspepsia was considered a FGID (Functional gastro-intestinal disorder) but in the newest version of the Rome-classification (2016) it is now a considered DGBI (disorders of gut-brain interactions) (23). Functional dyspepsia is described more in detail among the non-specific abdominal disorders (see below).

Non-specific abdominal pain (NSAP)

Among abdominal diagnoses, after investigating procedures, non-specific abdominal pain (NSAP) (ICD R104.0) is the most common discharge diagnosis eventually used in an emergency department (12, 24). This diagnosis can only be used when no organic findings have been found that can explain the symptoms. However, a long-term follow up comparing a group of patients with NSAP versus a group of patients with acute appendicitis found

that 29% of the group with NSAP vs 11% acute appendicitis still had abdominal complaints 22 years after the initial evaluation. Of the NSAP-group 20% developed chronic abdominal pain and 10% developed peptic ulcer (14). Patients with abdominal symptoms without an organic cause are now thought to have diseases of gut-brain interaction (DGBI) (23).

Gastrointestinal disorders are described in the Rome classification which is continually revised and the latest version, Rome IV, is from 2016 (23). The Rome IV classification divides gastrointestinal disorders into three domains; organic GI disorder, motility disorder, and functional GI disorder. Examples of these three domains concerning the same anatomical region would be peptic ulcer, gastroparesis and functional dyspepsia. Peptic ulcer can be identified by gastroscopy, gastroparesis (due to for example diabetes) can be visualized by x-rays but functional dyspepsia eludes objective description. In DGBI, it has been proposed that psychosocial factors (e.g. stress), psychiatric conditions (e.g. anxiety) and personality traits (e.g. neuroticism) play a role thereby introducing the concept of the "brain-gut axis". It is known that the central nervous system has direct contact, via axons, to myenteric plexus and that emotions and psychological states of mind can influence gut processes and *vice versa* in a vicious circle (25-28). Figure 1.

Figure 1. Diseases of Gut-Brain Interactions

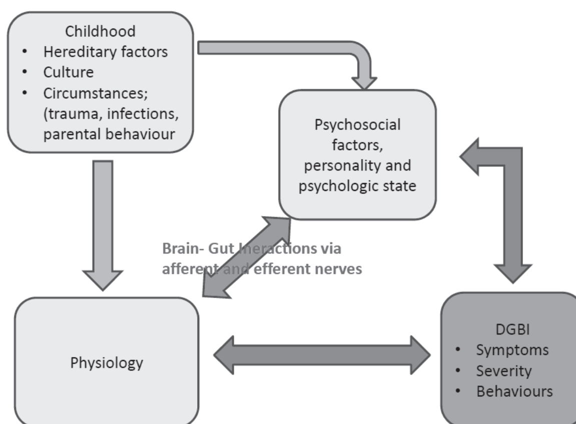


Figure influenced by Drossman, Gastroenterology 2016; 150:1262-1279.

Specific abdominal diagnoses (SAD)

For the purpose of this thesis, specific abdominal diagnoses (SAD) are all the diagnoses where a specific cause for the abdominal symptoms can be determined (with the exception mentioned earlier of organic dyspepsia that are non-acid related). The diagnostic process depends on routine investigations including x-rays, ultrasound, laboratory investigations and so forth. A detailed list of all diagnoses included in the studies can be seen in table 2.

Psychiatric comorbidity

Psychiatric comorbidity along with somatic disorders are common both among patients treated in primary care and in hospital in-patients. Depression and anxiety (with 12 months prevalence of 3-9% or 6-12% respectively) in European countries (29), has been shown to affect several chronic medical illnesses. In their review article Katon et al describes the prevalence of depression among patients treated in primary care to be 5-10% and 6-14% for inpatients in hospitals. The overall prevalence of depression in some chronic medical illnesses are estimated to be 41% (30).

A thorough review of 31 studies involving 16,922 patients showed depression and anxiety to affect diabetes, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, congestive heart failure and coronary artery disease. Not only were patients with these diseases affected by depression and anxiety, the psychiatric disorder had an impact on their wellbeing and more objective parameters like glucose levels (31).

In the case of coronary artery disease it has been shown that depression is not only a risk factor for acute myocardial infarction, but also that a depression present simultaneously with acute myocardial infarction worsens the course in terms of morbidity and even mortality (5, 32-34). Some studies report not only successful treatment of patients with depressive comorbidity and acute coronary disease, but also that the risk of death is diminished if both are treated simultaneously (35).

In addition ot overt psychiatric symptoms like excessive worrying, personality traits have also been shown to influence somatic diseases. In particular the combination of “negative affectivity” and “social inhibition” (together denoted as the “distressed” personality, or personality type D), has been identified as a risk factor for death in patients with coronary heart disease (36-39). A review from 2010 reports personality type D also influence several somatic diagnoses (chronic pain, asthma, tinnitus, sleep apnea, vulvovaginal candidiasis, mild traumatic brain injury, vertigo melanoma and diabetic foot syndrome).

Patients with personality type D also had poor physical health status, poor mental health status, and poor self-management of their disease (40).

The prevalence of psychiatric comorbidity among patients on in the hospital has varied. Among general medical hospital inpatients, Seltzer (41) and Silverstone (42) reported a prevalence of 27 % while Hansen (43) reported 38.7%. Even though the frequency might seem high, the detection rate is low among medical staff. Silverstone reported that only 41% of psychiatric cases were recognized by medical staff compared to 61% by nurses (42), while Seltzer reported that medical staff recognized 31.1% of cases (41).

Because the detection rate is low, so too is the referral rate. Rothenhäusler (44) reported referral rates between 2.6-3.3% and Huyse (45) in a European study reported the mean referral rate to be as low as 1%.

In addition to the increased suffering and possible complications due to psychiatric comorbidity discussed above, studies have reported an increased length of stay (LOS) in patients with psychiatric disorders. Bressi (46)reported increased LOS among patients with schizophrenia and mood disorders, while earlier Frederich (47) reported increases in LOS up to 8 days among patients with psychiatric comorbidity, and more recently Edmondson (48) reported increased LOS in an emergency department among patients with acute myocardial infarct (NSTEMI) or unstable angina and depression.
Whether or not *any* type of psychiatric comorbidity is the cause of increased LOS is debatable. In 2001 Wancata et al (49) found that only patients with dementia or drug-abuse had increased LOS, soon thereafter, Furanletto et al (50) reported increased LOS only for patients with cognitive impairment.

Whether or not psychiatric comorbidity increases LOS or not, there is general consensus about the benefits of early psychiatric consultation. In 2004 Kishi et al (51) reported that shorter LOS was associated with early psychiatric consultation, as did Desan et al in 2011 (52) and Sockalingam et al in 2016 (53).
A couple of decades earlier, in 1991, Strain et al (8) had showed that early psychiatric liaison screening of elderly patients with hip fractures resulted in higher rates of detection of psychiatric comorbidity, better psychiatric care, and earlier discharge.

Studies from emergency departments rarely report the total prevalence of psychiatric comorbidity. However, in 2005, Saliou et al (54) reported that among 500 consecutive patients to an emergency ward, the total number of patients with psychiatric problems were 189 (38%) and of these, 149 (79%) were not at the emergency department for psychiatric reasons. The most common diagnosis in this group was depression (41%) followed by generalized anxiety disorder (19.5%) and alcohol dependence (11.4%). Saliou et al concluded that patients seen in an emergency service are to be considered a population at risk for psychiatric disorders regardless of the reason for seeking care. In 2004 Ford et al (55) reported that, among patients with high utilization of primary care and emergency departments, there is a high prevalence of anxiety and depressive and addictive disorders and this is supported by Stockbridge et al a decade later (56). Two studies by the Wulsin group in 1991 focus on chest-pain in the emergency room and concludes that psychiatric morbidity are often present, either with or without, acute coronary syndrome, Wulsin et al (1991) (57, 58).

Abdominal pain is a common reason for seeking health care, in primary care estimated to be 8% of cases (59) and 5-8% of visits to emergency care, Ferlander et al (2018) and Hastings et al (2011) (11, 12). Abdominal pain associates with depression in 19% of cases and the same figure with anxiety according to Mussel et al (2008) (59). It therefore might be assumed that psychiatric comorbidity is associated with abdominal conditions but studies are lacking from emergency departments.

Diagnosis of depressive and anxiety disorders

Diagnostic procedures in general

Some diseases (like anemia) can be diagnosed by simple tests (like a hematological finding of low hemoglobin). In contrast, no biomarkers, physiological tests, or x-rays that can determine a psychiatric diagnosis. Instead psychiatric diagnoses are built on feelings, experiences, or assumptions that patients express; either they can notice these factors themselves, or the factors can be noticed by others.
Today psychiatric diagnoses are often determined by the Diagnostic and Statistical Manual of Mental disorders (DSM), which is published by the American Psychiatric Association (APA) and has been revised several times since its first edition in 1952. A diagnosis according to DSM is based on certain criteria, and if a patient fulfills a specific number of these criteria, a diagnosis can be determined. The version in use at the time of this writing is DSM-5 (60).
Psychiatric evaluation includes determining or excluding psychiatric diagnoses (axis I) and/or syndromes of personality (axis II) (60). The difference between these are that an axis I disorder is temporary, meaning that the symptoms started at a specific moment in time (e.g. "I started to feel depressed this spring"). For some axis I disorders, there is a distinct starting time but the condition remains for life (e.g. schizophrenia). An axis II diagnosis is a stabile pattern of personality traits that are troublesome for the patient because these traits diminishes the ability to interact with other people, which has consequences for almost all areas of life (education, relations, employment etc.). If an axis II diagnosis exists, there is an increased risk for an axis I diagnose (61-63).

The diagnostic procedure in general, includes interviews, structured or semi-structured, by trained personnel, often aided with questionnaires. There are many different interview guides, but the "the gold standard" is the structured clinical interview for the DSM (or SCID interviews) (DSM-5 and DSM-PD) (64). The interviews makes it possible to either conclude or dismiss a psychiatric diagnose according to the DSM-system. Evaluation of a possible syndrome of personality, or mapping of specific personality traits, can also be made with the help of the Temperament and Character Inventory, see below in

section Personality (65, 66). Questionnaires are developed for particular disorders (e.g. major depression) and are used to determine the depth, or seriousness, of the disorder. The Montgomery-Asberg depression rating scale (MADRS) questionnaire is one example used to differentiate depths of depression (67).

Depressive disorders

In a given community depressive disorders are relatively common. Estimates of prevalence vary among studies and procedures performed (i.e. which screening tools or clinical data are used), but prevalence of depressive disorders is generally thought to be between 2.4-9.1% (29). Risk factors for depressive disorders include for example chronic medical disorders (e.g. diabetes), the prevalence increases among primary care patients (5-10%) to medical/surgical inpatients (6-14%) (30).

Common symptoms of depression are; low mood, loss of interests that usually are joyful, diminished concentration, loss of appetite, disturbed night sleep (often waking up early in morning with anxiety), thoughts about death and so forth (60).

Diagnostic criteria of major depression according to DSM are that at least one of the core symptoms (low mood or loss of interest) must be present and additionally three or four other symptoms of depression must be present, in sum at least five symptoms in total. Also the condition must have been present for at least 14 days, most of the time and not have a somatic explanation (e.g. hypothyreosis) (60).

Depressive disorder might also be associated with somatic conditions e.g. chronic pain (68).

There are other diagnoses within the general concept of depressive disorders like minor depression and dysthymia. Significant differences between these includes fewer required criteria (for minor depression) and persistence for more than 2 years (for dysthymia) (60).

Several questionnaires aid in the diagnosting depression, like (MADRS (67), the Hamilton depression rating scale (Ham-D) (69), and the Hospital anxiety

and depression scale (HAD) (70). Some questionnaires (for example HAD and Prime-MD) can also be used for screening for depressive disorders for (71, 72).

Anxiety disorders

In a given community anxiety disorders are more common than depressive disorders, with a 12-month prevalence of 2.4-12.0 %, with the variation being due to differences among studies in procedure, screening tools, or clinical data (29). Like with depressive disorders anxiety disorders are associated with somatic conditions (73) and with increased health care utilization (74, 75).

Symptoms of an anxiety disorder vary depending on the type of disorder. Worrying about multiple things (generalized anxiety disorder), panic attacks (panic disorder), obsessive-compulsory disorder (OCD) where anxiety is evoked if certain actions not are taken (e.g. checking the door lock for a specific number of times), post-traumatic stress disorder (PTSD) (where anxiety is evoked by remembering a traumatic event) and finally phobias (where anxiety hinders a person from ordinary social interaction) (60).
Like with depressive disorders, it is not rare that anxiety is associated with somatic symptoms like palpitations and dyspnea (60).

The DSM-system discriminates among these different anxiety disorders and questionnaires that might be helpful in the diagnostic procedure e.g. Hamilton anxiety rating scale (Ham-A) (76), Generalized Anxiety Disorder 7-item scale (GAD-7) (77) and the Hospital anxiety and depression scale (70).

Personality

Early theories of Personality

Ever since Hippocrates' famous statement about impact of personality on disease (1), theories of what builds a personality and what a personality really is have occupied thinkers. Hippocrates is considered to be the inventor of the humoral theory of fluids, which is an idea about the origin personality that was further developed by others like Galen. According to the humoral theory, health depends on a delicate balance ("harmony") of black bile, yellow bile, blood, and phlegm, and whenever the equilibrium is distorted, symptoms of disease occur (2). For example, if a person has an excess of black bile, the person would suffer from melancholy; if there was excess of yellow bile, aggressive behavior would be expressed.

The theory that there is a balance of different entities that build personality has prevailed through the centuries, but as science has progressed, it has shaped the ideas about interactions of importance. In 1963, Eysenck published an article in Nature that used modern factor analysis of personality traits and the medieval humoral theory into two opposing dimensions, neuroticism vs extraversion. Neuroticism is diverted into "stable vs unstable" and extraversion is diverted into "extroversion vs introversion" (78) (Figure 2).

Figure 2. Personality model according to Eysenck.

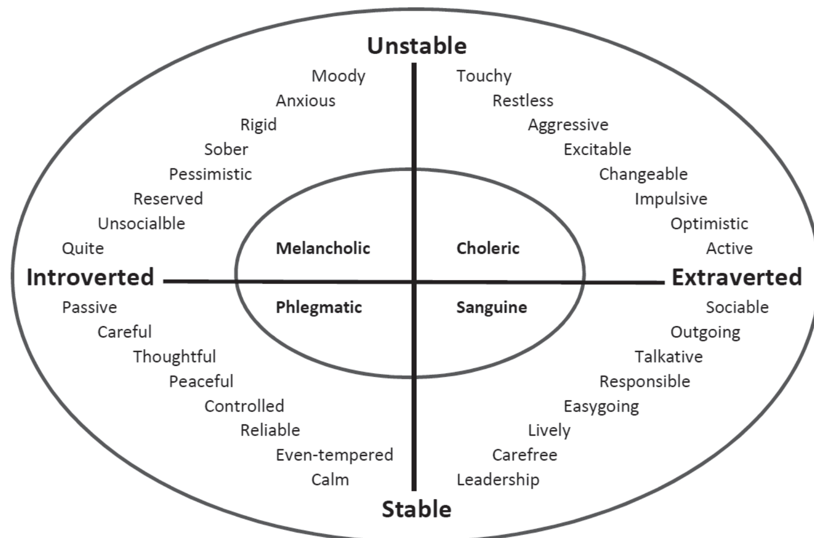


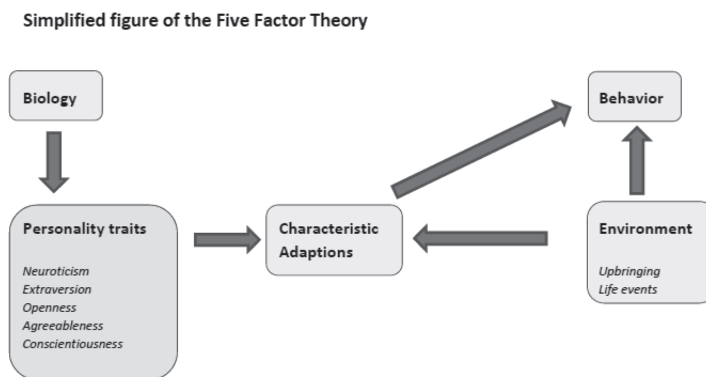
Figure inspired from Biological basis of personality, prof H.J. Eysenck (Nature 1963)

In his article, Eysenck argued that temperament is mainly inherited, but did not argue against the idea that personality is also influenced by the environment. His main hypothesis (and that of other contemporary scientists) was that temperament is inherited and forms the basis on which character (as measured by the extra- vs introversion dimension) develops under the influence of the environment and during upbringing. Eysenck noted the resemblance between the theory of neuroticism vs extraversion and the medieval humoral theory, and argued that criminals were "choleric" and thereby belong to the unstable extraverted personality type (Figure 2) (78). Eyneck's theories were based on Cattells work with factor analysis of ratings and self-ratings for personality and his work to pare these down to the sixteen words on the outer circle in the figure. Later Eysenck also added the dimension psychotism, and this three-dimensional theory about neuroticism, extraversion and psychotism eventually became the 'Eysenck personality questionnaire' or EPQ (79).

The Five Factor Theory (FFT) and the Five Factor Model (FFM)

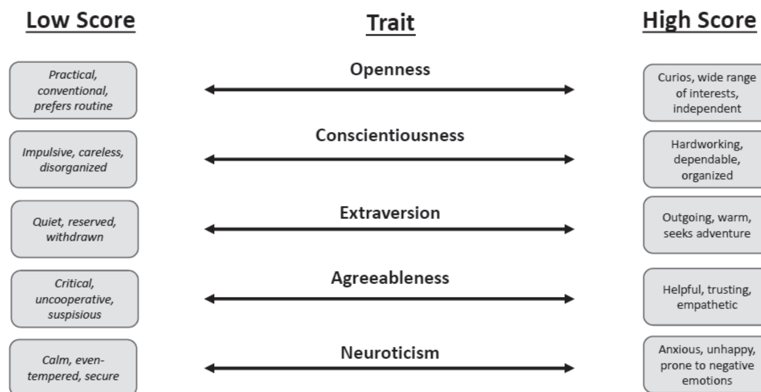
The Five Factor Theory (FFT) was developed by Costa & McCrae (80) when psychotism was replaced with agreeableness, openness and conscientiousness. The FFT therefore is based on neuroticism, extraversion, openness, agreeableness and conscientiousness. The Five Factor Model (FFM) evolved out of the FFT and became the base for the questionnaire NEO-PI by Costa & McCrae (80). Even though the FFT is derived from collected words about personality and subsequent factor analysis, it has been shown that neuroticism, extraversion, openness, agreeableness and conscientiousness are inherited traits. These traits can be termed as "basic tendencies" that will interact with the environment (upbringing, life events etc.) in dynamic processes and shape the individual personality (81) Figure 3.

Figure 3. The Five Factor Theory (FFT)



The questionnaire NEO-PI, offers the opportunity to map personality traits described by FFM and FFT. The system is hierarchical and each dimension (e.g. neuroticism) is scored into "higher" and "lower" (Figure 4) (82).

Figure 4. High and low scores in FFM.



The psychobiological personality model and the Temperament and Character Inventory (TCI) by Cloninger.

The psychobiological personality model

An alternative way to explore personality traits, was proposed in 1986 by Cloninger (83), who started to investigate associations between personality disorders (Axis II) and psychiatric diagnoses (Axis I). Cloninger was not satisfied with factor analysis as a foundation for describing personality, because factor analysis of words describing personality traits is based on both genotype (inherited) and phenotype (developed), which led to confusion when for example extraversion was proven to be inherited independently from two traits (impulsivity and sociability). In contrast Eysenck had treated extraversion as a single behavioral dimension caused by shared environmental circumstances. Contrary to Eysenck's theories (65), in Cloningers view, genetic and environmental influences do not influence behavior in the same way. Instead Cloninger formulated a psychobiological theory based on temperament

(inherited i.e. automatic responses to stimulus) and character (learned i.e. cognitive behavior in response to stimulus). Initially, based on empirical findings, it was proposed that three dimensions of temperament (novelty seeking, harm avoidance and reward dependence) were associated with dopamine, serotonine and noradrenaline respectively. These dimensions were associated with personality deviations and in return also with psychiatric diagnoses, e.g. histrionic personality profile (axis II) is associated with anxiety disorders (axis I) (83). On this basis the "Tridimensional Personality Questionnaire" (TPQ) was created. Further development led to persistence being associated with glutamate and a part of reward dependence and therefore became an own dimension. Finally, character dimensions (self-directedness, cooperativeness and self-transcendence) were added, resulting in a seven dimensional model that can be explored using the Temperament and Character Inventory (TCI). Peculiarly, the four dimensions of temperament can be seen as a modern version the humoral theory (Melancholic, harm avoidance; Choleric, novelty seeking; Sanguine, reward dependence; Phlegmatic, persistence)(65).

The psychobiological model of personality was now based on seven higher order dimensions; namely novelty seeking (NS), harm avoidance (HA), reward dependence (RD), persistence (P), self-directedness (SD, cooperativeness (CO) and self-transcendence (ST). Each of the higher order dimensions, except for persistence, also have lower order dimensions describing the dimension in detail. See below under the section "Temperament and Character Inventory (TCI) and table 1.

Subsequent studies have supported the theory of association between personality traits and psychiatric disorders. Depressive disorders have been associated with higher levels of harm avoidance and self-transcendence and lower levels of self-directedness and cooperativeness. Severity of depression has been associated with levels of harm avoidance, self-directedness and cooperativeness (61). Harm avoidance and self-directedness are associated with both depression and anxiety symptoms in the general population and also predict the risk for lifetime mental disorders (84). Harm avoidance is strongly associated with generalized anxiety disorder (85).

Cloninger's psychobiological theory stipulates that temperament is largely inherited and character develops mostly in interactions with the environment. Some authors question this, and suggest that character might also be inherited (86).
In sum temperament and character are distinct features that are part of an 'iterative epigenetic process' in which the factors interact with each other to motivate behavior (86, 87).

The character traits are thought to be formulated in process with the temperament traits which are facilitating, or suppressing, their development, under influence of the environment. So even as temperament and character are to be seen as distinct features there is a continuous interaction between them (88). For example it is known that high harm avoidance has a negative influence on the development of character (Figure 5) (86).

Figure 5. The iterative epigenetic process

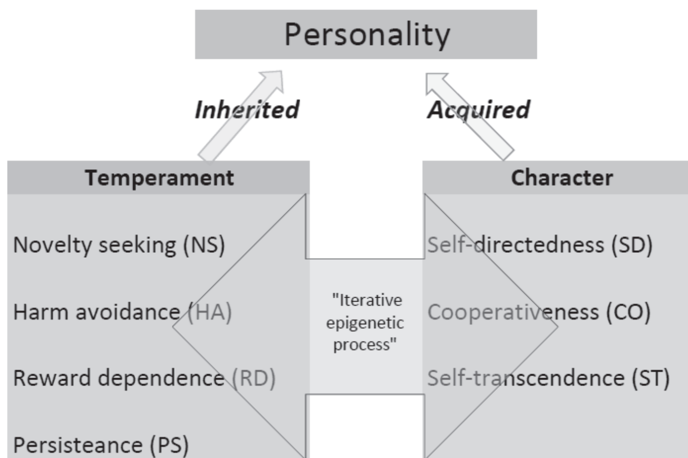


Figure is inspired by Prof Cloningers psychobiological theory about the structure of personality

The Temperament and Character Inventory (TCI).

The Temperament and Character Inventory (TCI) questionnaire, comes in different versions, but all have in common that statements have to be confirmed or denied. The statements covers different areas of personality (e.g. higher and lower dimensions) based on the psychobiological theory. Besides measuring separate higher and lower dimensions the TCI also have several validity scales. These scales measure how the test is performed and gives a probability of the validity in each test situation. There are five validity scales; rarity scale, runs scale, number true scale, like items scale and unlike items scale. These scales have been validated. The scales measures how the test have been performed which gives information about if the answers represents a probable profile of the person or if the test is to be considered invalid (65). The dimensions of TCI show little change during adult life. There might be some development (e.g. character matures to some extent) but the rank-order between the traits is sustained (88). The TCI is used for detection and categorizing syndromes of personality, but it can also be used to study specific personality traits (65, 89).

From the table 1 descriptors of the TCI can be seen. The high scores and low scores are divided into the lower order dimensions. Novelty seeking have four lower dimension (NS1-NS 4), harm avoidance have four lower dimensions (HA1-HA4), reward dependence have three (RD1, RD3, RD4) and persistence have only one (RD2). This because in the development of TCI it was discovered that persistence was an own dimension. Self-directedness and cooperativeness have five (SD1-SD5, CO1-CO5, respectively) and finally self-transcendence have three (ST1-ST3).

Table 1.

Temperament and Character Descriptors

		High scorers		Low scorers
TEMPERAMENT	**Novelty Seeking (NS)**	*exploratory, curious*	*NS 1*	*indifferent*
		impulsive	*NS 2*	*reflective*
		extravagant, enthusiastic	*NS 3*	*frugal, detached*
		disorderly	*NS 4*	*orderly, regimented*
	Harm Avodiance (HA)	*worrying, pessimistic*	*HA1*	*relaxed, optimistic*
		fearful, doubful	*HA2*	*bold, confident*
		shy	*HA3*	*outgoing*
		fatigable	*HA4*	*vigorous*
	Reward Dependence (RD)	*sentimental, warm*	*RD1*	*practical, cold*
		dedicated, attached	*RD3*	*withdrawn, detached*
		dependent	*RD4*	*independent*
	Persistance (P)	*industrious, diligent*	*RD2*	*inactive, indolent*
		hard-working		*gives up easily*
		ambitious, overachiever		*modest, underachiever*
		perseverant, perfectionist		*quitting, pragmatist*
CHARACTER	**Self-Directedness (SD)**	*mature, strong*	*SD1*	*immature, fragile*
		responsible, reliable		*blaming, unreliable*
		purposeful	*SD2*	*purposeless*
		resourceful, effective	*SD3*	*inert, ineffective*
		self-accepted	*SD4*	*self-striving*
		habits congurent with long term goals	*SD5*	*habits incongruent with long time goals*
	Cooperativeness (CO)	*socially tolerant*	*CO1*	*socially intolerant*
		emphatic	*CO2*	*critical*
		helpful	*CO3*	*unhelpful*
		compassionate, constructive	*CO4*	*revengeful, destructive*
		ethical, principled	*CO5*	*oppurtunistic*
	Self-Transcendence (ST)	*wise, patient*	*ST1*	*impatient*
		creative, self-forgetful	*ST2*	*unimaginative, self-consious*
		united with universe	*ST3*	*pride, lack of humility*

Table inspired from "The Temperament and Character Inventory (TCI): A guide to its Development and Use", Cloninger et al, 1994

The five factor model and the psychobiological model by Cloninger.

The five factor model (FFM) and Cloninger's psychobiological model have different foundations for their respective theories. The FFM is based on factor analysis of ratings of personality and the psychobiological model is based on psychiatric diagnoses and their association with personality traits. The two fields of psychiatry and psychology have evolved different preferences regarding the two theories. In general, the FFM is more popular among psychologists and the psychobiological model among psychiatrists (90). Although they are different theoretical ways of viewing personality, the results of NEO-PI (FFM) and TCI (the psychobiological model) show considerable overlap with each other. For example, harm avoidance (TCI) is strongly positively associated with neuroticism (NEO-PI) and negatively associated with extraversion (NEO-PI). The overlap of scores of dimensions between the two questionnaires is substantial (90).

Personality profile D

Studies have found that a specific personality profile is associated with morbidity and mortality in patients with cardiovascular diseases (36). This specific personality profile, type-D personality, is characterized by negative affectivity and high social inhibition. Persons with high negative affectivity tends to experience negative affect over time, regardless of actual situation. In this sense, high negative affectivity resembles high neuroticism. High social inhibition means a tendency to not share emotions and persons with high social inhibition tends to feel tense and inhibited in social situations (37). From the perspective of the FFM has been found that negative affectivity is positively associated with neuroticism and negatively associated with conscientiousness, agreeableness and extraversion. Social inhibition is positively associated with neuroticism and negatively associated with extraversion and conscientiousness (39). There is also an association between temperament and character dimensions of TCI and type-D personality. High affectivity has been found to associate negatively with self-directedness, reward dependence, persistence and

cooperativeness but positively with harm avoidance. Social inhibition is positively associated with harm avoidance and negatively with reward dependence, persistence and self-directedness (91).

Association between psychiatric disorders, personality and abdominal conditions

Organic dyspepsia

Despite the opinion that only organic causes are relevant in the etiology of organic dyspepsia (15), certain studies have shown the contrary. There are reports of psychosocial, psychiatric, personality traits and environmental factors for peptic ulcer, one of the diagnoses found in the concept of organic dyspepsia. Two contributions by Levenstein et al (92, 93) have reported that depression, maladjustment and the personality trait hostility, are associated with peptic ulcer. Two reports by Goodwin et al (94, 95) reported associate peptic ulcer with generalized anxiety and the personality trait neuroticism which were followed up 10 years later by Taha et al (96) who found associations of peptic ulcer with neuroticism and anxiety disorders. These studies depend on surveys based on patients self-reports. There is generally a good correlation between self-reports and medical chart notes for many disorders (e.g. asthma), but good correlation has not been shown for self-reports and gastrointestinal diseases (97, 98).
Objective examinations (gastroscopy) have been used, for instance by Pajala et al (99) who found patients with verified organic dyspepsia to have a higher prevalence of mental distress than the general population and interestingly found no difference between patients with organic or functional dyspepsia. Filipovic et al (100) compared gastroscopy of patients with functional dyspepsia and peptic ulcer, compared to healthy controls and found that people with functional dyspepsia had more depressive symptoms and higher levels of neuroticism compared to patients with peptic ulcer and controls.

Although these studies include objective examinations there is a lag time between symptom debut and actual examination, so the possibility of a gastric ulcer healing spontaneously cannot be excluded, which would give misleading result (101, 102).

Feldman et al (103) compared two groups of inpatients, one with complicated peptic ulcer disease and one with kidney or gallstone disease, and one group of out patients with uncomplicated ulcer disease. A control group of healthy men was used for comparison. Compared to patients with kidney or gallstone disorders and the controls, patients with peptic ulcer disease were found to be more pessimistic, dependent, and perceived life events more negatively. Patients with peptic ulcer were also found to be more immature and had more depression and anxiety. A weakness of this study is that it did not include women.

Environmental factors have also been reported to be associated with peptic ulcer. For example Levenstein et al (93) described higher incidence of peptic ulcer among shift-workers, lack of sleep, smoking, high alcohol consumption, and consumption of non-steroid anti-inflammatory drugs (NSAID). It is also known that the incidence of peptic ulcer increases with catastrophes e.g. the bombing of London during World War II which implies that stress may have an important role (93). It has been shown that patients who are considered psychologically usually have a favorable long-term course after a stress induced peptic ulcer (93). Jones (18) reports in a review that even after the discovery of *Helicobacter pylori* as a cause for peptic ulcer and the known impact of NSAIDs, 5-20% of patients that develop peptic ulcer lack an organic etiology for the condition.

Several authors (95, 96, 99, 103) discuss the personality trait neuroticism and its association to peptic ulcer. In addition in 1994 Wilhelmsen et al (104) performed a prospective randomized trial with short-term cognitive psychotherapy given to patients with recurrent peptic ulcer and compared to a control group with recurrent peptic ulcer. Interestingly, the patients receiving therapy relapsed in peptic ulcer significantly faster than the control group. When anti-ulcer treatment was given along therapy, there were no difference in relapse rate between the groups. However, neuroticism decreased in the therapy group. In a follow-up study 10 years later, Wilhelmsen and Berstad found that after eradicating *Helicobacter pylori*, neuroticism also declined, leading to the conclusion that high levels of neuroticism are consequences of peptic ulcer, not the other way around (105).

Gastroesophageal reflux disease (GERD)

Like with peptic ulcer, there are also reports associating GERD with psychosocial factors, psychiatric diagnoses, personality traits and environmental factors. In a review article Mizyed et al (106) described psychosocial factors (stress, cigarette smoking, alcohol consumption), psychological comorbidity (depression, anxiety) and personality traits (neuroticism) that were significantly associated with GERD. Patients who failed to respond to treatment were more likely to have low psychological well being, more anxiety, or depression and they suggested that patients with GERD refractory to treatment might benefit from psychological evaluation and even treatment. Similary, Rathi et al (107) compared 100 patients with confirmed GERD with 100 controls matched by age and sex, and found that patients with GERD had a prevalence of depression (46%) and anxiety (31%) compared to controls 19% and 11% respectively. No statistical difference were found among confounding factors (age, sex, alcohol, tobacco etc.). Lee et al (108) found that high neuroticism and low extraversion were statistically associated with symptoms of GERD but not necessary with esophagitis. Matic et al reports (109) that patients with depression and GERD had more psychiatric rehospitalizations than depressed patients without GERD.

Gastritis

Like with peptic ulcer and GERD there are also reports of an association between gastritis and mental disorders. Goodwin et al (110) reported significant association of gastritis and anxiety or mood disorders based on a population survey. Anxiety disorders had a prevalence of 27.0 % and affective disorders a prevalence of 20.1% among adults with gastritis compared, 15.3% and 11.5% respectively in adults without gastritis. The authors mention one major limitation that the study was based on self-reports.

Non-specific abdominal pain

As previously mentioned non-specific abdominal pain is the most common discharge diagnosis from an emergency department (24). Of those discharged with this diagnosis, it has been shown that about 20% will develop chronic abdominal pain (14). This diagnostic group is classified in Rome-IV as a DGBI (diseases of gut-brain interactions) and it is supposed that etiology of the abdominal pain comes from gut-brain interactions (23, 25) which are a

combination of biological, psychological and social factors (111). Among social factors, chronic stress, abuse, and severe life events (e.g. marital separation) have been reported in patients with irritable bowel syndrome (IBS) (27, 111). Depression and anxiety are also overrepresented in this group, and these diagnoses to affect on both symptom severity and the decision to seek health care (26, 59, 111). For example it has been found that patients with functional dyspepsia have motor dysfunctions compared to controls in emptying the ventricle to the duodenum, of disturbances in the propulsion of food in the ventricle towards pylorus and also an increased sensitivity to distension of the ventricle. The causes of these disturbances are unknown, but it is known that conditions like anxiety might amplify these dysfunctions. Studies have shown that functional dyspepsia is associated with anxiety disorders, depressive disorders, and somatoform disorders. Sometimes conditions like, for example sensitivity to gastric distension, are also found among people not seeking health care for functional dyspepsia, implying that mental disorders may play a role in the decision of seeking health care or not (15). Higher levels of neuroticism, more maladaptive illness behavior, and worse coping skills are found among patients seeking health care with IBS compared to those not seeking consultation (27, 28). Other studies have shown that higher levels of neuroticism are associated with less response to treatment (27).

Specific abdominal diagnoses

Few studies have reported psychiatric comorbidity among patients with specific abdominal diagnoses. An exception is a study by Ni Mhaolain et al (112) which estimated frequency of depression (12.5%) and anxiety (18.75%) based on screening of surgical in-patients. The studied cohort had of a variety of surgical diagnoses (gallstone disease, appendicitis, etc.) and there were also patients with coronary heart disease and peptic ulcer, conditions which are known to be associated with of psychiatric comorbidity (32, 34, 92-96). About 22.9% of the patients were referred to psychiatric consultation, but the results of those consultations was not reported. Feldman et al (103) compared inpatients with complicated peptic ulcer, inpatients with gallstone/kidneystone diseases, out patients with uncomplicated peptic ulcer disease and healthy controls. They

found that patients with peptic ulcer differed significantly from patients with gallstone/kidney stone diseases and healthy controls in terms of personality traits and psychiatric symptoms. Of the patients with peptic ulcer 18% were considered "normal", 33% were considered "neurotic" and 49% had some personality disorder, compared to 59%, 25% and 16% of patients with stone disease and 50%, 20% and 30% of healthy controls, respectively. One of the strengths of that study is that two of the groups, complicated peptic ulcer group and gallstone/kidney group, could be equally stressed by being hospitalized, and thereby differences in stress symptoms between the groups could be excluded. Two weaknesses were that the study only consisted of men and that psychiatric diagnoses were not set according to the DSM-system. A 1977 report from Gomez et al (113) concluded that only 15.6% of 96 patients who complained of recurrent pain, after thorough investigation did had an underlying organic cause for their symptoms, and in the rest depression, chronic tension, hysterical mechanisms and alcoholism was found as explanatory factors. Joyce et al (114) found that 18 patients, out of 105 inpatients, did not have an organic etiology for their symptoms; most of the 18 were women, and anxiety was concluded an important factor for the symptoms. It should be noted that these two last studies have nearly opposite results, which might be due to different study designs. Gomez et al. excluded all patients with apparent organic causes from their material, which might give a misleading result compared to Joyce et al. or Ni Mhaolain et al. Also, neither Gomez et al. nor Joyce et al. described the prevalence of psychiatric comorbidity, because both studies divided the patients into those with an organic cause and those with a non-organic cause. This division leaves the group of patients with an organic cause untested for psychiatric comorbidity. These studies are more than 30 years old and criteria for psychiatric diagnoses have changed since then. Especially with DSM-III-R (1987) when a lot of criteria was changed (115).

In summary the prevalence of psychiatric comorbidity among patients with specific abdominal diagnoses is not well studied.

Self-rated health

Self-rated health (SRH), regardless of whether it is a conclusion of multiple questions or a single question (e.g. “how would you consider your general health?”), has been found to be predictive for future morbidity and mortality (116-119), and the predictive value seems to be independent of objective physical or mental status. The exact formulation of the question also has minimal impact on the predictive value (116).
Finding out the self-rated health is done in many ways. There can be a single question in a questionnaire with a variety of items (e.g. Prime-MD), and the question can be placed at the beginning (e.g. SF-36) or at the end (e.g. Prime-MD). Alternatively, self-rated health can be evaluated with a specific questionnaire with several items about health (e.g. QLQ-C30, EQ-5D). The questions can be answered in different ways from choosing a specific category on a five-level Likert scale, from “excellent” to “poor”, (e.g. Prime-MD), to pointing to a visual analogue scale with end points “worst” and ”best” (e.g. EQ-5-D). Studies have shown that, regardless of these specific variations, the predictive value regarding future morbidity and mortality is the same (116).

Conflicting arguments claim that objective physical status (e.g. symptomatic coronary heart disease) affects on SRH but that does not change the predictive value of the answer (120).

SRH has been found to associate with personality traits both in the FFM and TCI. Several articles have reported that high levels of neuroticism and low levels of extraversion, conscientiousness and agreeableness are associated with low SRH; others report that high levels of harm avoidance and low levels of self-directedness and cooperativeness are associated with low SRH and subjective health complaints (121-125). For patients with manifest diseases, higher levels of neuroticism in combination with lower levels of extraversion, conscientiousness and agreeableness are associated with low general and low self-rated cardiovascular health (126). Among patients with cancer, harm avoidance and self-directedness, together with depression and anxiety, influenced SRH (127).
Patients with personality disorder, or sub-threshold personality disorder, reported low SRH and also multiple longstanding illnesses (128).

The previous section ("Psychiatric comorbidity") discussed personality profile D and its association with low SRH (129, 130) and that the association affects on several somatic diseases (40). It has also been shown that for patients with a "vulnerable personality profile" and a low SRH, SRH can improve by self-management interventions (130).

Medication

Treatment of depressive and anxiety disorders often includes prescription of drugs. The following description of treatment is in correspondence with Swedish guidelines in “Läkemedelsboken” (131).

Medication of depressive disorders.

Depressive disorders of moderate to serious strength are often treated with an antidepressant medication. The different diagnoses among the depression disorders might require different pharmaceutical compounds or differing durations of treatment.

The first line choice of an antidepressant drugs are SSRI.s (e.g. sertraline, citaloprame, escitaloprame). If medication with an SSRI is not effective or side-effects are intolerable, a SNRI might (e.g. venlafaxine, duloxetine) or a NaSSA (e.g. mirtazapine) be chosen. If there is a significant presence of anxiety in combination with depression, an adjuvant treatment with anxiolytics (e.g. oxazepam) might be necessary.

Medication of anxiety disorders

As with depression there are several different diagnoses within anxiety disorders that might require treatment with different medications. A patient with some kind of social phobia might need medication only when a social event is at hand. However, most patients with anxiety disorders need continuous treatment, at least for certain periods of time.

As listed above the first choices for treating anxiety disorders are with the antidepressant SSRIs or SNRI. The general recommendation is to avoid adjuvant treatment with anxiolytics, although there can be situations when it is needed (e.g. at the beginning of treatment with an SSRI, anxiety might increase).

AIM OF THE THESIS

The general aim of this thesis is to study the prevalence of psychiatric comorbidity among patients with abdominal pain in an emergency department and possible long term psychiatric problems.

Specific aims

Study I: To investigate whether personality traits differ among patients in an emergency ward with various abdominal conditions using the Temperament and Character Inventory (TCI) compared to a control group.

Study II: To study whether psychiatric symptoms differ in patients with various abdominal conditions in an emergency ward using Prime-MD.

Study III: To study the association between self-rated health (SRH) and personality traits among patients with various abdominal conditions in an emergency ward using Prime-MD and Temperament and Character Inventory (TCI).

Study IV: To study long-term psychiatric problems among patients admitted to an emergency department for abdominal pain by studying prescription of psycho-pharmaceutical drugs, and the associations among different abdominal conditions, personality traits, self-rated health, and psychiatric symptoms in a long-time perspective.

METHODS

Design

The overall design for the studies in this thesis was to investigate personality traits, psychiatric symptoms, and self-rated health among consecutive patients with abdominal conditions hospitalized for one night at the emergency department. In addition prescriptions were evaluated for anti-depressants and anxiolytic drugs 10-15 years after the initial hospitalization. All patients were given a letter with information about the study and the questionnaires (Prime-MD and TCI). If the patient approved participation, the questionnaires were filled in and left to the staff in a closed envelope. The envelopes were collected on regular basis by the researcher.

Material

Patients with abdominal pain may seek the emergency department in Kalmar by their own decision and do not need a referral from primary care. They are examined by the doctor on call on the emergency floor, and if needed hospitalized for further investigation or observation. Patients for whom the somatic condition is serious are directly admitted to a regular surgical floor, or operative, or intensive care unit. Only patients with a stable somatic situation will be admitted to the emergency ward.

The material for conclusions in this thesis is based on 165 consecutive patients hospitalized with abdominal pain at the emergency department for surgical diseases during one year. The patients voluntary participated by filling in two questionnaires (TCI and Prime-MD) and allowing investigation of their chart notes and prescriptions.

Initially 224 consecutive patients with abdominal pain were invited to participate in the study, and 43 (19.2%) declined participation. The TCI questionnaire was filled out by181 patients, but 16 (7.1%) of these were incomplete and had to be excluded.

The first study was based on voluntary participation of 165 patients (89 women and 76 men), who filled out TCI (study I), but not all patients also filled out Prime-MD (studies II and III). Studies II and III comprised 137 patients (77 women and 60 men), of the initial 165 (83%). It was possible to do a 10-15 year follow-up for 129 of the 165 patients (78%), (75 women and

54 men) concerning prescriptions, were possible to follow up 10-15 years after admission at the emergency department concerning prescriptions. Before follow-up, 23 had moved out of county, 12 patients had died and one could not be traced. For study I a control group of 122 persons (age and gender matched), was recruited from the local population in Kalmar. Figure 6 presents a flowchart of the studies and table 2 present patient's characteristics.

Figure 6.

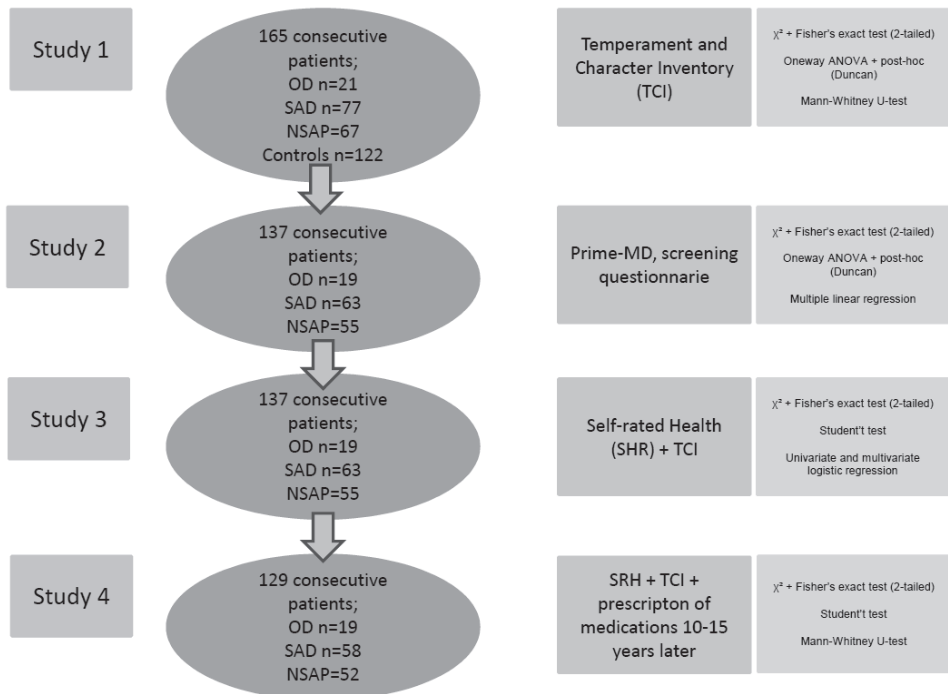


Table 2.

Abdominal diagnoses in studies I-IV.

		Study I	**Studies II and III**	**Study IV**
		n=165	**n=137**	**n=129**
Non-specific abdominal pain (NSAP)	Abdominal pain NOS	67	55	52
Organic Dyspepsia (OD)	Duodenal ulcer	10	10	9
	GERD	5	4	4
	Gastritis	4	3	4
	Ventricular ulcer	2	2	2
Specific Abdominal diagnoses (SAD)	Gallbladder disease	25	22	22
	Diverticulitis	21	14	14
	Appendicitis	8	7	8
	Gastroenteritis	7	6	1
	Ileus	5	4	4
	Chron´s disease	3	3	3
	Pancreatitits	3	3	3
	Ventricular tumor	1	1	0
	Mallory Weiss bleeding	1	0	0
	Gastrointestinal bleeding NOS	1	1	1
	Obstipation	1	1	1
	Ulceros colitis	1	1	1

Of the initial 165 patients (study 1), 12 patients were dead at the follow up study 10-15 years after admission to the emergency ward (study IV). One patient in the group of NSAP dead within a year of the admission of a non-abdominal cause. The rest of the patients died more than 7 year after the admission. 23 patients had moved out of the county and 1 patient could not be traced.

Instruments

Temperament and Character Inventory (TCI)

The TCI-questionnaire, developed by Cloninger et al., is based on a number of statements, in this thesis the 238-item version is used, that are to be answered "true" or "false"(65). The Swedish validated 238-item self-report questionnaire version of TCI (132) was utilized in the studies of this thesis. Cronbach α vales for the higher order dimensions were 0.56 to 0.85 and for the lower order dimensions 0.20 to 0.74 (132). The level of maturity of the character can be approximated by the sum of SD and CO and a mature character is said to be self-reliant, cooperative and self-transcendent (88) which is used in study I, III and IV. The Temperament and Character Inventory (TCI), shows good correlation with the Neuroticism-Extraversion-Openness Personality Inventory (NEO-PI). NEO-PI measures instead the traits neuroticism, extraversion, openness, agreeableness and conscientiousness as determinants of the personality, according to the Five Factor Model (FFM) (133). There is a good correlation between the dimensions of personality trait neuroticism (NEO-PI) and harm avoidance (TCI) (65, 90).

Details about the psychobiological theory and the TCI is to be found in the section Personality, The psychobiological theory and Temperament and Character Inventory, earlier in this thesis.

Prime –MD

Prime-MD was developed for use in primary care in US by Spitzer et al (134). The instrument screens and identifies diagnoses for common psychiatric conditions, is validated and have shown high correspondence with interviews performed by psychiatric personnel (134).

The first part of the instrument is a questionnaire with 28 questions, to be answered 'yes' or 'no', whether or not a specific symptom has often been present for the last month. There are six sections covering different psychiatric fields and each section has between one to fifteen questions. The first section of the questionnaire is about somatic symptoms e.g. palpitations, headache etc. The second section is about eating problems, the third about depressive conditions the forth about anxiety and so on.

It has been shown that if a patient answers more than five questions with 'yes' in the first section, besides the reason for attendance to a primary care facility, the risk of having a psychiatric condition is raised (135, 136).

The questionnaire also asks questions to screen for alcohol problems. For this purpose CAGE is used , which is an acronym for Cut-down, Annoyance, Guilt and Eye-opener. 'Cut-down', addresses whether the patient has tried to cut down the alcohol consumption. 'Annoyance', addresses whether people around the patient have complained or gotten annoyed about the patient's alcohol consumption. 'Guilt' addresses the possibility that the patient has feelings of guilt about current level of alcohol consumption. Finally, 'Eye-opener' addresses whether the patients has the need for a drink in the morning to cure a hang-over. In the Swedish version of CAGE this last question has been changed to a question about whether the patient has drunk 5 or more standardized glasses of alcohol.
If a person answers yes' twice or more on the CAGE-questionnaire a further evaluation of alcohol habits is recommended. The CAGE-questions have been shown to be very useful in hospital settings for screening of alcohol problems (137-140).

At the end of the Prime-MD questionnaire, the patient is asked to rate their general health over the last month with one of five options; Excellent, Very Good, Good, Not so good and Poor. Numerous studies have shown that questions about general health predict future morbidity and even mortality. Regardless of the actual physical condition (117-119, 141). In plain language, two groups of patients, with the equal physical status, will statistically differ in the future in terms of morbidity and mortality in proportion to their answers about their own on general health.

The full use of Prime-MD includes an interview following the protocol for psychiatric disorders of the DSM-system (115). However in study II-IV only results of the Prime-MD questionnaire has been used, as no interviews were performed. Also ratings of self-rated health has been simplified into poor and good by putting “excellent”, “very good” and “good” together to Good, and taking “not so good” and “poor” together to Poor.

Medical records

From medical records, patients were assessed for demographic data, length of stay (LOS), current psychiatric contacts and prescriptions of antidepressants and anxiolytics, both at admission and 10-15 years after admission. Records were also obtained regarding current admission and for a time-span of 7 years before and 7 years after admission for all 165 participants. The reason for this was to detect previous conditions and hospitalizations relevant for exploration of psychiatric comorbidity. High utilization of emergency care has previously shown to be associated with psychiatric comorbidity (55, 142).

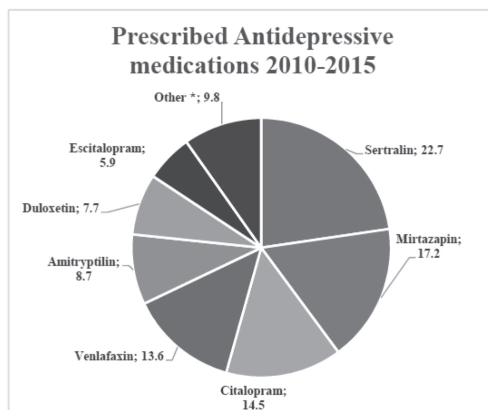
Prescribed medications at admission and 10-15 years after

Current medication at admission was assessed from reading chart notes from each participant. Medications prescribed 10-15 years after were assessed from the database system (Cosmic) used in the health care system of the Kalmar county. The database system Cosmic covers all health care, regardless where it is given (primary care (public and private), somatic hospital services or psychiatric services). The Cosmic system started in 2006 and by 2010 all health care was supposed to be connected to the system. It has therefore been possible to trace all prescriptions made after the admission. Choosing a time

span of 6 years (2010-2015) for controlling prescription was motivated by the fact that, for many patients, medication is prescribed one year at a time, and a window of a single year might miss a prescription. A longer time span was also chosen to be sure that possible private primary care centers were included in Cosmic, as it is possible that connection was delayed even after 2010.

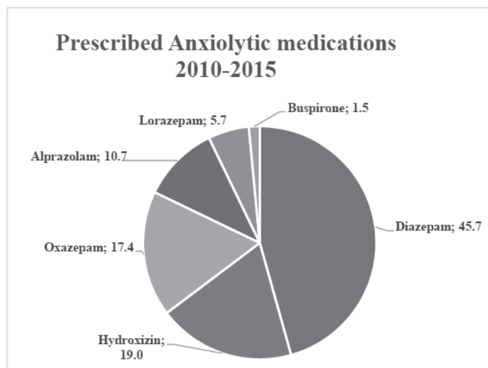
Example prescriptions of antidepressants and anxiolytics can be seen in table 4 and 5 respectively.

Table 4.



* Other; Paroxetin, Klomipramin, Mianserin, Fluoxetin, Buprion, Reboxetin, Agomelatin, Moklobemid, Vortioxetin

Table 5.



Ethical considerations

Studies I-IV were performed with approval of the Regional Ethical Review Board in Linköping, Sweden (D-nr 984 04). Informed consent was obtained from all participants and the procedures of the project comply with the ethical standards of the Helsinki Declaration of 1964.

Statistical analysis

All statistical analyses in this thesis were performed using the software Statistica ver.12. Significance levels were set to $p<0.05$ in all studies.

In general, χ^2-analyses were performed on categorical data (e.g. sex, diagnostic groups, etc.) and whenever possible followed by Fisher's two-tailed exact test. For continuous variables (e.g. age, T-scores of TCI) Studen-t test or one-way Anova was used, in case of significance followed by post-hoc Duncan. The Mann-Whitney U-test was used in attrition analysis to compare variables between participating and excluded patients. Non-normal distributed variabels (e.g. length of stay) were transformed by logarithm before analysis.

In study I, a higher order dimension, "maturity of character" was created by combining the higher order dimensions self-directedness and cooperativeness in accordance with Josefsson et al (88). In study II, multiple linear regression was used to explore possible associations between length of stay and extra-gastrointestinal symptoms. In study III, taking the shown association between NEO-PI and TCI in consideration (90) and the defined personality profile D (39), a distressed personality profile was created by harm avoidance in the upper quartile and the sum of SD and CO in the lower quartile. Univariate logistic regression revealing risk factors for poor SRH was performed on all TCI higher order dimensions showing significant association ($p<0.05$) with poor SRH and all corresponding TCI lower order dimensions together with sex, age categories and diagnostic groups. The univariate logistic regression was followed by multivariate logistic regression for all variables with $p<0.1$ in univariate logistic regression together with sex and age categories. A complete overview of used statistical methods in different studies is presented in table 6.

Table 6.

Statistical tools used in studies I-IV in thesis				
Type of statistic procedure	**Study I**	**Study II**	**Study III**	**Study IV**
χ^2-test, followed by Fisher's exakt test when possible	X	X	X	X
One-way Anova followed by post-hoc (Duncan) in cases of significance	X	X		
Student-t test			X	X
Mann-Whitney U-test	X	X	X	X
Multiple linear regression		X		
Univariate and multivariate logistic regression			X	

RESULTS

Study I

Temperament and character in patients with acute abdominal pain.

The aim of study I was to investigate whether patients with acute abdominal pain in an emergency department had differing personality traits, and whether these correlated with abdominal pain diagnosis.

One hundred sixty-five (165) consecutive patients admitted to emergency ward due to abdominal pain were divided into three diagnostic groups (organic dyspepsia (OD, N =21), specific abdominal diagnoses (SAD, N= 77), and non-specific abdominal pain (NSAP, N=67) and one hundred twenty-two (122) age- and gender-matched controls (C) performed the Temperament and Character Inventory (TCI). Data was also collected about smoking, alcohol habits and previous and forthcoming health care utilization (both somatic and psychiatric) for 7 years before and after the admission to the emergency ward.

All patients with the diagnosis OD had gone through gastroscopy. In this study, only patients for whom hydrochloric acid had a part in the etiology (e.g. duodenal ulcer) were considered to be in the OD-group. Patients with organic dyspepsia due to other reasons (e.g. ventricular tumor) were considered part of the SAD-group. This group, SAD, consisted only of diagnoses were a specific cause could be identified (e.g. diverticulosis). The group of NSAP comprised all patients for whom an organic cause could not be determined.

Results for higher order dimensions showed that patients with OD had significantly higher levels of harm avoidance than C and SAD ($p=0.003$ respectively), lower levels of cooperativeness than C and SAD ($p=0.004$ and $p=0.048$ respectively), higher levels of self-transcendence than C, SAD and NSAP ($p<0.001$, $p=0.048$ and $p=0.012$ respectively). Patients with OD also

had less matured character (self-directedness, SD, and cooperativeness, CO, taken together) than C and SAD (p=0.004 and p=0.026 respectively).

For lower order dimensions, patients with OD showed higher harm avoidance, HA 1, than C, SAD and NSAP (p=0.002, p=0.001 and p=0.011 respectively) and, higher harm avoidance HA 4 than C and SAD (p<0.001 and p=0.024 respectively). NSAP compared to C showed, higher levels of harm avoidance HA 4 (p=0.022). OD compared to C and NSAP, showed lower levels of cooperativeness CO 5 (p=0.035 and p=0.004, respectively), and when OD was compared to C, higher levels of ST 2 and ST 3 (p=0.002 and p=0.004 respectively. OD also showed higher levels of ST 3 compared to NSAP (p=0.007). NSAP showed lower levels of CO5 compared to C (p=0.004).

A analysis of personality traits showed that patients with organic dyspepsia, in the temperament, had higher levels of anxiety (HA), more pessimism (HA 1) and were more easy fatigued (HA 4). They also had a less matured character (SD and CO together). In character, patients with organic dyspepsia had less acceptance of other people (CO) and were less responsible (CO 5), but also had a higher sense of togetherness (ST 2) and spiritual acceptance (ST 3). These traits separated patients with organic dyspepsia mainly from controls and patients with specific abdominal diagnoses, and for some traits, also from patients with non-specific abdominal pain. Patients with non-specific abdominal pain also were less responsible (CO 5) and were more easy fatigued (HA 4) than controls.

Further analysis showed that slightly more than 70% of patients with OD had deviating HA, SD and CO or ST, more than one standard deviation, when same traits were compared to patients with SAD (38%, p=0.007), NSAP (37%, p=0.011) or C (33%, p=0.001).

In sum study I shows that the group of patients suffering from organic dyspepsia, where hydrochloric acid is part of the etiology, show a different pattern of personality traits compared to controls, patients with specific abdominal diagnoses, and patients with non-specific abdominal pain. Patients with non-specific abdominal pain show, to a lesser degree, different personality traits compared to controls.

Study II

Psychiatric symptoms among patients with acute abdominal pain.

The aim of study II was to further investigate whether the previously obtained differences in personality traits among patients with acute abdominal pain in an emergency department also had differences in psychiatric symptoms indicating psychiatric comorbidity, length of stay or in perceived general health.

Of the 165 consecutive patients in study I admitted to emergency ward due to abdominal pain 137 patients answered the Prime-MD questionnaire. The diagnostic procedures in this study was the same as in study I. The groups in this study consisted of participants with organic dyspepsia (OD, N= 19), specific abdominal diagnoses (SAD, N=63) and non-specific abdominal pain (NSAP, N=55). Data were from the Prime MD questionnaire and demographic and medical records.

Results revealed that during the last month, patients with OD reported more chest pain than patients with SAD or NSAP ($p=0.027$ and $p=0.023$ respectively), worries ($p=0.01$ and $p=0.002$ respectively) and palpitations ($p=0.005$ and $p=0.039$ respectively). Patients with OD also reported more dizziness ($p=0.004$), insomnia ($p=0.006$) and alcohol problems ($p=0.01$) than those with SAD. Patients with NSAP compared to both SAD and OD reported more headache ($p=0.048$) and compared to SAD more insomnia ($p=0.022$) and problems with alcohol ($p=0.05$).

Results from Prime-MD analysis revealed a positive association between the number of acknowledged extra-gastrointestinal symptoms and distinct psychiatric symptoms associated with anxiety or depression ($F [8,135]=30.6$, $p<0.001$). For example, among patients with three or more extra-gastrointestinal symptoms, 50% had problems with depressed mood ($p=0.005$), 55% with loss of interest in joyful things ($p=0.002$), and 55% with worrying too much about various issues ($p<0.001$).

Patients with OD had significantly more extra-gastrointestinal symptoms associated with anxiety or depression (chest pain, dizziness, palpitations, dyspnea, insomnia, nervousness, worry, decreased interest in joyful things and depressed mood) compared to patients with SAD ($p<0.001$) or NSAP ($p=0.002$), ($F[2, 126]=6.301$, $p=0.002$). Patients with OD reported self-rated health “not so good” in 63% of cases, significantly more often than SAD patients (19%), or NSAP patients (18%) ($p<0.001$).

Patients with OD and SAD had similar lengths of stay and these were significantly longer than for patients with NSAP ($p=0.002$).
However, there was no significant difference in length of stay between number of extra-gastrointestinal symptoms or self-rated health.

In sum study II shows that patients with organic dyspepsia, where hydrochloric acid is part in the etiology, have more extra-gastrointestinal symptoms associated with symptoms of depression or anxiety, compared to patients with specific abdominal diagnoses or non-specific abdominal pain. Patients with organic dyspepsia reported lower perceived health three times more often than patients with specific abdominal diagnoses or non-specific abdominal pain. Patients with organic dyspepsia had a length of stay comparable to those with specific abdominal diagnoses but there was no general association between number of extra-gastrointestinal symptoms or perceived health that could have indicated a more somatic serious condition. Patients with non-specific abdominal pain reported some extra-gastrointestinal symptoms significantly differently than patients with specific abdominal diagnoses and organic dyspepsia.

Study III

Personality traits are important for self-rated perceived health among patients with acute abdominal pain, especially in organic dyspepsia.

The aim of study III was to further investigate whether the previously studies that found low perceived health among patients with acute abdominal pain is associated with personality traits, especially among patients with organic dyspepsia.

Of the 165 consecutive patients in study I admitted to emergency ward due to abdominal pain 137 patients filled out the self-rated health questionnaire and the Temperament and Character Inventory (TCI). The diagnostic procedures in this study were the same as in study I. The groups in this study consisted of organic dyspepsia (OD, N= 19), specific abdominal diagnoses (SAD, N=63) and non-specific abdominal pain (NSAP, N=55), Data was obtained from the self-rated health in the Prime-MD questionnaire, the TCI, and demographic and medical records.

Results showed that patients rating their health as poor were also, were more harm avoidant ($p<0.001$), fearful ($p=0.039$) and fatigued ($p<0.001$) in temperament. They were less matured in character ($p=0.002$), less self-directed ($p<0.001$), less responsible ($p<0.001$), purposeful ($p=0.012$), resourceful ($p=0.003$) and goal-directed in behavior ($p=0.001$). Multivariate logistic regression showed that poor self-rated health was predicted by OD (OR7.1 (0.04 – 0.51), $p=0.003$), high fatigability (OR 11.9 (2.62 – 53.54), $p=0.002$) and low responsibility (OR 5.0 (0.05 – 0.85), $p=0.029$). Patients with a ‘distressed personality profile’ (high harm avoidance and less matured character) rated their health as poor in 91% of cases compared to 29% of patients with SAD ($p=0.002$) or 33% of those with NSAP ($p=0.003$).

In sum the results of study III show that perceived general health is influenced by several personality traits. Organic dyspepsia and the personality traits ‘easy fatigue” and ‘less responsible’ are among the important risk factors for having a perceived general health of poor. In the group of patients with a ‘distressed personality profile’ organic dyspepsia seems to be the most important for self-rated health poor.

Study IV

Increased psychopharmaceutic use among patients with abdominal pain 10-15 years after admission to emergency care.

The aim of study IV was to do a long-term follow-up on the participants and further explore whether previous findings of different personality traits, extra-gastrointestinal symptoms associated with depression or anxiety, and self-rated health affect prescription of anti-depressive or anxiolytic drugs.

Of the 165 consecutive patients in study I admitted to emergency ward due to abdominal pain who answered Prime-MD questionnaire and the Temperament and Character Inventory (TCI), it was possible to follow 129 patients after 10-15 years in regards to prescription of psycho-pharmaceutical drugs. The groups in this study consisted of 19 patients with acid-dependent organic dyspepsia (OD), 58 patients with specific abdominal diagnoses (SAD) and 52 patients with non-specific abdominal pain (NSAP). Data was collected from the the Prime-MD and TCI questionnaires and the computerized health care system (Cosmic) regarding prescriptions. Prescriptions were divided into three groups, total psycho-pharmaceutical drugs (PD), anti-depressive drugs (AD) and the unique combination of anti-depressive and anxiolytic drugs (ADAX).

Results showed that only few of the patients expressing psychiatric symptoms at admission were prescribed PD or AD. At follow up, 10-15 years later, 63% of patients with OD (compared to 31% of patients with SAD and 40% of patients with NSAP) were prescribed PD (p=0.047). The group of OD was significantly different from SAD (p=0.016) and from SAD and NSAP taken together (p=0.040). ADs were prescribed for 53% of OD, 19% patients with SAD and 23% patients with NSAP (p=0.018) and OD was significantly differed from SAD (p=0.007) and from SAD and NSAP taken together (p=0.027). ADAX were prescribed for 37%, of patients with OD, 7% of patients with SAD and 23% of patients with NSAP (p=0.005). Again, OD was significantly differenced from SAD (p=0.004) and from SAD and NSAP taken together (p=0.045). Patients with NSAP were significantly different from SAD (p=0.028). Increased prescriptions of PD, AD and ADAX was significantly

related to higher levels of harm avoidance (PD; p=0.001, AD; p=0.004 and ADAX; p=0.001), to significantly lower levels of self-directedness (PD; p=0.001, AD; p=0.004 and ADAX; p=0.003), and to less matured character (sum of self-directedness and cooperativeness) (PD; p=0.006, AD; p=0.024 and ADAX; p=0.009). Regarding the different diagnostic groups OD had the highest frequency of increase of ADAX, 37%, compared to 7% for SAD, and 23% for NSAP (p=0.005). Further analysis showed that OD was significantly different from SAD (p=0.004) and SAD and NSAP taken together (p=0.045). Also, NSAP was significantly different from SAD (p=0.028).

At follow up of 10-15 years the majority of patients who, on admission, expressed psychiatric symptoms or had more than 5 extra-gastrointestinal symptoms or had psychiatric contact or had alcohol problems or rated poor-self rated health or had a distressed personality had prescriptions of PD, AD or ADAX.

In sum study IV shows that many patients who come to an emergency department for abdominal symptoms and also have psychiatric symptoms do not have psychiatric prescriptions. These psychiatric symptoms do not seem to be temporary, as the majority of patients with these symptoms have increased psychiatric medications 10-15 years. Patients with acid-dependent organic dyspepsia and, to a lesser extent, patients with non-specific abdominal pain are overrepresented among those prescribed psycho-pharmaceuticals, antidepressants and the combination of antidepressants and anxiolytics compared to patients with specific abdominal diagnoses, which corresponds with previous findings in study I-III.

Attrition analysis for studies I-IV

Attrition analysis using Mann-Whitney U-test and χ^2-analysis revealed no statistical difference between participating patients (N=165) and declining patients (N=59) in study I, participating patients (N=137) and initial patients (N=165) in studies II and III and participating patients (N=129) compared to initial patients (N=165) in study IV, regarding age, gender or diagnostic groups.

DISCUSSION

Acid-dependent organic dyspepsia

The main finding of studies I-IV is that the group of patients with acid-dependent organic dyspepsia is different from the other two groups (specific abdominal diagnoses and non-specific abdominal pain) in all investigated aspects.
They differ in personality traits, in expressing numbers of extra-gastrointestinal symptoms, have more anxiety and depression symptoms, have lower self-rated health, have more problems with alcohol, and they are overrepresented in prescription of antidepressant and/or anxiolytic drugs 10-15 year after the initial admission.

In study I patients with acid-dependent organic dyspepsia showed personality traits in temperament that are associated with anxiety, worry, pessimism, doubt and susceptibility to fatigue. In character, these patients had traits associated with being intolerant, critical, self-orientated, opportunistic but also flexible, able to see 'wholeness' (about persons and nature), and being spiritually accepting. In an approximation of the level of maturity of character, (sum of self-directedness and cooperativeness) patients with acid-dependent organic dyspepsia scored lower than others. In study II the patients with acid-dependent organic dyspepsia presented more symptoms of anxiety and depression, more extra-gastrointestinal symptoms and rated low on their general health. In study III it was shown that, in combination with the distressed personality profile, these patients rated their general health as poor in 91% of cases.

Previous studies of patients with acid-dependent organic dyspepsia has shown that patients with this condition are overrepresented in having higher levels of neuroticism (95, 96, 103, 105, 106, 108) and psychiatric disorders of anxiety and depression (92-94, 96, 103, 106, 107, 109). Neuroticism, as has been discussed earlier in this thesis, is a counterpart to harm avoidance in TCI (90). Harm avoidance is associated with anxiety and depressive disorders which

might explain the overrepresentation of these symptoms in the group (Study II)(61, 84, 85). This finding corresponds with earlier findings of increased frequency of anxiety and depression among patients with peptic ulcer (92-94, 96, 103).

Among personality traits, patients with acid-dependent organic dyspepsia showed high harm avoidance and low cooperativeness (study I), high harm avoidance and low self-directedness (study III), and less mature character (sum of self-directedness and cooperativeness, studies I and III). These traits correspond to the FFM profile of distressed personality and were overrepresented among patients with acid-dependent organic dyspepsia compared to specific abdominal diagnoses and non-specific abdominal pain. This result has not been reported previously. The distressed profile has been associated with low self-rated health in many studies and is associated with depression and anxiety (129) . Patients with acid-dependent organic dyspepsia are also overrepresented in prescription of antidepressants and/or anxiolytic drugs (study IV).

These findings (traits expressed in the group of acid-dependent organic dyspepsia correspond with the risk of depressive and anxiety disorders) can at least in part be explained by the fact that personality traits are quite stable throughout life. From the perspective of 10-15 years after admission acid-dependent organic dyspepsia does not seem to be a temporal disease, instead data argues that it is, at least for some patients, a chronic disease. These findings contradicts the report about high levels of neuroticism declining after remission of acid-dependent organic dyspepsia (105). The group of patients that had prescription aimed to decrease depression and anxiety also had symptoms that are associated with harm avoidance (neuroticism).

Patients with acid-dependent organic dyspepsia also reported more extra-gastrointestinal symptoms and symptoms associated with depression and anxiety than the other two groups with abdominal pain. Single symptoms (e.g. depressed mood) are associated with depression (134), and also the number of extra-gastrointestinal symptoms is positively associated with the risk of depression or anxiety (135).

As mentioned previously peptic ulcer, gastritis and GERD have been associated with personality traits and psychiatric disorders. However most of these

associations are based on large surveys with non-controlled medical chart notes, which leaves uncertainty about the validity. Studies that did control personality traits and/or psychiatric symptoms with verified medical chart notes do not address the problem with self-healing of an ulcer. The studies in this thesis reports personality traits and psychiatric symptoms on patients where acid-dependent organic dyspepsia was confirmed by gastroscopy and thereby rules out false associations.

Non-specific abdominal pain

The group of patients with non-specific abdominal pain showed deviations in the lower order dimensions of exhaustibility and being opportunistic (study I). They expressed significantly more extra-gastrointestinal symptoms (headache, problems with sleeping, and problems with alcohol) than patients with specific abdominal diagnoses, but on the same level as acid-dependent organic dyspepsia (study II). They rated their general health at the same level as specific abdominal diagnoses, but significantly higher than those with acid-dependent organic dyspepsia (study II). At 10-15 years after admission they had a higher frequency of prescription of the combination of antidepressant and anxiolytic drugs compared to patients with specific abdominal diagnoses but not compared to patients with organic dyspepsia 10-15 years after admission (study IV).

Previous studies on patients with non-specific abdominal pain report that 29% of them had abdominal symptoms 20 years after admission, and that as many as 20% of them will develop chronic abdominal pain (14). It can be suspected that at least some patients who subsequently develop chronic pain have DGBI (disease of gut-brain interactions), as definition of this group includes that there is no organic finding to explain the symptoms. Patients with DGBI have higher prevalence of neuroticism, depression and anxiety (26-28, 59, 111). However, the frequency symptoms associated with depression or anxiety among patients with non-specific abdominal pain was comparable with the frequency among patients with specific abdominal diagnoses (study II). Concerning reported higher levels of neuroticism (28) it is of note that patients with non-specific abdominal pain had significantly higher levels of exhaustibility, a lower order dimension of harm avoidance that corresponds to

neuroticism (study I). Higher levels of harm avoidance do associate with depression and anxiety disorders which might explain the higher frequency of prescribed combinations of antidepressant and anxiolytic drugs 10-15 years later.

Specific abdominal diagnoses

The group of patients with specific abdominal diagnoses are significantly different from patients with non-specific abdominal pain or acid-dependent organic dyspepsia in a number of ways. They had no personality traits that differed from the control group (study I), had almost no psychiatric symptoms compared to patients with organic dyspepsia or non-specific abdominal pain (study II), had a self-rated health not significantly different from patients with non-specific abdominal pain (study II and III) and had the lowest prescription of psycho-pharmaceutical drugs compared to the other two groups (study IV). These observations do not exclude psychiatric comorbidity in individual cases but specific abdominal diagnoses could be interpreted as bearing diminished risk risk for psychiatric comorbidity compared to patients with acid-dependent organic dyspepsia or non-specific abdominal pain.

SRH – predictor of bad prognosis

Poor self-rated health has been associated with the personality traits easy exhaustibility, less responsibility, and the distressed personality profile (study III). In study II, self-rated health of 'poor' also was significantly associated with acid-dependent organic dyspepsia. In study III multivariate logistic regression showed that acid-dependent organic dyspepsia and the personality traits easy exhaustibility and less responsibility predicted a self-rated health of

‘poor’. Furthermore, patients with the distressed personality profile, together with acid-dependent organic dyspepsia, rated their general health as ‘poor’ three times more often than patients with the distressed personality profile together with specific abdominal diagnoses or non-specific abdominal pain (study III). Patients with poor self-rated health had a significantly higher frequency of prescription of antidepressants and/or anxiolytic drugs 10-15 years after admission (study IV).

It is known that the single question “How would you rate your general health” is prognostic for subsequent morbidity (116) and the results of studies II-IV support this conclusion, especially as self-rated health is associated with personality traits (123, 126, 128), which in turn is associated with depression and anxiety (61, 63, 85)

In sum, answering the one question “How would you rate your general health” with “poor” is associated with personality traits associating with the distressed personality in at least 29% of cases, and in 91% of cases with acid-dependent organic dyspepsia. Almost 60% of patients having a distressed personality profile do get some kind of psycho-pharmaceutical drug prescribed 10-15 years after admission, which promotes the single question about general health to a very important, and easy, question with a clear prognostic value. This lifts the single question about general health to a very important, and easy, question with a prognostic value. For patients with acid-dependent organic dyspepsia a heavy prognostic value – and for patients with acid-dependent organic dyspepsia, a very strong prognostic value.

Prime-MD and extra-gastrointestinal symptoms

The Prime-MD questionnaire has been (used in studies II, III and IV) in its full use (questionnaire and interview), has a high validity compared to investigation performed by trained psychiatric personnel (134). However, in the studies for this thesis, only the questionnaire was used, leaving some uncertainty about whether the collected symptoms also represents psychiatric disorders. It has been reported that 42% of patients acknowledging a positive answer on the Prime-MD questionnaire eventually turn out not to have a psychiatric disorder when an interview is performed. But sensitivity and specificity vary: sensitivity is good to excellent for anxiety and alcohol use but lower for mood disorders. In a previous study the specificity for anxiety was moderate but good for mood and alcohol disorders (134).

The number of admitted symptoms on the Prime-MD questionnaire has previously been associated with the increased risk for a psychiatric disorder, especially if the symptoms are considered somatoform (meaning they are not relatable to the cause of the consultation). In case of a somatoform symptom, the risk for an anxiety or depressive disorder ranges between 40-90% (135). In study II several psychiatric symptoms were associated with organic dyspepsia and increased number of extra-gastrointestinal symptoms. The extra-gastrointestinal symptoms were considered somatoform as they did not relate to abdominal pain.

Whether psychiatric symptoms and extra-gastrointestinal symptoms can be equated with a psychiatric disorder is of course uncertain. However, the results of the Prime-MD questionnaire do correspond with prescription of antidepressants and anxiolytic drugs 10-15 years later which gives the questionnaire some validity. The Prime-MD questionnaire was useful in the studies in this thesis as it screens for psychiatric symptoms and also somatic symptoms that are associated with psychiatric disorders.

Length of stay

Length of stay has previously been associated with psychiatric comorbidity in several studies (46-48) but other studies dismiss this association (49, 50) . In study II, there were no associations between data supporting psychiatric comorbidity (e.g. number of extra-gastrointestinal symptoms or self-rated health) and length of stay.
Patients with non-specific abdominal pain had significantly shorter length of stay than patients with acid-dependent organic dyspepsia or specific abdominal diagnoses (study II). Patients with acid-dependent organic dyspepsia had significantly higher numbers of extra-gastrointestinal symptoms and self-rated health conditions of 'poor', compared to patients with specific abdominal diagnoses, which a group of patients where some had serious diagnoses (e.g. cancer) or were going through surgery. Even though the data is inconclusive about whether psychiatric comorbidity has effect on length of stay, it is a fact that patients with acid-dependent organic dyspepsia had significantly more psychiatric symptoms. Other studies confirm that psychiatric consultation might decrease length of stay (8, 51-53) which argues that a psychiatric consultation might make a difference in length of stay and also argues for post-discharge interventions.

Limitations

The studies in this thesis had some limits. The first limitation is the small number of patients with acid-dependent organic dyspepsia. However all these patients were consecutive and had their diagnoses verified by gastroscopy which is a strength compared to earlier studies that associated acid-dependent organic dyspepsia with personality traits and/or psychiatric symptoms. Even though the group of acid-dependent organic dyspepsia is small, its uniqueness in terms of personality traits and psychiatric symptoms, was verified by three independent sources of information (TCI, Prime-MD, and prescription data) compared to specific abdominal diagnoses and non-specific abdominal pain.

Secondly, only one question was used concerning self-rated health. Several questionnaires could have been used to explore general health but studies have shown that the results are much the same regardless which questionnaire used

and that the sole question “How would you rate your general health?” is predictive for future health (116). Again the validity of the question in Prime-MD is supported by prescription data showing significantly higher prescription of antidepressants and anxiolytic drugs among patients rating their general health as poor.

Third, extra-gastrointestinal symptoms might be associated with somatic disease and not (as presumed in study II) associated with the risk for a psychiatric disorder. For example, palpitations or dizziness might be consequences of low blood pressure or low hemoglobin count due to gastrointestinal bleeding from a peptic ulcer. If extra-gastrointestinal symptoms were associated with a serious somatic disease, presumably the extra-gastrointestinal symptoms would also be associated with increased length of stay. However, the number of extra-gastrointestinal symptoms was not associated with longer length of stay in study II. Furthermore, if the extra-gastrointestinal symptoms were associated with a serious somatic disease, patients probably would not have been admitted to the emergency ward but rather to a regular surgical ward or intensive care. It might be assumed, that having a number of extra-gastrointestinal symptoms could be a risk factor for psychiatric disorders, especially as these symptoms might not be seen as somatoform it they were not the reason for the consultation in the first place. However, it cannot be excluded in every single case that the extra-gastrointestinal symptoms were associated with somatic disease rather than psychiatric disorder.

Another limitation is that only the questionnaire part (not the interview part) of Prime-MD was used in studies II, III and IV. The questionnaire is intended as a screening instrument to be followed by a structured interview. If the full sequence is performed (both questionnaire and interview), the procedure of Prime-MD has high validity compared to evaluation by trained psychiatric personnel (134) but it is known that patients acknowledging a psychiatric symptom do not qualify for a psychiatric diagnosis in 42% of cases (134) depending on the exact psychiatric disorders (see Discussion). Results of sole use of the questionnaire therefore can neither confirm nor disprove a current psychiatric disorder.

Finally, using prescribed antidepressants and/or anxiolytic drugs as a confirmation of psychiatric problems might not be warranted because for

example antidepressants might be prescribed for chronic pain (143). However, even though antidepressant medication is prescribed for both psychiatric and non-psychiatric conditions, the majority of prescriptions are for psychiatric reasons. Gardarsdottir et al (144) found that prescription of anti-depressive medications were for psychiatric indications (depression, anxiety, OCD) in 68.1% of cases, and Wong et al (145) measuring prescription of anti-depressive medications for a variety of conditions found that depression, anxiety, panic disorder, OCD and social phobia were specified in 79.5% of cases among 185 primary care physicians for 100,000 patients.

CONCLUSIONS

Studies I-IV, using different independent instruments, show that psychiatric comorbidity among patients with acute abdominal pain is common and also has an impact on a patient's future.

The results of studies I-IV corroborate previous results about acid-dependent organic dyspepsia and non-specific abdominal pain. However some new information has been revealed:

- Gastroscopy has confirmed the somatic diagnosis in acid-dependent organic dyspepsia and that it can be associated to personality traits, both in temperament and character, and psychiatric symptoms. Previous studies have not demonstrated this by certainity.

- The diagnosis of acid-dependent organic dyspepsia is associated with poor self-rated health.
- The risk for poor self-rated health, associated with acid-dependent organic dyspepsia, is aggravated by personality traits, both in temperament and character.
- Prescription of antidepressants and/or anxiolytics are significantly associated with acid-dependent organic dyspepsia and non-specific abdominal pain 10-15 years after admission indicating persisting psychiatric problems.

It is obvious that there is a need for routine screening of patients with acute abdominal pain, especially those having acid-dependent organic dyspepsia, and non-specific abdominal pain, for psychiatric comorbidity.

Screening on a regular basis might lead to early detection of psychiatric problems which could benefit patients suffering from psychiatric comorbidity.

One of the instruments used in the studies is the Prime-MD questionnaire, which has 28 “yes/no” questions on a single sheet of paper. This simple questionnaire gives information about the following:

- Possible psychiatric problems by specific questions about symptoms (e.g. worries).
- Somatic symptoms that might be associated with depression or anxiety (e.g. palpitations)
- Possible problems with alcohol
- The patient’s own perception of the general health – a very prognostic question, also associated with personality.

The results of the Prime-MD could be used for screening, for patients who might benefit from a psychiatric consultation.

The purpose of an emergency department is to handle acute conditions that cannot wait for a scheduled appointment or an out-patient facility, and it might not be possible for a full psychiatric consultation to take place at the emergency ward in every case. It is therefore important to have an effective

screening tool, and in study II, Prime-MD was shown to be valuable for screening for possible psychiatric consultation. If the prognostic value of the question about general health is taken into account, the value of Prime-MD is even higher.

Patients identified with possible psychiatric comorbidity can be referred to a specialist in psychiatry, and at this consultation a Temperament and Character Inventory can be made. The benefits of doing so are clearly shown in studies I, III and IV. It is important to identify possible personality traits that might influence the risk for developing depressive or anxiety disorders.

With a consultation of a psychiatrist comes the opportunity to intervene in possible psychiatric disorders which could take the form of prescription of antidepressants or anxiolytics but might also include psychotherapy.

Studies on patients with different somatic conditions have shown both a prevalence of psychiatric comorbidity and also the benefits of psychiatric interventions. We know for example that patients with acute myocardial infarction and depression have a worse prognosis in terms of both morbidity and mortality (32, 34), that treatment with antidepressants is both effective and safe for reducing depression (5) and might even decrease the risk for death (35).
It is also possible that for patients with acute abdominal pain, especially those with acid-dependent organic dyspepsia or non-specific abdominal pain, screening for psychiatric comorbidity might be beneficial.

Because the results from studies I-IV depend on a small number of patients, especially those with acid-dependent organic dyspepsia, it is important to repeat the studies with a larger patient population. Sample size can be increased by having parallel psychiatric consultation with suspected cases of acid-dependent organic dyspepsia and patients with other types of acute abdominal pain might benefit from such a study.

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